**SECTION 2.5**
**CLINICAL OVERVIEW**

---

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

Gilead Sciences

15 July 2015

---

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 4
LIST OF IN-TEXT FIGURES ..... 4
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 5
PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS ..... 8
1. PRODUCT DEVELOPMENT RATIONALE ..... 9
1.1. Scientific Background ..... 10
1.1.1. HIV-1 Infection and Current Treatment Options ..... 10
1.1.2. Rationale for FTC/RPV/TAF Development ..... 11
1.2. Overview of the Clinical Development Program ..... 13
1.2.1. Clinical Pharmacology Development Program ..... 13
1.2.2. Dose Selection ..... 14
1.2.3. Clinical Efficacy and Safety Development Program ..... 14
1.2.4. Regulatory Guidelines and Advice ..... 19
2. OVERVIEW OF BIOPHARMACEUTICS ..... 20
2.1. Formulation ..... 20
2.2. Dissolution Profile ..... 20
2.3. Bioavailability ..... 20
2.4. Food Effect on Exposure ..... 21
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 23
3.1. Mechanism of Action ..... 23
3.1.1. TAF ..... 23
3.1.2. RPV ..... 23
3.1.3. FTC ..... 23
3.2. In Vitro Activity ..... 24
3.2.1. TAF ..... 24
3.2.2. RPV ..... 25
3.2.3. FTC ..... 25
3.3. ADME Characteristics ..... 25
3.3.1. Absorption ..... 26
3.3.2. Distribution ..... 27
3.3.3. Metabolism and Elimination ..... 27
3.4. Clinical Pharmacokinetics ..... 28
3.4.1. Pharmacokinetics After Single- and Multiple-Dose Administration in HIV-Infected and Healthy Subjects ..... 29
3.4.2. Comparison of Exposure Between Healthy and HIV-Infected Subjects ..... 30
3.5. Intrinsic Factors ..... 30
3.5.1. Renal Impairment ..... 30
3.5.2. Hepatic Impairment ..... 31
3.5.3. Hepatitis B and/or Hepatitis C Virus Coinfection ..... 32
3.5.4. Pediatrics ..... 32
3.5.5. Pharmacokinetics/Pharmacodynamics ..... 33
3.5.6. Demographic Factors ..... 34
3.5.7. Potential for Drug Interactions ..... 35
3.6. Summary of Clinical Pharmacology ..... 36
4. OVERVIEW OF EFFICACY ..... 38
4.1. Rationale for Primary Efficacy Endpoint ..... 38

4.2. Efficacy in ART-Naive Adults ..... 39
4.2.1. E/C/F/TAF ..... 39
4.2.2. RPV ..... 41
4.3. Efficacy in Virologically Suppressed Adults ..... 43
4.3.1. E/C/F/TAF ..... 43
4.3.2. Eviplera ..... 45
4.4. Efficacy in Adults with Mild to Moderate Renal Impairment ..... 46
4.5. Efficacy in ART-Naive Adolescent Subjects ..... 46
4.5.1. E/C/F/TAF ..... 46
4.5.2. RPV ..... 47
4.6. Efficacy Discussion and Conclusions ..... 47

5. OVERVIEW OF SAFETY ..... 49

5.1. Extent of Exposure ..... 50
5.2. Criteria for Evaluation and Statistical Methods ..... 50
5.3. Overall Safety ..... 51
5.3.1. Adverse Events ..... 52
5.3.2. Clinical Laboratory Evaluations ..... 59
5.4. Analysis of Adverse Drug Reactions ..... 61
5.5. Bone Safety ..... 64
5.6. Renal Safety ..... 68
5.7. Ocular Safety ..... 70
5.8. Neuropsychiatric Events ..... 71
5.9. Fasting Glucose and Lipid Parameters ..... 71
5.10. Postmarketing Data ..... 73
5.11. Safety in Special Groups and Situations ..... 73
5.12. Safety Discussion and Conclusions ..... 74

6. BENEFITS AND RISKS CONCLUSIONS ..... 76

6.1. Benefits ..... 76
6.2. Risks ..... 78
6.3. Conclusions ..... 79

7. REFERENCES ..... 80

## LIST OF IN-TEXT TABLES

Table 1. Studies Supporting Clinical Efficacy and Safety for the FTC/RPV/TAF FDC Marketing Application ..... 15
Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Pooled Data (FAS) ..... 40
Table 3. RPV Studies Pooled C209 and C215 Data (FTC/TDF Subset Populations): Virologic Outcome (< 50 HIV-1 RNA copies/mL, TLOVR) at Weeks 48 and 96 ..... 42
Table 4. GS-US-292-0109: Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Week 48 FAS) ..... 44
Table 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set) ..... 54
Table 6. RPV Studies C209 and C215 (FTC/TDF Subset): Summary of Treatment-Emergent Adverse Events (Phase 3 Week 96 Pooled Analysis) ..... 56
Table 7. RPV Study C213: Adverse Events Summary (Intent-to-Treat) ..... 57
Table 8. Eviplera Study GS-US-264-0111: Overall Summary of Adverse Events (Safety Analysis Set) ..... 58
Table 9. Eviplera Study GS-US-264-0106: Overall Summary of Adverse Events (Safety Analysis Set) ..... 59
Table 10. Tabulated Summary of Adverse Reactions Associated with the Components of FTC/RPV/TAF ..... 62
Table 11. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 48 Analysis) ..... 67
Table 12. GS-US-292-0109: Key Measures of BMD (Week 48 Analysis) ..... 67
Table 13. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments (Excluding Subjects Receiving a Lipid Modifying Agent) Change from Baseline at Week 48 (Safety Analysis Set) ..... 72
Table 14. RPV Studies C209 and C215 (FTC/TDF Subset): Mean Change from Baseline in Lipid Values Reported in Subjects in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)[a] ..... 72

## LIST OF IN-TEXT FIGURES

Figure 1. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set) ..... 66

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| 3TC | lamivudine |
| ABC | abacavir |
| ABC/3TC | abacavir/lamivudine (coformulated) |
| ACTH | adrenocorticotropic hormone |
| ADR | adverse drug reaction |
| aGFR | actual glomerular filtration rate |
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ALT | alanine aminotransferase |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATV | atazanavir |
| AZT | zidovudine |
| AZT/3TC | zidovudine/lamivudine (coformulated) |
| B2M | beta-2-microglobulin |
| BLQ | below the limit of quantitation |
| BMD | bone mineral density |
| BMI | body mass index |
| CatA | cathepsin A |
| CD | cluster determinant |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CK | creatine kinase |
| CMH | Cochran-Mantel-Haentzel |
| COBI; C | cobicistat (Tybost®) |
| CPK | creatine phosphokinase |
| CRF | case report form |
| CSR | clinical study report |
| CV | coefficient of variation |
| CYP | cytochrome P450 |
| DDI | drug-drug interaction |
| DLV | delavirdine |
| DNA | deoxyribonucleic acid |
| $EC_{XX}$ | dose that produced a therapeutic response in XX% of subjects |
| ECG | electrocardiogram |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) |
| EFV | efavirenz |
| EFV/FTC/TDF | efavirenz/emtricitabine/tenofovir disoproxil fumarate (coformulated; Atripla®) |

| | |
|---|---|
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| EU | European Union |
| EVG; E | elvitegravir (Vitekta®) |
| EVG/COBI/FTC/TDF | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| FTC; F | emtricitabine (Emtriva®) |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated) |
| FTC/RPV/TDF | emtricitabine/rilpivirine/tenofovir disoproxil fumarate (coformulated; Eviplera®) |
| FTC/TDF | emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) |
| FTC-TP | emtricitabine 5′-triphosphate |
| Gilead | Gilead Sciences |
| HBV | hepatitis B virus |
| HCl | hydrochloride |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV, HIV-1, HIV-2 | human immunodeficiency virus, type 1, type 2 |
| $IC_{XX}$ | concentration that resulted in XX% inhibition |
| ICH | International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use) |
| INSTI | integrase strand-transfer inhibitor |
| ISE | Integrated Summary of Efficacy |
| ITT | intent-to-treat |
| $K_i$ | kinetic inhibition constant |
| LDL | low-density lipoprotein |
| LDV/SOF | ledipasvir/sofosbuvir (coformulated; Harvoni®) |
| LOCF | last observation carried forward |
| m | module |
| M = F | missing = failure |
| MAA | Marketing Authorization Application |
| MDZ | midazolam |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MH | Mantel-Haenszel |
| N or n | number of subjects in a population (N) or subset (n) |
| NDA | New Drug Application |
| NNRTI | nonnucleoside reverse transcriptase inhibitor |
| N(t)RTI | nucleos(t)ide reverse transcriptase inhibitor |
| NVP | nevirapine |

| | |
|---|---|
| P1NP | procollagen type 1 N-terminal propeptide |
| PBMC | peripheral blood mononuclear cell |
| PD | pharmacodynamic(s) |
| P-gp | P-glycoprotein |
| PI | protease inhibitor |
| PI/r | ritonavir-boosted protease inhibitor |
| PK | pharmacokinetic(s) |
| PP | per protocol |
| PRT | proximal renal tubulopathy |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| QTc | QT interval (electrocardiographic interval between the beginning of the Q wave and termination of the T wave, representing the time for both ventricular depolarization and repolarization to occur) corrected for heart rate |
| RBC | red blood cell |
| RMP | Risk Management Plan |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |
| RPV | rilpivirine (Edurant®; also known as TMC278) |
| RT | reverse transcriptase |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| TAM | thymidine analog-associated mutation |
| TLOVR | time to loss of virologic response |
| TMC278 | rilpivirine (see RPV) |
| SBR | stay on baseline regimen |
| SD | standard deviation |
| SE | standard error |
| SmPC | Summary of Product Characteristics |
| SOC | system organ class |
| STB | Stribild® (see EVG/COBI/FTC/TDF) |
| TAF | tenofovir alafenamide |
| TBLH | total body less head |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| TFV-DP | tenofovir diphosphate |
| TVD | Truvada® (see FTC/TDF) |
| UACR | urine albumin to creatinine ratio |
| ULN | upper limit of normal |
| UPCR | urine protein to creatinine ratio |
| US, USA | United States, United States of America |
| WBC | white blood cell |

## PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| AUC | area under the plasma/serum concentration versus time curve |
| $AUC_{last}$ | area under the plasma/serum concentration versus time curve from time zero to the last quantifiable concentration |
| $AUC_{xx}$ | partial area under the plasma/serum concentration versus time curve from time zero to time xx |
| $AUC_{inf}$ | area under the plasma/serum concentration versus time curve extrapolated to infinite time, calculated as $AUC_{0-last} + (C_{last}/\lambda_z)$ |
| $AUC_{tau}$ | area under the plasma/serum/PBMC concentration versus time curve over the dosing interval |
| $C_x$ | quantifiable plasma/serum concentration of the drug at observed time point |
| CL/F | apparent oral clearance after administration of the drug: $CL/F = Dose/AUC_{inf}$, where "Dose" is the dose of the drug |
| $C_{last}$ | last observed quantifiable plasma/serum concentration of the drug |
| $C_{max}$ | maximum observed plasma/serum concentration of drug |
| $C_{min}$ | minimum observed plasma/serum concentration of drug |
| F | estimated oral bioavailability of the drug (%), calculated as $100(AUC_{PO} \times Dose_{IV})/(AUC_{IV} \times Dose_{PO})$ |
| PBMC | peripheral blood mononuclear cell |
| $t_{½}$, $t_{½,\,term}$ | estimate of the terminal elimination half-life of the drug in plasma |
| $T_{max}$ | time (observed time point) of $C_{max}$ |

# 1. PRODUCT DEVELOPMENT RATIONALE

Gilead Sciences (Gilead) is submitting this dossier in support of a new marketing application for a fixed-dose combination (FDC) of emtricitabine (FTC; F), rilpivirine (RPV; Tibotec Medicinal Compound 278 [TMC278]), and tenofovir alafenamide (TAF): the FTC/RPV/TAF FDC tablet (200/25/25 mg). The proposed indication for the FTC/RPV/TAF FDC tablet is for use as a complete regimen for the treatment of HIV-1 infection in adult and pediatric patients aged 12 years and above, without known mutations associated with resistance to the nonnucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir (TFV) or FTC, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

This marketing application for FTC/RPV/TAF is based on a pivotal bioequivalence study (GS-US-366-1159) comparing FTC/RPV/TAF to Edurant® (marketed RPV 25-mg tablet) and Gilead's FDC tablet containing the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), FTC, and TAF (E/C/F/TAF 150/150/200/10 mg). E/C/F/TAF was selected as the reference because the pivotal clinical data establishing the safety and efficacy of TAF in combination with FTC were generated using the E/C/F/TAF FDC in Phase 3 studies. Edurant was selected as a reference because the safety and efficacy of RPV have been established from the Edurant Phase 3 registrational studies. Study GS-US-366-1159 demonstrated the following:

- Bioequivalence of TAF and FTC exposures between the FTC/RPV/TAF FDC (200/25/25 mg) and Gilead's E/C/F/TAF (150/150/200/10 mg) FDC tablet, thereby supporting extrapolation of the demonstrated safety and efficacy of TAF and FTC exposures in the FTC/RPV/TAF FDC to those from E/C/F/ TAF
- Bioequivalence of RPV exposure between the FTC/RPV/TAF FDC tablet and the marketed product Edurant (RPV 25-mg tablet), thereby supporting extrapolation of the demonstrated safety and efficacy of RPV exposures in the FTC/RPV/TAF FDC to those from Edurant

In accordance with the bioequivalence approach outlined above, the safety and efficacy of FTC/RPV/TAF in various patient populations is supported by the safety and efficacy of the individual components in those populations as follows:

- Antiretroviral treatment (ART)-naive adult subjects
  - Two pivotal Phase 3 studies conducted with E/C/F/TAF (Studies GS-US-292-0104 and GS-US-292-0111)
  - Two pivotal Phase 3 studies conducted with RPV in combination with a nucleos(t)ide reverse transcriptase inhibitor (N[t]RTI) backbone, which included FTC and tenofovir disoproxil fumarate (TDF; Viread) (Studies TMC278-TiDP6-C209 [C209] and TMC278-TiDP6-C215 [C215]).
- Virologically suppressed adult subjects
  - One Phase 3 E/C/F/TAF study (GS-US-292-0109)
  - Two Phase 2b and 3 FTC/RPV/TDF studies (GS-US-264-0111 and GS-US-264-0106)

- Adult subjects with mild to moderate renal impairment
  - One Phase 3 E/C/F/TAF study (GS-US-292-0112)
  - RPV is approved without dose adjustment for patients with mild to moderate renal impairment
- Adolescent subjects
  - One Phase 2/3 E/C/F/TAF study (GS-US-292-0106)
  - One Phase 2 RPV study (TMC278-TiDP38-C213 [C213])

At the time of writing, the studies conducted with E/C/F/TAF and the RPV study in adolescent subjects (Study C213) are under review in multiple countries, including the EU and US, as parts of marketing applications. The studies conducted with RPV (with the exception of Study C213) or FTC/RPV/TDF have been reviewed by regulatory authorities in multiple countries, including the EU and US, leading to the current indications for these products.

The registration of FTC/RPV/TAF is also supported by a comprehensive package of clinical and nonclinical pharmacology data collected using the component agents (either alone or in combination) and by postmarketing data. Together, the data support the proposed prescribing information for the FTC/RPV/TAF FDC tablet.

This overview presents the clinical rationale for the development of FTC/RPV/TAF and reviews the information that is relevant to the benefit:risk assessment for the use of this FDC in the treatment of HIV-1 infection. This overview includes biopharmaceutic, clinical pharmacology, efficacy, and safety data that support the proposed labeling and patient information.

## 1.1. Scientific Background

### 1.1.1. HIV-1 Infection and Current Treatment Options

HIV-1 infection is a life-threatening and serious disease of major public health significance, with approximately 35 million people infected worldwide {27071}.

Standard of care for the treatment of HIV-1 infection uses combination ART to suppress viral replication, increase cluster determinant (CD)4 cell counts, and stop disease progression. For ART-naive HIV-infected patients, initial therapy generally consists of 2 N[t]RTIs in combination with a third active antiretroviral (ARV) from one of 3 drug classes: an INSTI; an NNRTI; or a protease inhibitor (PI). Virologically suppressed, HIV-infected patients can benefit by switching from their current regimen to improve safety or tolerability or to simplify the regimen {27621}, {32519}, {34898}, {34940}. All patient populations may benefit from once-daily FDC regimens as these have been shown to provide increased adherence and improved clinical and virologic outcomes {20372}.

### 1.1.2. Rationale for FTC/RPV/TAF Development

The success of potent and well-tolerated ART, including licensed products such as Eviplera, means that morbidity and mortality in the HIV-infected population is increasingly driven by non–AIDS-associated comorbidities. Clinical attention has become more focused on optimizing tolerability, long-term safety, and adherence to potent ART regimens {29705}. There remains a significant medical need for effective and safe therapies that take into consideration the limitations of currently available regimens, non–HIV-related comorbidities, virologic resistance, and regimen simplification.

Tenofovir (TFV) is a nucleotide analog with limited oral bioavailability that inhibits HIV-1 reverse transcription. Tenofovir disoproxil fumarate (TDF) is an oral prodrug of TFV that has improved bioavailability, and delivers systemic exposures of TFV with favorable efficacy and safety data. TDF is a recommended NtRTI for use in combination with other antiretroviral agents for the treatment of HIV-1 infection {27621}, {34797}, {34898}, {34940}.

Despite its advantages over other NRTIs, TDF is associated with nephrotoxicity (Viread and Eviplera Risk Management Plans [RMPs]), which manifests as increased serum creatinine, increased protein loss (particularly tubular), and occasional cases of proximal renal tubulopathy (PRT) (including Fanconi syndrome). These TDF-associated renal risks necessitate renal monitoring, placing burden on the patient and healthcare provider. In addition, TDF is associated with early onset bone demineralization in adults, specifically reductions in bone mineral density (BMD).

TAF is an investigational oral prodrug of TFV that is more stable in plasma than TDF. TAF achieves higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP) and > 90% lower circulating levels of TFV relative to TDF. TAF offers an improved clinical profile as shown in the safety and efficacy clinical studies conducted with E/C/F/TAF, which is attributed to lower plasma TFV exposures compared with the approved dose of TDF.

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are widely used in the treatment of HIV-1 infection. RPV, a diarylpyrimidine derivative, is a potent NNRTI with in vitro activity against wild type HIV-1 and NNRTI-resistant mutants. RPV is an NNRTI that is approved as a single agent for use in combination with other ART agents for the treatment of HIV-1 infection in ART-naive adult patients with HIV-1 RNA ≤ 100,000 copies/mL at the start of therapy {29500}.

TDF and RPV are also components of Eviplera, an FDC tablet containing FTC/RPV/TDF (200/25/300 mg). Eviplera is a well-tolerated, once-daily regimen that is approved in the EU as a complete regimen for the treatment of HIV-1 infection in adult patients without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

RPV has an improved safety profile compared with other approved NNRTIs in the EU and/or US for use in treatment-naive adult patients; nevirapine (NVP; Viramune®) {28148}, delavirdine (DLV; Rescriptor®) {15967}, and efavirenz (EFV; Sustiva®) {22637}. These NNRTIs are associated with hepatotoxicity, central nervous system symptoms, and/or the risk of

teratogenicity {34898}. FTC (Emtriva®) is an NRTI that is approved for use in combination with other agents for the treatment of HIV-1 infection in adults and children (~3 months of age or older) in the EU, US, and other regions worldwide.

Gilead has coformulated TAF (as TAF fumarate) with FTC and RPV into an FDC tablet, FTC/RPV/TAF (200/25/25 mg) that is suitable for once daily use. The FDC addresses the need for a highly efficacious, once-daily, complete regimen that combines an N(t)RTI backbone that has an improved renal and bone safety profile compared with TDF-containing backbones with an NNRTI, RPV, that has established safety and tolerability benefits compared with other NNRTIs.

Exposures of the FTC and TAF components of the FTC/RPV/TAF FDC have been shown to be bioequivalent to that of E/C/F/TAF, and exposures of the RPV component of the FTC/RPV/TAF FDC have been shown to be bioequivalent to that of Edurant. Therefore, the clinical efficacy and safety of E/C/F/TAF and RPV-containing regimens support the efficacy and safety of FTC/RPV/TAF in a broad range of populations.

The clinical efficacy and safety data for E/C/F/TAF and RPV-containing regimens demonstrate the following:

- In treatment-naive, HIV-infected adults, virologic responses were noninferior to approved regimens for the FTC/TAF-containing regimen E/C/F/TAF (vs EVG/COBI/FTC/TDF [Stribild®; STB]) and RPV-containing regimen (vs EFV).

- Efficacy was maintained in virologically suppressed subjects switching from standard-of-care regimens to an FTC/TAF- (E/C/F/TAF) or RPV-containing regimen (Eviplera).

- The PK of TAF and FTC in HIV-infected adolescent subjects was consistent with the range of exposure associated with antiviral activity of E/C/F/TAF in adults, and the PK of RPV in HIV-infected adolescent subjects was comparable with that of adults, supporting the use of FTC/RPV/TAF in pediatric patients ≥ 12 years of age. No new safety findings were observed in treatment-naive adolescents treated with either E/C/F/TAF or RPV.

- The FTC/TAF-containing regimen E/C/F/TAF was associated with improved bone safety compared with TDF-containing regimens, specifically, less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for virologically suppressed subjects.

- The FTC/TAF-containing regimen E/C/F/TAF was associated with an improved renal safety profile compared with TDF-containing regimens; specifically, there was less change in serum creatinine, proteinuria, and renal tubular proteinuria for ART-naive subjects compared with STB, and there was a reduction in serum creatinine levels and improvements in renal tubular protein parameters for virologically suppressed subjects who switched from a TDF-based regimen. These results support renal safety monitoring for TAF-containing regimens that is consistent with standard clinical practice (and with other non–TDF-containing ARV regimens).

- Safety and efficacy in renally impaired subjects supports the use of FTC/TAF without dose adjustment in patients with an estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 30 mL/min. RPV can be used without dose adjustment in these patients.

- RPV is associated with an improved safety/tolerability profile (neuropsychiatric symptoms, serum lipids) compared with EFV.

- No interaction was observed when FTC/RPV/TAF was coadministered with ledipasvir/sofosbuvir (LDV/SOF), suggesting that no dose adjustment is required when they are coadministered.

## 1.2. Overview of the Clinical Development Program

This submission is based on a pivotal bioequivalence study (Study GS-US-366-1159) that demonstrated bioequivalent exposure of TAF and FTC between the FTC/RPV/TAF and E/C/F/TAF FDCs, and bioequivalent exposure of RPV between the FTC/RPV/TAF FDC and Edurant.

### 1.2.1. Clinical Pharmacology Development Program

The clinical pharmacology of the FTC/RPV/TAF FDC has been extensively characterized through in vitro or nonclinical studies with single-agent TAF, RPV, or FTC, and clinical studies conducted with single-agent TAF, RPV, or FTC, or the FDCs FTC/RPV/TAF, E/C/F/TAF, F/TAF, FTC/TDF, or FTC/RPV/TDF. The clinical studies that provide PK and/or pharmacodynamic (PD) data to support this marketing application are listed and described in m2.7.2, Section 1.2.3. Extrapolation to the FTC/RPV/TAF FDC is based on the bioequivalence of TAF and FTC exposure between FTC/RPV/TAF and E/C/F/TAF and the bioequivalence of RPV exposure between FTC/RPV/TAF and Edurant (Study GS-US-366-1159), and is further supported by the bioequivalence of RPV exposure between Eviplera and Edurant (Study GS-US-264-0103), which supported the registration of Eviplera.

Data provided from Phase 1 studies conducted with the FTC/RPV/TAF FDC are new for this Marketing Authorization Application (MAA), as follows:

- Study GS-US-366-1159, the pivotal bioequivalence study that forms the basis for determining the safety and efficacy of FTC/RPV/TAF through a pharmacokinetic bridge to the established safety and efficacy of E/C/F/TAF and Edurant

- Study GS-US-366-1651, which evaluated the effect of food on TAF, RPV, and FTC exposure following administration of FTC/RPV/TAF

- Study GS-US-366-1689, which investigated the DDI potential between FTC/RPV/TAF and LDV/SOF

### 1.2.2. Dose Selection

The proposed commercial FTC/RPV/TAF FDC tablet contains FTC 200 mg, RPV 25 mg, and TAF 25 mg. The 200-mg dose of FTC represents the marketed dose of the single agent Emtriva. The 25-mg dose of RPV is the marketed dose of the single agent Edurant and is the approved dose in Eviplera. The 25-mg dose of TAF provides an equivalent exposure to the TAF selected doses in E/C/F/TAF and F/TAF that are currently under regulatory review.

Cumulative assessment of exposure:response data from proof-of-concept Study GS-US-120-0104 indicates that the exposure associated with TAF 25-mg dose provides potent and near-maximal antiviral activity. Relative to TDF 300 mg, TAF 25 mg demonstrates no loss in efficacy, but 90% reduction in TFV plasma levels, translating to an improvement in off-target side effects. The recommended dose of TAF is based on ensuring that patients have a TAF systemic exposure that is within the range of the reference exposure achieved with TAF 25 mg, or with TAF 10 mg when administered with a boosting agent such as COBI in E/C/F/TAF, for which an extensive safety and efficacy database exists. RPV does not have a clinically relevant effect on TAF exposure (Study GS-US-120-1554); therefore, the dose of TAF 25 mg is appropriate for the FTC/RPV/TAF FDC.

### 1.2.3. Clinical Efficacy and Safety Development Program

The efficacy and safety of FTC/RPV/TAF in HIV-infected subjects are supported by data in the populations outlined below (Table 1).

- ART-naive, HIV-infected adults with screening HIV-1 RNA ≥ 1000 copies/mL (E/C/F/TAF Phase 3 Studies GS-US-292-0104 and GS-US-292-0111) or ≥ 5000 copies/mL (RPV Phase 3 Studies C209 and C215, and E/C/F/TAF Phase 2 Study GS-US-292-0102)

- Virologically suppressed, HIV-1 infected adults switching from a TDF-based regimen to E/C/F/TAF (E/C/F/TAF Phase 3 Study GS-US-292-0109); or from EFV/FTC/TDF (Atripla®) to the RPV-containing regimen Eviplera (Study GS-US-264-0111); and HIV-1 infected patients suppressed on a regimen consisting of 2 N(t)RTIs + a ritonavir-boosted protease inhibitor (PI/r) switching to the RPV-containing regimen Eviplera (Study GS-US-264-0106)

- HIV-1 infected adults with mild to moderate renal impairment receiving E/C/F/TAF (Study GS-US-292-0112)

- ART-naive, HIV-infected adolescents 12 to < 18 years of age treated with E/C/F/TAF (Phase 2/3 Study GS-US-292-0106) or RPV (Phase 2 Study C213)

No efficacy or safety data are currently available for the FTC/RPV/TAF FDC in HIV-infected patients. The Phase 1 studies with FTC/RPV/TAF FDC in healthy subjects provide additional safety information (Section 1.2.1).

Exposure data are provided in m2.7.4, Section 1.

**Table 1. Studies Supporting Clinical Efficacy and Safety for the FTC/RPV/TAF FDC Marketing Application**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR Reference and Study Narrative Locations |
|---|---|---|---|---|
| **E/C/F/TAF Studies** | | | | |
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 435)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 432) | Week 48 efficacy, PK, and safety | **CSR:** GS-US-292-0104 Interim Week 48 CSR<br>**Narrative:** m2.7.3, Section 2.1.1.1 |
| GS-US-292-0111 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 431)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 435) | Week 48 efficacy, PK, and safety | **CSR:** GS-US-292-0111 Interim Week 48 CSR<br>**Narrative:** m2.7.3, Section 2.1.1.2 |
| GS-US-292-0102 | Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB<br>Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102 | Randomized phase:<br>E/C/F/TAF FDC + placebo-to-match STB (N = 112)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 58)<br>Open-label extension phase:<br>Continued on E/C/F/TAF FDC (N = 105)<br>Switch to E/C/F/TAF FDC (N = 161)<br>from STB to E/C/F/TAF FDC (N = 53)<br>from D/C/F/TAF to E/C/F/TAF FDC (N = 70)<br>from DRV+COBI+TVD to E/C/F/TAF FDC (N = 38) | Week 48[b] efficacy, PK, and safety | **CSR:** GS-US-292-0102 Interim Week 96 CSR<br>**Narrative:** m2.7.3, Section 2.1.1.3 |

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR Reference and Study Narrative Locations |
|---|---|---|---|---|
| **HIV-Infected, Virologically Suppressed Adult Subjects** | | | | |
| GS-US-292-0109 | Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC | Switch to E/C/F/TAF FDC (N = 959)<br>Stay on TVD+3rd Agent (N = 477) | Week 48 efficacy and safety | **CSR:** GS-US-292-0109 Interim Week 48 CSR<br>**Narrative:** m2.7.3, Section 2.1.2 |
| **HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment** | | | | |
| GS-US-292-0112 | Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC | E/C/F/TAF FDC (N = 248) | Week 24 efficacy and safety | **CSR:** GS-US-292-0112 Interim Week 24 CSR<br>**Narrative:** m2.7.4, Section 1.1.4.1.1 |
| **HIV-Infected, ART-Naive Adolescent Subjects** | | | | |
| GS-US-292-0106 | Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC | E/C/F/TAF FDC (N = 48)<br>PK substudy: N = 24 | Week 24 efficacy, PK, and safety | **CSR:** GS-US-292-0106 Interim Week 24 CSR<br>**Narrative:** m2.7.4, Section 1.1.4.1.2 |

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR Reference and Study Narrative Locations |
|---|---|---|---|---|
| **RPV Studies** | | | | |
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| TMC278-TiDP6-C209 (also referred to as C209 or ECHO) | Phase 3, randomized, double-blind, double-dummy, active controlled international study to assess the long-term efficacy, safety, and tolerability of RPV compared to EFV, each in combination with a fixed background N(t)RTI regimen containing TDF and FTC, in HIV-1 infected, ARV treatment-naive subjects. | RPV + FTC/TDF (N = 346)<br>EFV + FTC/TDF (N = 344) | Week 48 and 96 efficacy and safety | **CSR:** TMC278-TiDP6-C209<br>**Narrative:** m2.7.3 Section 2.2.1.1. |
| TMC278-TiDP6-C215 (also referred to as C215 or THRIVE) | Phase 3, randomized, double-blind, double-dummy, active-controlled international trial to compare the long-term efficacy, safety, and tolerability of RPV vs. EFV, each in combination with a background regimen containing 2 N(t)RTIs in HIV-1 infected, ARV treatment-naive subjects. The investigator-selected N(t)RTIs were either abacavir (ABC)/lamivudine (3TC), zidovudine (AZT)/3TC, or FTC/TDF. | RPV + background regimen of 2 N(t)RTIs (N = 340)<br>EFV + background regimen of 2 N(t)RTIs (N = 338)<br><br>Subjects included in FTC/TDF subset<br>RPV + FTC/TDF (N = 204)<br>EFV + FTC/TDF (N = 202) | Week 48 and 96 select[c] safety<br><br>FTC/TDF subset: Week 48 and 96 efficacy and select[c] safety | **CSR: :** TMC278-TiDP6-C215<br><br>**Narrative:** m2.7.3, Section 2.2.1.2 |
| **HIV-Infected, ART-Naive Adolescent Subjects** | | | | |
| TMC278-TiDP38-C213 (also referred to as C213 or PAINT) | Phase 2, open-label, single arm trial to evaluate the PK, safety, tolerability, and antiviral activity of RPV in antiretroviral-naive HIV-1 infected adolescents aged 12 to < 18 years. | RPV + investigator-selected background regimen of 2 N(t)RTIs (N = 36) | Week 48 efficacy, PK, and safety | **CSR:** TMC278-TiDP38-C213<br>**Narrative:** m2.7.4, Section 1.1.4.2.1 |

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR Reference and Study Narrative Locations |
|---|---|---|---|---|
| **Eviplera Studies** | | | | |
| **HIV-Infected, Virologically Suppressed Adult Subjects** | | | | |
| GS-US-264-0111 | Phase 2b, open-label, multicenter study to evaluate switching from EFV/FTC/TDF STR to FTC/RPV/TDF (Eviplera) in virologically suppressed HIV-1 infected subjects on EFV/FTC/TDF desiring change in regimen due to EFV intolerance | Eviplera Group: (N = 49) | Week 48 efficacy, PK, and safety | **CSR:** GS-US-264-0111<br>**Narrative:** m2.7.3, Section 2.3.1.1 |
| GS-US-264-0106 | Phase 3, randomized, open-label, multicenter study to evaluate the safety and efficacy of switching from regimens consisting of a PI/r and 2 NRTIs to FTC/RPV/TDF (Eviplera) in virologically suppressed, HIV-1 infected subjects. | Eviplera Group: (N = 317)<br>Stay on Baseline Regimen (SBR) Group:<br>Remained on baseline regimen for 24 weeks, then switched to Eviplera for 24 weeks (N = 159)<br>Delayed Switch Group:<br>Subjects in the SBR group who switched to Eviplera after 24 weeks on their baseline regimen (N = 152)<br>Total Eviplera Group:<br>The Eviplera group +the Delayed Switch Group (N = 469) | Week 48 efficacy and safety | **CSR:** GS-US-264-0106<br>**Narrative:** m2.7.3, Section 2.3.1.2 |

TVD = Truvada® (FTC/TDF).
a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b The randomized phase was 48 weeks; most ART-naive subjects who continued E/C/F/TAF in the extension completed 96 weeks of treatment.
c In some instances, the subset of subjects receiving FTC/TDF with RPV from Studies C209 and C215 is presented, as it provides data for RPV and FTC administered with a TFV prodrug and therefore contains relevant data for the FTC/RPV/TAF combination.
Source: m2.7.3, Table 2

### 1.2.4. Regulatory Guidelines and Advice

All studies conducted in the development program were conducted in accordance with International Conference on Harmonization (ICH) guidelines. As required under a US Investigational New Drug application, investigators were required to ensure that the basic principles of "Good Clinical Practice" were adhered to, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, "Protection of Human Subjects," and 21 CFR, part 56, "Institutional Review Boards." These standards are consistent with the requirements of the European Community Directive 2001/20/EC. All study designs were endorsed by the regulatory agencies of the countries in which the studies were conducted. As such, data are considered applicable across regions without need for further bridging studies.

All Phase 2 and Phase 3 studies included in this submission were of an adequate design and duration, as recommended in applicable regulatory guidance (ICH E8 and E10; {28155}, {27447}), with well-established endpoints to characterize efficacy and safety in the treatment of HIV-1 infection {13932}.

Advice was sought from the Committee for Medicinal Products for Human Use (CHMP) on 2 aspects of the nonclinical development plan for TAF (m2.4). Advice on overall development was sought from the US Food and Drug Administration (FDA). As a result of these discussions, and in accordance with the industry guidance, the registration strategy for FTC/RPV/TAF is based on a pivotal bioequivalence study that pharmacokinetically bridges the exposure of FTC and TAF to the E/C/F/TAF FDC tablet, and pharmacokinetically bridges the exposure of RPV to the approved agent Edurant. Both E/C/F/TAF and Edurant have been shown to be efficacious, safe, and well tolerated in a broad spectrum of HIV-infected patients; these data are presented in this MAA to support the use of FTC/RPV/TAF.

The FTC/RPV/TAF clinical development program includes an agreed Initial Pediatric Study Plan in the US and an approved Paediatric Investigational Plan in the EU (EMEA-001679-PIP01-14).

Gilead is seeking registration of the FTC/RPV/TAF FDC tablet for use as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients aged 12 years and above, without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

# 2. OVERVIEW OF BIOPHARMACEUTICS

Biopharmaceutical studies are summarized in detail in m2.7.1. The formulation and dissolution profile of FTC/RPV/TAF is described in m2.7.1, Sections 1.1 and 1.2.

## 2.1. Formulation

The commercial drug product is an immediate-release fixed-dose combination tablet containing 200 mg of emtricitabine, 25 mg of rilpivirine, and 25 mg of tenofovir alafenamide (FTC/RPV/TAF 200/25/25 mg). RPV is incorporated into the drug product as the RPV hydrochloride (HCl) salt, and TAF is incorporated into the drug product as the hemifumarate form (referred to as TAF fumarate). The FTC/RPV/TAF 200/25/25-mg tablet is a bilayer tablet with one layer containing RPV and the other layer containing FTC and TAF.

FTC/RPV/TAF tablets are manufactured in a series of steps. RPV HCl is fluid-bed granulated with intragranular excipients to produce RPV granules, which are subsequently dried, milled, and blended with extragranular excipients to produce RPV final powder blend. FTC and TAF fumarate are co-dry granulated with intragranular excipients and lubricated with extragranular magnesium stearate to produce FTC/TAF final powder blend. The RPV final powder blend and the FTC/TAF final powder blend are compressed into bilayer tablet cores that are then film coated using Opadry II Gray 85F17636.

## 2.2. Dissolution Profile

The dissolution profile for the commercial tablet formulation of FTC/RPV/TAF showed that greater than 75% of FTC and TAF were dissolved within 30 minutes and greater than 75% RPV was dissolved within 60 minutes.

## 2.3. Bioavailability

Although the absolute bioavailability of TAF has not been evaluated in humans, it is estimated to be approximately 40%. TAF is transported by P-glycoprotein (P-gp) and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI) reduces P-gp–mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from Studies GS-US-366-1159 (m2.7.1, Section 2.1.1), GS-US-292-0103 (m2.7.1, Section 2.2.1), and GS-US-292-0101 (m2.7.2, Section 2.2.2.1), indicated that TAF exposure following administration of TAF 10 mg with a boosting agent (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg without a boosting agent, including following administration of the FTC/RPV/TAF FDC.

The RPV PK profile following single and multiple doses has been characterized in healthy and HIV-infected individuals at doses ranging from 12.5 to 300 mg. RPV is orally available, with the $C_{max}$ attained approximately 4 hours after administration. The rate of RPV absorption is not influenced by dose (m2.7.2, Section 3.3.1.1.2).

FTC is rapidly and extensively absorbed after oral administration and peak plasma concentrations reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multiexponential decay. Greater than 85% of an oral dose of FTC is absorbed with little first-pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93% as shown in Study FTC-110; m2.7.2, Section 3.3.1.1.3).

Results from Study GS-US-366-1159 demonstrate bioequivalence in TAF and FTC exposures between FTC/RPV/TAF (200/25/25 mg) and E/C/F/TAF (150/150/200/10 mg), and bioequivalence in RPV exposure between FTC/RPV/TAF (200/25/25 mg) and Edurant (25 mg). Statistical comparisons of plasma FTC, RPV, and TAF PK parameters ($AUC_{last}$, $AUC_{inf}$, and $C_{max}$) are presented in m2.7.1, Section 2.1.1, Table 16.

## 2.4. Food Effect on Exposure

The effect of food on FTC/RPV/TAF exposure is discussed in detail in m2.7.2, Section 3.3.3.1.

The effect of food on the absorption/bioavailability of FTC/RPV/TAF (200/25/25 mg) was evaluated in Study GS-US-366-1651, which is summarized below (m2.7.1, Section 3.3).

### TAF

When FTC/RPV/TAF was administered under fed conditions compared with fasted conditions, TAF $AUC_{last}$ increased by 45% and 54% after moderate-fat and high-calorie, high-fat food, respectively. TAF $C_{max}$ decreased by 23% and 31% under moderate-fat and high-calorie, high-fat conditions, respectively, compared with fasted conditions. There was also a delay in $T_{max}$ (increase from 0.5 hours under fasted conditions to 1.3 hours under moderate-fat conditions and to 1.5 hours under high-calorie, high-fat conditions).

The TAF exposures when the FTC/RPV/TAF tablet is administered with and without food fall within the wide range of safe and efficacious TAF exposure established in the Phase 3 E/C/F/TAF studies; therefore, the differences in TAF PK parameters upon administration with food (versus fasted) are not considered clinically relevant.

### RPV

When FTC/RPV/TAF was administered under fed conditions compared with fasted conditions, RPV $AUC_{inf}$ increased by 13% and 73% after moderate-fat and high-calorie, high-fat food, respectively. RPV $C_{max}$ increased by 39% and 107% when administered under moderate-fat and high-calorie, high-fat conditions, respectively, compared with fasted conditions. There was also a delay in median $T_{max}$ under moderate-fat conditions (increase from 3 hours under fasted conditions to 4 hours under moderate-fat conditions) and no change under high-calorie, high-fat conditions (4 hours for both fasted and high-calorie, high-fat conditions).

Bioequivalence of RPV exposure has been demonstrated under fed conditions between FTC/RPV/TAF and Edurant, the marketed product with clinical efficacy and safety established when administered under fed conditions {27873}, {29500}, {30163}, {34797}.

**FTC**

When FTC/RPV/TAF was administered under fed conditions compared with fasted conditions, FTC $AUC_{inf}$ decreased by 9% and 12% after moderate-fat and high-calorie, high-fat food, respectively. FTC $C_{max}$ decreased by 24% and 26% when administered under moderate-fat and high-calorie, high-fat conditions, respectively, compared with fasted conditions. There was also a delay in median $T_{max}$ (increase from 1.0 hour under fasted conditions to 2.0 hours under moderate-fat conditions and 2.0 hours under high-calorie, high-fat conditions).

The differences in FTC PK parameters upon administration with food (versus fasted) are not considered clinically relevant.

**FTC/RPV/TAF**

The results from Study GS-US-366-1651 are consistent with previous studies of TAF and FTC, supporting administration of these compounds without regard to food. The bioequivalence study, GS-US-366-1159 was conducted in the fed state per the proposed clinical use of FTC/RPV/TAF and in a setting for which safety and efficacy of the reference products have been established. Based on the established safety and efficacy of RPV from the Edurant Phase 3 studies, it is recommended that FTC/RPV/TAF be administered with food. Furthermore, the reference treatment E/C/F/TAF is also recommended for administration with food (for the EVG component), forming the basis of the safety and efficacy of TAF. Therefore, fasted bioequivalence data are not relevant for the FTC/RPV/TAF FDC.

Therefore, the FTC/RPV/TAF FDC should be administered with food.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

The clinical studies characterizing the PK of FTC/RPV/TAF and its components are described in m2.7.2, Section 1.2. The analyses of the clinical PK data are described in detail in m2.7.2, Section 3.

The available nonclinical and clinical virology data in support of this submission are summarized in m2.7.2, Section 4; clinical virology data are incorporated with efficacy data in this overview (Section 4).

## 3.1. Mechanism of Action

### 3.1.1. TAF

TAF is a phosphonoamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). TAF is permeable into cells and due to increased plasma stability and intracellular activation by cathepsin A (CatA), TAF is more efficient than TDF in loading TFV into peripheral blood mononuclear cells (PBMCs) (including lymphocytes, macrophages, and other HIV target cells). Intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV-DP. TFV-DP inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain termination.

TFV has activity that is specific to HIV-1, HIV-2, and hepatitis B virus (HBV). In vitro studies have shown that TFV can be fully phosphorylated when combined in cells. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ, and there is no evidence of toxicity to mitochondria in vitro.

### 3.1.2. RPV

Rilpivirine is a diarylpyrimidine NNRTI of HIV-1 and inhibits HIV-1 replication by non-competitive inhibition of HIV-1 RT. Rilpivirine does not inhibit the human cellular DNA polymerases α, β, and mitochondrial DNA polymerase γ.

### 3.1.3. FTC

FTC, an NRTI, is converted intracellularly through 3 phosphorylation reactions to its active phosphorylated anabolite, FTC 5′-triphosphate (FTC-TP). FTC-TP inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate), and after incorporation into DNA, by DNA chain termination. FTC has activity that is specific to HIV (HIV-1 and HIV-2) and HBV. In vitro studies have shown that FTC can be fully phosphorylated when combined in cells. FTC-TP is a very weak inhibitor of mammalian DNA polymerases α, β, ε, and mitochondrial DNA polymerase γ. There was no evidence of toxicity to mitochondria in vitro and in vivo.

## 3.2. In Vitro Activity

Nonclinical virology is summarized in m2.7.2, Section 4.1.

### 3.2.1. TAF

The kinetic inhibition constant ($K_i$) values for TFV-DP against HIV-1 reverse transcription (RNA-dependent DNA synthesis) and the second strand DNA synthesis (DNA-dependent DNA synthesis) are 0.02 and 1.6 μM, respectively {1131}. TFV alone, or in combination with other NRTIs, ABC, didanosine, or lamivudine, has no effect on either the intracellular 2'-deoxynucleoside triphosphate (dNTP) or ribonucleoside triphosphate (rNTP) pool concentrations {8573}.

In resting human PBMCs in vitro, the $t_{1/2}$ of TFV-DP was approximately 50 hours; whereas, the $t_{1/2}$ in activated PBMCs was approximately 10 hours {1574}. Consistent with the in vitro studies, TFV is efficiently taken up by PBMCs in monkeys and is metabolized to TFV-DP, with the intracellular concentrations of the active metabolite TFV-DP reaching 0.9 μM. The $t_{1/2}$ of TFV-DP in the monkey PBMCs was > 50 hours and significant levels of TFV and its metabolites were observed in the lymph nodes 48 hours after dosing. The long intracellular $t_{1/2}$ supports once-daily dosing.

TAF showed broad anti-HIV activity in human PBMCs against all HIV-1 groups (M, N, O), including M subtypes A to G, with average $EC_{50}$ values ranging from 0.10 to 12.0 nM and an overall mean $EC_{50}$ of 3.6 nM. TAF also has potent antiviral activity against HIV-2, with $EC_{50}$ values ranging from 0.91 to 2.63 nM.

As TAF is a prodrug of TFV, resistance analyses of the parent compound, TFV, are relevant to the TAF in vitro resistance profile. As expected, the HIV-1 resistance profile of TAF was nearly identical to that of TFV, under in vitro dose-escalation drug selection with wild-type HIV-1. Treatment with TAF or TFV led to the development of the reverse transcriptase (RT) mutation K65R ± S68N with moderate phenotypic resistance to TFV and no additional resistance after extended culturing time. In addition, limited viral evolution and phenotypic changes were observed after 6 months of resistance selection with either TAF or TFV in viruses with preexisting TFV-resistance mutations (K65R, 3TAMs, and Q151M complex), suggesting a lack of alternative resistance pathways for these viruses under selective pressure from TAF (or TFV). Susceptibility to TAF for a panel of HIV-1 mutants from ART-experienced patients was almost identical to TFV, with fold change compared with wild-type virus ranging from 0.34- to 23-fold of the $EC_{50}$ (correlation coefficient between TFV and TAF of 0.97).

Although the resistance profile for TAF was nearly the same as that for TFV in vitro, the in vivo resistance profile may differ between the 2 drugs since the level of TFV-DP achieved in vivo upon loading with TAF is significantly higher than that with TDF. When the in vivo condition was modeled, the results showed that physiologically relevant concentrations of TAF inhibited breakthrough for most of the viruses tested, including those with 3 thymidine analog mutations (TAMs), K65R, Q151M complex, 4 TAMs, or T69 insertion. In contrast, viral breakthrough was only inhibited for a few viruses in the presence of TFV. For viruses with the highest resistance

(5 TAMs), neither TAF nor TFV could achieve inhibition of viral breakthrough. These results suggest that treatment with TAF may lead to antiviral efficacy against previously defined TDF-resistant viruses.

TFV demonstrated additive to synergistic activity with a variety of other ARV drugs in vitro. The combination of TAF with TFV resulted in an additive effect, as expected since both deliver TFV-DP to cells. TAF exhibited moderate to high synergistic effects when combined with other N(t)RTIs or NNRTIs. The combination of TAF with PIs resulted in moderate synergy, and the combination of TAF with INSTIs resulted in the highest level of synergy. As expected, the combination of TAF with COBI, a pharmacokinetic enhancer coformulated with TAF in E/C/F/TAF and devoid of antiviral activity, resulted in an additive effect.

### 3.2.2. RPV

RPV exhibited activity against laboratory strains of wild-type HIV-1 in an acutely infected T-cell line with a median $EC_{50}$ value for HIV-$1_{IIIB}$ of 0.73 nM (0.27 ng/mL). RPV demonstrated limited activity in cell culture against HIV-2 with a median $EC_{50}$ value of 5220 nM (range, 2510 to 10830 nM) (920 to 3970 ng/mL).

RPV demonstrated antiviral activity against a broad panel of HIV-1 group M (subtype A, B, C, D, F, G, H) primary isolates with $EC_{50}$ values ranging from 0.07 to 1.01 nM (0.03 to 0.37 ng/mL) and was less active against group O primary isolates with $EC_{50}$ values ranging from 2.88 to 8.45 nM (1.06 to 3.10 ng/mL).

The antiviral activity of rilpivirine was not antagonistic when combined with the NNRTIs efavirenz, etravirine, or nevirapine; the N(t)RTIs abacavir, didanosine, FTC, lamivudine, stavudine, tenofovir, or zidovudine; the PIs amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, or tipranavir; the fusion inhibitor enfuvirtide; the chemokine (C-C motif) receptor 5 (CCR5) co-receptor antagonist maraviroc; or the INSTI raltegravir.

### 3.2.3. FTC

The $EC_{50}$ of FTC against laboratory adapted strains of HIV-1 ranged from 0.0013 to 0.64 μM depending on cell type and virus strain used in the assay. With clinical isolates of HIV-1, $EC_{50}$ values range from 0.002 to 0.028 μM. FTC displays antiviral activity in vitro against HIV-1 subtypes A, B, C, D, E, F, and G with $EC_{50}$ values ranging from 0.002 to 0.075 μM, and shows activity against HIV-2 (with an $EC_{50}$ of 0.007 to 1.5 μM). Reduced susceptibility to FTC was associated with M184V/I mutations in HIV-1 reverse transcriptase (RT).

## 3.3. ADME Characteristics

TAF is more stable in plasma than TDF, provides higher intracellular levels of the active phosphorylated metabolite TFV-DP, and at the 10-mg dose contained within the E/C/F/TAF FDC tablet yields > 90% lower circulating levels of TFV relative to TDF.

### 3.3.1. Absorption

Absorption is described in detail in m2.7.2, Section 3.2.1.

**TAF**

TAF PK is characterized by rapid absorption, with a median plasma $T_{max}$ of approximately 0.50 hours.

TAF is transported by P-gp and subject to metabolism by esterases expressed in the intestine {21545}, {21546}. Inhibition of P-gp by a boosting agent (eg, COBI) reduces P-gp–mediated TAF cycling across the brush border membrane of the intestine, thereby increasing the fraction of the TAF dose absorbed to approximately 90%. Cumulative results from studies with FTC/RPV/TAF and E/C/F/TAF indicated that TAF exposure following administration of TAF 10 mg with a boosting agent (either as a single agent coadministered with COBI 150 mg or as a component of E/C/F/TAF) was comparable with the exposure achieved following administration of TAF 25 mg without a boosting agent, including following administration of the FTC/RPV/TAF FDC.

**RPV**

The RPV PK profile following single and multiple doses has been characterized in healthy and HIV-infected individuals at doses ranging from 12.5 to 300 mg. RPV is orally available, with the $C_{max}$ attained approximately 4 hours after administration. The rate of RPV absorption is not influenced by dose.

The highest solubility of RPV is obtained at pH 2.0, and at pH values above 2.0, solubility decreases markedly.

Drugs that alter intragastric pH affect the solubility of RPV and thus can also indirectly affect the absorption of RPV. Studies exploring the effect of coadministration of RPV with omeprazole (a drug that increases intragastric pH), and the interaction between RPV and famotidine (a histamine $H_2$-receptor antagonist that inhibits gastric acid production), demonstrated that the absorption of RPV is pH-dependent.

**FTC**

Single- and multiple-dose PK studies have shown that FTC is rapidly and extensively absorbed after oral administration. Plasma FTC concentrations were measurable at the earliest sampling time (15 minutes postdose) and reached a maximum within 1 to 2 hours of dosing over a wide dose range (25 to 1200 mg) and then followed an apparent multiexponential decay. Greater than 85% of an oral dose of FTC is absorbed with little first-pass elimination prior to reaching the systemic circulation, resulting in a high absolute bioavailability value (93%).

FTC is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours postdose. Following multiple dose oral administration of FTC to 20 HIV-1 infected subjects, the mean ± SD AUC over a 24-hour dosing interval was 10.0 ± 3.1 h•µg/mL. The mean steady state plasma trough concentration at 24 hours postdose was equal to or greater than the mean in vitro $IC_{90}$ value for anti-HIV-1 activity.

### 3.3.2. Distribution

Distribution is described in detail in m2.7.2, Section 3.2.2.

**TAF**

The protein binding of TAF was moderate in human plasma with percent unbound TAF values ranging from 14% to 23%.

**RPV**

RPV and its metabolites were not distributed to blood cells to any significant extent. The distribution of RPV into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been evaluated in humans.

**FTC**

In vitro binding of FTC to human plasma proteins was < 4% and independent of concentration over the range of 0.02 to 200 µg/mL. At peak plasma concentration, the mean plasma to blood drug concentration ratio was ~1.0 and the mean semen to plasma drug concentration ratio was ~4.0.

### 3.3.3. Metabolism and Elimination

Metabolism and elimination, interaction with drug transporters, and biotransformation are described in detail in m2.7.2, Section 3.2.3.

**TAF**

Metabolism is a major elimination pathway for TAF in humans, accounting for > 80% of an oral dose. TAF has a distinct metabolism profile designed to maximize both antiviral potency and clinical safety. Inside cells, TAF is converted by intracellular enzymes to form the pharmacologically active metabolite TFV-DP. Due to increased plasma stability and activation by CatA, as compared with TDF, TAF is more efficiently loaded into PBMCs (including lymphocytes and other HIV-target cells) and macrophages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV, its major metabolite, to the systemic circulation and undesired tissues, including the kidney and bone. In human clinical studies, a 10-mg oral dose of TAF in E/C/F/TAF resulted in TFV-DP concentrations > 4-fold higher in PBMCs and > 90% lower concentrations of TFV in plasma as compared with a 300-mg oral dose of TDF in STB.

In vitro, TAF had little or no inhibitory effect (concentration that resulted in 50% inhibition [$IC_{50}$] > 25 µM) on the human enzymes evaluated other than cytochrome P450 enzyme (CYP) 3A, the inhibition of which was relatively weak ($IC_{50}$ ~7.5 µM). In primary human hepatocytes, TAF showed little or no potential for induction of CYP activity at clinically relevant concentrations. In assays with recombinant enzymes, TAF was not a substrate for CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6; metabolism of TAF with CYP3A4 was detectable

in assays but was comparatively low. Since TAF did not affect the exposure to CYP3A substrates, midazolam or RPV, in clinical drug-drug interaction studies (Studies GS-US-120-1538 and GS-US-120-1554), TAF is not expected to have clinically meaningful CYP-mediated interaction potential.

TAF is eliminated following metabolism to its major metabolite TFV. TAF and TFV have a median plasma $t_{1/2}$ of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of intact TAF is a minor pathway with less than ≤ 2% of the dose eliminated in urine. In clinical PK studies, the pharmacologically active metabolite, TFV-DP, has a $t_{1/2}$ of 150 to 180 hours within PBMCs {7878}, {8461}.

**RPV**

In vitro experiments indicate that RPV primarily undergoes oxidative metabolism mediated by the CYP 3A system.

The terminal elimination half-life of RPV is approximately 45 hours.

A mass balance study (Study C119) showed that most of the [$^{14}$C]TMC278-related radioactivity from a single 150-mg dose administered as oral solution was excreted in feces. At 168 hours after dosing, a mean of 85.1% of the administered radioactivity was recovered in feces, and a mean of 6.1% of the administered radioactivity was recovered in urine. Unchanged TMC278 accounted for a mean of 25.5% of the dose in feces. Only trace amounts (< 1%) of unchanged TMC278 were detected in urine.

**FTC**

In vitro studies indicate that FTC is not an inhibitor of human CYP450 enzymes. Following administration of [$^{14}$C]FTC, complete recovery of the FTC dose was achieved in urine (~86%) and feces (~14%). The biotransformation of FTC includes oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of dose) and conjugation with glucuronic acid to form 2'-O-glucuronide (~4% of dose). No other metabolites were identifiable. The plasma FTC $t_{1/2}$ was approximately 10 hours. Following FTC dosing, the steady-state mean intracellular $t_{1/2}$ of FTC-TP (the active drug moiety) in PBMCs was 39 hours. FTC is primarily excreted by the kidney by both glomerular filtration and active tubular secretion.

## 3.4. Clinical Pharmacokinetics

Details on PK after single- and multiple-dose administration in HIV-infected and healthy subjects are presented in m2.7.2, Section 3.3.1.1.

### 3.4.1. Pharmacokinetics After Single- and Multiple-Dose Administration in HIV-Infected and Healthy Subjects

**TAF**

The TAF PK profile has been characterized following single doses and at steady state in healthy and HIV-infected individuals at doses ranging from 8 to 125 mg. Overall, TAF behaved dose proportionally and in a linear manner across the range of doses studied. The TAF PK profile is characterized by rapid absorption, with a median plasma $T_{max}$ of approximately 0.50 hours, and rapid elimination, with a median plasma $t_{1/2}$ of approximately 0.40 hours and plasma concentrations below the limit of quantitation by approximately 5 hours postdose (Study GS-US-120-0104). Due to the short plasma $t_{1/2}$, TAF does not accumulate in plasma.

**TFV**

The TFV PK profile is characterized by rapid emergence in plasma following TAF dosing, with a median plasma $T_{max}$ ranging from 0.25 to 3 hours postdose, and slow elimination, with a median plasma $t_{1/2}$ of 32.37 hours.

**RPV**

The RPV PK profile has been characterized following single doses and at steady state in healthy and HIV-infected individuals at doses ranging from 12.5 to 300 mg.

After single-dose administration in healthy subjects, the exposure to RPV increased dose proportionally across a dose range of 12.5 to 200 mg, and less than dose proportional between the 200- and 300-mg doses. The rate of RPV absorption was not influenced by the dose; the median $T_{max}$ was 4 to 4.5 hours.

The rate of RPV absorption was not influenced by the dose; the median $T_{max}$ was 4 to 5 hours. The pharmacokinetic profile of RPV in plasma was generally similar after multiple-dose administration of different formulations.

After single-dose administration of RPV as an oral solution in HIV-1 infected subjects, the exposure to RPV appeared to increase in a less than dose proportional fashion across a dose range of 25 to 150 mg. The rate of RPV absorption was not influenced by the dose; the median $T_{max}$ was 3 to 4 hours at all dose levels.

Plasma concentrations of RPV accumulated between the first dose and steady state. After 7 days of treatment with RPV as oral solution, the $AUC_{24h}$ was 2- to 3-fold higher compared to Day 1.

**FTC**

The multiple-dose PK of FTC are dose proportional over the dose range of 25 to 200 mg.

### 3.4.2. Comparison of Exposure Between Healthy and HIV-Infected Subjects

**TAF**

HIV disease status did not have an effect on TAF exposure in healthy and HIV-infected subjects and was not a statistically or clinically relevant covariate based on population PK analyses. Based on population PK covariate analyses, a statistically significant effect of HIV disease status on TFV PK parameters was observed; however, the range of TFV exposures across healthy and HIV-infected was comparable and the observed relationship between disease status and TFV exposure is therefore unlikely to be clinically relevant.

**RPV**

Regardless of the oral formulation or dose of RPV administered, the exposure to RPV was generally lower in HIV-1 infected subjects compared to healthy subjects, at all dose levels. The reason for this lower exposure to RPV in HIV-1 infected subjects has not been identified; this observation is not uncommon for antiretrovirals {15852}. Elevated gastric pH has been observed in HIV-1 infected patients {15889}, which could have contributed to the lower exposure to RPV observed in HIV-1 infected subjects, as the absorption of RPV is pH-dependent (Study C140), with decreasing oral bioavailability at higher pH.

**FTC**

In general, FTC PK parameter estimates following oral administration are characterized by relatively low intersubject variability, and consistent PK data have been observed between healthy volunteers and HIV-infected subjects.

## 3.5. Intrinsic Factors

The effects of intrinsic factors on PK of TAF are described in detail in m2.7.2, Section 3.3.2 and are summarized below.

### 3.5.1. Renal Impairment

Details on the PK in subjects with renal impairment are summarized in m2.7.2, Section 3.3.2.1.1.

**TAF**

No clinically relevant differences in TAF or TFV PK were observed between healthy subjects and subjects with severe renal impairment. Plasma TFV exposure in subjects with mild to moderate renal impairment were within or below the range of TFV plasma exposure after administration of TDF 300 mg in both healthy, HIV-uninfected subjects and in HIV-infected patients with normal renal function. Additionally, population PK analyses of TAF and TFV from pooled Phase 1, 2, and 3 study populations showed that baseline estimated glomerular filtration rate (eGFR) was not a statistically or clinically relevant covariate influencing TAF PK.

**RPV**

In view of the negligible renal excretion of RPV (Study C119) (< 1%), no dose adjustment of RPV is required in patients with renal impairment.

A univariate analysis for the 96-week pooled Phase 3 data (Studies C209 and C215; TMC278-C904-Anal-PKPD, Display PKDP.3), evaluating the impact of different intrinsic factors on the PK parameters of RPV, indicated that the factor of eGFR had no statistically significant effect on the exposure to RPV in HIV-1 infected subjects. This was confirmed in the covariate analysis of the pooled Phase 3 pharmacokinetic data, where eGFR was not retained as a significant covariate affecting the CL/F of RPV (W48-PopPK-Report).

RPV is approved in subjects with mild and moderate renal impairment ($eGFR_{CG} \geq 30$ mL/min), supporting the use of FTC/RPV/TAF without dose adjustment in this population.

**FTC**

In an intensive PK substudy in Study GS-US-292-0112, the exposure of FTC following administration of E/C/F/TAF to HIV-infected subjects with $eGFR_{CG}$ of 30 to 69 mL/min was comparable with that shown in subjects with mild renal impairment (50-80 mL/min) who do not require dose adjustment. In addition, the safety profile of FTC administered as E/C/F/TAF was comparable for subjects with $eGFR_{CG} < 50$ mL/min or $eGFR_{CG} \geq 50$ mL/min in Study GS-US-292-0112. These data in HIV-infected patients support the use of FTC without dose adjustment in patients with $eGFR_{CG} \geq 30$mL/min (supplanting existing recommendations to modify the dosing interval for FTC in patients with $eGFR_{CG} < 50$ mL/min).

**FTC/RPV/TAF**

Based on the results of the FTC, RPV, and TAF components, FTC/RPV/TAF may be administered once daily without dose adjustment in patients with $eGFR_{CG} \geq 30$ mL/min. FTC/RPV/TAF should not be initiated in patients with eGFR < 30 mL/min.

### 3.5.2. Hepatic Impairment

Details on the PK in subjects with hepatic impairment are summarized in m2.7.2, Section 3.3.2.1.2.

**TAF**

No clinically relevant differences in TAF or TFV PK were observed in subjects with mild to moderate hepatic impairment; therefore, no TAF dose adjustment is required in patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment on the PK of TAF has not been studied.

**RPV**

A univariate analysis for the 96-week pooled Phase 3 data (TMC278-C904-Anal-PKPD, Display PKDP.3), evaluating the impact of different intrinsic factors on the PK parameters of RPV, indicated that the factor of HBV and/or hepatitis C virus (HCV) coinfection status had no statistically significant effect on the exposure to RPV in HIV-1 infected subjects.

In Trial TMC278-TiDP-C130, the steady-state exposure to RPV at doses of 25 mg once daily was higher in subjects with mild hepatic impairment compared to matched healthy control subjects; the mean $C_{max}$ and $AUC_{24h}$ were 1.27- and 1.47-fold higher, respectively. In subjects with moderate hepatic impairment, the exposure to RPV after a single dose was lower compared to healthy subjects ($C_{max}$: 30% lower; $AUC_{24h}$: 24% lower). Based on the shape of the plasma concentration profiles, this appeared to be due to a difference in the absorption of RPV. However, at steady state, due to the longer $t_{½, term}$ in subjects with moderate hepatic impairment compared to matched healthy control subjects, the exposure to RPV was comparable in subjects with moderate hepatic impairment and healthy subjects.

These data suggest that no dose adjustment of RPV is needed in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment on the exposure to RPV has not been studied.

**FTC**

The PK of FTC has not been studied in subjects with hepatic impairment; however, FTC is not significantly metabolized by liver enzymes, so the impact of liver impairment should be limited.

**FTC/RPV/TAF**

Based on the results of the FTC, RPV, and TAF components, no dose adjustment of FTC/RPV/TAF is required in patients with mild to moderate hepatic impairment. No PK or safety data are available for FTC/RPV/TAF in severe hepatic impairment.

### 3.5.3. Hepatitis B and/or Hepatitis C Virus Coinfection

The PK of FTC, RPV, and TAF have not been fully evaluated in patients coinfected with HBV or HCV. There no clinical data yet available on the use of FTC/RPV/TAF in subjects with HBV or HCV coinfection.

### 3.5.4. Pediatrics

Details on the PK in pediatric subjects are summarized in m2.7.2, Section 3.3.2.5.

**TAF**

The effect of age of pediatric subjects on the PK of TAF and TFV was assessed based on data from Study GS-US-292-0106, where E/C/F/TAF was administered to HIV-infected, ART-naive adolescents (12 to < 18 years). TAF and TFV exposures were in the range of values observed in HIV-infected, ART-naive adults following E/C/F/TAF administration, indicating that the 12- to

< 18-year-old range had no relevant effects on the exposure of TAF. Additionally, in the pooled Phase 2 and Phase 3 study populations used for TAF population PK analyses, HIV-infected adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, respectively, again confirming that age (12 to < 18 years) was not a clinically relevant covariate.

**RPV**

The pharmacokinetics of RPV in adolescent subjects was assessed in Study TMC278-C213.

Data from intensive PK analysis (noncompartmental analysis) indicated that RPV pharmacokinetics were similar in adults and adolescents. Also the interindividual variability (% coefficient of variation [CV]) of the RPV pharmacokinetic parameters $C_{0h}$, $C_{min}$, $C_{max}$ and $AUC_{24h}$ in adolescents was similar to that observed in adults (pooled data of RPV Phase 3 Studies C209/C215 pharmacokinetic substudies), and ranged between 35% and 50% in adolescents and between 48% and 58% in adults.

Data from population PK analysis (sparse sampling) also indicated that the RPV PK and variability were similar in adults and adolescents.

**FTC**

There were no relevant effects of age (≥ 12 years) on the exposure of FTC.

### 3.5.5. Pharmacokinetics/Pharmacodynamics

Details on the PK/PD relationships are presented in m2.7.2, Section 3.4.

**TAF**

Based on PK/PD analysis for efficacy parameters, TAF 25 mg is expected to provide near-maximal activity (HIV-1 RNA decreases of approximately 1.7 to 1.8 $log_{10}$ copies/mL). Phase 2 data in Study GS-US-292-0102 with TAF 10 mg in the E/C/F/TAF FDC (which achieves exposure equivalent to TAF 25 mg) demonstrated efficacy, based on high proportions of subjects with plasma HIV-1 RNA < 50 copies/mL. The E/C/F/TAF FDC was shown to be effective with a favorable safety and tolerability profile in Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106). Moreover, TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111) using results from the snapshot algorithm showed uniformly high virologic success across the quartile categories of TAF $AUC_{tau}$ ($AUC_{tau}$ from 47 to 1869 ng•h/mL) with no trends in exposure-response relationship observed.

**RPV**

The plasma and intracellular PK and PK-PD correlation, and long-term efficacy and safety data obtained from Phase 2/3 clinical studies and postmarketing experience, support the approved 25-mg once-daily dose for RPV.

**FTC**

The plasma and intracellular PK and PK-PD correlation, and long-term efficacy and safety data obtained from Phase 2/3 clinical studies and postmarketing experience, support the approved 200-mg once-daily dose for FTC.

### 3.5.6. Demographic Factors

Details on the effects of demographic factors on PK are presented in m2.7.2, Sections 3.3.1.2 and 3.3.2.

**TAF**

Population PK analyses indicated no statistically significant or clinically relevant influence on TAF exposure based on body size measures (body weight, body surface area, or body mass index), age (range, 12 to 82 years), sex, race, $eGFR_{CG}$, and population (healthy subjects versus treatment-naive versus treatment-experienced HIV-infected subjects). A modest, statistically significant effect of race (black versus nonblack) and sex on TFV PK parameters was observed. However, the range of TFV exposure across race and across males and females was comparable and, as such, these observed relationships are not considered to be clinically relevant.

In adolescents (n = 24), TAF and TFV exposures were comparable with historical values observed in HIV-infected, treatment-naive adults following E/C/F/TAF treatment. Similarly, in the population PK analyses, adolescent subjects had comparable TAF and TFV exposures versus HIV-infected adult subjects, confirming that age was not a clinically relevant covariate.

**RPV**

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for RPV.

The pharmacokinetics of RPV in antiretroviral treatment-naive HIV-1 infected pediatric patients 12 to less than 18 years of age receiving RPV 25 mg once daily was comparable to that in treatment-naive HIV-1 infected adults receiving RPV 25 mg once daily. There was no impact of body weight on RPV pharmacokinetics in pediatric patients in Study C213 (33 to 93 kg), similar to what was observed in adults. Population pharmacokinetic analysis in HIV-1 infected patients showed that RPV pharmacokinetics is not different across the age range (12 to 78 years) evaluated.

**FTC**

No clinically relevant pharmacokinetic differences due to gender or ethnicity have been identified for FTC.

### 3.5.7. Potential for Drug Interactions

Drug interaction information is summarized in m2.7.2, Section 3.3.3.2.

TAF is not an inhibitor or inducer of CYP3A4 in vivo. Coadministration of TAF single agent with a modest CYP inducer resulted in slightly lower TAF exposure and a commensurate lowering of TFV exposure; as such, administration of TAF with a modest CYP3A inducer may result in lower TAF exposure. TAF is transported by P-gp and metabolized by esterases expressed in the intestine. As such, drugs that strongly affect P-gp activity may lead to changes in TAF availability.

In vitro, RPV is an inducer of CYP3A4 and an inhibitor of CYP3A4 activity. Most of the clinical drug-drug interaction trials were performed with an RPV dose of 150 mg once daily. Overall, RPV at the dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of coadministered drugs.

Based on the results of the in vitro experiments, in vivo assessments, and the known elimination pathways of FTC, the potential for clinically relevant drug-drug interactions involving FTC with other medicinal products is low.

Study GS-US-366-1689 investigated the DDI potential between FTC/RPV/TAF and LDV/SOF. No interaction was observed; therefore, no dose adjustment is required when FTC/RPV/TAF is coadministered with LDV/SOF.

#### 3.5.7.1. Potential for FTC/RPV/TAF to Affect Other Drugs

**TAF**

The potential for TAF and TFV to affect human CYP-mediated drug metabolism was examined in vitro using hepatic microsomal fractions and enzyme-selective activities. The inhibitory activity of TAF with human liver microsomal CYP isozymes, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A were assessed at concentrations up to 25 μM. The inhibition constant ($IC_{50}$) values calculated for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were greater than 25 μM. TAF weakly inhibited CYP3A-mediated oxidation of midazolam or testosterone with $IC_{50}$ values of 7.6 and 7.4 μM, respectively. TFV at 100 μM did not inhibit CYP1A2, CYP2C9, CYP2D6, CYP2E1, and CYP3A.

The potential for TAF to be a mechanism-based inhibitor of the human CYP enzymes CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 was assessed at TAF concentration at 50 μM (AD-120-2040). There was no evidence for time- or cofactor-dependent inhibition of any enzyme by TAF, with the maximum change in activity of 17.4% with CYP2C8 relative to control.

Clinical evaluation of TAF as a CYP3A4 inhibitor or inducer (Study GS-US-120-1538) showed no clinically relevant differences in midazolam (MDZ) PK relative to MDZ alone following coadministration of MDZ (oral or intravenous) and TAF; these data indicate that multiple-dose TAF does not exhibit CYP3A inhibition or induction activity, either presystemically or systemically.

#### 3.5.7.2. Potential for Other Drugs to Affect FTC/RPV/TAF

**TAF**

TAF is transported by P-gp and metabolized by esterases expressed in the intestine {21545}, {21546}. Intestinal P-gp cycles TAF, mediating metabolism of the prodrug by esterases. As such, drugs that strongly affect P-gp activity (eg, COBI) may lead to changes in TAF bioavailability. Coadministration with COBI or ritonavir (RTV) can lead to near maximal inhibition of P-gp, resulting in an increase in TAF exposure.

As TAF is not metabolized by CYP enzymes except for weak metabolism observed for CYP3A4 in vitro, CYP inducers are not expected to have a relevant effect on TAF PK; however, most CYP inducers are also P-gp inducers, and coadministration with P-gp inducers may decrease the absorption of TAF. Coadministration with a moderate CYP3A and P-gp inducer (ie, EFV) resulted in slightly lower TAF exposure (14% to 22%), and coadministration with a weak CYP3A and P-gp inducer (ie, RPV) resulted in no change to TAF exposure. As such, minimal effect on TAF exposure is expected when administered as part of the FTC/RPV/TAF FDC.

**RPV**

In general, the exposure to RPV can be affected by modulators of CYP3A enzyme activity and by drugs that increase the gastric pH.

## 3.6. Summary of Clinical Pharmacology

The PK profiles of FTC/RPV/TAF and its components have been well characterized in healthy subjects, HIV-infected subjects, and special populations. The following are the major clinical pharmacology findings for the FTC/RPV/TAF FDC:

- TAF, RPV, and FTC exposures were bioequivalent when comparing FTC/RPV/TAF to E/C/F/TAF and Edurant (25 mg) tablets, as applicable, following single-dose administration to healthy subjects (N = 96).

- Relative to fasting conditions, the administration of FTC/RPV/TAF to healthy adult subjects with either moderate-fat or high-calorie, high-fat food resulted in increased exposure of RPV and TAF. The effect of food on TAF exposure is not clinically relevant but the clinical relevance of the effect of food on RPV exposure is not known. In the absence of more definitive data, the FTC/RPV/TAF FDC tablet should be administered with food.

- No clinically relevant differences were observed in the PK of the individual components of FTC/RPV/TAF with respect to any demographic variable. Further, the PK of TAF and FTC in HIV-infected adolescent subjects was consistent with the range of exposure associated with antiviral activity of E/C/F/TAF in adults, and the PK of RPV in HIV-infected adolescent subjects was comparable with that of adults. These data support the extrapolation of efficacy and safety data from adult subjects to pediatric subjects and support the use of FTC/RPV/TAF in patients > 12 years of age.

- No dose adjustment of FTC/RPV/TAF is necessary in patients with estimated creatinine clearance ≥ 30 mL/min. Renal excretion of RPV is negligible, and Study GS-US-292-0112 showed that FTC and TAF can be safely administered in HIV-infected subjects with $eGFR_{CG} \geq 30$ mL/min.

- No dose adjustment of FTC/RPV/TAF is necessary in patients with mild or moderate hepatic impairment as no clinically relevant changes in PK were observed in these subjects. Neither FTC/RPV/TAF nor its individual components have been studied in patients with severe hepatic impairment.

- The PK of TAF, RPV, and FTC have not been fully evaluated in patients coinfected with HBV and/or HCV.

- TAF PK/PD analyses evaluating TAF exposure versus response in the 2 pivotal Phase 3 studies (Studies GS-US-292-0104 and GS-US-292-0111) using results from the snapshot algorithm showed uniformly high virologic success across the quartile categories of TAF $AUC_{tau}$ with no trends in exposure-response relationship observed.

- FTC/RPV/TAF is a complete regimen for the treatment of HIV-1 infection; therefore, FTC/RPV/TAF should not be administered with other HIV ARV medications. Information regarding potential drug-drug interactions with other HIV ARV medications is not provided. The drug-drug interaction studies described were conducted with TAF, RPV, or FTC as individual agents or combinations; limited drug-drug interaction studies have been conducted using FTC/RPV/TAF.

  — Clinical studies have shown no clinically relevant drug-drug interactions between TAF and RPV.

  — The solubility of RPV is pH dependent. Therefore, drugs that alter intragastric pH may affect the solubility of RPV. As such, the FTC/RPV/TAF FDC tablet should not be coadministered with proton pump inhibitors as coadministration may cause significant decreases in RPV plasma concentrations. For drugs with a short-lived effect on intragastric pH, such as the $H_2$-antagonists and antacids, an effect on RPV exposure can be circumvented by separating the intake of the drugs in time.

  — The FTC/RPV/TAF FDC tablet should not be administered with CYP3A inducers as these could decrease RPV plasma concentrations, and potentially reduce the therapeutic effect of RPV. Following the switch from an EFV-based regimen (a known CYP3A inducer with a long plasma half-life) to a RPV-based regimen, the briefly lower exposures of RPV had no impact on antiviral efficacy in stably suppressed patients.

  — TAF is transported by P-gp. Therefore, drugs that induce P-gp activity may lead to a decreased plasma concentration of TAF, whereas, drugs that inhibit P-gp may increase the absorption and plasma concentration of TAF. The proposed prescribing information for FTC/RPV/TAF reflects these potential interaction concerns. Although RPV is an inhibitor of P-gp, no clinically relevant drug-drug interaction with TAF has been observed in clinical studies.

# 4. OVERVIEW OF EFFICACY

Evidence to support the clinical efficacy of FTC/RPV/TAF is provided by a comprehensive program of 6 clinical studies of E/C/F/TAF, 3 clinical studies of RPV, and 2 clinical studies of Eviplera, in combination with the demonstration of PK bioequivalence of exposures of FTC and TAF to E/C/F/TAF and RPV to Edurant. This section provides an overview of the pooled analysis of efficacy that was conducted for the pivotal E/C/F/TAF Phase 3 studies in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111) and an overview of the pooled analysis of efficacy that was conducted for the pivotal RPV Phase 3 studies in ART-naive subjects (Studies C209 and C215). In some instances, the subset of subjects receiving FTC/TDF with RPV from Studies C209 and C215 is presented, as it provides data for RPV and FTC administered with a TFV prodrug and therefore contains relevant data for the FTC/RPV/TAF combination.

An overview of the studies for E/C/F/TAF and the RPV-containing regimen, Eviplera, that were conducted in virologically suppressed subjects is also provided, along with the individual studies in renally impaired or adolescent subjects (Table 1; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Pooling of the efficacy data for Studies GS-US-292-0104 and GS-US-292-0111 is appropriate due to their identical study design, including eligibility criteria (m2.7.3, Section 2.1). Statistical methods for pooling and analysis of efficacy data are provided in the E/C/F/TAF Integrated Summary of Efficacy (ISE) Statistical Analysis Plan (E/C/F/TAF ISE SAP). Pooling of the efficacy data for Studies C209 and C215, including pooling of the FTC/TDF subset, is appropriate due to their identical study design, including eligibility criteria (m2.7.3, Section 2.2). Statistical methods for pooling and analysis of efficacy data are provided for the pooled C209 and C215 studies in TMC278-TiDP6-904.

No other data were pooled (unless otherwise stated), due to differences in the subject populations studied, treatment durations, and randomization. The clinical virology analyses are described in m2.7.2, Section 4.2.

Key demographic and baseline characteristics across all populations are summarized in Section 5.

## 4.1. Rationale for Primary Efficacy Endpoint

The primary efficacy endpoint in the E/C/F/TAF studies was the percentage of subjects with HIV-1 RNA < 50 copies/mL using the snapshot algorithm (at Week 48 for ART-naive and virologically suppressed subjects, at Week 24 for subjects with renal impairment; and for the randomized portion of the Phase 2 E/C/F/TAF Study GS-US-292-0102). Secondary efficacy analyses including the percentage of subjects with HIV-1 RNA < 50 copies/mL using the missing = failure (M = F) method, the percentage of subjects with HIV-1 RNA < 20 copies/mL using the snapshot algorithm, and changes in CD4 cell count, are summarized in this overview to support the primary efficacy endpoint results.

The primary efficacy endpoint for the RPV Phase 3 studies in ART-naive adult subjects was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the time to loss of virologic response (TLOVR) algorithm. Secondary efficacy analyses that support the primary efficacy endpoint results are summarized and include the percentage of subjects with HIV-1 RNA < 50 copies/mL using the snapshot algorithm at Weeks 48 and 96, the percentage of subjects with HIV-1 RNA < 50 copies/mL using TLOVR algorithm at Week 96, and changes in CD4 cell count.

In the Eviplera Phase 2b and 3 studies (GS-US-264-0111 and GS-US-264-0106) in virologically suppressed subjects, the primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 12 (GS-US-264-0111) or Week 24 (GS-US-264-0106) using the snapshot algorithm. Secondary efficacy analyses that support the primary efficacy endpoint results are summarized and include the proportion of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 48 as defined by the snapshot algorithm and using missing data imputation methods, and changes in CD4 cell count.

## 4.2. Efficacy in ART-Naive Adults

### 4.2.1. E/C/F/TAF

Details on the individual efficacy results from the E/C/F/TAF Phase 2 Study GS-US-292-0102, and the Phase 3 Studies GS-US-292-0104 and GS-US-292-0111 are provided in m2.7.3, Section 3.2.1.

The percentages of subjects with virologic success based on the pooled Phase 3 data (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the snapshot algorithm) were E/C/F/TAF 92.4% versus STB 90.4% (Table 2).

E/C/F/TAF was determined to be noninferior to STB because the lower bound of the 2-sided confidence interval (CI) of the difference in the success rate (E/C/F/TAF – STB) was greater than the prespecified −12% margin (difference in percentages: 2.0%; 95% CI: −0.7% to 4.7%).

These pooled results confirmed those from the individual Studies GS-US-292-0104 and GS-US-292-0111, where noninferiority of E/C/F/TAF versus STB was determined using the full analysis set (FAS) (GS-US-292-0104: difference in percentages: 1.0%, 95.002% CI: −2.6% to 4.5%; GS-US-292-0111 difference in percentages: 3.1%, 95.002% CI −1.0% to 7.1%) and confirmed using the per-protocol (PP) Analysis Set.

**Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL – Pooled Data (FAS)**

| | | | E/C/F/TAF vs. STB | |
|---|---|---|---|---|
| | E/C/F/TAF (N=866) | STB (N=867) | p-value[a] | Difference in Percentages (95% CI) [b] |
| Virologic success at Week 48[c] | | | | |
| HIV-1 RNA < 50 copies/mL | 800 (92.4%) | 784 (90.4%) | 0.13 | 2.0% (−0.7% to 4.7%) |
| Virologic failure at Week 48[c] | 31 (3.6%) | 35 (4.0%) | — | — |
| HIV-1 RNA >= 50 copies/mL | 20 (2.3%) | 23 (2.7%) | — | — |
| Discontinued study drug due to lack of efficacy | 2 (0.2%) | 3 (0.3%) | — | — |
| Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL[d] | 8 (0.9%) | 8 (0.9%) | — | — |
| Added New ARV | 1 (0.1%) | 1 (0.1%) | — | — |
| No virologic data in Week 48 window [c] | 35 (4.0%) | 48 (5.5%) | — | — |
| Discontinued study drug due to AE/death | 8 (0.9%) | 14 (1.6%) | — | — |
| Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d] | 21 (2.4%) | 31 (3.6%) | — | — |
| Missing data during window but on study drug | 6 (0.7%) | 3 (0.3%) | — | — |

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA, region and study stratum. Baseline HIV-1 RNA stratum: <= 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.
b Difference in percentages of virologic success between treatment groups and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA, region, and study stratum.
c Week 48 window is between Day 294 and 377 (inclusive).
d Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.
Source: m2.7.3, Table 38

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- In the pooled subgroup analysis, the rates of virologic success at Week 48 for the subgroups age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, region (US versus ex-US), or study drug adherence were similar for the E/C/F/TAF and STB groups. For female subjects and subjects with baseline HIV-1 RNA ≤ 100,000 copies/mL, the lower bound of 95% CI for the virologic success was > 0, favoring the E/C/F/TAF group over the STB group.

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the M = F method for the pooled data were as follows: E/C/F/TAF 93.0%; STB 92.3%.

- The emergence of resistance mutations was rare across the E/C/F/TAF and STB groups (E/C/F/TAF group 0.7%, 7 of 978 subjects; STB group 0.8%, 7 of 925 subjects) (integrated analysis of Studies GS-US-292-0102, GS-US-292-0104, and GS-US-292-0111; m2.7.2, Section 4.2.1.2.2.1).

- The mean (SD) increases from baseline in CD4 cell counts at Week 48 (observed data) using the pooled data were as follows: E/C/F/TAF 230 [177.3] cells/μL; STB 211 [170.7] cells/μL (similar results were shown for the last observation carried forward [LOCF] analysis).

The efficacy data from the Phase 2 Study GS-US-292-0102 supported those for the Phase 3 studies and demonstrated evidence of durable efficacy; 87.5% of subjects who received E/C/F/TAF from baseline achieved and maintained HIV-1 RNA < 50 copies/mL at Week 96 (M = F).

### 4.2.2. RPV

Details on the individual efficacy results from the FTC/TDF subset of subjects in the individual studies and pooled analysis of the RPV Phase 3 Studies C209 and C215 are provided in m2.7.3, Section 3.2.2.

In the pooled intent-to-treat (ITT) population for the FTC/TDF subset at Week 48, 83.5% of subjects in the RPV group and 82.4% of subjects in the control group were virologic responders (Table 3). At Week 96, 76.9% of subjects in the RPV group and 77.3% of subjects in the control group were virologic responders. The difference in virologic response [95% CI] between the RPV + FTC/TDF and control groups was 1.0 [−3.4; 5.5]. The lower limit of the 95% CI of the difference between the treatment groups was well above −12%; therefore, noninferiority of RPV versus control was established at the 12% noninferiority margins.

**Table 3. RPV Studies Pooled C209 and C215 Data (FTC/TDF Subset Populations): Virologic Outcome (< 50 HIV-1 RNA copies/mL, TLOVR) at Weeks 48 and 96**

| Virologic Outcome, n (%) | Week 48 | | Week 96 | |
|---|---|---|---|---|
| | RPV N = 550 | Control N = 546 | RPV N = 550 | Control N = 546 |
| **Responders**[a] | 459 (83.5) | 450 (82.4) | 423 (76.9) | 422 (77.3) |
| Baseline viral load ≤ 100,000 c/mL | 258/288 (89.6) | 217/256 (84.8) | 241/288 (83.7) | 206/255 (80.8) |
| Baseline viral load > 100,000 c/mL | 201/262 (76.7) | 233/290 (80.3) | 182/262 (69.5) | 216/291 (74.2) |
| **Nonresponders** | | | | |
| Virologic Failure | 52 (9.5) | 23 (4.2) | 63 (11.5)[b] | 28 (5.1)[c] |
| Baseline viral load ≤ 100,000 c/mL | 12/288 (4.2) | 6/256 (2.3) | 17/288 (5.9) | 6/255 (2.4) |
| Baseline viral load > 100,000 c/mL | 40/262 (15.3) | 17/290 (5.9) | 46/262 (17.6) | 22/291 (7.6) |
| Rebounder[d] | 20 (3.6) | 11 (2.0) | 33 (6.0) | 20 (3.7) |
| Resuppressed[e] | 4 (0.7) | 3 (0.5) | 14 (2.5) | 7 (1.3) |
| Never suppressed[f] | 32 (5.8) | 12 (2.2) | 30 (5.5) | 8 (1.5) |
| Initial lack of response[g] | 3 (0.5) | 1 (0.2) | 4 (0.7) | 1 (0.2) |
| Death[h] | 0 | 1 (0.2) | 0 | 4 (0.7) |
| Discontinued due to AE | 12 (2.2) | 39 (7.1) | 20 (3.6) | 44 (8.1) |
| Discontinued for non-AE reason[i] | 27 (4.9) | 33 (6.0) | 44 (8.0) | 48 (8.8) |

N = number of subjects per treatment group; n = number of observations
a Subject with 2 consecutive viral load values < 50 copies/mL (ITT TLOVR)
b There were 17 new virologic failures between Weeks 48 and 96 (6 patients with baseline viral load ≤ 100,000 copies/mL and 11 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.
c There were 10 new virologic failures between Weeks 48 and 96 (3 patients with baseline viral load ≤ 100,000 copies/mL and 7 patients with baseline viral load > 100,000 copies/mL). There were also reclassifications in the Week 48 primary analysis with the most common being reclassification from virologic failure to discontinued for non-AE reasons.
d Subjects with 2 consecutive results < 50 copies/mL before Week 48, and subsequently 2 consecutive results ≥ 50 copies/mL before/at Week 48
e Subjects who had a rebound and who subsequently had 2 consecutive viral load values < 50 copies/mL
f Subjects who never had 2 consecutive viral load values < 50 copies/mL before Week 48
g Subjects who were never suppressed and who never achieved 2 consecutive results showing > 1 log10 decrease from baseline by Week 12
h One subject in the control group died after Week 48 (and hence is not included in this table) but before the date of data cut-off, and is included in the total number of deaths in the Week 96 Eviplera Summary of Clinical Safety
i For example, lost to follow up, noncompliance, withdrew consent
Source: m 2.7.3, Tables 44 and 46; {30163}

In the Phase 3 pooled TLOVR analysis for the FTC/TDF subset at Week 48, 9.5% of subjects in the RPV group and 4.2% of subjects in the control group were virologic failures. Discontinuation due to an AE was reported for a greater proportion of subjects in the control group (7.1% of subjects) than the RPV group (2.2%).

The majority of virologic failures occurred within the first 48 weeks of the studies in both groups. From Week 48 to Week 96, there were similar and low rates of virologic failure observed between the treatment groups: 2.7% in the RPV group and 2.6% in the EFV group.

The virologic failure rates at Weeks 48 and 96 in the RPV group were 9.5% and 11.5%, respectively, and in the control group were 4.2% and 5.1%, respectively. The difference in the rate of new virologic failures from Week 48 to Week 96 between RPV and control groups was not statistically significant (3.6% and 2.1%, respectively, p = 0.242).

Results for the FTC/TDF subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the snapshot algorithm were as follows: RPV + FTC/TDF 82.5%; control + FTC/TDF 80.8%; 12.9% of subjects in the RPV + FTC/TDF group and 7.9% of subjects in the control group were virologic failures.
- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using the TLOVR algorithm (subjects with 2 consecutive viral load values < 50 copies/mL) were as follows: RPV + FTC/TDF 76.9%; control + FTC/TDF 77.3%. The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using the snapshot algorithm for the FTC/TDF subset of the pooled data were as follows: RPV + FTC/TDF 77.3%; control + FTC/TDF 76.7%.
- The mean (SD) increases from baseline in CD4 cell counts at Week 96 were as follows: Week 96, the mean increase from baseline was 225.5 cells/μL in the RPV group (n = 549) and 222.1 cells/μL in the control group (n = 546).
- The proportion of virologic responders at Week 96 in the RPV group was greater in subjects with baseline viral load ≤ 100,000 copies/mL (83.7%) than in those with baseline viral load > 100,000 copies/mL (69.5%).
- Fewer subjects in the RPV group with baseline viral load ≤ 100,000 copies/mL had virologic failure with resistance compared with > 100,000 copies/mL. Through Week 48, there were more subjects in the RPV group that had emergent resistance than the control for both viral load strata. Between Weeks 48 and 96, however, the number of subjects with virologic failure and resistance was low and comparable between treatment groups in both baseline viral load strata.

## 4.3. Efficacy in Virologically Suppressed Adults

### 4.3.1. E/C/F/TAF

Key treatment outcomes for Study GS-US-292-0109 are described below; full details are provided in m2.7.3, Section 3.2.1.2.

- The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the snapshot algorithm) were as follows: E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9% (Table 4).

Switching to E/C/F/TAF was determined to be noninferior to maintaining FTC/TDF+3rd Agent at Week 48 because the lower bound of the 2-sided CI of the difference in success rate (E/C/F/TAF − comparator) was greater than the prespecified −12% margin (difference in percentages: 2.7%, 95.01% CI: −0.3% to 5.6%). Noninferiority of E/C/F/TAF versus FTC/TDF+3rd Agent was confirmed by the analysis using the PP Analysis Set.

**Table 4. GS-US-292-0109: Virologic Outcome at Week 48 Using Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Week 48 FAS)**

| | | | E/C/F/TAF vs. FTC/TDF+3rd Agent | |
|---|---|---|---|---|
| | E/C/F/TAF (N=799) | FTC/TDF+3rd Agent (N=397) | p-value[a] | Difference in Percentages (95.01% CI)[b] |
| Virologic success at Week 48[c] | | | | |
| HIV-1 RNA < 50 copies/mL | 764 (95.6%) | 369 (92.9%) | 0.051 | 2.7% (−0.3% to 5.6%) |
| Virologic failure at Week 48[c] | 9 (1.1%) | 5 (1.3%) | — | — |
| HIV-1 RNA >= 50 copies/mL | 6 (0.8%) | 5 (1.3%) | — | — |
| Discontinued study drug due to lack of efficacy | 1 (0.1%) | 0 | — | — |
| Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL[d] | 0 | 0 | — | — |
| Added new ARV | 2 (0.3%) | 0 | — | — |
| No virologic data in Week 48 window[c] | 26 (3.3%) | 23 (5.8%) | — | — |
| Discontinued study drug due to AE/death | 8 (1.0%) | 3 (0.8%) | — | — |
| Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[d] | 5 (0.6%) | 15 (3.8%) | — | — |
| Missing data during window but on study drug | 13 (1.6%) | 5 (1.3%) | — | — |

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by the prior treatment regimen (STB, ATR, ATV/boosted+TVD).
b Difference in percentages of virologic success and its 95.01% CI were calculated based on the MH proportion adjusted by the prior treatment regimen.
c Week 48 window is between Day 294 and 377 (inclusive). The Week 48 FAS is defined as subjects randomized by 31OCT2013 and received at least 1 dose of study drug.
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
Source: m2.7.3, Table 40

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- Virologic success rates using the Week 48 FAS were balanced in both treatment groups for the age, sex, race, geographic regions, prior treatment regimen, and study drug adherence subgroups.

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the M = F method were as follows: E/C/F/TAF 96.4%, FTC/TDF+3rd Agent 94.7%.

- The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 48 using the snapshot algorithm were as follows: E/C/F/TAF 92.2%; FTC/TDF+3rd Agent 90.4%.

- One subject (0.1%) from the E/C/F/TAF group (no subjects from the FTC/TDF+3rd Agent group) experienced confirmed virologic rebound; this subject did not have resistance detected to any study drug (m2.7.2, Section 4.2.1.1.4).

- The mean (SD) increases from baseline in CD4 cell counts at Week 48 (observed data) were as follows: E/C/F/TAF 33 (166.6) cells/μL; FTC/TDF+3rd Agent 27 (160.2) cells/μL (similar results were shown for the LOCF).

### 4.3.2. Eviplera

Key treatment outcomes for Eviplera Studies GS-US-264-0111 and GS-US-264-0106 are described below; full details are provided in m2.7.3, Section 3.2.3.1.

The primary endpoint in both studies was the percentages of subjects with virologic success (plasma HIV-1 RNA < 50 copies/mL in Studies GS-US-264-0111 and GS-US-264-0106 at Week 12 or Week 24, respectively, using the snapshot algorithm).

In Study GS-US-264-0111, all 49 subjects (100%) in the FAS had virologic success at Week 12. At Week 48, 93.9% of subjects (95% CI: 83.1%, 98.7%) had virologic success.

In Study GS-US-264-0106, virologic success was maintained at Week 24: Eviplera 93.7%; stay on baseline regimen (SBR) 89.9%. There was a 3.8% treatment difference (95% CI: −1.6%, 9.1%), and the lower bound of the 95% CI of the treatment difference was above the predefined −12% margin for noninferiority of Eviplera to SBR. Virologic success for Eviplera was maintained at Week 48 (89.3%).

Results for subgroup analyses and key secondary efficacy endpoints are summarized below:

- In Study GS-US-264-0111, using the M = F method, the proportion of subjects with HIV-1 RNA levels < 50 copies/mL at Week 48 was 93.9% (95% CI: 83.1%, 98.7%). In Study GS-US-264-0106, similar proportions of subjects in the Eviplera group (93.7%) and the SBR group (89.9%) had HIV-1 RNA < 50 copies/mL at Week 24 using the M = F method. The proportion of subjects in the Delayed Switch group with HIV-1 RNA < 50 copies/mL after 24 weeks of treatment was 92.1%.

- In Study GS-US-264-0111, the median first quartile (Q1), third quartile (Q3) change from baseline in CD4 cell counts was −2 (–76, 104) cells/μL at Week 48. In Study GS-US-264-0106, the median (Q1, Q3) increase from baseline to Week 24 in CD4 cell count was 10 (−61, 82) cells/μL in the Eviplera group and 22 (–40, 106) cells/μL in the SBR group.

## 4.4. Efficacy in Adults with Mild to Moderate Renal Impairment

Key treatment outcomes for E/C/F/TAF Study GS-US-292-0112 are described below; full details are provided in m2.7.3, Section 3.2.1.3.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 24 using the snapshot algorithm) were as follows:

- Cohort 1 (switch subjects) 95.0% (baseline $eGFR_{CG}$ < 50 mL/min: 95.0%; baseline $eGFR_{CG}$ ≥ 50 mL/min: 95.1%). Virologic success in Cohort 1 was maintained at Week 48 (93.7%).
- Cohort 2 (ART-naive subjects) 5 of 6 subjects

Results for subgroup analyses and key secondary efficacy endpoints are summarized below:

- There were no clinically relevant differences in virologic success at Week 24 (snapshot algorithm, HIV-1 RNA < 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate) for Cohort 1
- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the M = F method was 97.5% in Cohort 1.
- The percentage of subjects with HIV-1 RNA < 20 copies/mL at Week 24 using the FAS was 93.0% for Cohort 1 (baseline $eGFR_{CG}$ < 50 mL/min 92.5%; baseline $eGFR_{CG}$ ≥ 50 mL/min 93.2%). Five of 6 subjects in Cohort 2 also had HIV-1 RNA < 20 copies/mL.
- In Cohort 1, 2 subjects (0.8%, 2 of 242) were analyzed and showed resistance to multiple drug classes; 1 subject had the same resistance documented in an historic genotype and 1 subject appeared to have had reinfection with a resistant virus. In Cohort 2, no subject met the criteria for resistance analysis (0%, 0 of 6) (m2.7.2, Section 4.2.1.1.5).
- CD4 cell counts remained stable during treatment with E/C/F/TAF for Cohort 1 (mean [SD] change from baseline in CD4 cell counts at Week 24 using the FAS [observed data] was −7 [159.2] cells/μL and at Week 48 [observed data] was 16 [158.0] cells/μL) and increased during treatment for Cohort 2 (mean [SD] change from baseline in CD4 cell count at Week 24 [observed data] was 126 [106.3] cells/μL and at Week 48 was 144 [169.7] cells/μL).

## 4.5. Efficacy in ART-Naive Adolescent Subjects

### 4.5.1. E/C/F/TAF

Key treatment outcomes for E/C/F/TAF Study GS-US-292-0106 are described below; full details are provided in m2.7.3, Section 3.2.1.4.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 24 using snapshot algorithm) was 91.3% (21 of 23 subjects in the Week 24 FAS).

Two subjects who had HIV-1 RNA > 50 copies/mL at Week 24 had HIV-1 RNA < 50 copies/mL at earlier visits and at Week 32.

Results for the key secondary endpoints are shown below:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the M = F method was identical to the primary endpoint: 91.3%.
- There was no virologic resistance to E/C/F/TAF in any subject.
- The mean (SD) increase from baseline in CD4 cell count was 212 (144.3) cells/μL.

### 4.5.2. RPV

Key treatment outcomes for the RPV Study C213 are described below; full details are provided in m2.7.3, Section 3.2.2.2.

The observed proportion of virologic responders based on the ITT population (plasma HIV-1 RNA < 50 copies/mL at Week 48 using TLOVR) was 26 of 36 subjects (72.2%) while 8 of 36 subjects (22.2%) were considered virologic failures.

Of the subjects who experienced virologic failure at Week 48, 4 of 36 subjects (11.1%) were never suppressed (of whom 1 of 36 subjects [2.8%] experienced initial lack of virologic response) and 4 of 36 subjects (11.1%) rebounded.

Results for the key secondary endpoints were as follows:

- The virologic response rate (< 50 copies/mL) at Week 48 obtained by the snapshot approach was the same as for TLOVR imputation (26 of 36 subjects [72.2%]), while 9 of 36 subjects (25.0%) were considered virologic failures.
- The mean (standard error [SE]) increase from baseline in CD4 cell count was 201.2 (32.87) cells/μL at Week 48.

## 4.6. Efficacy Discussion and Conclusions

The FTC/TAF- and RPV-containing regimens produced high rates of virologic success/response in all HIV-infected populations studied.

Potent antiviral efficacy, noninferior to comparators was demonstrated over 48 weeks in ART-naive adults. E/C/F/TAF was noninferior to STB (virologic success: E/C/F/TAF 92.4%; STB 90.4% from pooled analysis [snapshot] of Studies GS-US-292-0104 and GS-US-292-0111). RPV administered with FTC/TDF was noninferior to EFV+FTC/TDF (virologic response: RPV 83.5%; EFV 82.4% from pooled analysis [TLOVR] in Studies C209 and C215).

High rates of virologic suppression/response were achieved and maintained through 96 weeks of treatment, providing evidence for durable efficacy of FTC/TAF- (Study GS-US-292-0102) and RPV- (Studies C209 and C215) containing regimens. The percentages of subjects with HIV-1 RNA < 50 copies/mL through Week 96 were as follows: E/C/F/TAF: 87.5% (M = F); RPV+FTC/TDF 76.9% (TLOVR).

FTC/TAF- and RPV-containing regimens maintained efficacy in virologically suppressed subjects switching from standard-of-care regimens. In Study GS-US-292-0109, switching to E/C/F/TAF was noninferior to continuing FTC/TDF+3rd Agent (STB, EFV/FTC/TDF [Atripla], atazanavir [ATV]/boosted+TVD) at Week 48 (E/C/F/TAF 95.6%; FTC/TDF+3rd Agent 92.9%). In Eviplera Study GS-US-264-0106, switching to Eviplera was noninferior to SBR at the Week 24 primary endpoint (Eviplera 93.7%; SBR: 89.9%), and Eviplera Study GS-US-264-0111, all 49 subjects (100%) maintained HIV-1 RNA < 50 copies/mL at the Week 12 primary endpoint.

In subjects with mild to moderate renal impairment (Study GS-US-292-0112), those who switched to E/C/F/TAF maintained virologic suppression at Week 24 as evidenced by high rates of virologic success (E/C/F/TAF 95.0%), supporting the use of FTC/TAF-containing regimen in patients with $eGFR_{CG}$ ≥30 mL/min without dose modification.

In ART-naive adolescent subjects, high rates of virologic success were seen at Week 24 (91.3%) for E/C/F/TAF (Study GS-US-292-0106), similar to those observed in ART-naive adults. In ART-naive adolescent subjects, virologic response at Week 48 (72.2%) supports the efficacy of RPV (Study C213).

Across all of the E/C/F/TAF and RPV studies, analyses of the secondary HIV-1 RNA endpoints supported the primary efficacy analyses. In addition, the immunologic benefit of treatment with FTC/TAF- and RPV-containing regimens was demonstrated by improvements in CD4 cell counts. Generally, there was no difference in efficacy across the different demographic subpopulations evaluated, indicating that FTC/TAF- and RPV-containing regimens are efficacious in all populations without regard to demographic characteristics or underlying renal function. However, for RPV (Studies C209 and C215) the proportion of virologic responders at Week 96 was greater in subjects with baseline viral load ≤ 100,000 copies/mL than in those with baseline viral load > 100,000 copies/mL. FTC/RPV/TAF should not be used in patients with a baseline HIV-1 RNA >100,000 copies/mL.

Overall, clinical data from FTC/TAF- and RPV-containing studies demonstrate efficacy in the treatment of HIV-1 infection. The demonstration of PK bioequivalence of FTC and TAF to E/C/F/TAF and of RPV to Edurant (m2.7.2) in combination with the comprehensive demonstration of efficacy indicates that the FTC/RPV/TAF FDC will provide a highly effective treatment for HIV-1 in ART-naive adults and adolescents, virologically suppressed subjects, and subjects with mild to moderate renal impairment.

# 5. OVERVIEW OF SAFETY

No data are available from studies of FTC/RPV/TAF in HIV-1 infected patients. The clinical safety of FTC/RPV/TAF was established through the E/C/F/TAF and RPV clinical development programs. To date, 197 healthy volunteers have received FTC/RPV/TAF in three Phase 1 studies.

This section provides an overview of the pooled analysis of safety that was conducted for the E/C/F/TAF (Studies GS-US-292-0104 and GS-US-292-0111) and RPV (Studies C209 and C215) pivotal Phase 3 studies in ART-naive subjects. For the Phase 3 RPV studies, the subset of subjects receiving FTC/TDF in these 2 studies (referred to as the FTC/TDF subset) is presented in some instances because it provides data for RPV and FTC administered with a TFV prodrug and therefore contains relevant data for the FTC/RPV/TAF combination. Safety results for other individual studies of FTC/TAF- and RPV-containing regimens are also presented for virologically suppressed subjects (E/C/F/TAF Study GS-US-292-0109, and Eviplera Studies GS-US-264-0111 and GS-US-264-0106), renally impaired subjects (E/C/F/TAF Study GS-US-292-0112), and adolescent subjects (E/C/F/TAF Study GS-US-292-0106 and RPV Study C213) (Table 1; m2.7.4, Section 2). In addition, safety results from the Phase 1 FTC/RPV/TAF studies in healthy subjects are included (m2.7.4, Section 2.1.9.3.5).

A comprehensive nonclinical pharmacology and virology, PK, and toxicology program for TAF, RPV, and FTC was undertaken to support the clinical evaluation of the FTC/RPV/TAF FDC for the treatment of HIV-1 infection.

In the E/C/F/TAF, RPV, and Eviplera clinical studies, demographic and baseline characteristics were generally similar between treatment groups within each randomized study; characteristics were also generally similar in the E/C/F/TAF and RPV studies in each HIV-infected population (m2.7.4, Section 1.3). Results for E/C/F/TAF are summarized as follows:

- The median ages of subjects who were ART-naive or virologically suppressed ranged from 33 to 41 years at baseline. Switch subjects (Cohort 1) in the renal impairment study had a median age of 58 years. The median age of adolescent subjects was 15 years and 23 adolescent subjects were in the Week 24 Full Analysis Set (FAS).

- Most subjects in each study were male (80%-90%), except for Study GS-US-292-0106 (41.7% male, 58.3% female).

- Across studies of adult subjects, the most common races were white (approximately 55% to 70%) and black (approximately 20% to 30%), and approximately 15% to 25% subjects were Hispanic or Latino. In adolescents, most subjects were black (~90%) and none were Hispanic or Latino.

Generally, the studied populations are representative of both ART-naive and virologically suppressed HIV-infected subjects in the general population.

## 5.1. Extent of Exposure

A total of 2394 subjects received the FTC/TAF-containing regimen E/C/F/TAF in Phase 2 and Phase 3 studies, with a median (Q1, Q3) exposure of 48.1 weeks (42.3, 60.0). The median exposure to E/C/F/TAF was similar in subjects who were ART-naive (Studies GS-US-292-0104 and GS-US-292-0111), subjects who were virologically suppressed (Study GS-US-292-0109), and subjects with mild to moderate renal impairment (Study GS-US-292-0112). The median (Q1, Q3) exposure was shorter in adolescent subjects in Study GS-US-292-0106 (12.1 weeks [4.1, 32.1]); however, approximately half of the subjects in the study received E/C/F/TAF for ≥ 24 weeks. In the E/C/F/TAF studies with comparators, exposure between groups was similar within each study.

The median (Q1, Q3) duration of exposure was 105.3 weeks (98.0, 108.1) for ART-naive subjects who received E/C/F/TAF through the extension phase of Study GS-US-292-0102, with 92.0% of subjects completing 96 weeks of treatment.

A total of 722 ART-naive subjects received at least 1 dose of RPV in the Phase 2 and Phase 3 studies, including 686 subjects in the RPV Phase 3 studies and 36 subjects in the RPV Phase 2 study. In the pooled Phase 3 studies in ART-naive adult subjects (Studies C209 and C215), RPV was taken for at least 96 weeks by 566 subjects (82.5%). In Study C209, 346 received RPV and 344 received control, each in combination with FTC/TDF. In Study C215, 340 subjects received RPV and 338 received control, each with a regimen containing 2 investigator-selected N(t)RTIs (FTC/TDF, AZT/3TC, or ABC/3TC). In the pooled RPV Phase 3 studies, 550 of 686 subjects in the RPV group and 546 of 682 subjects in the control group received a background N(t)RTI regimen of FTC/TDF (ie, the FTC/TDF subset). In both studies combined, 450 subjects (81.8%) received RPV plus FTC/TDF for a total of 96 weeks. In the Phase 2 RPV study in ART-naive adolescent subjects (Study C213), 36 subjects received RPV. At the Week 48 analysis cutoff date, the majority of subjects (66.7%) were ongoing in the study, and the mean (SD) and median (range) durations of exposure to RPV were 71.6 (43.09) and 63.50 (1.0-179.0) weeks, respectively. The total patient-years of RPV exposure was 49.40.

A total of 518 virologically suppressed subjects received Eviplera in Phase 2b Study GS-US-264-0111 and Phase 3 Study GS-US-264-0106. Cumulative patient exposure to Complera/Eviplera since first marketing approval in the US on 10 August 2011 to 28 February 2015 is estimated to be 206,654 patient-years.

In Phase 1 studies, a total of 197 healthy subjects received at least 1 dose of the FTC/RPV/TAF FDC.

## 5.2. Criteria for Evaluation and Statistical Methods

Pooling of the safety data for the E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 was considered appropriate due to their identical study design, including eligibility criteria (m2.7.4, Section 1.1.3). Pooling of the individual Phase 3 RPV data for Studies C209 and C215 was also considered appropriate due to the similarity in the trials' designs. Analyses for the FTC/TDF subset are presented for select analyses, as these data are relevant to the FTC/RPV/TAF FDC; the overall pooled data for Studies C209 and C215 are presented where the subset analyses are not available. No other data were pooled (unless otherwise stated), due to differences in the subject populations studied, treatment durations, and randomization.

For selected safety data (eg, bone and renal parameters) in the randomized E/C/F/TAF studies, comparisons between groups were performed using appropriate statistical tests.

To control for the overall type I error in the assessment of the primary efficacy endpoint and the key safety endpoints in the E/C/F/TAF Studies GS-US-292-0104, GS-US-292-0111, and GS-US-292-0109; hypothesis testing was performed in sequential order. The primary hypothesis of noninferiority of E/C/F/TAF relative to the active comparator, with respect to the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (as defined by the snapshot algorithm) was tested first. If noninferiority was established, multiplicity adjustments were performed for the following safety endpoints with a fallback procedure in the sequential order given below, with prespecified 2-sided alpha levels {23531}:

a) Hip BMD (alpha = 0.02)

b) Spine BMD (alpha = 0.01)

c) Serum creatinine (alpha = 0.01998 for Studies GS-US-292-0104 and GS-US-292-0111; and 0.0199 for Study GS-US-292-0109)

d) Treatment-emergent proteinuria for Studies GS-US-292-0104 and GS-US-292-0111; EFV-related symptom assessment score for Study GS-US-292-0109 (alpha = 0.00)

Further details on the statistical methods, safety data definitions, and grading scales are provided in E/C/F/TAF integrated summary of safety (ISS) SAP (E/C/F/TAF ISS SAP) and are included in sections below when appropriate. The RPV Phase 3 Week 96 pooled safety analysis is described in TMC278-TiDP6-904. Additional details on the statistical methods, safety data definitions, and grading scales for all studies are provided in the individual SAPs.

## 5.3. Overall Safety

### FTC/RPV/TAF

The safety of FTC/RPV/TAF has been evaluated in healthy volunteers in Studies GS-US-366-1159, GS-US-366-1651, and GS-US-366-1689. FTC/RPV/TAF was well tolerated in those 3 studies; there were no Grade 3 or 4 AEs, deaths or serious adverse events (SAEs) reported. Only 1 subject permanently discontinued any study drug due to an AE related to LDV/SOF (nonserious, Grade 2 colitis) in Study GS-US-366-1689. The maximum postdose toxicity for the majority of laboratory abnormalities was Grade 1. The most frequently reported Grade 3 laboratory abnormality was occult blood on urinalysis in female subjects (the majority of whom had confirmed menses). One subject with Grade 1 amylase at screening had Grade 3 amylase and Grade 3 and 4 lipase without clinical symptoms (m2.7.4; Section 3.4); the remaining Grade 3 or 4 abnormalities occurred in 1 subject each (Grade 3 increased aspartate aminotransferase [AST], Grade 3 increased low-density lipoprotein [LDL], and Grade 4 increased creatine kinase).

### 5.3.1. Adverse Events

**E/C/F/TAF**

**Key Safety Endpoints**

Statistically significant differences (alpha protected using the fallback procedure described in Section 5.2) favoring E/C/F/TAF over STB or TDF-containing regimens were observed at Week 48 for all key secondary safety endpoints in both ART-naive and virologically suppressed subjects: mean percentage changes from baseline in hip BMD ($p < 0.001$ for both ART-naive and virologically suppressed subjects) and spine BMD ($p < 0.001$ for both ART-naive and virologically suppressed subjects; Section 5.5), mean change from baseline in serum creatinine ($p < 0.001$ for both ART-naive and virologically suppressed subjects; Section 5.6), change from baseline in treatment-emergent proteinuria (ART-naive subjects, $p = 0.022$), and change from baseline in EFV-related symptom assessment composite score (virologically suppressed subjects; $p < 0.001$; m2.7.4, Section 2.1.9.1.

**Adverse Events**

In E/C/F/TAF clinical studies, the AE profile was generally similar in ART-naive adults, virologically suppressed adults, adults with mild to moderate renal impairment, and ART-naive adolescents (Table 5). In ART-naive adults, the most commonly reported AEs were diarrhea, nausea, headache, and upper respiratory tract infection; these events-are generally consistent with those from prior studies of STB and other TVD-based regimens {21102}, {21057}. Most subjects across all studies reported at least 1 AE. The percentage of subjects reporting any AE was generally as expected for the respective study populations and differences between studies in exposure to study drug. A similar percentage of subjects reported any AE between treatment groups within each randomized study. Across all studies, AEs leading to study drug discontinuation were uncommon.

Five ART-naive subjects in the E/C/F/TAF studies died (E/C/F/TAF 2 subjects [embolic stroke and alcohol poisoning]; STB 3 subjects [cardiac arrest, recreational drug and alcohol overdose, and acute myocardial infarction]). Two virologically suppressed subjects in the E/C/F/TAF group of Study GS-US-292-0109 died during the study (septic shock and Stage 4 lung adenocarcinoma). There were no deaths in the renally impaired population (Study GS-US-292-0102) nor in the ART-naive adolescent study (GS-US-292-0106). None of the events that led to death were considered by the investigator as related to study drug.

Both E/C/F/TAF and STB were well tolerated in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111), with comparably low rates of Grade 3 or 4 AEs, SAEs, SAEs considered related to study drugs, and AEs leading to drug discontinuations in both treatment groups.

As expected, among virologically suppressed subjects who were stable on their treatment regimen before participating in open-label Study GS-US-292-0109, subjects who switched to E/C/F/TAF had a higher incidence of any AE considered by the investigator as related to study drug than subjects who stayed on their existing regimen (E/C/F/TAF 19.3%, 185 subjects; FTC/TDF+3rd Agent 12.8%, 61 subjects). Most of the AEs considered related to study drug were Grade 1 in severity. The incidences of AEs related to study drug were lower in both treatment groups in Study GS-US-292-0109 than those in other studies.

With longer exposure to study drug in the open-label extension of Study GS-US-292-0102, the AE profile for the E/C/F/TAF group was consistent with that in the randomized phase.

No cases of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy were reported for subjects who received E/C/F/TAF.

**Table 5. GS-US-292-0104, GS-US-292-0111, GS-US-292-0102, GS-US-292-0109, GS-US-292-0112, and GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ART-Naive Adult Subjects | | | | Virologically Suppressed Subjects | | Subjects with Renal Impairment | | ART-Naive Adolescent Subjects |
|---|---|---|---|---|---|---|---|---|---|
| | GS-US-292-0104/ GS-US-292-0111 | | GS-US-292-0102[a] | | GS-US-292-0109 | | GS-US-292-0112 | | GS-US-292-0106 |
| **Subjects Experiencing Any** | **E/C/F/TAF (N=866)** | **STB (N=867)** | **E/C/F/TAF (N=112)** | **STB (N=58)** | **E/C/F/TAF (N=959)** | **FTC/TDF+ 3rd Agent (N=477)** | **Cohort 1: ART-Experienced (N=242)** | **Cohort 2: ART-Naive (N=6)** | **E/C/F/TAF (N=48)** |
| Adverse Event | 778 ( 89.8%) | 782 ( 90.2%) | 107 ( 95.5%) | 57 ( 98.3%) | 764 ( 79.7%) | 368 ( 77.1%) | 209 (86.4%) | 5 (83.3%) | 39 (81.3%) |
| Grade 2, 3, or 4 Adverse Event | 419 ( 48.4%) | 380 ( 43.8%) | 72 ( 64.3%) | 29 ( 50.0%) | 389 ( 40.6%) | 177 ( 37.1%) | 114 (47.1%) | 3 (50.0%) | 13 (27.1%) |
| Grade 3 or 4 Adverse Event | 71 ( 8.2%) | 75 ( 8.7%) | 13 ( 11.6%) | 3 ( 5.2%) | 61 ( 6.4%) | 32 ( 6.7%) | 18 (7.4%) | 0 | 4 (8.3%) |
| Study-Drug-Related Adverse Event | 342 ( 39.5%) | 364 ( 42.0%) | 43 ( 38.4%) | 19 ( 32.8%) | 185 ( 19.3%) | 61 ( 12.8%) | 62 (25.6%) | 1 (16.7%) | 18 (37.5%) |
| Grade 2, 3, or 4 Study-Drug-Related Adverse Event | 84 ( 9.7%) | 75 ( 8.7%) | 9 ( 8.0%) | 1 ( 1.7%) | 46 ( 4.8%) | 20 ( 4.2%) | 24 (9.9%) | 1 (16.7%) | 2 (4.2%) |
| Grade 3 or 4 Study-Drug-Related Adverse Event | 12 ( 1.4%) | 9 ( 1.0%) | 1 ( 0.9%) | 0 | 3 ( 0.3%) | 6 ( 1.3%) | 3 (1.2%) | 0 | 1 (2.1%) |
| Serious Adverse Event | 70 ( 8.1%) | 59 ( 6.8%) | 12 ( 10.7%) | 3 ( 5.2%) | 42 ( 4.4%) | 21 ( 4.4%) | 26 (10.7%) | 0 | 4 (8.3%) |
| Study-Drug-Related Serious Adverse Event | 3 ( 0.3%) | 2 ( 0.2%) | 0 | 0 | 0 | 1 ( 0.2%) | 0 | 0 | 1 (2.1%) |
| Adverse Event Leading to Premature Study Drug Discontinuation | 8 ( 0.9%) | 13 ( 1.5%) | 4 ( 3.6%) | 0 | 9 ( 0.9%) | 7 ( 1.5%) | 8 (3.3%) | 0 | 0 |
| Death | 2 ( 0.2%) | 3 ( 0.3%) | 0 | 0 | 2 ( 0.2%) | 0 | 0 | 0 | 0 |

a Includes subjects in the randomized phase of Study GS-US-292-0102; subjects in the open-label extension are not included. The AE profile of subjects in the open-label extension was similar to the AE profile observed in the randomized phase.

Source: m2.7.4, Table 24

**RPV**

In the RPV clinical studies, the AE profile was generally similar in ART-naive adults (FTC/TDF subset of Studies C209 and C215) and ART-naive adolescents (Study C213) (Table 6 and Table 7 respectively). In ART-naive adults, the most commonly reported AEs were diarrhea, headache, nasopharyngitis, upper respiratory tract infection, nausea, dizziness and insomnia (m2.7.4, Table 39). Most subjects across all RPV studies reported at least 1 AE. A similar percentage of subjects reported any AE between treatment groups in both Phase 3 studies.

A total of 7 subjects died during the course of the RPV Phase 3 trials, 1 in the RPV group in Study C215 and 6 in the control groups (3 in Study C209 and 3 in Study C215). Four of the deaths occurred in the FTC/TDF subset. The AEs leading to death were from a variety of causes, with some cases being associated with disease progression or HIV-related. None were assessed by the investigator as related to study medication. Only 1 of these subjects received RPV and FTC/TDF prior to death. No deaths were reported in the Phase 2 study in adolescents (Study C213).

RPV was generally well tolerated in in ART-naive subjects. The Phase 3 Week 96 pooled analysis also showed that incidences of AEs leading to permanent discontinuation were lower in subjects in the RPV group compared with subjects in the control group (3.8% vs 8.6%, respectively). Incidences of treatment-related AEs were also lower in subjects in the RPV group compared with subjects in the control group (46.7% vs 64.7%, respectively).

Overall, RPV was associated with a favorable safety/tolerability profile over EFV. Adverse events of interest are described in m2.7.4, Sections 2.1.2 and 2.1.9.

**Table 6. RPV Studies C209 and C215 (FTC/TDF Subset): Summary of Treatment-Emergent Adverse Events (Phase 3 Week 96 Pooled Analysis)**

| AE Summary, n (%) | Pooled | |
|---|---|---|
| | **RPV N = 550** | **Control N = 546** |
| Treatment duration (weeks) Median (range) | 104.1 (0.1; 135) | 103.9 (0.3; 136) |
| Subject-years of exposure | 1017.1 | 984.4 |
| Any AE | 502 (91.3) | 510 (93.4) |
| Any Grade 3 or 4 AE | 84 (15.3) | 106 (19.4) |
| Grade 3 | 74 (13.5) | 98 (17.9) |
| Grade 4 | 22 (4.0) | 19 (3.5) |
| Any treatment-related[a] AE | 257 (46.7) | 353 (64.7) |
| Any treatment-related[a] AE of at least Grade 2 | 94 (17.1) | 181 (33.2) |
| Death | 0 | 4 (0.7) |
| Any SAE[b] | 52 (9.5) | 61 (11.2) |
| AE leading to permanent discontinuation | 21 (3.8) | 47 (8.6) |
| AE leading to temporary discontinuation | 26 (4.7) | 36 (6.6) |

a Defined as possibly, probably, or very likely related to treatment in the opinion of the investigator.
b Includes SAEs with an outcome of death.
c AEs of interest were not identified from single relevant SOCs, but were based on selected AE preferred terms from a number of relevant SOCs.
Source: m2.7.4, Table 25

**Table 7. RPV Study C213: Adverse Events Summary (Intent-to-Treat)**

| Number of subjects n (%) | RPV 25 mg QD |
|---|---|
| In intent-to-treat population | 36 |
| with at least one AE | 35 (97.2%) |
| with at least one SAE | 6 (16.7%) |
| who died due to an AE | 0 |
| with a grade 1 AE or mild AE | 32 (88.9%) |
| with a grade 2 AE or moderate AE | 26 (72.2%) |
| with a grade 3 AE or severe AE | 5 (13.9%) |
| with a grade 4 AE or potentially life-threatening AE | 2 (5.6%) |
| with a grade 2-4 AE | 28 (77.8%) |
| with a grade 3-4 AE | 7 (19.4%) |
| with a missing grade | 0 |
| with at least one AE for which the study drug was permanently stopped | 1 (2.8%) |
| with at least one AE for which the study drug was temporarily stopped | 0 |
| with an AE which is possibly, probably or very likely related to RPV | 13 (36.1%) |
| with an AE which is possibly, probably or very likely related to the underlying ARV treatment | 7 (19.4%) |
| with an SAE which is possibly, probably or very likely related to RPV | 1 (2.8%) |

Source: m2.7.4, Table 26

In the Eviplera studies in virologically suppressed, HIV-1 infected subjects for up to 48 weeks (Studies GS-US-264-0111 and GS-US-264-0106) there were no changes in the tolerability profile (frequency, nature, or severity of AEs) (Table 8 and Table 9).

**Table 8. Eviplera Study GS-US-264-0111: Overall Summary of Adverse Events (Safety Analysis Set)**

| Adverse Event Category, n (%) | FTC/RPV/TDF (N = 49) |
|---|---|
| Subjects Experiencing Any Treatment-Emergent AE | 43 (87.8%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE | 3 (6.1%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent AE | 21 (42.9%) |
| Subjects Experiencing Any Treatment-Emergent AE Related to Study Drug | 12 (24.5%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent AE Related to Study Drug | 0 |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent AE Related to Study Drug | 3 (6.1%) |
| Subjects Experiencing Any Treatment-Emergent SAE | 1 (2.0%) |
| Subjects Experiencing Any Treatment-Emergent SAE Related to Study Drug | 0 |
| Subjects Experiencing Any Treatment-Emergent AE That Caused Permanent Discontinuation or Temporary Interruption From Study Drug | 0 |
| Subjects Who Died | 0 |

Source: m2.7.4, Table 27

**Table 9. Eviplera Study GS-US-264-0106: Overall Summary of Adverse Events (Safety Analysis Set)**

| | FTC/RPV/TDF (N=317) | SBR (N=159) | Delayed Switch to FTC/RPV/TDF (N=152) | Total FTC/RPV/TDF (N=469)[a] |
|---|---|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 253 (79.8%) | 91 (57.2%) | 109 (71.7%) | 362 (77.2%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 18 (5.7%) | 11 (6.9%) | 12 (7.9%) | 30 (6.4%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event | 138 (43.5%) | 39 (24.5%) | 47 (30.9%) | 185 (39.4%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug | 79 (24.9%) | 4 (2.5%) | 35 (23.0%) | 114 (24.3%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 3 (0.9%) | 0 | 4 (2.6%) | 7 (1.5%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 31 (9.8%) | 1 (0.6%) | 11 (7.2%) | 42 (9.0%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 18 (5.7%) | 8 (5.0%) | 9 (5.9%) | 27 (5.8%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event Related to Study Drug | 3 (0.9%) | 0 | 0 | 3 (0.6%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Permanent Discontinuation of Study Drug | 7 (2.2%) | 0 | 6 (3.9%) | 13 (2.8%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Temporary Interruption of Study Drug | 3 (0.9%) | 0 | 2 (1.3%) | 5 (1.1%) |

a. Total FTC/RPV/TDF group includes subjects from the FTC/RPV/TDF and Delayed Switch to FTC/RPV/TDF groups.
Safety Analysis Set includes subjects who were enrolled into the study and received at least one dose of study drug. Adverse events are mapped according to MedDRA Version 15.
Source: m2.7.4, Table 28

### 5.3.2. Clinical Laboratory Evaluations

**E/C/F/TAF**

In the E/C/F/TAF Phase 2 and Phase 3 studies, approximately 20% of subjects across all studies had a Grade 3 or 4 laboratory abnormality, with the exception of adolescent subjects in Study GS-US-292-0106 (4 subjects, 8.3%). Among the most common Grade 3 or 4 laboratory abnormalities across studies were elevated creatine kinase and fasting LDL (Section 5.9; m2.7.4, Section 3.1).

In the E/C/F/TAF group from Studies GS-US-292-0104 and GS-US-292-0111, 4 of 90 subjects (4.4%) who experienced lipase abnormalities had Grade 3 or 4 lipase abnormalities. Given that lipase testing was only performed in subjects with serum amylase > 1.5 × upper limit of normal (ULN) and the low number of subjects with Grade 3 or 4 lipase abnormalities, lipase abnormalities were not proposed for inclusion in the FTC/RPV/TAF Prescribing Information.

In ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111, there were no clinically relevant changes from baseline within groups, or differences between the treatment groups in median values for hematology or clinical chemistry parameters, and all median values were within normal ranges. The majority of subjects had at least 1 laboratory abnormality, the majority of which were Grade 1 or 2. Grade 3 or 4 creatine kinase abnormalities (E/C/F/TAF 6.8%, 59 subjects; STB 5.7%, 49 subjects) occurred at a variety of time points, were not consistently present for individual subjects, and no case of clinical rhabdomyolysis was reported. The incidences of Grade 3 or 4 creatine kinase abnormalities were similar across the 2 treatment groups in Study GS-US-292-0109.

Among virologically suppressed subjects in Study GS-US-292-0109, a lower percentage of subjects in the E/C/F/TAF group compared with the FTC/TDF+3rd Agent group had Grade 3 or 4 abnormalities (E/C/F/TAF 19.8%, FTC/TDF+3rd Agent 25.4%), predominantly driven by the higher incidence of Grade 3 or Grade 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group (E/C/F/TAF 0.1%, 1 of 959 subjects; FTC/TDF+3rd Agent 14.3%, 68 of 477 subjects). Almost all cases (66 of 68) of Grade 3 or 4 hyperbilirubinemia in the FTC/TDF+3rd Agent group occurred in subjects taking ATV.

Among subjects with mild to moderate renal impairment in Study GS-US-292-0112, Grade 3 or 4 hypercholesterolemia, serum glucose (nonfasting, hyperglycemia), and urine glucose (glycosuria) were reported in a higher percentage of subjects than in other E/C/F/TAF studies.

**RPV**

In the RPV Phase 3 studies, most laboratory abnormalities were Grade 1 or Grade 2. For the FTC/TDF subset, the incidence of Grade 3 or 4 laboratory abnormalities was lower in the RPV group (12.2%) than in the control group (18.8%) (2.7.4, Section 3.2.1). The most common Grade 3 and 4 laboratory abnormalities in the RPV group compared with the control group were increased pancreatic amylase, increased AST, and increased ALT. No Grade 4 laboratory abnormalities were reported in more than 5 subjects in the RPV group and in more than 7 subjects in the control group. In the RPV study in ART-naive adolescents (Study C213), the most common Grade 3-4 laboratory abnormalities were neutrophils and precursors decreased, and neutrophils segmented decreased (3 subjects).

In the Eviplera studies in virologically suppressed subjects, most laboratory abnormalities were Grade 1 or Grade 2. Grade 3 or 4 treatment-emergent laboratory abnormalities reported in the Eviplera group in Study GS-US-264-0111 were Grade 3 increased creatine kinase (2 subjects. All other Grade 3 or 4 laboratory abnormalities occurred in 1 subject each. In Study GS-US-264-0106, Grade 3 or 4 treatment-emergent laboratory abnormalities reported in more than 2 subjects in the Eviplera group included increased creatine kinase (8 subjects), elevated

ALT (5 subjects), elevated AST (5 subjects), decreased absolute neutrophil count (3 subjects), increased amylase (3 subjects), increased lipase (3 subjects), and hematuria (5 subjects). There were no clinically meaningful mean changes from baseline overall in these laboratory parameters in any treatment group during the study.

*Cortisol*

In the RPV Phase 3 studies, there was an overall mean change from baseline in basal cortisol at Week 96: -19.1 nmol/L (95% CI: -30.85; -7.37) in the RPV group and -0.6 nmol/L (95% CI: -13.29, 12.17) in the control group {30163}. At Week 96, the mean change from baseline in adrenocorticotropic hormone (ACTH)−stimulated cortisol levels was lower in the RPV group (18.4 ± 8.36 nmol/L) than in the control group (54.1 ± 7.24 nmol/L). Mean values for the RPV group for both basal and ACTH-stimulated cortisol at Week 96 were within the normal range. These changes in adrenal safety parameters were not clinically relevant. There were no clinical signs or symptoms suggestive of adrenal or gonadal dysfunction in adults.

## 5.4. Analysis of Adverse Drug Reactions

No data are available from clinical trials of FTC/RPV/TAF in HIV-1 infected patients.

The key data source supporting the Undesirable Effects section of the FTC/RPV/TAF prescribing information is the Week 48 pooled data from the pivotal E/C/F/TAF Phase 3 studies in ART-naive subjects (Studies GS-US-292-0104 and GS-US-292-0111), the pooled pivotal RPV Phase 3 studies in ART-naive subjects (Studies C209 and C215), and postmarketing experience with Eviplera. Supporting data are also provided from studies of virologically suppressed adults switching treatment to E/C/F/TAF (Study GS-US-292-0109), virologically suppressed adults switching treatment to an RPV-containing regimen (Eviplera Studies GS-US-264-0111 and GS-US-264-0106), adults with mild to moderate renal impairment (E/C/F/TAF Study GS-US-292-0112), and ART-naive adolescents (E/C/F/TAF Study GS-US-292-0106 and RPV Study C213).

**E/C/F/TAF**

Based on an assessment for a potential causal relationship, 9 AEs from studies GS-US-292-0104 and GS-US-292-0111 are included as possible adverse drug reactions (ADRs) for the FTC and TAF components of FTC/RPV/TAF. This is in line with what was proposed for the E/C/F/TAF Summary of Product Characteristics (SmPC).

The most commonly reported adverse reactions through Week 48 from the pooled E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111 in ART-naive adults were diarrhoea (17%), nausea (15%), and headache (14%).

No new adverse reactions to FTC/TAF were identified through Week 48 in Study GS-US-292-0109 of virologically suppressed patients who switched from a TDF-containing regimen to E/C/F/TAF (n=959).

Based on the data presented in m2.7.4, the safety profile of the FTC/TAF-containing regimen E/C/F/TAF in subjects with mild to moderate renal impairment from Study GS-US-292-0112 is similar to that in subjects with normal renal function, and the safety profile of E/C/F/TAF in ART-naive adolescent subjects aged 12 to < 18 years from Study GS-US-292-0106 is similar to that in adults.

**RPV**

The safety assessment of RPV-based regimens is based on the Week 96 pooled data in Studies C209 and C215 in ART-naive HIV-1 infected adult patients. The most frequently reported adverse reactions through Week 96 in the FTC/TDF subset were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%) and insomnia (5%). Clinical ADRs of at least moderate intensity (≥ Grade 2) and selected treatment-emergent clinical laboratory abnormalities are considered as ADRs for the RPV component of FTC/RPV/TAF, based on the pooled data from the 686 patients who received RPV in trials C209 and C215. No new adverse reactions to RPV in combination with FTC/TDF were identified in virologically suppressed patients switching to RPV in combination with FTC/TDF in clinical Studies GS-US-264-0106 and GS-US-264-0111. The proposed ADRs are in line with those in the approved Eviplera SmPC for the RPV component {30163}.

The assessment of adverse reactions in adolescents is based on Week 48 data from one single-arm, open-label study (Study C213) in 36 pediatric patients of 12 to < 18 years of age and weighing at least 32 kg. No new adverse reactions were identified compared with those seen in adults. Adverse reactions (all grades) ≥10% frequency were headache, depression, somnolence, and nausea.

Adverse reactions to FTC/RPV/TAF from clinical studies are listed in Table 10 below, by system organ class and highest frequency observed. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), or rare (≥ 1/10,000 to < 1/1,000).

**Table 10. Tabulated Summary of Adverse Reactions Associated with the Components of FTC/RPV/TAF**

| Adverse Reactions | AE Frequency with FTC/TAF[a] | AE Frequency with RPV[b] |
|---|---|---|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Decreased haemoglobin | — | Common |
| Decreased platelet count | — | Common |
| Decreased white blood cell count | — | Common |
| GASTROINTESTINAL DISORDERS | | |
| Abdominal discomfort | — | Common |
| Abdominal Pain | Common | Common |
| Diarrhea | Very common | — |
| Dry mouth | — | Common |

| Adverse Reactions | AE Frequency with FTC/TAF[a] | AE Frequency with RPV[b] |
|---|---|---|
| Dyspepsia | Common | — |
| Flatulence | Common | — |
| Increased lipase | — | Common |
| Increased pancreatic amylase | — | Very common |
| Nausea | Very common | Very common |
| Vomiting | Common | Common |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Fatigue | Common | Common |
| HEPATOBILIARY DISORDERS | | |
| Increased bilirubin | — | Common |
| Increased transaminases (AST and/or ALT) | — | Very common |
| IMMUNE SYSTEM DISORDERS | | |
| Immune reactivation syndrome | — | Uncommon |
| METABOLISM AND NUTRITION DISORDERS | | |
| Decreased appetite | — | Common |
| Increased LDL cholesterol (fasted) | — | Very common |
| Increased total cholesterol (fasted) | — | Very common |
| Increased triglycerides (fasted) | — | Common |
| NERVOUS SYSTEM DISORDERS | | |
| Dizziness | — | Very common |
| Headache | Very common | Very common |
| Somnolence | — | Common |
| PSYCHIATRIC DISORDERS | | |
| Abnormal dreams | — | Common |
| Depressed mood | — | Common |
| Depression | — | Common |
| Insomnia | — | Very common |
| Sleep disorders | — | Common |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| Rash | Common | Common |

a Adverse reactions identified from FTC/TAF clinical studies
b Adverse reactions identified from RPV clinical studies
Source: {30163}

In addition to adverse reaction reports from clinical trials, weight gain (common) and severe skin reactions with systemic symptoms (uncommon) have been identified as adverse drug reactions during postapproval use of Eviplera (Section 5.10) and are included in the FTC/RPV/TAF SmPC.

## 5.5. Bone Safety

### E/C/F/TAF

HIV-infected adults are at risk of low BMD, with up to 60% prevalence of osteopenia and up to 15% prevalence of osteoporosis {34940}. The initiation of treatment in ART-naive adults is associated with a decrease in BMD in the first 12 to 24 months of use {14194}, {14253}, {16915}, {16604}. The observed changes are similar whether the regimen includes an NNRTI, an INSTI, or a PI; however, the decrease in BMD appears to be greater with TDF than with other NRTIs {10655}, {11882}, {17561}, {18854}, {25126}, {29368}.

HIV-1 treatment with TDF-containing regimens represents a concern for pediatric patients who initiate lifelong HIV therapy, particularly those in the pre- or peri-pubertal stage and those building bone mass. In the EU, TDF is only indicated for pediatric subjects from 2 years of age with NRTI resistance or toxicities precluding the use of first-line agents {35312}, and pediatric treatment guidelines recommend TDF as first-line only in pediatric subjects > 12 years with high viral loads {34421}.

The totality of results from bone safety analyses in HIV-infected subjects across the clinical development program demonstrated that treatment with E/C/F/TAF is associated with an improved bone safety profile compared with STB or with other TDF-containing regimens, with statistically significant differences in multiple tests of bone metabolism. The percentage changes from baseline in BMD at the hip or at the spine at Week 48 were the first and second key alpha-protected safety endpoints for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111, respectively (Section 5.2). Statistical analysis using the fallback procedure confirmed that there were significant differences in the changes from baseline using adjusted alphas that were dependent on the results from preceding tests.

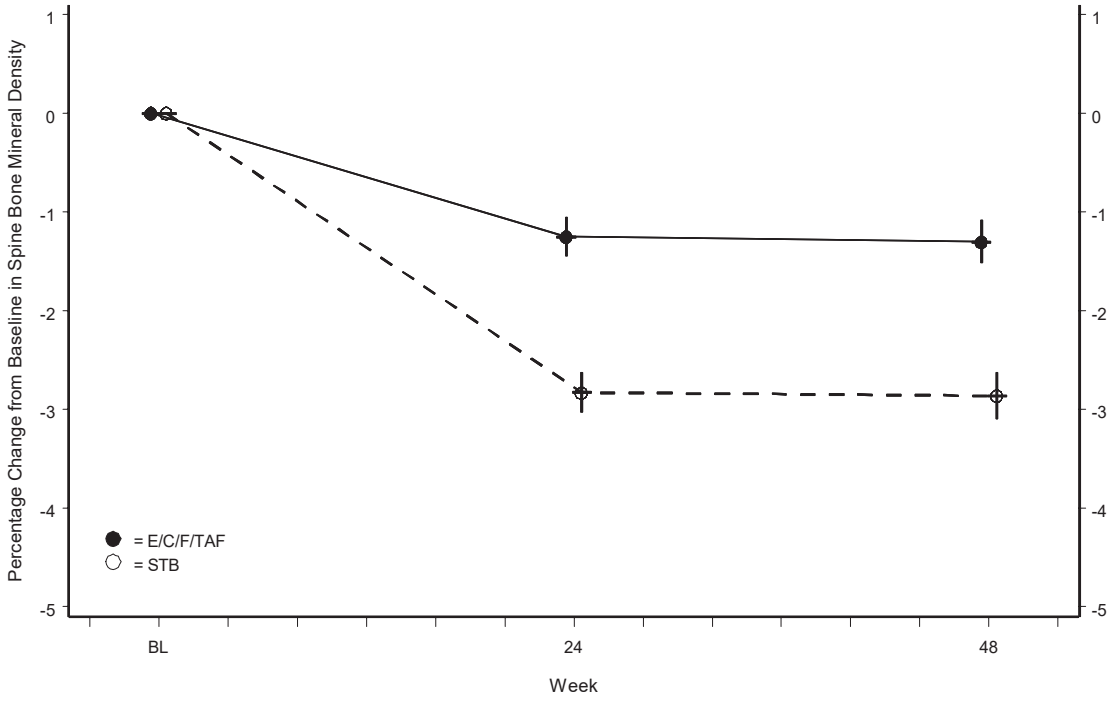
Specifically, the following results were noted (m2.7.4, Section 2.1.9.2):

- Statistical analysis using the fallback procedure showed statistically significant differences in ART-naive adults favoring E/C/F/TAF over STB at Week 48 for the first and second alpha-protected key safety endpoints: mean percentage decreases from baseline in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$ for the differences between the 2 groups) (Table 11, Figure 1 [spine]).
- Compared with subjects receiving STB, fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in BMD; more subjects in the E/C/F/TAF group had a > 3% increase from baseline in BMD. In addition, fewer subjects in the E/C/F/TAF group had worsening BMD clinical status from baseline (normal to osteopenia, normal to osteoporosis, or osteopenia to osteoporosis).
- For virologically suppressed adults who switched to E/C/F/TAF from a TDF-based regimen, improvements in both hip and spine BMD were observed (Table 12). Compared with subjects receiving TDF, fewer subjects in the E/C/F/TAF group had a > 3% decrease from baseline in BMD; more subjects in the E/C/F/TAF group had a > 3% increase from baseline in BMD. In addition, a higher percentage in the E/C/F/TAF group than the TDF group had an improvement in BMD clinical status, and a lower percentage of subjects in the E/C/F/TAF group than the TDF group had worsening BMD clinical status.

- Similar improvements in BMD were noted in virologically suppressed adults with renal impairment who switched to E/C/F/TAF from a TDF-based regimen, an older study population with a median age of 58 years. Moreover, minimal changes or small increases were observed in virologically suppressed subjects with renal impairment who switched to E/C/F/TAF from a non–TDF-based regimen, demonstrating the minimal effect of E/C/F/TAF itself on BMD.
- In ART-naive adolescent subjects, treatment with E/C/F/TAF resulted in minimal changes from baseline in height-age adjusted spine (mean [SD] change: −0.08 [0.391]) and total body less head (TBLH) (mean [SD] change: −0.10 [0.256]) BMD Z-scores at Week 24. The results suggest no impact on bone mineralization relative to the reference population. Mean (SD) percentage decreases from baseline at Week 48 in BMD at the hip or spine were smaller in the E/C/F/TAF group compared with the STB group ($p < 0.001$).
- Across comparative studies, reduced bone turnover was observed with E/C/F/TAF compared with STB or TDF-regimens, as shown by less change in parathyroid hormone (PTH), type I collagen C telopeptide (C-telopeptide), and procollagen type 1 N-terminal propeptide (P1NP). Subjects who switched to E/C/F/TAF from a TDF-based regimen experienced a decrease from baseline in serum levels of the P1NP and PTH.

These bone safety results demonstrate that treatment with an FTC/TAF-containing regimen is associated with an improved bone profile, particularly relative to TDF-based regimens.

**Figure 1.** **GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | |
|---|---|---|---|
| E/C/F/TAF (n=): | 845 | 797 | 784 |
| STB (n=): | 850 | 816 | 773 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 03SEP2014, Lab Data: 04SEP2014, s292-0111: CRF,DXA Data: 22SEP2014, Lab Data: 23SEP2014
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out 26SEP2014:17:41

Source: E/C/F/TAF ISS, Figure 3.2.2

## Table 11. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 48 Analysis)

| | E/C/F/TAF (N = 866) | STB (N = 867) | E/C/F/TAF vs STB[a] | |
|---|---|---|---|---|
| | | | p-value | Difference in LSM (95% CI) |
| **Hip DXA Analysis** | **(N = 780)** | **(N = 767)** | | |
| Mean (SD) % Change in BMD | −0.657 (3.2646) | −2.948 (3.4095) | p < 0.001 | 2.291 (1.958 , 2.624) |
| Subjects with Categorical Change (%): | | | | |
| > 3% Decrease in BMD | 17% | 50% | — | — |
| > 3% Increase in BMD | 7% | 3% | | |
| Subjects with No Decrease in BMD | 35% | 14% | — | — |
| **Lumbar Spine DXA Analysis** | **(N = 784)** | **(N = 773)** | | |
| Mean % Change in BMD | −1.301 (3.0823) | −2.862 (3.2460) | p < 0.001 | 1.561 (1.247 , 1.876) |
| Subjects with Categorical Change (%): | | | | |
| > 3% Decrease in BMD | 27% | 46% | — | — |
| > 3% Increase in BMD | 7% | 3% | | |
| Subjects with No Decrease in BMD | 34% | 17% | — | — |

a P-values, difference in least squares means, and its 95% CI were from the analysis of variance (ANOVA) model including treatment as fixed effect.

Source: E/C/F/TAF ISS, Tables 20.1.2, 20.2.2, 22.1, and 22.2

## Table 12. GS-US-292-0109: Key Measures of BMD (Week 48 Analysis)

| | E/C/F/TAF (N = 902) | FTC/TDF+3rd Agent (N = 452) | E/C/F/TAF vs STB[a] | |
|---|---|---|---|---|
| | | | p-value | Difference in LSM (95% CI) |
| **Hip DXA Analysis** | **(N = 733)** | **(N = 350)** | | |
| Mean Percent Change in BMD | 1.949 (2.9956) | −0.136 (2.9890) | p < 0.001 | 2.078 (1.697 , 2.459) |
| Subjects with Categorical Change (%): | | | | |
| >3% Decrease in BMD | 2% | 11% | — | — |
| >3% Increase in BMD | 25% | 9% | | |
| Subjects with No Decrease in BMD | 80% | 47% | — | — |
| **Lumbar Spine DXA Analysis** | **(N = 742)** | **(N = 356)** | | |
| Mean Percent Change in BMD | 1.861 (3.0889) | −0.110 (3.7415) | p < 0.001 | 1.970 (1.551 , 2.390) |
| Subjects with Categorical Change (%): | | | | |
| >3% Decrease in BMD | 6% | 17% | — | — |
| >3% Increase in BMD | 34% | 14% | | |
| Subjects with No Decrease in BMD | 75% | 49% | — | — |

a P-values, difference in least squares means, and its 95% CI were from the analysis of variance (ANOVA) model including treatment as fixed effect.

Source: GS-US-292-0109, Section 15.1, Tables 40.2, 41.2

**RPV**

Dual energy X-ray absorptiometry scans were performed in substudies of the individual trials, C209 and C215, at baseline, Week 48, and Week 96 (or at the time of withdrawal from the main trial for subjects who discontinued the trial after 64 weeks of treatment). Analyses from pooled BMD data showed that both treatment groups showed a small but statistically significant median decrease from baseline in BMD (1.4% and 1.5% in the RPV group and 1.4% and 1.5% in the control group at Week 48 and Week 96, respectively). No statistically significant differences were observed between treatment groups (m2.7.4, Section 2.1.9.2.3).

## 5.6. Renal Safety

**E/C/F/TAF**

Treatment with TDF in HIV-infected patients has been associated with nephrotoxicity, including an elevated risk of proteinuria and decline in kidney function, as well as proximal tubular dysfunction in some subjects {19884}, {22018}, {34898}. Because of these associations and that between significant proteinuria and morbidity/mortality in the HIV-infected population {4195}, {6964}, {17105}, renal events and renal laboratory parameters were comprehensively evaluated.

Renal parameters were assessed in all Phase 2 and 3 studies with E/C/F/TAF and Eviplera as renal toxicity has been associated with TDF use. COBI inhibits tubular secretion of creatinine, leading to an increase in serum creatinine and a decrease in eGFR without an effect on actual GFR (aGFR).

Standard renal assessments of changes in serum creatinine, eGFR, and emergence of proteinuria (by dipstick) were complemented by more sensitive evaluations of tubular dysfunction, ie, quantitative assessment of proteinuria (urine protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR], urine retinol binding protein [RBP] to creatinine ratio, and beta-2-microglobulin [B2M] to creatinine ratio).

As expected, increases in serum creatinine were seen after initiation of E/C/F/TAF in ART-naive subjects. The magnitude of these increases was similar to those noted after initiation of treatment with other regimens including RTV and RPV {18038}, {19105}, {25886}, {28739}.

The totality of results from renal assessments in HIV-infected adult and adolescent subjects across the clinical development program demonstrated that treatment with E/C/F/TAF is associated with an improved renal safety profile compared with STB or with other TDF-containing regimens, with statistically significant differences in multiple tests of renal function. The change from baseline in serum creatinine at Week 48 and change from baseline in treatment emergent proteinuria were the third and fourth alpha-protected key safety endpoints, respectively, for the pooled analysis of Studies GS-US-292-0104 and GS-US-292-0111. Statistical analysis using the fallback procedure confirmed significance using an adjusted alpha, which was dependent on the results from preceding tests. Specifically, the following results were noted (m2.7.4, Section 2.1.9.3.1):

- Statistical analysis using the fallback procedure showed statistically significant differences favoring E/C/F/TAF over STB at Week 48 for the third and fourth alpha-protected key safety endpoints. In ART-naive adults, treatment with E/C/F/TAF was associated with less change in serum creatinine and eGFR and less proteinuria (by dipstick) compared with treatment with STB. Overall, increases from baseline in mean values for serum creatinine were smaller in the E/C/F/TAF group compared with the STB group. The difference between the treatment groups was statistically significant at all time points in the studies (m2.7.4, Section 2.1.9.3).

- In ART-naive adults, E/C/F/TAF was associated with decreases from baseline in tubular proteinuria (UPCR) and albuminuria (UACR), while increases from baseline in UPCR and UACR were seen with STB. There was a decrease from baseline in median UPCR for the E/C/F/TAF group that was observed at Week 2 and persisted through Week 48. In contrast, there was an increase from baseline in UPCR in the STB group. The difference between groups was statistically significant from baseline through Week 48 ($p < 0.001$ at each time point).

- For virologically suppressed adults who switched to E/C/F/TAF from a TDF-based regimen, there were minimal changes in serum creatinine and eGFR, and there were decreases in proteinuria and tubular proteinuria (RBP and B2M to creatinine ratios) (by dipstick). The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% to 21% and 49% to 27%, respectively, through Week 24. Decreases from baseline in proteinuria (UPCR), albuminuria (UACR), and tubular proteinuria also occurred as soon as 1 week after switch to E/C/F/TAF from a TDF-containing regimen in renally impaired subjects, strongly suggesting a reduction in TFV-associated toxicity. Renally impaired subjects who switched from a non-TDF containing regimen had a mild increase in serum creatinine but had significant improvements in UPCR, UACR, and tubular proteinuria (median percentage changes from baseline in UPCR and UACR were 0.1% and −19.5%, respectively).

- An iohexol substudy of adult subjects with stable, mild to moderate renal impairment (eGFR ≥ 30 mL/min) who switched to E/C/F/TAF had no change in aGFR through 24 weeks, regardless of baseline $eGFR_{CG}$ or pre-switch TDF use.

- In ART-naive adolescent subjects, changes in serum creatinine and eGFR calculated using the Schwartz formula were seen as early as Week 1 and subsequently stabilized and were nonprogressive. These changes are consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion, which results in an increase in serum creatinine and a decrease in eGFR without an effect on aGFR.

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) or laboratory findings consistent with subclinical renal tubulopathy were reported for subjects who received E/C/F/TAF.

Overall, across studies in different patient populations, there was an improved renal safety profile for an FTC/TAF-containing regimen, likely a result of the decrease in systemic TFV exposure relative to that with TDF-containing regimens.

**RPV**

Renal parameters were assessed in the Phase 2 and 3 studies with RPV and Eviplera (m2.7.4, Sections 2.1.9.3.3 and 2.1.9.3.4)

The pooled data from the RPV Phase 3 studies C209 and C215 demonstrated that serum creatinine increased and eGFR decreased over 96 weeks of treatment with RPV {30163}. Most of the increase in creatinine and decrease in eGFR occurred within the first 4 weeks of treatment. Over 96 weeks of treatment with RPV, mean changes of 0.1 mg/dL (range: -0.3 mg/dL to 0.6 mg/dL) for creatinine and -13.3 mL/min/1.73 $m^2$ (range: -63.7 mL/min/1.73 $m^2$ to 40.1 mL/min/1.73 $m^2$) for eGFR were observed. Creatinine increases were comparable by background N(t)RTIs. In patients who entered the RPV Phase 3 studies with mild or moderate renal impairment, the serum creatinine increase observed was similar to that seen in patients with normal renal function. These changes are not considered to be clinically relevant, as they do not reflect a change in aGFR. Small increases in serum creatinine for RPV are likely due to inhibition of renal transporters, as described below.

Changes in serum creatinine and eGFR observed at Week 48 in the Eviplera Study GS-US-264-0106 were consistent with those observed in the RPV Phase 3 studies.

RPV may inhibit tubular secretion of creatinine, but has no effect on the actual glomerular filtration. Hence, mean changes from baseline in serum creatinine and $eGFR_{CG}$ values in the RPV group are not considered clinically relevant and are not indicative of RPV-induced nephrotoxicity {30163}. RPV is approved for subjects with $eGFR_{CG} \geq 30$ mL/min.

## 5.7. Ocular Safety

A minimal infiltration of histiocytes was present in some organs (eye [choroid plexus, ciliary body], lung, and spleen) in some animals in a nonclinical study with dogs treated at a high dose of TAF, which was at 3.7- and 17-fold higher exposure to TAF and TFV, respectively, than that observed in human subjects administered a 25-mg dose (m2.4, Section 4.2.2.3). Therefore, in the E/C/F/TAF clinical program, analyses were conducted to evaluate the system organ class (SOC) term eye disorders to detect AEs where the symptoms reported may potentially represent posterior uveitis.

There have been no reports of posterior uveitis in human clinical studies to date.

Overall, in the E/C/F/TAF studies, there were similar incidences between treatment groups for events potentially related to uveitis, other eye disorders and conjunctivitis (m2.7.4, Section 2.1.9.4.1). Clinically, none of the AEs potentially related to uveitis in adults in the E/C/F/TAF groups were considered representative of an actual case of posterior uveitis. In an ophthalmologic substudy conducted as part of Study GS-US-292-0109, no subjects had fundoscopic findings consistent with uveitis. One adolescent subject treated with E/C/F/TAF developed intermediate uveitis. Symptoms and fundoscopic examination findings improved significantly with eye drops, and oral steroid and antihistamine therapy while treatment with E/C/F/TAF continued.

The ocular findings in Phase 3 clinical studies do not suggest that nonclinical finding in dogs are of clinical relevance in humans.

## 5.8. Neuropsychiatric Events

The Phase 3 RPV Week 96 analysis showed the incidence of neurologic events of interest was lower with RPV (28.4%) than with the control (EFV; 46.6%; $p < 0.0001$ Fisher exact test). The most commonly reported neurologic events of interest (in > 3.0% of subjects in either treatment group) were headache (15.5% with RPV vs 14.1% with control), dizziness (10.2% vs 29.6%, respectively; $p < 0.0001$ Fisher exact test), and somnolence (4.4% vs 7.5%, respectively). Neurologic events of interest were reported with lower severity grades in the RPV group than in the control group and were considered by the investigator to be treatment-related in a smaller proportion of subjects in the RPV group compared with the control group.

Neurologic events of interest mainly emerged in the first 4 weeks of treatment, when they were seen at approximately half the incidence in the RPV group than in the control group.

Psychiatric events of interest in the RPV Week 96 pooled analysis were reported for 27.7% of subjects in the RPV group compared with 31.8% of subjects in the control group. The most commonly reported psychiatric events of interest on RPV (in > 5.0% of RPV-treated subjects) were insomnia (10.5% vs 8.5% on control), abnormal dreams/nightmare (8.9% vs 13.6%, on control; $p = 0.0061$ Fisher exact test), and depression (6.9% vs 6.0% on control).

Psychiatric events of interest emerged mainly in the first 4 weeks of treatment, when they were seen at a lower incidence in the RPV group than in the control group.

## 5.9. Fasting Glucose and Lipid Parameters

For ART-naive and virologically suppressed subjects in the randomized E/C/F/TAF studies, greater increases in the fasting lipid parameters total cholesterol, direct LDL, high-density lipoprotein (HDL), total cholesterol to HDL ratio, triglycerides, and glucose were observed in subjects treated with E/C/F/TAF compared with those treated with a TDF-comparator (m2.7.4, Section 3.6.1). Similar results were seen in an analysis excluding subject receiving lipid modifying agents for total cholesterol, direct LDL, HDL, and triglycerides (Table 13). In the comparative E/C/F/TAF studies, the percentages of subjects who received concomitant lipid-modifying agents were comparable between treatment groups. A similar trend for fasting lipid results was seen in ART-naive adolescents who received E/C/F/TAF.

Higher percentages of subjects treated with E/C/F/TAF than those treated with a TDF-based comparator had categorical changes from baseline in the National Cholesterol Education Program (NCEP) ATP III lipid classifications; these categorical changes were not clinically meaningful and were similar to data from studies of ABC and other non-TDF-based regimens in ART-naive patients{11417}, {15957}, {15585}, {15975}, {18679}, {25972}, {26007}.

The mechanism underlying the differences in metabolic laboratory parameters observed between treatment with E/C/F/TAF compared with TDF-containing regimens (including STB) is unknown but may be associated with an effect of TFV on lipids{16173}, {27870}, and the previously discussed markedly lower plasma concentrations of TFV in subjects receiving E/C/F/TAF.

**Table 13. E/C/F/TAF Studies GS-US-292-0104 and GS-US-292-0111: Summary of Fasting Metabolic Assessments (Excluding Subjects Receiving a Lipid Modifying Agent) Change from Baseline at Week 48 (Safety Analysis Set)**

| Laboratory Parameter (mg/dL) | E/C/F/TAF (N=832) | | STB (N=827) | |
|---|---|---|---|---|
| | Baseline | Week 48 | Baseline | Week 48 |
| | mg/dL | Change[a] | mg/dL | Change[a] |
| Total Cholesterol (fasted) | 162 [N=757] | 30 [N=757] | 166 [N=742] | 13 [N=742] |
| HDL-cholesterol (fasted) | 46 [N=757] | 7 [N=757] | 45 [N=742] | 4 [N=742] |
| LDL-cholesterol (fasted) | 104 [N=753] | 15 [N=753] | 107 [N=744] | 3 [N=744] |
| Triglycerides (fasted) | 113 [N=757] | 29 [N=757] | 119 [N=742] | 10 [N=742] |

a The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.
A lipid modifying agent was defined as medication with Drug Class = 'LIPID MODIFYING AGENTS' and CMDECOD containing the wording of 'STATIN'
Source: m2.7.4, Table 83

For RPV, mean change from baseline in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides for the FTC/TDF subset are presented in Table 14.

**Table 14. RPV Studies C209 and C215 (FTC/TDF Subset): Mean Change from Baseline in Lipid Values Reported in Subjects in the RPV or Control Group (Phase 3 Week 96 Pooled Analysis)[a]**

| Laboratory Parameter (mg/dL) | Pooled | | | |
|---|---|---|---|---|
| | RPV N = 550 | | Control N = 546 | |
| Week 96 | Week 96 | Change from baseline[b] | Week 96 | Change from baseline[b] |
| Total Cholesterol (fasted) | 162 [N=430] | 2 [N=430] | 160 [N=401] | 26 [N=401] |
| HDL-Cholesterol (fasted) | 42 [N=429] | 4 [N=429] | 40 [N=399] | 11 [N=399] |
| LDL-Cholesterol (fasted) | 97 [N=427] | -1 [N=427] | 96 [N=397] | 14 [N=397] |
| Triglycerides (fasted) | 123 [N=430] | -14 [N=430] | 127 [N=401] | 6 [N=401] |

a Subjects who received lipid-lowering agents during the treatment period were excluded.
b The change from baseline is the mean of within-patient changes from baseline for patients with both baseline and Week 96 values
Source: m2.7.4, Table 90

For the FTC/TDF subset, there were no changes from baseline at Week 96 for TC, LDL, and HDL in the RPV group, compared with increases in the control group. Mean decreases from baseline were observed for triglyceride values over the 96-week treatment period in the RPV group, compared with mean increases from baseline in the control group. Similar results were seen in an analysis excluding subject receiving lipid modifying agents (m2.7.4, Section 3.6.2.1.1).

In Eviplera Study GS-US-264-0111, significant decreases from baseline in fasting total cholesterol, direct LDL cholesterol, and fasting triglycerides were observed starting as early as Week 12 and continuing through Week 48. There were statistically significant decreases in fasting total cholesterol, triglycerides, and direct LDL cholesterol from baseline to Week 48 (median change of –17 mg/dL from baseline in total cholesterol and –26 mg/dL in triglycerides [$p < 0.001$], and –8 in direct LDL cholesterol [$p = 0.016$]) (m2.7.4, Section 3.6.3.1.1). Similar changes were observed in Study GS-US-264-0106 through 24 weeks of treatment. Differences between these treatment groups for all 5 of these lipid parameters were statistically significant at Week 24 ($p < 0.001$). The mean reductions from baseline in lipid parameters observed at Week 24 in the FTC/RPV/TDF group were generally maintained through Week 48 of therapy (m2.7.4, Section 3.6.3.1.2).

## 5.10. Postmarketing Data

Postmarketing adverse reactions of severe skin reactions with systemic symptoms and weight gain have been identified for Eviplera (Section 5.4; m2.7.4, Section 6) and are included in the proposed FTC/RPV/TAF prescribing information. Severe skin reactions are an important potential risk for RPV in the Edurant RMP, and have not been identified during extensive postapproval use of other FTC- and TDF-containing products. Severe skin reactions are considered an important identified risk for RPV-containing FDC products, including FTC/RPV/TAF.

## 5.11. Safety in Special Groups and Situations

Safety information pertinent to the use of FTC/RPV/TAF in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the proposed prescribing information. Key findings are as follows:

The AE profile for subjects receiving the components of FTC/RPV/TAF was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count. The safety profile for the components of FTC/RPV/TAF in adults is consistent with that for adolescents. Guidance is provided in the prescribing information that the FTC/RPV/TAF FDC should not be administered to patients under the age of 12 years or weighing < 35 kg.

The exposure of FTC following administration of E/C/F/TAF to HIV-infected subjects with $eGFR_{CG}$ of 30 to 69 mL/min in an intensive PK substudy in Study GS-US-292-0112 was comparable with that shown historically in subjects with mild renal impairment (50-80 mL/min) who did not require dose adjustment. In addition, the safety profile of FTC administered as E/C/F/TAF was comparable for subjects with $eGFR_{CG} < 50$ mL/min or $eGFR_{CG} \geq 50$ mL/min in Study GS-US-292-0112. These data in HIV-infected patients support the use of FTC without dose adjustment in patients with $eGFR_{CG} \geq 30$mL/min (supplanting existing recommendations to modify the dosing interval for FTC in patients with $eGFR_{CG} < 50$ mL/min). Overall, FTC/RPV/TAF may be administered once daily without dose adjustment in patients with $eGFR_{CG} \geq 30$ mL/min.

Based on available PK data (Section 3.5.2), no dose adjustment of FTC/RPV/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B). Treatment with FTC/RPV/TAF is not recommended for use in patients with severe hepatic impairment.

The PK of FTC, RPV, and TAF have not been fully evaluated in patients coinfected with HBV or HCV. Due to a lack of data with the appropriately suppressive dose of TAF for use in subjects with HIV and HBV coinfection, these subjects were excluded from the E/C/F/TAF clinical development program. Subjects with HCV coinfection were also excluded due to incomplete DDI data. In the Phase 3 pooled analysis (Studies C209 and C215), approximately 9% of subjects were reported to be coinfected with HBV and/or HCV at baseline or on treatment. As expected, hepatic events of interest and elevated hepatic parameters were observed at a higher incidence in subjects who were coinfected with HBV and/or HCV than in subjects who were not coinfected. The incidence of hepatic events of interest and the incidence of elevated hepatic laboratory parameters in coinfected subjects were comparable in both the RPV and control groups.

Discontinuation of therapy with FTC/RPV/TAF in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis.

No adequate and well-controlled studies of FTC/RPV/TAF or its components have been conducted in pregnant women. Animal studies do not indicate direct or indirect harmful effects of FTC, RPV, or TAF with respect to pregnancy, embryonal and fetal development, parturition, or postnatal development. FTC/RPV/TAF should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving FTC/RPV/TAF.

## 5.12. Safety Discussion and Conclusions

The safety and tolerability of FTC/RPV/TAF is supported by Phase 1 studies of the FTC/RPV/TAF FDC in healthy subjects; FTC/RPV/TAF was generally safe and well-tolerated in healthy volunteers in those studies. Since exposures of the FTC/RPV/TAF FDC components are bioequivalent to the FTC/TAF-containing regimen E/C/F/TAF and the RPV-containing regimen Edurant, the safety and tolerability profile of the FTC/RPV/TAF FDC is supported by a safety database using Phase 2 and Phase 3 E/C/F/TAF, RPV, and Eviplera studies. This safety database is robust in terms of numbers of subjects receiving the recommended dose of each component and the length of treatment. The proposed prescribing information for FTC/RPV/TAF is based on the Phase 3 E/C/F/TAF and RPV studies, and postmarketing data from RPV-containing regimens.

Treatment with FTC/TAF- and RPV-containing regimens was well tolerated across all patient populations evaluated, as demonstrated by the low overall incidences of SAEs considered related to drug or study drug discontinuation due to AEs. The most commonly reported adverse reactions for E/C/F/TAF were diarrhoea (17%), nausea (15%), and headache (14%). The most commonly reported adverse reactions for RPV (when administered with FTC/TDF) were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%) and insomnia (5%). The AE profile for subjects receiving FTC/TAF or RPV was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count.

The FTC/RPV/TAF FDC is expected to be safe and well tolerated; to provide improvements in BMD and proteinuria in patients switching from TDF-based regimens; and to provide smaller BMD decreases and changes in proteinuria in ART-naive adult patients compared with patients initiating a TDF-containing regimen. For FTC/RPV/TAF, changes from baseline in lipids and serum creatinine are unknown. The FTC/RPV/TAF FDC can be taken without dose adjustment in patients with $eGFR_{CG} \geq 30$ mL/min.

In conclusion, exposure to the components of FTC/RPV/TAF demonstrated an acceptable safety profile in HIV-infected subjects, and offers the favorable tolerability of RPV and FTC with renal and bone advantages compared with TDF-based regimens.

# 6. BENEFITS AND RISKS CONCLUSIONS

FTC/RPV/TAF is a new FDC that combines TAF, an investigational prodrug of TFV with the approved NRTI FTC and approved NNRTI RPV for the treatment of HIV-infection in a broad range of patients. TAF is more stable in plasma than TDF. It achieves higher intracellular levels of the active phosphorylated metabolite TFV-DP and > 90% lower circulating levels of TFV relative to TDF. TAF has demonstrated an improved bone and renal safety profile compared with TDF in clinical studies, which is attributed to lower plasma TFV exposures compared to the approved dose of TDF. RPV, in combination with other ARVs, provides a safe and effective alternative ART option with an improved tolerability profile over other NNRTIs. Therapy with the FTC/RPV/TAF FDC should be initiated by a physician experienced in the management of HIV infection. The following considerations support a favorable benefit:risk profile for the FTC/RPV/TAF FDC for the treatment of HIV-infected patients.

## 6.1. Benefits

For individual patients living with HIV infection, the success of potent ART is based on many factors, including tolerability, convenience, adherence, resistance barrier, aging, and non-AIDS comorbidities. Non-AIDS comorbidities are increasingly accountable for morbidity and mortality. Consequently, clinical attention has become focused on the optimization of regimens and the development of novel therapies that address these critical factors {29705}. In addition, there remains a significant medical need for new safe and effective therapies for the treatment of pediatric patients, including adolescents.

FTC/RPV/TAF FDC tablets have many benefits for patients living with HIV infection, including the following:

- **FTC/RPV/TAF is an FDC that Combines an NNRTI with a Novel N(t)RTI Backbone that is Highly Effective in ART-Naive, Virologically Suppressed, and Renally Impaired Adults**

Treatment with FTC/TAF- and RPV-containing regimens has demonstrated durable ARV activity in multiple Phase 2 (Studies GS-US-292-0102, GS-US-264-0111, and C213), and Phase 3 studies (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, GS-US-292-0112, C209, C215, and GS-US-264-0106). Using the snapshot algorithm at Week 48, the FTC/TAF-containing regimen E/C/F/TAF was noninferior to standard-of-care regimens in ART-naive and virologically suppressed patients. In ART-naive adults, RPV administered with FTC/TDF was noninferior to EFV in Studies C209 and C215. Results for virologic outcomes were consistent across multiple treatment populations and were supported by several sensitivity analyses. Immunologic benefits of treatment were largely demonstrated by increases in CD4 cell counts.

Therefore, replacement of TDF with TAF in the FTC/RPV/TAF regimen is expected to result in similar efficacy to the existing FTC/RPV/TDF FDC (Eviplera) in treatment-naive patients initiating therapy and in virologically suppressed patients.

- **FTC/TAF- and RPV-Containing Regimens are Well Tolerated in a Broad Spectrum of Patients**

Treatment with the FTC/TAF-containing regimen E/C/F/TAF and an RPV-containing regimen in combination with FTC and the TFV prodrug TDF was well tolerated across a broad range of patient populations with different prior treatment paradigms (ART-naive or virologically suppressed), various degrees of renal function (normal function to moderate renal impairment), and a broad range of ages, as demonstrated by the low overall incidences of SAEs considered related to study drug, or study drug discontinuation due to AEs. The most frequently reported adverse reactions for E/C/F/TAF were diarrhoea (17%), nausea (15%), and headache (14%). The most commonly reported adverse reactions for RPV (when administered with FTC/TDF) were nausea (9%), dizziness (8%), abnormal dreams (8%), headache (6%), diarrhoea (5%), and insomnia (5%). Eviplera, which contains the FTC and RPV components, was well tolerated in virologically suppressed subjects. Replacement of the TDF component with TAF in FTC/RPV/TAF is likely to result in an improved bone and renal safety profile relative to Eviplera.

- **FTC/TAF-Containing Regimens have an Improved Bone and Renal Safety Profile Compared with TDF-Containing Regimens**

Treatment with an FTC/TAF-containing regimen was associated with an improved bone safety profile, as compared with TDF-containing regimens. Specifically, treatment with FTC/TAF-containing regimens resulted in less change in BMD at both the hip and spine for ART-naive subjects, and improvements in BMD for subjects who switched from a TDF-based regimen. Patients with HIV have increased risk for bone disease and this improved bone profile represents a clinically meaningful advancement in therapeutic options, particularly for patients with other risks for osteoporotic bone disease, for patients aged more than 50 years, and for adolescents.

Treatment with FTC/TAF-containing regimens is associated with an improved renal safety profile, as compared with TDF-containing regimens. Specifically, treatment with FTC/TAF-containing regimens resulted in less change in serum creatinine for ART-naive subjects compared with STB and a reduction in serum creatinine levels for subjects who switched from a TDF-based regimen. Treatment with FTC/TAF-containing regimens is also associated with less proteinuria and less renal tubular proteinuria for ART-naive subjects compared with a TDF-based regimen, and improvements in these renal protein parameters in subjects who switched from a TDF-based regimen.

- **FTC/TAF- and RPV-Containing Regimens are Efficacious in ART-Naive Adolescents; FTC/TAF-Containing Regimens have a Renal Safety Profile Consistent with that in Adults and No Impact on Bone Mineralization Relative to a Reference Population**

Treatment of adolescents with an FTC/TAF- and RPV-containing regimens demonstrated efficacy, robust immunological response, and tolerability similar to results from studies in ART-naive adults. The lack of notable changes from baseline in height-age adjusted spine and TBLH BMD Z-scores in E/C/F/TAF-treated adolescents indicates that subjects mineralized bone at rates consistent with those of the reference population.

## 6.2. Risks

The clinical safety database supporting this new marketing application for FTC/RPV/TAF is robust and includes data originating from E/C/F/TAF, RPV, and Eviplera studies conducted in a broad range of HIV-infected subjects, including those who are ART-naive, virologically suppressed, or renally impaired, and adolescents.

Treatment with E/C/F/TAF, RPV, and Eviplera was well tolerated across all patient populations evaluated (Section 6.1). The important identified and potential risks for FTC/RPV/TAF, either directly related to the use of FTC/RPV/TAF as an FDC, or attributable to one or more of the components of FTC/RPV/TAF, are detailed in the FTC/RPV/TAF RMP and reflected in the proposed prescribing information as appropriate.

*Important Identified Risks*

Important identified risks for one or more components of FTC/RPV/TAF or for RPV-containing FDC products are as follows: posttreatment hepatic flares in HIV/HBV coinfected patients (FTC, TAF), development of drug resistance (RPV), depression (RPV), and severe skin reactions (RPV-containing FDC regimens).

The efficacy and safety of FTC/RPV/TAF FDC have not been established in HIV-infected patients coinfected with HBV. Discontinuation of therapy with FTC/RPV/TAF FDC in patients coinfected with HIV-1 and HBV may be associated with severe acute exacerbations of hepatitis due to the FTC and TAF components of FTC/RPV/TAF, and therefore is included as an important identified risk in the FTC/RPV/TAF RMP.

Severe skin reactions with systemic symptoms have been identified as ADRs during postapproval use of Eviplera (but not during the extensive postapproval use of other FTC- and TDF-containing products), and so are considered an important identified risk for RPV-containing FDC products including FTC/RPV/TAF.

*Important Potential Risks*

Overdose (including overdose through accidental concurrent use of FTC/RPV/TAF with RPV-containing products) and off-label use in patients with a baseline viral load > 100,000 HIV-1 RNA copies/mL are considered important potential risks for FTC/RPV/TAF as an FDC tablet and for the RPV component. The important potential risk of overdose is related to the possibility of QT interval prolongation with overdose of RPV. FTC/RPV/TAF and Edurant are not currently indicated for use in patients with a viral load > 100,000 HIV-1 RNA copies/ml due to an increased risk of such patients developing virologic failure.

Important potential risks attributable to only the RPV component of FTC/RPV/TAF are as follows: QT interval prolongation, hepatotoxicity, and blood cortisol decreased. The inclusion of these safety concerns as important potential risks is in alignment with the Edurant RMP. There are no important potential risks associated with the FTC or TAF components of FTC/RPV/TAF.

The robust data from the E/C/F/TAF study program, summarized in Sections 5.6 and 6.1, do not support renal toxicity or loss of BMD being safety concerns for FTC/RPV/TAF.

Coadministration of potent CYP3A inducers or medicinal products that increase gastric pH with FTC/RPV/TAF is contraindicated as significant decreases in RPV plasma concentrations may occur, which may result in loss of therapeutic effect of FTC/RPV/TAF.

The FTC/RPV/TAF FDC should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving FTC/RPV/TAF.

The FTC/RPV/TAF FDC may be used without dose adjustment in patients with mild or moderate hepatic impairment, but is not recommended for use in patients with severe hepatic impairment due to lack of clinical data in this population.

Immune reconstitution syndrome, opportunistic infections, and osteonecrosis have been reported with combination ART. In HIV-infected patients with severe immune deficiency, an inflammatory reaction to asymptomatic or residual opportunistic infections may arise after the time of initiation of any effective ART. HIV-infected patients receiving ART may also continue to develop opportunistic infections and other complications of HIV infection. Cases of osteonecrosis have been reported particularly in patients with advanced HIV disease and/or long-term exposure to combination ART although the etiology is considered to be multifactorial (including corticosteroid use, alcohol consumption, severe immunosuppression, higher body mass index). Relevant information on immune reconstitution syndrome (including autoimmune disorders), opportunistic infections, and osteonecrosis has been included in the proposed prescribing information.

Precautionary language has also been included in the proposed prescribing information for the following class labeling effects: increase in blood lipids and glucose, and mitochondrial dysfunction, which are not considered to be safety concerns in the FTC/RPV/TAF RMP.

## 6.3. Conclusions

The FTC/RPV/TAF FDC provides FTC and TAF exposures that are bioequivalent to those from E/C/F/TAF, and RPV exposure that is bioequivalent to that in Edurant; thereby establishing the safety and efficacy of FTC/RPV/TAF by extrapolation to the safety and efficacy of these reference products in the treatment of a broad population of patients infected with HIV-1.

The FTC/RPV/TAF FDC is a once-daily complete regimen that provides the improved safety profile of TAF over TDF together with the established tolerability of FTC and RPV. FTC/RPV/TAF is proposed for use in HIV-1 infected adults and pediatric patients aged 12 years and above, without known mutations associated with resistance to the NNRTI class, tenofovir or emtricitabine, and with a viral load ≤ 100,000 HIV-1 RNA copies/mL.

# 7. REFERENCES

**1131** Cherrington JM, Allen SJW, Bischofberger N, Chen MS. Kinetic interaction of the diphosphates of 9-(2-phosphonylmethoxyethyl)adenine and other anti-HIV active purine congeners with HIV reverse transcriptase and human DNA polymerases α, β, and γ. Antivir Chem Chemother 1995;6 (4):217-21.

**1574** Robbins BL, Srinivas RV, Kim C, Bischofberger N, Fridland A. Anti-human immunodeficiency virus activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-*R*-(2-phosphonomethoxypropyl)adenine (PMPA), Bis(isopropyloxymethylcarbonyl) PMPA. Antimicrob Agents Chemother 1998;42 (3):612-7.

**4195** Gardner LI, Holmberg SD, Williamson JM, Szczech LA, Carpenter CCJ, Rompalo AM, et al. Development of proteinuria or elevated serum creatinine and mortality in HIV-infected women. J Acquir Immune Defic Syndr Hum Retrovirol 2003;32 (2):203-9.

**6964** Szczech LA, Gange SJ, van der Horst C, Bartlett JA, Young M, Cohen MH, et al. Predictors of proteinuria and renal failure among women with HIV infection. Kidney Int 2002;61 (1):195-202.

**7878** Pruvost A, Negredo E, Benech H, Theodoro F, Puig J, Grau E, et al. Measurement of intracellular didanosine and tenofovir phosphorylated metabolites and possible interaction of the two drugs in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2005;49 (5):1907-14.

**8461** Hawkins T, Veikley W, St. Claire RLI, Guyer B, Clark N, Kearney BP. Intracellular Pharmacokinetics of Tenofovir Diphosphate, Carbovir Triphosphate, and Lamivudine Triphosphate in Patients Receiving Triple-Nucleoside Regimens. J Acquir Immune Defic Syndr 2005;39 (4):406-11.

**8573** Vela JE, Miller MD, Rhodes GR, Ray AS. Effect of tenofovir in combination with other anti-HIV NRTIs on intracellular nucleotide pools [poster number H-1901]. 45th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2005 December 16-19; Washington, DC, USA.

**10655** Amiel C, Ostertag A, Slama L, Baudoin C, N'Guyen T, Lajeunie E, et al. BMD is reduced in HIV-infected men irrespective of treatment. J Bone Miner Res 2004;19 (3):402-9.

**11417** Anastos K, Lu D, Shi Q, Tien PC, Kaplan RC, Hessol NA, et al. Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens. J Acquir Immune Defic Syndr Hum Retrovirol 2007;45 (1):34-42.

**11882** Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. Tenofovir Disoproxil Fumarate, Emtricitabine, and Efavirenz Compared With Zidovudine/Lamivudine and Efavirenz in Treatment-Naive Patients: 144-Week Analysis. J Acquir Immune Defic Syndr 2008;47 (1):74-8.

**13932** U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER); Center for Biologics Evaluation and Research (CBER). Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements — Clinical Considerations for Accelerated and Traditional Approval Oct, 2002.

**14194** Duvivier C, Kolta S, Assoumou L, Ghosn J, Rozenberg S, Murphy RL, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS 2009;27 (7):817-24.

**14253** Brown TT, McComsey GA, King M, Qaqish RB, Bernstein B, da Silva BA. Bone Mineral Density (BMD) 96 Weeks after Antiretroviral Therapy (ART) Initiation: A Randomized Trial Comparing Efavirenz (EFV)-Based Therapy to a Lopinavir/ritonavir (LPV/r)-Containing Regimen with Simplification to LPV/r Monotherapy [Poster 966]. 15th Conference on Retroviruses and Opportunistic Infections (CROI); 2008 February 3-6; Boston, Mass, USA.

**15585** Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D, Fisher M, et al. Randomized Comparison of Renal Effects, Efficacy, and Safety With Once-Daily Abacavir/Lamivudine Versus Tenofovir/Emtricitabine, Administered With Efavirenz, in Antiretroviral-Naive, HIV-1-Infected Adults: 48-Week Results From the ASSERT Study [e-publication]. J Acquir Immune Defic Syndr 2010.

**15852** Dickinson L, Khoo S, Back D. Differences in the pharmacokinetics of protease inhibitors between healthy volunteers and HIV-infected persons. Curr Opin HIV AIDS 2008;3 (3):296-305.

**15889** Welage LS, Carver PL, Revankar S, Pierson C, Kauffman CA. Alterations in gastric acidity in patients infected with human immunodeficiency virus. Clin Infect Dis 1995;21 (6):1431-8.

**15957** Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, et al. Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009;361 (23):2230-40.

**15967** RESCRIPTOR® (brand of delavirdine mesylate tablets), US Prescribing Information. Agouron Pharmaceuticals Inc. LaJolla, CA, Revised May 2001.

**15975** Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching from Kivexa [ABC/3TC ]+Kaletra [LPV/r] to Truvada [TDF/FTC]+Kaletra [LPV/r] Reduces High Cholesterol: Results of a 12 Week Randomized, Controlled Study (ROCKET II) [Poster WEPE0110]. XVIII International AIDS Conference; 2010 July 18-23; Vienna, Austria.

**16173** Tungsiripata M, Kitchb D, Glesbyc MJ, Guptad SK, Mellorse JW, Moranf L, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: A CTG5206. AIDS 2010;24 (1):1781-4.

**16604** Madruga JV, Cassetti I, Etzel A ea. The 10-Year Safety and Efficacy of Tenofovir DF (TDF)-Containing HAART in Antiretroviral Naïve Patients [Poster #P086]. 10th International Congress on Drug Therapy in HIV Infection; 2010 November 7-11; Glasgow, UK.

**16915** McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis 2010;51 (8):937-46.

**17105** Gupta SK, Mamlin BW, Johnson CS, Dollins MD, Topf JM, Dube MP. Prevalence of proteinuria and the development of chronic kidney disease in HIV-infected patients. Clinical nephrology 2004;61 (1):1-6.

**17561** Grund B, Peng G, Gibert CL, Hoy JF, Isaksson RL, Shlay JC, et al. Continuous antiretroviral therapy decreases bone mineral density. AIDS 2009;23 (12):1519-29.

**18038** Molina JM, Cahn P, Grinsztejn B, Lazzarain A, Mills A, Saag M, et al. Rilpivirine versus efavirenz with tenofovir and emtricitabine in treatment-naive adults infected with HIV-1 (ECHO): a phase 3 randomised double-blind active-controlled trial. Lancet 2011;378 (9787):238-46.

**18679** Campo R, DeJesus E, Khanlou H, Wang H, Dau L, Fralich T, et al. SWIFT study: Switching from lamivudine/abacavir (3TC/ABC) to emtricitabine/tenofovir DF (FTC/TDF) based regimen improves lipid parameters while maintaining virologic suppression [Poster Presentation H2-786]. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2011 September 17-20; Chicago, IL.

**18854** Qaqish R, Trinh R, Tian M, Fredrick L, Podsadecki T, Norton M, et al. Bone mineral density (BMD) analysis in antiretroviral (ART)-naïve subjects taking Lopinavir/Ritonavir (LPV/R) combined with Raltegravir (RAL) or Tenofovir/Emtricitabine (TDF/FTC) for 96 weeks in the PROGRESS study [Abstract O09]. Presented at:13th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV; 2011 July 14-16; Rome, Italy. Antivir Ther 2011;16 (Suppl. 2):A8.

**19105** Cohen CJ, Andrade-Villanueva J, Clotet B, Fourie J, Johnson MA, Ruxrungtham K, et al. Rilpivirine versus efavirenz with two background nucleoside or nucleotide reverse transcriptase inhibitors in treatment-naive adults infected with HIV-1 (THRIVE): a phase 3, randomised, non-inferiority trial. Lancet 2011;378 (9787):229-37.

**19884** Scherzer R, Estrella M, Li Y, Deeks SG, Grunfeld C, Shlipak MG. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012;26 (7):867–75.

**20372** Llibre JM, Arribas JR, Domingo P, Gatell JM, Lozano F, Santos JR, et al. Clinical implications of fixed-dose coformulations of antiretrovirals on the outcome of HIV-1 therapy. AIDS 2011;25 (14):1683-90.

**21057** DeJesus E, Rockstroh J, Henry K, Molina J-M, Gathe J, Ramanathan S, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet 2012;379:2429-38.

**21102** Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet 2012;379 (9835):2439-48.

**21545** Williams FM. Clinical significance of esterases in man. Clin Pharmacokinet 1985;10 (5):392-403.

**21546** Inoue M, Morikawa M, Tsuboi M, Ito Y, Sugiura M. Comparative study of human intestinal and hepatic esterases as related to enzymatic properties and hydrolizing activity for ester-type drugs. Japanese journal of pharmacology 1980;30 (4):529-35.

**22018** Calza L, Trapani F, Tedeschi S, Piergentili B, Manfredi R, Colangeli V, et al. Tenofovir-induced renal toxicity in 324 HIV-infected, antiretroviral-naive patients. Scand J Infect Dis 2011;43 (8):656-60.

**22637** SUSTIVA® (efavirenz) capsules and tablets for oral use. US Prescribing Information. Bristol-Myers Squibb Company. Princeton, NJ. August 2012.

**23531** Wiens BL, Dmitrienko A. The fallback procedure for evaluating a single family of hypotheses. J Biopharm Stat 2005;15 (6):929-42.

**25126** McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. J Infect Dis 2011;203 (12):1791-801.

**25886** Gallant JE, Koenig E, Andrade-Villanueva J, Chetchotisakd P, DeJesus E, Antunes F, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. J Infect Dis 2013;208 (1):32-9.

**25972** Campo R, DeJesus E, Bredeek UF, Henry K, Khanlou H, Logue K, et al. SWIFT: prospective 48-week study to evaluate efficacy and safety of switching to emtricitabine/tenofovir from lamivudine/abacavir in virologically suppressed HIV-1 infected patients on a boosted protease inhibitor containing antiretroviral regimen. Clin Infect Dis 2013;56 (11):1637-45.

**26007** Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS 2013;27 (11):1771-8.

**27071** Joint United Nations Programme on HIV/AIDS (UNAIDS). Global report: UNAIDS report on the global AIDS epidemic. 2013.

**27447** EMA. Committee for Medicinal Products for Human Use (CHMP), Guideline on the clinical development of medicinal products for the treatment of HIV infection. September, 2013.

**27621** Williams I, Churchill D, Anderson J, Boffito M, Bower M, Cairns G, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012 (Updated November 2013. All changed text is cast in yellow highlight.). HIV Med 2014;15 Suppl 1:1-85.

**27870** Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. Antivir Ther 2012;17 (6):1011-20.

**27873** Janssen-Cilag Ltd. EDURANT 25 mg tablets. European Union Summary of Product Characteristics. Bucks, UK. Revised December 2013:

**28148** Boehringer Ingelheim (Canada) Ltd. VIRAMUNE® (nevirapine) Immediate-Release Tablets 200 mg and VIRAMUNE® XR (nevirapine) Extended-Release Tablets 400 mg. Product Monograph. Burlington, ON. Revised November 2013. 2013:

**28155** U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment. DRAFT GUIDANCE. June, 2013.

**28739** Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013;382 (9893):700-8.

**29368** Moyle GJ, Stellbrink HJ, Compston J, Orkin C, Arribas JR, Domingo P, et al. 96-Week results of abacavir/lamivudine versus tenofovir/emtricitabine, plus efavirenz, in antiretroviral-naive, HIV-1-infected adults: ASSERT study. Antivir Ther 2013;18 (7):905-13.

**29500** Janssen-Cilag SpA. EDURANT® (rilpivirine) tablets for oral use. U.S. Prescribing Information. Latina, Italy. Revised May 2014. 2014:

**29705** Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

**30163** Gilead Sciences International Limited. EVIPLERA (emtricitabine, rilpivirine, tenofovir DF) 200 mg/25 mg/245 mg Film Coated Tablets. Summary of Product Characteristics. United Kingdom. Updated 07 April 2014. 2014:

**32519** Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Available at: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revised 13 November 2014.

**34421** Bamford A, Turkova A, Lyall H, Foster C, Klein N, Bastiaans D, et al. Paediatric European Network for Treatment of AIDS (PENTA) guidelines for treatment of paediatric HIV-1 infection 2015: optimizing health in preparation for adult life. HIV Med 2015.

**34797** Gilead Sciences Inc. COMPLERA® (emtricitabine, rilpivirine, tenofovir disoproxil fumarate) Tablets. US Prescribing Information. Foster City, CA. Revised May 2015:

**34898** Department for Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC). Downloaded from http://aidsinfo.nih.gov/guidelines on 5/11/2015. Last Updated 08 April, 2015.

**34940** European AIDS Clinical Society (EACS). European Treatment Guidelines Version 7.1. November, 2014.

**35312** Gilead Sciences Inc. VIREAD® (tenofovir disoproxil fumarate) 123 mg, 163 mg, 204 mg, and 245 mg film-coated tablets, and 33 mg/g granules. Summary of Product Characteristics. Gilead Sciences Limited. Revised May. 2015:

## Justification for Absent Clinical Data in Module 5

| Section | | Comment |
|---|---|---|
| 5.3.1.1 | Bioavailability Study Reports | An absolute bioavailability study has not been conducted with RPV or TAF. |
| 5.3.1.3 | *In vitro-In vivo* Correlation Study Reports | *In vitro* dissolution profiles are discussed in m2.7.1 Section 1.2. Reports of *in vitro* dissolution tests can be found in the Quality section of the eCTD, see m3.2.P.5.4. |
| 5.3.2.1 | Plasma Protein Binding Reports | The plasma protein binding study conducted with FTC is located in Section 5.3.2.2. The plasma protein binding studies conducted with RPV and TAF are located in Section 5.3.2.1 and 5.3.3.3., respectively. |
| 5.3.2.3 | Reports of Studies Using Other Human Biomaterials | There are no additional studies conducted with FTC and TAF using other human biomaterials. |
| 5.3.3.2 | Patient PK and Initial Tolerability Study Reports | No reports for TAF or RPV are included as these are provided in 5.3.4.1 and 5.3.5.1., respectively. |
| 5.3.3.5 | Population PK Study Reports | No population PK report is included for FTC; a regression analysis report is provided in section 5.3.4.2 (13542v1). A RPV population PK report is located in Section 5.3.5.3 and a RPV adolescent population PK report is located in Section 5.3.5.2. |
| 5.3.4.1 | Healthy Subject PD and PK/PD Study Reports | FTC studies are located in Section 5.3.4.2 as conducted in healthy volunteers and patients (combined analysis). |
| 5.3.4.2 | Patient PD and PK-PD Study Reports | RPV studies are located in Section 5.3.4.1 as conducted in healthy volunteers. |
| 5.3.7 | Case Report Forms and Individual Patient Listings | Not applicable. |

**SECTION 2.5**
**CLINICAL OVERVIEW ADDENDUM**

---

# EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE FIXED-DOSE COMBINATION (FTC/RPV/TAF FDC)

Gilead Sciences

**24 May 2016**

---

**CONFIDENTIAL AND PROPRIETARY INFORMATION**

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
TABLE OF TABLES ..... 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 4
1. INTRODUCTION ..... 6
2. UPDATED EFFICACY AND SAFETY DATA ..... 10
2.1. Efficacy data ..... 10
2.1.1. Updated Extension 96 week Results from Studies GS-US-292-0104 and GS-US-292-0111 ..... 10
2.1.2. Full Week 48 Results from Study GS-US-292-0109 ..... 10
2.1.3. Week 48 Results from study GS-US-311-1089 ..... 12
2.1.4. Week 48 Results from Study GS-US-292-0112 ..... 13
2.1.5. Week 48 Results from Study GS-US-292-0106 ..... 15
2.1.6. Week 48 Results from Study GS-US-292-1249 ..... 15
2.1.7. Conclusion ..... 19
2.2. Safety data ..... 19
2.2.1. ART-Naive Subjects ..... 19
2.2.2. Virologically Suppressed Subjects ..... 19
2.2.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112 ..... 24
2.2.4. ART-Naive Adolescent Subjects: week 48 Results from study GS-US-292-0106 ..... 28
2.2.5. HIV/HBV-Coinfected Adults: Study GS-US-292-1249 ..... 28
2.2.6. Conclusion ..... 32
3. PHARMACOKINETIC DRUG INTERACTIONS ..... 33
3.1. Study GS-US-311-1387 ..... 33
3.1.1. Pharmacokinetic Results ..... 33
3.1.2. Safety Results ..... 34
4. REFERENCES ..... 36
5. ATTACHMENTS ..... 37

# LIST OF IN TEXT TABLES

Table 1. Additional Study Reports Providing Key Clinical Safety & Efficacy Information for the FTC/RPV/TAF FDC ..... 7
Table 2. GS-US-292-0109: Virologic Outcome at Week 48 (All Subjects) Using FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Week 48 [All Subjects] FAS) ..... 12
Table 3. GS-US-292-0112: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) ..... 14
Table 4. GS-US-292-1249: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) ..... 16
Table 5. GS-US-292-1249: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) ..... 17
Table 6. GS-US-292-0109: Bone Mineral Density – Week 48 (All Subjects) Analysis (Observed Data, Hip or Spine DXA Analysis Set) ..... 23
Table 7. GS US 292 0112: Change from Baseline in Renal Laboratory Tests at Week 48 in Virologically Suppressed Subjects with Renal Impairment who Switched to E/C/F/TAF (Safety Analysis Set) ..... 27
Table 8. GS-US-311-1387: Summary Statistics and Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Test (F/TAF FDC Administered with Steady-State CBZ) and Reference (F/TAF FDC Alone) (Part A) (TAF and TFV PK Analysis Set) ..... 34

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| ART | antiretroviral therapy |
| ATR | Atripla® |
| ATV | atazanavir |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| COBI, C | cobicistat (Tybost®) |
| DXA | dual-energy x-ray absorptiometry |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated) |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ | estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine method |
| $eGFR_{CKD\text{-}EPI,\ cysC}$ | estimated glomerular filtration rate calculated using the Chronic Kidney Disease Epidemiology Collaboration cystatin C method |
| EU | European Union |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| FTC, F | emtricitabine (Emtriva®) |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated) |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HIV, HIV-1, HIV-2 | human immunodeficiency virus, type 1, type 2 |
| LDL | low-density lipoprotein |
| MAA | Marketing Authorization Application |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N or n | number of subjects in a population (N) or subset (n) |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NtRTI | nucleotide reverse transcriptase inhibitor |
| PT | preferred term |
| Q1, Q3 | first quartile, third quartile |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |

| | |
|---|---|
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TmP/GFR | renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate |
| TVD | Truvada® |
| UGT | UDP glucuronosyl transferase |
| US | United States |

# 1. INTRODUCTION

A Marketing Authorisation Application (MAA) for the FTC/RPV/TAF Fixed Dose Combination (FDC) tablet was submitted in the European Union (EU) on 29 July 2015 and in the United States (US) on 1 July 2015, for the treatment of human immunodeficiency virus-1 (HIV-1) infection in combination with other antiretroviral agents in adults and adolescents 12 years of age and older without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine, and with a viral load ≤100,000 HIV-1 RNA copies/mL.

The FTC/RPV/TAF FDC tablet contains 200 mg of the nucleoside reverse transcriptase inhibitor (NRTI), emtricitabine (FTC, F); 25 mg of rilpivirine (RPV) and 25 mg of the new active substance and nucleotide reverse transcriptase inhibitor (NtRTI), tenofovir alafenamide (TAF).This addendum to the Clinical Overview (m2.5 dated [redacted]) provides an overview of the additional efficacy and safety data that has become available since the original EU MAA submission and was submitted during the MAA review. The updated clinical efficacy and safety data in ART-naive E/C/F/TAF studies do not impact on the overall risk:benefit of FTC/RPV/TAF, however they do support the FTC/RPV/TAF labeling (which contains these longer term data).

The longer term efficacy and safety data are from 6 ongoing Phase 2 and Phase 3 studies (week 96 report for studies GS-US-292-0104 and GS-US-292-0111, final 48 week report for study GS-US-292-0109, 48 week data from study GS-US-292-0112, 48 week report for study GS-US-292-1249 and week 48 report for study GS-US-292-0106) and one Phase 1 drug-drug interaction study.

Three virology reports are included in this submission as they describe the resistance data from these longer term studies. Rates of resistance in the updated dataset were consistent with those in the original submission, and no novel mutations to the study drugs were detected.

The integrated Week 96 virology analyses for the Genvoya® (GEN) Phase 3 studies GS-US-292-0104 and GS-US-292-0111 in treatment-naive, HIV-1 infected subjects are described in PC-120-2027 (m5.3.5.4, PC-120-2027). The virology analyses for study GS-US-292-0112 are also described in PC-120-2027 (m5.3.5.4, PC-120-2027). Virology data from study GS-US-292-0109 are described in PC-120-2025 (m5.3.5.4, PC-120-2025), and virology data from study GS-US-292-1249 are described in PC-120-2024 (m5.3.5.4, PC-120-2024) (Table 1).

**Table 1. Additional Study Reports Providing Key Clinical Safety & Efficacy Information for the FTC/RPV/TAF FDC**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Cut Dates (Primary Analyses to Safety Update) | Data Location |
|---|---|---|---|---|
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 435)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 432) | [redacted] to [redacted] | **CSR w96** m5.3.5.1, GS-US-292-0104, |
| PC-120-2027 | Integrated Week 96 virology analyses for GEN phase 3 studies | | | m5.3.5.4 |
| GS-US-292-0111 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB | E/C/F/TAF FDC + placebo-to-match STB (N = 431)<br>STB + placebo-to-match E/C/F/TAF FDC (N = 435) | [redacted] to [redacted] | **CSR w96:** m5.3.5.1, GS-US-292-0111, |
| PC-120-2027 | Integrated Week 96 virology analyses for GEN phase 3 studies | | | m5.3.5.4 |
| **HIV-Infected, Virologically Suppressed Adult Subjects** | | | | |
| GS-US-292-0109 | Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to E/C/F/TAF FDC | Switch to E/C/F/TAF FDC (N = 959)<br>Stay on FTC/TDF+3rd Agent (N = 477) | [redacted] to [redacted] | m5.3.5.3, GS-US-292-0109, 48w Final CSR |
| PC-120-2025 | | | | m5.3.5.4 |

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Cut Dates (Primary Analyses to Safety Update) | Data Location |
|---|---|---|---|---|
| GS-US-311-1089 | A Phase 3, Randomized, Open-Label Switch Study to Evaluate<br>F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed<br>on Regimens containing FTC/TDF | Switch to F/TAF +3rd Agent (N=330)<br>Stay on FTC/TDF +3rd Agent (N=330) | [redacted] to [redacted] | **CSR w48** m5.3.5.1, |
| **HIV-Infected Adult Subjects with Mild to Moderate Renal Impairment** | | | | |
| GS-US-292-0112<br><br>PC-120-2027 | Phase 3, open-label, multicenter, multiple cohort study evaluated the safety, efficacy, and tolerability of E/C/F/TAF FDC | Integrated Summary of Efficacy and Safety | [redacted] | **Tables & Listings:** m5.3.5.3, GS-US-292-0112,<br><br>m5.3.5.4 |
| **HIV-Infected, ART-Naive Adolescent Subjects** | | | | |
| GS-US-292-0106 | Phase 2/3, open-label, multicenter, 2-part, single-group study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC | GEN (N=50)<br>Week 48 efficacy and safety, PBMC PK | [redacted] to [redacted] | **CSR:** m5.3.5.2, GS-US-292-0106, Week 48 Analysis |

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Cut Dates (Primary Analyses to Safety Update) | Data Location |
|---|---|---|---|---|
| **HIV-HBV-Coinfected Adult Subjects** | | | | |
| GS-US-292-1249<br><br>PC-120-2024 | Phase 3b, open-label, single-arm, multicenter, dual-cohort study to assess the safety, efficacy, and tolerability of E/C/F/TAF FDC | E/C/F/TAF FDC<br>HIV Suppressed (N = 74)<br>HIV/HBV Treatment Naive (N = 3) | [redacted] to | **CSR:** m5.3.5.2, GS-US-292-1249,<br><br>m5.3.5.4 |
| **Pharmacokinetic drug interactions** | | | | |
| GS-US-311-1387 | A Phase 1, Open-Label, Adaptive, Two-Part, Three Period, Fixed<br>Sequence Study to Evaluate the Effect of Carbamazepine on the<br>PK of TAF and GS-9883 in Healthy Adult Subjects | N=52 subjects | [redacted]<br>to<br>[redacted] | **CSR:** m5.3.1.4 |

AE = adverse event; AE to DC = AE leading to discontinuation; ART = antiretroviral therapy; COBI = cobicistat; DC = discontinuation; DRV = darunavir; E/C/F/TAF = EVG/COBI/FTC/TAF; FDC = fixed-dose combination; FTC = emtricitabine; LoQ = list of questions; GEN= Genvoya; STB = Stribild; TDF = tenofovir disoproxil fumarate; TVD = Truvada

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

# 2. UPDATED EFFICACY AND SAFETY DATA

The original m2.5 Clinical Overview, dated [redacted], is based on a pivotal bioequivalence study (GS-US-366-1159) comparing FTC/RPV/TAF to Edurant® (marketed RPV 25-mg tablet) and Gilead's FDC tablet containing the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), FTC, and TAF (E/C/F/TAF 150/150/200/10 mg). E/C/F/TAF was selected as the reference because the pivotal clinical data establishing the safety and efficacy of TAF in combination with FTC were generated using the E/C/F/TAF FDC in Phase 3 studies. Edurant was selected as a reference because the safety and efficacy of RPV have been established from the Edurant Phase 3 registrational studies.

Results provided in this Addendum demonstrate the continued potent and durable efficacy and continued safety profile of FTC/RPV/TAF. Interpretation of safety data after the longer duration of exposure remains unchanged relative to the data provided in the original m2.5 Clinical Overview dated [redacted].

## 2.1. Efficacy data

### 2.1.1. Updated Extension 96 week Results from Studies GS-US-292-0104 and GS-US-292-0111

The clinical efficacy and safety data for ART-naive adults for studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks treatment (vs 48 weeks in the original application) are presented in m2.5 Clinical Overview (Genvoya type II variation EMA/H/C/004042/II/0001, see Attachment 1). The clinical overview provides an updated evaluation of the benefits risks of E/C/F/TAF for use in the treatment of HIV-1 infection. These updated data also support the proposed FTC/RPV/TAF labeling.

The integrated Week 96 virology analyses for the GEN Phase 3 studies (Studies GS-US-292-0104 and GS-US-292-0111) in treatment-naive, HIV-1 infected subjects are described in m5.3.5.4, PC-120-2027.

### 2.1.2. Full Week 48 Results from Study GS-US-292-0109

The primary analyses reported efficacy results for all virologically suppressed, HIV-1 infected adult subjects who switched from TDF-containing ART regimen and were randomized in Phase 3 Study GS-US-292-0109 through 31 October 2013. Subjects included in efficacy analyses had been followed through the lower limit of the Week 48 analysis window (ie, Week 42) or had discontinued study treatment before the data cutoff on [redacted]. As a consequence, at the time of the primary analyses, the Week 48 Full Analysis Set (FAS) did not include all subjects. Of the 1436 subjects who received at least 1 dose of study drug in the study, 1196 subjects were included in the primary analyses Week 48 FAS, and 1122 subjects were included in the Week 48 PP Analysis Set.

Through the data cutoff for the primary analyses, the percentage of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Week 48 using the

FDA-defined snapshot algorithm) was 95.6% for E/C/F/TAF and 92.9% for FTC/TDF+3rd Agent. Switching to E/C/F/TAF was determined to be noninferior to maintaining FTC/TDF+3rd Agent at Week 48 because the lower bound of the 2-sided CI of the difference in success rate (E/C/F/TAF – comparator) was greater than the prespecified –12% margin (difference in percentages: 2.7%, 95.01% CI: –0.3% to 5.6%). Noninferiority of E/C/F/TAF versus FTC/TDF+3rd Agent was confirmed by the analysis using the PP Analysis Set.

Following the completion of all subjects in this study through Week 48, updated analyses were performed for key efficacy results for all 1436 randomized subjects who received at least 1 dose of study drug (E/C/F/TAF 959 subjects; FTC/TDF+3rd Agent 477 subjects). The updated Week 48 (All Subjects) FAS primary efficacy results are presented in Table 2 and the full clinical study report is included in m5.3.5.1; key findings were as follows:

The percentages of subjects with virologic success based on the FAS (HIV-1 RNA < 50 copies/mL at Week 48 [All Subjects] using the FDA-defined snapshot algorithm) were 97.2% (932 of 959 subjects) for E/C/F/TAF and 93.1% (444 of 477 subjects) for FTC/TDF+3rd Agent (difference in percentages: 4.1%, 95% CI: 1.6% to 6.7%; $p < 0.001$). The lower bound of the 2-sided 95% CI was greater than the prespecified -12% margin and also > 0, indicating that switching to E/C/F/TAF was both noninferior to maintaining FTC/TDF+3rd Agent and also statistically superior at Week 48 ($p < 0.001$).

The percentages of subjects with virologic success (HIV-1 RNA < 50 copies/mL at Week 48 [All Subjects] using the FDA-defined snapshot algorithm) based on the PP Analysis Set were 99.1% (913 of 921 subjects) for E/C/F/TAF and 98.9% (435 of 440 subjects) for FTC/TDF+3rd Agent (difference in percentages: 0.3%, 95% CI: −1.0% to 1.6%; $p = 0.6$; m5.3.5.3,).

**Table 2. GS-US-292-0109: Virologic Outcome at Week 48 (All Subjects) Using FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Week 48 [All Subjects] FAS)**

| | | | E/C/F/TAF vs. FTC/TDF+3rd Agent | |
|---|---|---|---|---|
| | E/C/F/TAF (N=959) | FTC/TDF+3rd Agent (N=477) | p-value[a] | Difference in Percentages (95% CI)[b] |
| Virologic Success at Week 48[c]; n (%) | | | | |
| HIV-1 RNA < 50 copies/mL | 932 (97.2) | 444 (93.1) | <0.001 | 4.1% (1.6% to 6.7%) |
| Virologic Failure at Week 48[c]; n (%) | 10 (1.0) | 6 (1.3) | | |
| HIV-1 RNA >= 50 copies/mL | 6 ( 0.6) | 4 ( 0.8) | | |
| Discontinued Study Drug Due to Lack of Efficacy | 1 (0.1) | 0 | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL[d] | 1 (0.1) | 0 | | |
| Added New ARV | 2 ( 0.2) | 2 ( 0.4) | | |
| No Virologic Data in Week 48 Window[c]; n (%) | 17 (1.8) | 27 (5.7) | | |
| Discontinued Study Drug Due to AE/Death | 10 (1.0) | 6 (1.3) | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d] | 7 (0.7) | 20 (4.2) | | |
| Missing Data During Window but on Study Drug | 0 | 1 (0.2) | | |

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by the prior treatment regimen (STB, ATR, ATV/boosted+TVD).
b Difference in percentages of virologic success and its 95% CI were calculated based on the MH proportion adjusted by the prior treatment regimen.
c Week 48 window is between Day 294 and 377 (inclusive).
d Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
Source: m5.3.5.3, EMA Day 120, GS-US-292-0109, Week 48 Analysis, Table 8

The Week 48 virology analyses for the GEN study GS-US-292-0109 are described in m5.3.5.4, PC-120-2025.

### 2.1.3. Week 48 Results from study GS-US-311-1089

Study GS-US-311-1089 is an ongoing, Phase 3, randomized, double-blind study to evaluate the efficacy, safety, and tolerability of switching FTC/TDF to F/TAF in virologically suppressed, HIV-1 infected adult subjects.

Efficacy and safety data for HIV-1 positive adult subjects virologically suppressed on regimens containing FTC/tenofovir disoproxil fumarate (TDF) who switch to a regimen containing F/TAF

(Study GS-US-311-1089); results through 48 weeks of treatment are presented in m2.5 Clinical Overview (Study GS-US-311-1089, see Attachment 2).

### 2.1.4. Week 48 Results from Study GS-US-292-0112

The primary analyses included in the original MAA Clinical Overview, included data through Week 24 in Study GS-US-292-0112 from HIV-infected adult subjects with mild to moderate renal impairment, including 242 subjects who switched treatment to E/C/F/TAF and 6 ART-naive subjects. At the time of data cutoff in the primary analyses, the percentages of subjects with virologic success based on the FAS at Week 24 (plasma HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm), which represented the prespecified primary study endpoint, were as follows:

- Cohort 1 (virologically suppressed switch subjects): 95.0% (baseline $eGFR_{CG}$ < 50 mL/min [n = 80]: 95.0%; baseline $eGFR_{CG} \geq 50$ mL/min [n = 162]: 95.1%).

- Cohort 2 (ART-naive subjects; n = 6): 83.3%

Following the completion of all subjects in this study at Week 48, updated analyses were performed for key efficacy results for all enrolled subjects who received at least 1 dose of study drug. The updated Week 48 efficacy results for the FAS are presented in Table 3 ; key findings are as follows:

- Cohort 1: 91.7% (baseline $eGFR_{CG}$ < 50 mL/min: 90.0%; baseline $eGFR_{CG} \geq 50$ mL/min: 96.2%)

- Cohort 2: 100%

**Table 3. GS-US-292-0112: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**

| | Cohort 1: Switch | | | Cohort 2: ART-Naive |
|---|---|---|---|---|
| | Baseline $eGFR_{CG}$ < 50 mL/min (N = 80) | Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162) | Total (N = 242) | Total (N = 6) |
| Virologic success at Week 48[a]; n (%) | | | | |
| HIV-1 RNA < 50 copies/mL | 72 (90.0) | 150 (96.2) | 222 (91.7) | 6 (100.0) |
| 95% CI[b] | 81.2% to 95.6% | 87.4% to 96.1% | 87.5% to 94.9% | 54.1% to 100.0% |
| Virologic failure at Week 48[a]; n (%) | 0 | 3 (1.9) | 3 (1.2) | 0 |
| HIV-1 RNA ≥ 50 copies/mL | 0 | 1 (0.6) | 1 (0.4) | 0 |
| Discontinued study drug due to lack of efficacy | 0 | 1 (0.6) | 1 (0.4) | 0 |
| Discontinued study drug due to other reasons and last available HIV-1 RNA >= 50 copies/mL[c] | 0 | 0 | 0 | 0 |
| Added new ARV | 0 | 1 (0.6) | 1 (0.4) | 0 |
| No virologic data in Week 48 window[a]; n (%) | 8 (10.0) | 9 (5.6) | 17 (7.0) | 0 |
| Discontinued study drug due to AE/death | 5 (6.3) | 2 (1.2) | 7 (2.9) | 0 |
| Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[c] | 1 (1.3) | 6 (3.7) | 7 (2.9) | 0 |
| Missing data during window but on study drug | 2 (2.5) | 1 (0.6) | 3 (1.2) | 0 |

a Week 48 window is between Day 294 and 377 (inclusive).
b The 95% CIs for virologic success rate in each cohort and baseline eGFR category was obtained using Exact method.
c Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Source: m5.3.5.3, GS-US-292-0112, SU analysis, Table 14.2

Overall, updated results for Study GS-US-292-0112 demonstrate continued maintenance of virologic success through Week 48 and support the efficacy of E/C/F/TAF in a renally impaired population.

The Week 48 virology analyses for the GEN study GS-US-292-0112 are described in m5.3.5.4, PC-120-2027.

### 2.1.5. Week 48 Results from Study GS-US-292-0106

The week 48 report for Study GS-US-292-0106 presents an updated evaluation of the benefits and risks of E/C/F/TAF for use in the treatment of HIV-1 infection in adolescent (12 to <18 years of age). The updated data information also supports the proposed FTC/RPV/TAF labelling.

Clinical efficacy and safety data in ART-naive adolescent evaluated in Study GS-US-292-0106 through 48 are presented in m 2.5 Clinical Overview (Genvoya Type II variation II/0011, see Attachment 3).

### 2.1.6. Week 48 Results from Study GS-US-292-1249

The primary analyses reported efficacy results for all HIV-HBV-coinfected adult subjects who were enrolled in the Phase 3b Study GS-US-292-1249, through January 2015. Efficacy results are primarily presented using the FAS, which included all HIV suppressed subjects who were enrolled, received at least 1 dose of study drug, had at least 1 post-Day 1 plasma HBV DNA or HIV-1 RNA result while on study drug, and had no major protocol violations of eligibility criteria (3 treatment naïve subjects and 72 HIV-supressed subjects) (GS-US-292-1249 Week 48, Section 15.1, Table 1.3).

Detailed efficacy results for HIV/HBV-coinfected subjects are presented in the CSR (GS-US-292-1249 Week 48, Section 9). The following efficacy endpoints at Weeks 24 and 48 are summarized: HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL using missing data imputation methods (M = F and M = E), change from baseline in CD4 cell count, HBV DNA < 29 IU/mL (M = F and M = E), HBV surface antigen (HBsAg) loss and seroconversion to antibody against HBsAg (anti-HBs), HBV e-antigen (HBeAg) loss and seroconversion to antibody against HBeAg (anti-HBe), alanine aminotransferase (ALT) normalization, and FibroTest score.

A total of 3 Cohort 1 treatment-naive subjects were enrolled; therefore, limited summaries are provided for these subjects and interpretation of their data should be made with caution.

#### 2.1.6.1. Percentage of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 Using FDA Snapshot Algorithm

The HIV co-primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm (Table 4). At Week 24, virologic success (HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm) among HIV-suppressed subjects (Cohort 2) was high (94.4%). One subject (1.4%) was classified as a virologic failure (HIV-1 RNA ≥ 50 copies/mL); the subject was subsequently discontinued due to lack of efficacy. All 3 treatment-naive subjects in Cohort 1 had virologic success (HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm) at Week 24.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm was a secondary HIV efficacy endpoint. At Week 48, virologic success (HIV-1 RNA < 50 copies/mL using the FDA snapshot algorithm) was high among the Cohort 2 HIV-suppressed subjects (91.7%) (Table 5). Two subjects (2.8%) were classified as virologic

failures (HIV-1 RNA ≥ 50 copies/mL). Of those 2 subjects, 1 subject discontinued study drug due to lack of efficacy after Week 24 (described above), and 1 subject had HIV-1 RNA ≥ 50 copies/mL at Week 48 and was subsequently withdrawn from the study due to noncompliance with study drug. At Week 48, 2 subjects in Cohort 1 (treatment-naive subjects) had virologic success. One subject had missing data during the Week 48 analysis window, but had an HIV-1 RNA level of 39 copies/mL at the last time point assessed (Week 36).

**Table 4. GS-US-292-1249: Virologic Outcome at Week 24 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**

| | E/C/F/TAF Cohort 1 (N = 3) | E/C/F/TAF Cohort 2 (N = 72) |
|---|---|---|
| Virologic Success at Week 24 | | |
| HIV-1 RNA < 50 copies/mL | 3/3 (100.0%) | 68/72 (94.4%) |
| 95% CI | 29.2% to 100.0% | 86.4% to 98.5% |
| Virologic Failure at Week 24 | 0 | 1 (1.4%) |
| HIV-1 RNA ≥ 50 copies/mL | 0 | 1 (1.4%) |
| Discontinued Study Drug Due to Lack of Efficacy | 0 | 0 |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL | 0 | 0 |
| Added New ARV | 0 | 0 |
| No Virologic Data in Week 24 Window | 0 | 3 (4.2%) |
| Discontinued Study Drug Due to AE/Death | 0 | 1 (1.4%) |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL | 0 | 2 (2.8%) |
| Missing Data During Window but on Study Drug | 0 | 0 |

Week 24 window was between Days 126 and 209 (inclusive).
Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
95% CI is the 2-sided exact 95% CI for binomial proportions.
Source: GS-US-292-1249 Week 48, Section 15.1, Table 4.1.1

**Table 5. GS-US-292-1249: Virologic Outcome at Week 48 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**

| | E/C/F/TAF Cohort 1 (N = 3) | E/C/F/TAF Cohort 2 (N = 72) |
|---|---|---|
| Virologic Success at Week 48 | | |
| HIV-1 RNA < 50 copies/mL | 2/3 (66.7%) | 66/72 (91.7%) |
| 95% CI | 9.4% to 99.2% | 82.7% to 96.9% |
| Virologic Failure at Week 48 | 0 | 2 (2.8%) |
| HIV-1 RNA ≥ 50 copies/mL | 0 | 1 (1.4%) |
| Discontinued Study Drug Due to Lack of Efficacy | 0 | 1 (1.4%) |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL | 0 | 0 |
| Added New ARV | 0 | 0 |
| No Virologic Data in Week 48 Window | 1 (33.3%) | 4 (5.6%) |
| Discontinued Study Drug Due to AE/Death | 0 | 1 (1.4%) |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL | 0 | 2 (2.8%) |
| Missing Data During Window but on Study Drug | 1 (33.3%) | 1 (1.4%) |

Week 48 window was between Days 294 and 377 (inclusive).
Discontinuation due to other reasons includes subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
95% CI is the 2-sided exact 95% CI for binomial proportions.
Source: GS-US-292-1249 Week 48, Section 15.1, Table 4.1.3

### 2.1.6.2. Percentage of Subjects with HBV DNA < 29 IU/mL at Weeks 24 and 48

The HBV co-primary efficacy endpoint was the percentage of subjects with HBV DNA < 29 IU/mL at Week 24 calculated using the M = F method. A secondary analysis was the percentage of subjects with HBV DNA < 29 IU/mL at Week 24 calculated using the M = E method.

At baseline, 62 of 72 Cohort 2 HIV-suppressed subjects (86.1%) had HBV DNA < 29 IU/mL and 10 of 72 subjects (13.9%) had HBV DNA ≥ 29 IU/mL. At Week 24, the overall percentage of subjects with HBV DNA < 29 IU/mL (M = F) was 86.1% (62 subjects; 95% CI: 75.9% to 93.1%). Using the M = E method, the overall percentage at Week 24 was 89.9% (62 of 69 subjects; 95% CI: 80.2% to 95.8%). Of the 62 subjects with baseline HBV DNA < 29 IU/mL, 57 subjects remained HBV suppressed (HBV DNA < 29 IU/mL), 3 subjects had HBV DNA ≥ 29 IU/mL at Week 24 (each < 69 IU/mL), 1 subject discontinued the study due to an AE prior to Week 24, and 1 subject withdrew from the study prior to Week 24. Of the 10 subjects with baseline HBV DNA ≥ 29 IU/mL, 5 subjects had HBV DNA < 29 IU/mL, 4 subjects had HBV DNA ≥ 29 IU/mL (2 of which were < 69 IU/mL), and 1 subject withdrew from the study prior to Week 24.
At Week 24, 1 treatment-naive subject (Cohort 1) had HBV DNA < 29 IU/mL.

At Week 48, 66 of 72 Cohort 2 HIV-suppressed subjects (91.7%) had HBV DNA < 29 IU/mL and 66 of 68 subjects (97.1%) had HBV DNA < 29 IU/mL using the M = F and M = E methods, respectively. Two subjects had detectable levels of HBV DNA at baseline and did not achieve suppression to < 29 IU/mL by Week 48. The Week 48 HBV DNA level was 51 IU/mL for 1 subject and 170 IU/mL for the other subject. Four subjects were missing data at Week 48: 2 subjects withdrew consent; 1 subject discontinued due to AEs; and 1 subject was missing Week 48 data, but had HBV DNA < 20 IU/mL at all prior visits and at Week 60. At Week 48 in treatment-naive subjects (Cohort 1), 2 of 3 subjects and 2 of 2 subjects had HBV DNA < 29 IU/mL, as assessed using the M = F and M = E methods, respectively.

#### 2.1.6.3. Percentage of Subjects with HBsAg Loss and Seroconversion at Weeks 24 and 48

Of the 70 HIV-suppressed subjects (Cohort 2) who were HBsAg positive and anti-HBs negative at baseline, 1 subject (1.4%) experienced HBsAg loss with seroconversion to anti-HBs at Week 24. At Week 48, 2 other subjects (2.9%) experienced HBsAg loss and 1 of these subjects (1.4%) also achieved seroconversion to anti-HBs. No treatment-naive subjects (Cohort 1) experienced HBsAg loss or seroconversion to anti-HBs at Week 24 or 48.

#### 2.1.6.4. Percentage of Subjects with HBeAg Loss and Seroconversion at Weeks 24 and 48

Of the 30 HIV-suppressed subjects (Cohort 2) who were HBeAg positive and anti-HBe negative at baseline, 1 subject (3.3%) experienced HBeAg loss with seroconversion to anti-HBe at Week 24. At Week 48, 1 other subject (3.3%) experienced HBeAg loss. One treatment-naive subject (Cohort 1) experienced HBeAg loss with seroconversion to anti-HBe at Week 24, which was maintained at Week 48.

#### 2.1.6.5. Change from Baseline in FibroTest Score at Weeks 24 and 48

The 8 HIV-suppressed subjects (Cohort 2) with baseline ATV treatment were excluded from the analyses of FibroTest scores since the FibroTest score calculation included serum bilirubin concentration, and ATV is known to cause reversible, asymptomatic elevations in indirect (unconjugated) bilirubin related to inhibition of UDP-glucuronosyl transferase (UGT) {Bristol Myers Squibb 2015}.

The median (first quartile [Q1], third quartile [Q3]) FibroTest score was 0.35 (0.21, 0.51) at baseline, and the median (Q1, Q3) change from baseline was −0.02 (−0.11, 0.05; p = 0.064) at Week 24 and −0.04 (−0.11, 0.03; p = 0.018) at Week 48.

All 3 treatment-naive subjects (Cohort 1) continued in the no/minimal fibrosis FibroTest category at Week 24. Two subjects continued in the no/minimal fibrosis FibroTest category and 1 subject was missing FibroTest data at Week 48.

The Week 48 virology analyses for the GEN study GS-US-292-1249 are described in m5.3.5.4, PC-120-2024.

### 2.1.7. Conclusion

Updated long-term efficacy data are available for Studies GS-US-292-0104 and GS-US-292-0111 (ART-naive adults), GS-US-292-0106 (adolescent ART-naive subjects), GS-US-292-0109 (subjects who switched from TDF-containing ART regimen), GS-US-292-0112 (subjects with mild-to-moderate renal impairment) and GS-US-292-1249 (subjects HIV/ hepatitis B virus (HBV)-coinfected. Results demonstrate the continued potent and durable efficacy of TAF in combination with FTC and this can be extrapolated to FTC/RPV/TAF.

## 2.2. Safety data

An overview of updated long-term safety data from studies GS-US-292-0104 and GS-US-292-0111 (Phase 3, adult ART-Naïve Subjects), GS-US-292-0106 (adolescent ART-naive subjects), GS-US-292-0109 (subjects who switched from TDF-containing ART regimen), GS-US-292-0112 (subjects with mild-to-moderate renal impairment) and GS-US-292-1249 ((subjects HIV/ hepatitis B virus (HBV)-coinfected ) is provided below.

### 2.2.1. ART-Naive Subjects

2.2.1.1. 96 week Results from studies GS-US-292-0104 and GS-US-292-0111

The clinical efficacy and safety data for ART-naive adults for studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks treatment (vs 48 weeks in the original application) are presented in m2.5 Clinical Overview (Genvoya type II variation II/0001, see Attachment 2). The clinical overview provides an updated evaluation of the benefits risks of E/C/F/TAF for use in the treatment of HIV-1 infection. These updated data also support the proposed FTC/RPV/TAF labeling.

### 2.2.2. Virologically Suppressed Subjects

Updated safety data from Study GS-US-292-0109 are summarized below. The Week 48 Final CSR is provided in m5.3.5.1, GS-US-292-0109, Week 48 Final.

2.2.2.1. Study GS-US-292-0109

**Subject Disposition**

For the data discussed in m2.5 Clinical Overview (dated [redacted]), Study GS-US-292-0109 was fully enrolled. A total of 1436 subjects received at least 1 dose of study drug (E/C/F/TAF 959 subjects; FTC/TDF+3rd Agent 477 subjects).

Through the data cut date for this safety update, 1360 subjects are continuing study drug treatment (E/C/F/TAF 96.5%, 925 subjects; FTC/TDF+3rd Agent 91.2%, 435 subjects), and 1378 subjects remain on study (E/C/F/TAF 96.9%, 929 subjects; FTC/TDF+3rd Agent 94.1%, 449 subjects) (m5.3.5.1, GS-US-292-0109, Week 48 Analysis, Table 1). Four subjects (2 per treatment group) have completed the 96-week randomized phase of the study. Seventy-two

subjects discontinued study drug (E/C/F/TAF 3.3%, 32 subjects; FTC/TDF+3rd Agent 8.4%, 40 subjects), and 54 subjects prematurely discontinued from the study (E/C/F/TAF 2.9%, 28 subjects; FTC/TDF+3rd Agent 5.5%, 26 subjects) prior to the data cutoff date. The reasons for premature discontinuation of study drug were generally balanced between treatment groups, although a lower percentage of subjects discontinued E/C/F/TAF (0.8%, 8 subjects) compared with FTC/TDF+3rd Agent (3.4%, 16 subjects) due to withdrawal of consent, which is possibly a reflection of the open-label study design.

2.2.2.1.1. Safety Results

In subjects switching from their baseline regimen, E/C/F/TAF was generally well tolerated through a median of 82.9 weeks of exposure, as evidenced by the infrequent discontinuations due to AEs and the absence of study drug-related SAEs. In subjects who stayed on their baseline regimen, study drugs were generally well tolerated through a median of 80.1 weeks of exposure.

2.2.2.1.2. Adverse Events

The most common AEs by PT considered by the investigator as related to study drug, reported for ≥ 1% of subjects in either group were as follows:

- **E/C/F/TAF:** diarrhea (2.5%, 24 of 959 subjects), nausea (2.3%, 22 subjects), flatulence(1.9%, 18 subjects), headache (1.8%, 17 subjects), abnormal dreams (1.3%, 12 subjects), dizziness (1.1%, 11 subjects), osteopenia

- **FTC/TDF+3rd Agent:** jaundice (1.9%, 9 of 477 subjects), insomnia (1.5%, 7 subjects), ocular icterus (1.5%, 7 subjects), osteopenia (1.5%, 7 subjects), abnormal dreams (1.3%, 6 subjects), diarrhea (1.3%, 6 subjects), dizziness (1.3%, 6 subjects), fatigue (1.0%, 5 subjects), and osteoporosis (1.0%, 5 subjects),

Among the common study drug-related AEs, there were no notable differences between treatment groups. All reports of study drug-related jaundice and ocular icterus were for subjects taking ATV/boosted+TVD regimens.

2.2.2.1.3. Serious Adverse Events

Serious AEs were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 6.8%,

65 subjects; FTC/TDF+3rd Agent 7.3%, 35 subjects). The following SAEs were reported for > 1 subject in either treatment group: sepsis (E/C/F/TAF 0.4%, 4 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); pneumonia (E/C/F/TAF 0.4%, 4 subjects; FTC/TDF+3rd Agent 0%); suicide attempt (E/C/F/TAF 0.4%, 4 subjects; FTC/TDF+3rd Agent 0%); appendicitis (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); aseptic meningitis (E/C/F/TAF 0.3%, 3 subjects; FTC/TDF+3rd Agent 0%); non-cardiac chest pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0.2%, 1 subject); diarrhea (E/C/F/TAF 0.1%; 1 subject; FTC/TDF+3rd Agent 0.4%, 2 subjects); osteomyelitis (E/C/F/TAF 0.1%, 1 subject; FTC/TDF+3rd Agent 0.4%, 2 subjects); abdominal pain (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); convulsion (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); coronary artery disease (E/C/F/TAF 0.2%, 2

subjects; FTC/TDF+3rd Agent 0%); sinusitis (E/C/F/TAF 0.2%, 2 subjects; FTC/TDF+3rd Agent 0%); cellulitis (E/C/F/TAF 0%; FTC/TDF+3rd Agent 0.4%, 2 subjects); depression (E/C/F/TAF 0%; FTC/TDF+3rd Agent 0.4%, 2 subjects); and myocardial infarction (E/C/F/TAF 0%; FTC/TDF+3rd Agent 0.4%, 2 subjects).

None of the SAEs reported in the E/C/F/TAF group were considered by the investigator as related to study drug. The FTC/TDF+3rd Agent group had an SAE of Fanconi Syndrome that was considered by the investigator as related to study drugs. In addition, 1 subject (Subject [redacted]) in the FTC/TDF+3rd Agent group had an SAE of acute cholecystitis that was considered by the investigator as related to study drugs.

2.2.2.1.4. Discontinuations

Few subjects in either group discontinued study drug due to AEs (E/C/F/TAF 0.9%, 9 subjects; FTC/TDF+3rd Agent 2.5%, 12 subjects). In the E/C/F/TAF group, no AE by preferred term (PT) that led to study drug discontinuation was reported for more than 1 subject. In the FTC/TDF+3rd Agent group, 3 subjects, all of whom were taking ATV/boosted+TVD regimens, had jaundice that led to study drug discontinuation. Two subjects (each) in the FTC/TDF+3rd Agent group discontinued for AEs of depression, increased blood creatinine, or insomnia.

Most of the AEs leading to study drug discontinuation were nonserious and considered by the investigator as related to study drug.

2.2.2.1.5. Deaths

Four subjects in the E/C/F/TAF group died during the study. None of events was considered by the investigator to be related to study drug. No subject in the FTC/TDF+3rd Agent group died during the study.

2.2.2.1.6. Ocular safety

Adverse events in the SOC of eye disorders were reported for similar percentages of subjects in the 2 groups (E/C/F/TAF 6.7%; FTC/TDF+3rd Agent 5.2%). One subject in the E/C/F/TAF group had an SAE of retinal detachment during the study; the event resolved with treatment and was considered by the investigator as unrelated to the study drug. Nonserious, treatment-related

AEs in the SOC of Eye disorders were reported for 3 subjects in the E/C/F/TAF group (eye irritation, visual acuity reduced, and vision blurred) and for 7 subjects in the FTC/TDF+3rd Agent group (ocular icterus, all subjects taking ATV/boosted+TVD). All other eye disorder AEs were considered by the investigator as not related to study drugs. Most eye disorder SOC AEs resolved and none resulted in discontinuation of study drugs.

Twenty (2.1%) subjects in the E/C/F/TAF group and 5 (1.0%) subjects in the FTC/TDF+3rd Agent group had an AE prespecified as potential symptom of uveitis; however, there were no cases of uveitis reported, and no subjects in the ophthalmic substudy had fundoscopic findings consistent with uveitis.

#### 2.2.2.1.7. Renal Safety

##### 2.2.2.1.7.1. Renal Events

Two subjects, 1 in each treatment group, had renal SAEs. One subject in the E/C/F/TAF group had an SAE of acute renal failure that was considered unrelated to study drug; no action was taken with respect to study drug for this event. One subject in the FTC/TDF+3rd Agent group (receiving ATV/co+TVD) had a study drug-related SAE of Fanconi syndrome that resulted in discontinuation of study drugs. In the E/C/F/TAF group, 2 subjects had nonserious renal AEs (ie, MedDRA renal and urinary disorder SOC) (tubulointerstitial nephritis [subject had recurrent hematuria on and off treatment and was diagnosed with Hodgkin's disease after treatment discontinuation] and acute renal failure [event was prerenal, linked to Hodgkin's disease and generalized worsening]) that resulted in discontinuation of study drug; both events were considered by the investigator as not related to study drugs. In addition to the subject who discontinued study drug for an SAE of Fanconi syndrome, 2 subjects in in the FTC/TDF+3rd Agent group discontinued for nonserious renal AEs (renal colic and chronic renal failure), and 2 subjects in the FTC/TDF+3rd Agent group discontinued study drug due to AEs of "blood creatinine increased".

There were no AEs of proximal renal tubulopathy (including Fanconi Syndrome in the E/C/F/TAF group).

#### 2.2.2.1.8. Bone Safety – Percentage Change from Baseline in Hip and Spine BMD

There were increases from baseline in mean (SD) BMD at the hip and at the spine in the E/C/F/TAF group as compared with minimal changes from baseline in both parameters in the FTC/TDF+3rd Agent group ($p < 0.001$ for the differences between groups at Weeks 24 and 48; Table 6).

**Table 6. GS-US-292-0109: Bone Mineral Density – Week 48 (All Subjects) Analysis (Observed Data, Hip or Spine DXA Analysis Set)**

| | | E/C/F/TAF | FTC/TDF+3rd Agent | E/C/F/TAF vs FTC/TDF+3rd Agent | |
|---|---|---|---|---|---|
| | | | | P-Value[a] | Diff in LSM (95% CI)[a] |
| **Hip BMD[b]** | | | | | |
| Baseline | N | 902 | 452 | | |
| | Mean (SD) | 1.000 (0.1398) | 0.993 (0.1432) | 0.40 | 0.007 (−0.009, 0.023) |
| % Change at Week 24 | N | 863 | 432 | | |
| | Mean (SD) | 0.994 (2.0915) | −0.219 (1.8926) | < 0.001 | 1.210 (0.976, 1.444) |
| % Change at Week 48 | N | 869 | 428 | | |
| | Mean (SD) | 1.468 (2.7136) | −0.340 (2.8280) | < 0.001 | 1.807 (1.488, 2.126) |
| **Spine BMD[c]** | | | | | |
| Baseline | N | 912 | 457 | | |
| | Mean (SD) | 1.093 (0.1703) | 1.087 (0.1734) | 0.56 | 0.006 (−0.013, 0.025) |
| % Change at Week 24 | N | 874 | 437 | | |
| | Mean (SD) | 1.496 (2.8022) | −0.192 (3.0048) | < 0.001 | 1.686 (1.356, 2.016) |
| % Change at Week 48 | N | 881 | 436 | | |
| | Mean (SD) | 1.557 (3.8441) | −0.443 (4.1387) | < 0.001 | 2.000 (1.549, 2.452) |

% Change = Change from baseline at a postbaseline visit/baseline * 100%; Diff = difference

a P-values, difference in least squares means (Diff in LSM), and its 95% CI were from the analysis of variance (ANOVA) model including treatment (E/C/F/TAF vs FTC/TDF+3rd Agent) and prior treatment regimen (STB, ATR, or ATV/boosted+TVD) as fixed effects.

b The Hip DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing hip BMD for the baseline visit.

c The Spine DXA Analysis Set is defined as subjects who received at least 1 dose of study drug and had nonmissing spine BMD for the baseline visit.

Source: m5.3.5.3, EMA Day 120, GS-US-292-0109, Week 48 Analysis, Tables 38 and 39

There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF. When assessed using a threshold of 3% for changes from baseline, there were higher percentages of subjects in the E/C/F/TAF group who had increases from baseline in BMD of > 3% relative to the FTC/TDF+3rd Agent group at Week 24 (hip: E/C/F/TAF 11.7%; FTC/TDF+3rd Agent 2.8%; spine: E/C/F/TAF 28.4%, FTC/TDF+3rd Agent 11.2%) and at Week 48 (hip: E/C/F/TAF 21.4%; FTC/TDF+3rd Agent 7.5%; spine: E/C/F/TAF 33.0%, FTC/TDF+3rd Agent 13.3%; m5.3.5.3, EMA Day 120, GS-US-292-0109, Week 48 Analysis, Tables 41.1 and 41.2).

### 2.2.3. Subjects with Mild to Moderate Renal Impairment: Study GS-US-292-0112

Updated safety data from Study GS-US-292-0112 are summarized below. Tables, figures, and listings for this updated analysis are provided in m5.3.5.2, GS-US-292-0112, SU analysis.

**Subject Disposition**

The majority of subjects in each Cohort have received study treatment for ≥ 48 weeks (Table 7). A total of 231 subjects (Cohort 1 [switch] 93.0%, 225 subjects; Cohort 2 [ART naive] 100.0%, 6 subjects) were continuing study drugs. A total of 17 subjects (6.9%) discontinued study drugs, all of whom were in Cohort 1 (switch) (m5.3.5.2, GS-US-292-0112, SU analysis, Table 1). The reasons for premature discontinuation of study drugs in Cohort 1 (switch) were AE (3.3%, 8 subjects), withdrew consent (1.2%, 3 subjects), lost to follow-up (0.8%, 2 subjects), death (0.4%, 1 subject), lack of efficacy (0.4%, 1 subject), protocol violation (0.4%, 1 subject), and investigator's discretion (0.4%, 1 subject).

**Extent of Exposure**

The median (Q1, Q3) duration of exposure to study drug was 48.1 (43.1, 60.1) weeks for Cohort 1 (switch) and 48.4 (46.7, 60.0) weeks for Cohort 2 (ART naive). The majority of subjects in each cohort had received study drugs for ≥ 48 weeks (Cohort 1 [switch] 56.2%, 136 subjects; Cohort 2 [ART naive] 66.7%, 4 subjects).

**Deaths and Serious Adverse Events**

There was one death in the switch Cohort 1 (m5.3.5.2, GS-US-292-0112, SU analysis, Table 3.3), however this was considered unrelated to study drug.The cumulative incidence of SAEs was 12.0% (29 subjects) in Cohort 1 (switch), with similar percentages reported in subjects with baseline $eGFR_{CG} \geq 50$ mL/min (12.3%, n = 20) and $eGFR_{CG} < 50$ mL/min (11.3%, n = 9). No SAEs have been reported in Cohort 2 (ART naive) (m5.3.5.2, GS-US-292-0112, SU analysis, Table 3.1.1 and 3.1.2).

#### 2.2.3.1. Renal Safety

##### 2.2.3.1.1. Renal Events

No new renal SAEs or AEs in the renal and urinary disorders SOC that led to study drug discontinuation were reported for subjects in Cohorts 1 or 2 (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 3.1.2 and 3.2.2).

There were no AEs of proximal renal tubulopathy (including Fanconi Syndrome).

2.2.3.1.2. Renal Laboratory Parameters

**Serum Creatinine, Cystatin C, and Phosphorus**

In Cohort 1 (switch), overall median changes from baseline at each time point through Week 48 ranged from -0.01 to 0.04 mg/dL for serum creatinine, -0.05 to -0.01 mg/dL for serum cystatin C, and 0 to 0.3 mg/dL for serum phosphorus (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.1.4 to 4.1.6), indicating no clinically significant increases or decreases in these parameters. In subjects whose last prior antiretroviral regimen did not include TDF (N = 84), mean (standard deviation [SD]) change from baseline in serum creatinine at Week 48 was 0.07 (0.310) mg/dL (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.2.4).

In Cohort 2 (ART naive), median changes from baseline in serum creatinine at each time point through Week 48 ranged from -0.01 to 0.18 mg/dL (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.4). Median changes from baseline at each time point through Week 48 ranged from -0.13 to 0.19 mg/dL for serum cystatin C and -0.6 to 0.2 mg/dL for serum phosphorus (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.1.5 and 4.1.6).

**Estimated Glomerular Filtration Rate**

No clinically relevant changes from baseline eGFR through Week 48 were observed using any of the 3 equations ($eGFR_{CG}$, $eGFR_{CKD\text{-}EPI,\ cysC}$, and $eGFR_{CKD\text{-}EPI,\ creatinine}$) in the Cohort 1 switch and Cohort 2 ART naive subjects (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.1.1 to 4.1.3).

In Cohort 1 (switch), the overall median (Q1, Q3) change from baseline in eGFR at Week 48 was -0.6 (-5.4, 5.4) mL/min for $eGFR_{CG}$, -1.8 (-7.9, 4.1) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 1.6 (-7.4, 11.9) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$. When subgroups by baseline $eGFR_{CG}$ (< or ≥ 50 mL/min) were assessed, no significant changes from baseline eGFR through Week 48 were observed using any of the 3 equations (Cockcroft-Gault [$eGFR_{CG}$], Chronic Kidney Disease Epidemiology Collaboration cystatin C method [$eGFR_{CKD\text{-}EPI,\ cysC}$], and Chronic Kidney Disease Epidemiology Collaboration creatinine method [$eGFR_{CKD\text{-}EPI,\ creatinine}$]) in Cohort 1.

In Cohort 2 (ART naive), the median (Q1, Q3) change from baseline in eGFR at Week 48 was -0.6 (-1.9, 4.2) mL/min for $eGFR_{CG}$, -3.0 (-4.9, 0.6) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ creatinine}$, and 7.3 (-0.1, 12.2) mL/min/1.73 $m^2$ for $eGFR_{CKD\text{-}EPI,\ cysC}$.

**Proteinuria by Urinalysis (Dipstick)**

Most subjects in Cohort 1 had either no change or an improvement (toxicity grade decreased at least 1 grade from baseline) from the baseline proteinuria toxicity grade at Week 48 (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.7). For 4.0% of subjects (9 of 223) with nonmissing values, proteinuria grade worsened from baseline at Week 48, of whom 5 of 73 (6.8%) had baseline $eGFR_{CG}$ < 50 mL/min and 4 of 150 (2.7%) had baseline $eGFR_{CG}$ ≥ 50 mL/min. For 82.4% of subjects (61 of 74) with nonmissing values, the proteinuria grade improved from baseline at Week 48, of whom 24 of 32 (75.0%) had baseline $eGFR_{CG}$

< 50 mL/min and 37 of 42 (88.1%) had baseline $eGFR_{CG} \geq 50$ mL/min. At Week 48, most subjects had either no change or an improvement (decrease) from the baseline proteinuria toxicity grade irrespective of pre-switch TDF use. In subjects whose last prior antiretroviral regimen did not include TDF, 12 of 18 (66.7%) of subjects had an improvement (ie, decrease at least 1 toxicity grade) from baseline in proteinuria as measured by urine dipstick at Week 48 (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.2.7). In subjects whose last prior antiretroviral regimen did include TDF, 49 of 56 (87.5%) of subjects had an improvement (ie, decrease at least 1 toxicity grade) from baseline in proteinuria as measured by urine dipstick at Week 48.

No changes from the baseline proteinuria toxicity grade were observed for 4 of 5 Cohort 2 ART naive subjects with nonmissing values. One subject in Cohort 2 worsened from Grade 0 at baseline to Grade 1 at Week 48.

**Proteinuria by Quantitative Assessment**

In Cohort 1 (switch subjects), decreases in the urine protein to creatinine ratio (UPCR) from the baseline median of 160.6 mg/g were observed at Week 1 (median of 110.3 mg/g) and persisted through Week 48 (median of 84.8 mg/g) (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.10.1). Median (Q1, Q3) UPCR percentage change from baseline at Week 48 was -45.1% (-64.3%, 2.0%). For subjects with baseline $eGFR_{CG} < 50$ mL/min, median (Q1, Q3) baseline UPCR was 270.0 (105.5, 499.5) mg/g, and median (Q1, Q3) percentage change from baseline at Week 48 was -33.3% (-63.5%, 7.0%); for subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UPCR was 138.5 (68.4, 269.3) mg/g, and median (Q1, Q3) percentage change from baseline at Week 48 was -47.4% (-64.5%, -4.4%). Similar to UPCR, decreases in urine albumin to creatinine ratio (UACR) from the baseline median (Q1, Q3) of 28.8 (7.9, 83.9) mg/g were observed at Week 1 (median of 16.6 mg/g) and persisted through Week 48 (median of 10.0 mg/g) (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.11.1). Median (Q1, Q3) UACR percentage changes from baseline at Week 48 was -49.5% (-77.3%, 2.0%). For subjects with baseline $eGFR_{CG} < 50$ mL/min, median (Q1, Q3) baseline UACR was 53.2 (14.6, 240.8) mg/g, and median (Q1, Q3) percentage change from baseline at Week 48 was -42.6% (-78.7%, 22.0%). For subjects with baseline $eGFR_{CG} \geq 50$ mL/min, median (Q1, Q3) baseline UACR was 22.7 (6.0, 60.6) mg/g, and median (Q1, Q3) percentage changes from baseline at Week 48 was -52.3% (-76.0%, -16.3%). In subjects whose last prior antiretroviral regimen did not include TDF, median percentage change from baseline at Week 48 was 4.4% and -16.2%, respectively, for UPCR and UACR (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.2.10.1 and 4.2.11.1). In subjects whose last prior antiretroviral regimen did include TDF, median percentage change from baseline at Week 48 was -54.5% and -60.5%, respectively, for UPCR and UACR.

At baseline, clinically significant proteinuria (UPCR > 200 mg/g) was reported for 42.3% of subjects (101 of 239) with nonmissing values at baseline and 15.8% of subjects (34 of 215) at Week 48 among subjects with nonmissing values at both baseline and Week 48 (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.10.2). Clinically significant albuminuria (UACR ≥ 30 mg/g) was reported for 48.9% of subjects (115 of 235) with nonmissing values at baseline and 25.7% of subjects (55 of 214) with nonmissing values at Week 48 (m5.3.5.2, GS-US-292-0112, SU analysis, Table 4.1.11.2).

In Cohort 2 (ART naive), changes from baseline in median UPCR were observed, but no subject developed new clinically significant proteinuria (UPCR > 200 mg/g). Changes in UPCR from the baseline median of 45.9 mg/g were observed from Weeks 1 to 48, with medians of 50.8, 48.8, 48.7, 48.4, 55.0, 43.2, 58.2, 48.9, and 71.2 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.1.10.1 and 4.1.10.2). One of 4 subjects (25%) with nonmissing values at both baseline and Week 48 developed clinically significant albuminuria (UACR ≥ 30 mg/g). Changes in UACR from the baseline median of 12.3 mg/g were observed from Weeks 1 to 48, with medians of 5.3, 7.8, 10.4, 8.1, 8.9, 7.2, 12.4, 7.1, and 10.2 mg/g at Weeks 1, 2, 4, 8, 12, 16, 24, 36, and 48, respectively (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 4.1.11.1 and 4.1.11.2).

**Summary of Key Renal Laboratory Parameters in Virologically Suppressed Subjects with Renal Impairment who Switched to E/C/F/TAF (Cohort 1)**

For Cohort 1 (switch subjects), multiple assessments indicate improvements in renal function that persisted through Week 48. These included improvements in proteinuria, albuminuria, and tubular proteinuria (Table 7). The prevalence of clinically significant proteinuria (UPCR > 200 mg/g) decreased from 42% at baseline to 15.8% at Week 48. The prevalence of clinically significant albuminuria (UACR ≥ 30 mg/g) decreased from 49% at baseline to 26% at Week 48. Other renal assessments, including serum cystatin C and serum phosphorus, showed small median changes from baseline at each time point through Week 48.

**Table 7. GS US 292 0112: Change from Baseline in Renal Laboratory Tests at Week 48 in Virologically Suppressed Subjects with Renal Impairment who Switched to E/C/F/TAF (Safety Analysis Set)**

| | Cohort 1: Switch (N = 242) |
|---|---|
| Serum Creatinine (mg/dL)[a] | 0.03 (0.264) |
| Improvement in Proteinuria by Urine Dipstick[b] | 61/74 (82.4%) |
| Urine Protein to Creatinine Ratio [c] | -45.1% |
| Urine Albumin to Creatinine Ratio[c] | -49.5% |
| Urine RBP to Creatinine Ratio[c] | -68.9% |
| Urine Beta-2-Microglobulin to Creatinine Ratio [c] | -76.5% |

a Mean change (SD)
b An improvement of at least 1 toxicity grade from baseline
c Median percent change
Source: m5.3.5.3, GS-US-292-0112, SU analysis, Tables 4.1.4, 4.1.7, 4.1.8, 4.1.9, 4.1.10.1, and 4.1.11.1

### 2.2.3.2. Bone Safety – Percentage Change from Baseline in Hip and Spine BMD

Overall, hip and spine bone mineral density (BMD) increased for Cohort 1 subjects after switching to E/C/F/TAF. Mean (SD) percentage increases from baseline were observed in hip BMD (Week 24: 0.733% [2.7674]; Week 48: 1.465% [4.1872]) and spine BMD (Week 24: 1.643% [3.6250]; Week 48: 2.286% [4.2417]) (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 6.1 and 6.2). Mean percentage changes from baseline in hip and spine BMD for

those with pre-switch TDF use compared with those without pre-switch TDF use were 1.151% versus -0.071% for hip BMD and 2.370% versus 0.291% for spine BMD at Week 24 and 1.846% versus 0.702% for hip BMD and 2.945% versus 0.985% for spine BMD at Week 48.

There was evidence for an improvement in hip and spine BMD after switch to E/C/F/TAF. When assessed using a threshold of 3% for changes from baseline, higher percentages of subjects had increases versus decreases from baseline in BMD at both the hip (Week 24: 13.8% versus 7.1%; Week 48: 21.8% versus 6.0%) and the spine (Week 24: 33.6% versus 8.0%; Week 48: 36.9% versus 3.7%) (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 6.3 and 6.4).

Mean (SD) percentage decreases from baseline were observed in hip BMD (Week 24: -0.022% [1.6853]; Week 48: -0.068% [1.6092]) and spine BMD (Week 24: -2.686% [4.5755]; Week 48: -4.140% [4.5911]) for Cohort 2 ART-naive subjects. A decrease from baseline in spine BMD of > 3% was observed for 2 of 6 subjects (33.3%) at Week 24 and 4 of 6 (66.7%) of subjects at Week 48; no subjects had a > 3% increase in spine BMD (m5.3.5.2, GS-US-292-0112, SU analysis, Tables 6.1 to 6.4).

### 2.2.4. ART-Naive Adolescent Subjects: week 48 Results from study GS-US-292-0106

The week 48 report for Study GS-US-292-0106 presents an updated evaluation of the benefits and risks of E/C/F/TAF for use in the treatment of HIV-1 infection in adolescent (12 to < 18 years of age). The updated data information also supports the proposed FTC/RPV/TAF labeling.

Clinical efficacy and safety data in ART-naive adolescent evaluated in Study GS-US-292-0106 through 48 are presented in m 2.5 Clinical Overview (Genvoya Type II variation EMA/H/C/004042/II/0011, see Attachment 3).

### 2.2.5. HIV/HBV-Coinfected Adults: Study GS-US-292-1249

Safety data from Study GS-US-292-1249 are summarized below.

**Subject Disposition**

Through the data cut for this study update, a total of 79 subjects were enrolled in the study and 77 subjects received at least 1 dose of study drug (74 HIV-suppressed subjects [Cohort 2], 3 treatment naive subjects [Cohort 1]). Seventy-one subjects (92.2%) (68 [91.9%] HIV-suppressed subjects, 3 [100%] treatment naive subjects) were still receiving study drug up to the Week 48 visit. As of the data cut-off date, 70 subjects (90.9%) (67 [90.5%] HIV-suppressed subjects, 3 [100%] treatment naive subjects) were still receiving study drug. All of these subjects, except 1 treatment naive subject, were participating in the extension phase.

Six subjects (7.8%) discontinued study drug before the Week 48 visit due to withdrawn consent (3 subjects [3.9%]), AE (1 subject [1.3%]), lack of efficacy (1 subject [1.3%]), or lost to follow up (1 subject [1.3%]). One additional subject (1.3%) discontinued study drug in the extension

phase due to noncompliance. The subject who discontinued study drug due to lack of efficacy remained in the study; the other 6 subjects also discontinued the study.

**Extent of Exposure**

For the HIV-suppressed subjects, the median (Q1, Q3) duration of exposure to study drug was 49.1 (48.1, 59.4) weeks . Seventy-one subjects (95.9%) received study drug for ≥ 24 weeks, and 60 subjects (81.1%) received study drug for ≥ 48 weeks. Seven subjects discontinued study drug prior to the data cutoff date, as discussed in Section 8.1. The Kaplan-Meier (KM) estimates of the percentage of subjects discontinuing study drug by Weeks 24 and 48 were 4% (95% CI: 0.0%-8.6%) and 12% (95% CI: 3.1%-21.3%), respectively. The KM median time to premature study drug discontinuation could not be estimated due to the low number of events.

For the HIV/HBV treatment-naive subjects, all 3 subjects received study drug for ≥ 24 weeks, and 2 subjects received study drug for ≥ 36 weeks. No subject discontinued study drug prior to the data cutoff date.

2.2.5.1. Adverse Events

Cohort 2: HIV-Suppressed Subjects

Twelve subjects (16.2%) had AEs considered related to study drug by the investigator. The most common AEs were diarrhea (3 subjects [4.1%]) and increased appetite (2 subjects [2.7%]); each of the other AEs was reported in 1 subject (1.4%).

The majority of AEs considered related to study drug by the investigator were Grade 1. Three subjects had a single nonserious Grade 2 AE considered related to study drug by the investigator: increased appetite, insomnia, or acute prerenal failure. None of the AEs considered related to study drug by the investigator were Grade 3 or 4 in severity or considered serious by the investigator.

Cohort 1: HIV/HBV Treatment-Naive Subjects

No subjects had AEs considered related to study drug by the investigator.

2.2.5.2. Serious Adverse Events

Through the data cut of this safety update, the cumulative incidence of SAEs was 8.1% (6 subjects) for the HIV-suppressed subjects (Cohort 2). These six subjects had a total of 10 SAEs, none of which were considered related to study drug by the investigator. Twelve subjects (16.2%) had AEs considered related to study drug by the investigator, none of which were Grade 3 or 4. None of the HIV/HBV treatment-naive subjects (Cohort 1) had AEs which were considered SAEs.

2.2.5.3. Discontinuation due to Adverse Events

One HIV-suppressed subject (Cohort 2) had 2 AEs leading to study drug discontinuation (Grade 1 weight increased and Grade 2 increased appetite) (GS-US-292-1249 Week 48, Section 11.5). Neither AE was considered serious, but both were considered related to study drug by the investigator. No HIV/HBV treatment naïve patients (Cohort 2) had an AE leading to study drug discontinuation during this study.

2.2.5.4. Death

No deaths have been reported (GS-US-292-1249 Week 48, Section 11.3).

2.2.5.5. Renal Safety

**HIV-Suppressed Subjects**

No subject had an AE of proximal renal tubulopathy or discontinued study drugs due to a renal AE.

No change from baseline in serum creatinine was observed through Week 48; the median (Q1, Q3) change from baseline in serum creatinine at Week 48 was −0.03 (−0.12, 0.06) mg/dL. Graded serum creatinine laboratory abnormalities were reported for 8 subjects (10.8%), most of which were Grade 1 (5 subjects [6.8%]) or Grade 2 (2 subjects [2.7%]). One of the Grade 1 abnormalities (elevation) corresponded to an AE of acute prerenal failure considered related to study drug (drug-drug interaction between the COBI component of E/C/F/TAF andamlodipine) by the investigator. In addition, Grade 2 abnormalities were observed in a subject who had renal cell carcinoma. One subject had a Grade 3 serum creatinine abnormality at Week 48. The subject's serum creatinine returned to within the normal range approximately 1.5 months later. The subject had Grade 3 SAEs of prostatitis and benign prostatic hyperplasia that began 10 days after the initial increase in serum creatinine. The prostatitis resolved within 2 days, and the benign prostatic hyperplasia was ongoing as of the database cutoff date. Neither AE was considered related to study drug by the investigator.

Median changes from baseline in serum cystatin C at each time point through Week 48 ranged from 0.01 to 0.03 mg/dL.

In these subjects with normal median renal function (baseline $eGFR_{CG}$ of 93.9 mL/min), a median increase of 3.3 mL/min (Q1, Q3: -3.5, 14.1; p = 0.013) was observed at Week 48. Four of 68 subjects (5.9%) with non-missing values developed clinically significant proteinuria (ie, UPCR > 200 mg/g) at Week 48, and 2 subjects (2.9%) had significant proteinuria at baseline and at Week 48. Four of 7 subjects (57.1%) with significant proteinuria at baseline had improved at Week 48. Results were generally similar at Week 24 and at the last on-treatment assessment for all subjects.

Three of 68 subjects (4.4%) with non-missing values developed clinically significant albuminuria (ie, UACR ≥ 30 mg/g) at Week 48, and 6 subjects (8.8%) had significant albuminuria at baseline and at Week 48. Three of 11 subjects (27.3%) with significant

albuminuria at baseline had improved at Week 48. Results were generally similar at Week 24 and at the last on-treatment assessment for all subjects.

The median (Q1, Q3) percentage change from baseline in urine RBP to creatinine ratio (median baseline of 98.8 μg/g) was -12.5% (-53.1%, 20.2%), -22.0% (-41.5%, 10.7%), and -5.8% (-38.1%, 32.0%) at Weeks 12, 24, and 48, respectively. The decrease from baseline at Week 24 was significant (p = 0.024). The median (Q1, Q3) percentage change from baseline in urine beta-2-microglobulin to creatinine ratio (median baseline of 138.8 μg/g) was -21.9% (-62.8%, 14.1%), -35.8% (-67.7%, 15.5%), and -21.5% (-70.7%, 17.0%) at Weeks 12, 24, and 48, respectively. The decreases from baseline at Weeks 12 and 24 were significant (p = 0.011 and 0.003, respectively).

**HIV/HBV Treatment-Naive Subjects**

No subject had an AE in the renal and urinary disorders SOC.

2.2.5.6. Hepatic Safety

**HIV-Suppressed Subjects**

No subjects had a hepatic AE or confirmed on-treatment ALT flare. Two subjects (2.7%) had elevated AST or ALT levels > 3 × ULN during this study; 1 subject (1.4%) had AST and ALT levels > 5 × ULN. The liver enzyme abnormalities for this subject were due to a nonserious, Grade 1 AE of HCV infection. The HCV infection was not considered related to study drug by the investigator, and was continuing as of the data cutoff date. Neither of these subjects had an elevation in total bilirubin > 1 × ULN. Three subjects (4.1%) had elevations in total bilirubin > 1 × ULN, but ≤ 2 × ULN. No subject had an elevation in ALP > 1.5 × ULN.

**HIV/HBV Treatment-Naive Subjects**

No subject had a hepatic AE or confirmed on-treatment ALT flare. Two subjects had elevated AST or ALT levels > 5 × ULN during this study; 1 subject had an ALT level > 10 × ULN, which was > 9 × ULN upon repeat and, therefore, not a confirmed on-treatment ALT flare. No subject had elevations in total bilirubin > 1 × ULN or ALP> 1.5 × ULN. None of these liver enzyme abnormalities were reported as an AE.

2.2.5.7. Laboratory abnormalities

Laboratory abnormalities were reported in HIV-suppressed subjects (Cohort 1). Most subjects (90.5% [67 subjects]) had at least 1 laboratory abnormality. Most laboratory abnormalities were Grade 1 or 2 in severity. Thirteen subjects (17.6%) and 3 subjects (4.1%) had at least 1 laboratory abnormality with a maximum severity of Grade 3 or 4, respectively. Grade 3 and 4 laboratory abnormalities were reported as AEs for 4 subjects. One subject had Grade 3 nonfasting hyperglycemia and hyperglycosuria reported as a Grade 2, nonserious AE of diabetes mellitus, which was ongoing as of the data cutoff date and was not considered related to study drug by the investigator. One subject had Grade 3 hematuria reported as a Grade 2, nonserious AE, which resolved within 8 days and was not considered related to study drug by the

investigator. One subject had Grade 3 elevated amylase reported as a Grade 1, nonserious AE, which was ongoing as of the data cutoff date and was not considered related to study drug by the investigator. One subject had Grade 3 ALT and AST and Grade 4 GGT due to an AE of HCV infection, as summarized above. In addition to those 4 subjects, 1 subject with Grade 3 elevated serum creatinine (discussed above) and 1 subject with Grade 3 hematuria had concurrent AEs of benign prostatic hyperplasia and prostatitis.

#### 2.2.5.8. Metabolic Laboratory Parameters

Changes in metabolic laboratory parameters were reported in HIV-suppressed patients.

There were increases from baseline to Week 48 in total cholesterol and direct LDL cholesterol, but not in the total cholesterol to HDL ratio.

Two subjects (2.8%; N = 72) had Grade 3 fasting hypercholesterolemia, 2 subjects (2.8%) had Grade 3 fasting LDL, and 1 subject (1.4%) each had Grade 3 and 4 fasting triglycerides. None of these abnormalities were reported as AEs by the investigators.

### 2.2.6. Conclusion

In conclusion, the aggregate long-term data reviewed for inclusion in this safety update do not alter the benefit:risk profile of FTC/RPV/TAF, as provided in the original m2.5 Clinical Overview (dated [redacted]). The totality of cumulative results from renal and bone safety analyses in HIV-infected subjects across the TAF clinical development program continues to demonstrate that treatment with TAF-containing regimens is associated with a preferential renal and bone safety profile compared with TDF-containing regimens, as reported in the primary analyses.

# 3. PHARMACOKINETIC DRUG INTERACTIONS

## 3.1. Study GS-US-311-1387

Data are now available from Study GS-US-311-1387, a Phase I open-label, adaptive, two-part, three period, fixed sequence study evaluating the effect of carbamazepine (CBZ) on the pharmacokinetics (PK) of TAF and GS-9883 in healthy adult subjects.

The primary objective of this study was to evaluate the effect of steady-state CBZ on the pharmacokinetics (PK) of tenofovir alafenamide (TAF) when administered as F/TAF FDC.

The secondary objectives for Part A of the study were to i) evaluate the effect of steady-state CBZ on the PK of TFV when administered as F/TAF FDC, ii) examine the safety and tolerability of F/TAF FDC when administered alone or with CBZ. The secondary objectives for Part B of the study were to i) evaluate the effect of steady-state CBZ on the PK of GS-9883 and TAF when administered as GS-9883/F/TAF FDC, ii) evaluate the effect of steady-state CBZ on the PK of TFV when administered as GS-9883/F/TAF FDC, iii) examine the safety and tolerability of GS-9883/F/TAF FDC when administered alone or with CBZ. Another secondary objective was to evaluate the steady-state PK of CBZ and its metabolite carbamazepine-10,11-epoxide (CBZE) when administered alone or in the presence of F/TAF FDC (Part A) or GS-9883/F/TAF FDC (Part B).

### 3.1.1. Pharmacokinetic Results

Mean (%CV) TAF $AUC_{last}$ was 223.4 (41.7) h*ng/mL and 110.4 (61.2) h*ng/mL following the administration of F/TAF FDC alone and with steady-state CBZ, respectively; mean (%CV) TAF $C_{max}$ was 219.6 (37.3) ng/mL and 99.4 (47.8) ng/mL, respectively. Mean (%CV) TFV $AUC_{inf}$ was 245.1 (15.8) h*ng/mL and 186.3 (15.5) h*ng/mL following the administration of F/TAF FDC alone and with steady-state CBZ, respectively; mean (%CV) TFV $C_{max}$ was 7.3 (19.4) ng/mL and 5.0 (18.9) ng/mL, respectively.

The statistical comparisons of TAF and TFV plasma PK parameters, following the administration of a single dose of F/TAF FDC alone and with CBZ at steady-state, are presented in Table 8 below.

**Table 8. GS-US-311-1387: Summary Statistics and Statistical Comparisons of TAF and TFV PK Parameter Estimates Between Test (F/TAF FDC Administered with Steady-State CBZ) and Reference (F/TAF FDC Alone) (Part A) (TAF and TFV PK Analysis Set)**

| | GLSM | | |
|---|---|---|---|
| **TAF PK Parameter** | **CBZ 300 mg BID+ F/TAF FDC 200/25mg (Test) (N = 22)** | **F/TAF FDC 200/25mg (Reference) (N = 26)** | **GLSM Ratio (%) (90% CI) Test/Reference** |
| $AUC_{last}$ (h*ng/mL) | 92.08 | 204.61 | 45.00 (39.66, 51.06) |
| $AUC_{inf}$ (h*ng/mL) | 103.81[a] | 224.68[b] | 46.21 (39.68, 53.81) |
| $C_{max}$ (ng/mL) | 87.80 | 204.59 | 42.92 (35.87, 51.35) |
| **TFV PK Parameter** | **CBZ 300 mg BID+ F/TAF FDC 200/25mg (Test) (N = 22)** | **F/TAF FDC 200/25mg (Reference) (N = 26)** | **GLSM Ratio (%) (90% CI) Test/Reference** |
| $AUC_{last}$ (h*ng/mL) | 157.05 | 208.91[c] | 75.18 (71.39, 79.17) |
| $AUC_{inf}$ (h*ng/mL) | 185.06[d] | 239.47[b] | 77.28 (73.51, 81.24) |
| $C_{max}$ (ng/mL) | 4.96 | 7.13[e] | 69.61 (65.18, 74.34) |

a n = 13.
b n = 23.
c n = 24.
d n = 21.
Source: GS-US-311-1387, Section 15.1, Table 5.1

TAF is a P-gp substrate. TAF exposure was decreased when used in combination with CBZ, a potent P-gp inducer. When coadministered with CBZ 300 mg at steady-state, TAF $AUC_{inf}$, $AUC_{last,}$ and $C_{max}$ decreased by approximately 54%, 55%, and 57%, respectively, compared with administration of F/TAF FDC alone. Similarly, a decrease in TFV exposures were observed when F/TAF FDC was coadministered with CBZ; TFV $AUC_{inf}$, $AUC_{last}$, and $C_{max}$ decreased by approximately 23%, 25%, and 30%, respectively. Alternative anticonvulsants should be considered.

### 3.1.2. Safety Results

Of the 26 enrolled subjects, 73.1% (19 subjects) had at least 1 AE (F/TAF 26.9%, 7 of 26 subjects; CBZ 57.7%, 15 of 26 subjects; and CBZ+F/TAF 31.8%, 7 of 22 subjects). The most commonly reported AEs were as follows: vomiting (7.7%, 2 subjects) following F/TAF; somnolence (38.5%, 10 subjects), headache (30.8%, 8 subjects), and dizziness (15.4%, 4 subjects) following CBZ; and nausea and headache (each 9.1%, 2 subjects) following CBZ+F/TAF.

AEs that were considered by the investigator to be related to study drug were reported for 69.2% (18 subjects); all related AEs were reported following CBZ (57.7%, 15 subjects) or CBZ+F/TAF (31.8%, 7 subjects).

The majority of AEs were Grade 1. Grade 3 or Grade 4 AEs were reported for 11.5% (3 subjects) (CBZ 7.7%, 2 subjects; and CBZ+F/TAF 4.5%, 1 subject), all of which were considered by the investigator to be related to study drug; 1 subject had Grade 4 thrombocytopenia (also an SAE, described below) following CBZ, which led to discontinuation of the study drugs, 1 subject had Grade 3 myositis following CBZ, which led to discontinuation of the study drugs, and 1 subject had Grade 3 angioedema and Grade 4 Stevens-Johnson syndrome (also an SAE, described below), both following CBZ+F/TAF.

SAEs were reported for 7.7% (2 subjects) (CBZ 3.8%, 1 subject; and CBZ+F/TAF 4.5%, 1 subject). Both SAEs (thrombocytopenia and Stevens-Johnson syndrome, following CBZ and CBZ+F/TAF, respectively) were considered by the investigator to be related to study drug; the investigator assessed the events as not related to F/TAF but to CBZ. Both thrombocytopenia and Stevens-Johnson syndrome are adverse reactions known to be associated with CBZ.

AEs leading to study drug discontinuation were reported for 15.4% (4 subjects), all following CBZ (thrombocytopenia and headache in 1 subject, hyponatremia in 1 subject, rash maculo-papular in 1 subject, and myositis in 1 subject). These were all considered by the investigator to be related to study drug; all AEs that led to study drug discontinuation are adverse reactions known to be associated with CBZ.

There were no clinically relevant changes in median laboratory values during the study. For the majority of subjects who had laboratory abnormalities, the maximum postdose toxicity was Grade 1. One subject had a Grade 4 laboratory abnormality (low platelet count, also reported as an SAE of thrombocytopenia and described above). Two subjects had Grade 3 laboratory abnormalities; these were elevated creatine kinase (following CBZ dosing), and occult blood in urine (following CBZ+F/TAF dosing).

There were no clinically relevant changes from baseline in vital signs or other safety findings. Overall, a single dose of the F/TAF FDC tablet (200/25 mg) was generally well tolerated when administered alone, and there were no relevant difference in tolerability when the F/TAF FDC tablet was coadministered with CBZ at steady-state.

# 4. REFERENCES

Bristol Myers Squibb. REYATAZ (Atanazavir Sulfate) Capsules, for oral use: US Prescribing Information. New York, NY. Revised March 2015.

# 5. ATTACHMENTS

| | |
|---|---|
| **Attachment 1** | **m2.5 Clinical Overview Genvoya type II variation EMA/H/C/004042/II/0001 (Study GS-US-292-0104 96 week and GS-US-292-0111 96 week)** |
| **Attachment 2** | **m2.5 Clinical Overview Study GS-US-311-1089** |
| **Attachment 3** | **m.2.5 Clinical Overview Genvoya type II variation EMA/H/C/004042/II/0011 (Study GS-US-292-0106 48 week)** |

# SECTION 2.5—CLINICAL OVERVIEW

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

Gilead Sciences

19 November 2015

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 3
LIST OF IN-TEXT FIGURES ..... 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 4
1. PRODUCT DEVELOPMENT RATIONALE ..... 5
1.1. Introduction and Background ..... 5
2. OVERVIEW OF BIOPHARMACEUTICS ..... 7
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 8
3.1. Pharmacology/Virology ..... 8
3.2. Clinical Pharmacokinetics ..... 8
4. OVERVIEW OF EFFICACY ..... 9
5. OVERVIEW OF SAFETY ..... 13
5.1. Extent of Exposure ..... 13
5.2. Overall Safety ..... 13
5.3. Analysis of Adverse Drug Reactions ..... 14
5.4. Bone Safety ..... 16
5.5. Renal Safety ..... 17
5.6. Suicidal Ideation and Suicide Attempt ..... 18
5.7. Fasting Glucose and Lipid Parameters ..... 19
5.8. Safety in Special Groups and Situations ..... 19
6. BENEFITS AND RISKS CONCLUSIONS ..... 20
6.1. Benefits ..... 20
6.2. Risks ..... 21
6.3. Conclusions ..... 21
7. REFERENCES ..... 22

## LIST OF IN-TEXT TABLES

Table 1. Studies Included in this Submission ..... 6
Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 96 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS) ..... 10
Table 3. GS-US-292-0104 and GS-US-292-0111: Treatment Difference in Virologic Success by Subgroup at Week 96 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS) ..... 12
Table 4. GS-US-292-0104 and GS-US-292-0111: Overall Summary of Adverse Events (Week 96 Analysis, Safety Analysis Set) ..... 14
Table 5. GS-US-292-0104 and GS-US-292-0111: Adverse Events (All Grades) Related to Study Drug for ADRs to Genvoya (Week 96 Analysis) ..... 15
Table 6. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 96 Analysis) ..... 17
Table 7. GS-US-292-0104 and GS-US-292-0111: Key Renal Laboratory Parameters (Week 96 Analysis) ..... 18
Table 8. GS-US-292-0104 and GS-US-292-0111: Summary of Suicide Events by Suicide/Self-Injury SMQ (Week 96 Analysis) ..... 19

## LIST OF IN-TEXT FIGURES

Figure 1. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set) ..... 16

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ART | antiretroviral treatment or therapy |
| ARV | antiretroviral |
| BL | baseline |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| COBI or C | cobicistat (Tybost®) |
| CSR | clinical study report |
| DXA | dual-energy x-ray absorptiometry |
| EVG or E | elvitegravir (Vitekta®) |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FTC | emtricitabine (Emtriva®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated; Genvoya® (previously referred to as E/C/F/TAF) |
| $eGFR_{CG}$ | glomerular filtration rate, estimated, by Cockcroft-Gault method |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| HDL | high-density lipoprotein |
| INSTI | integrase strand-transfer inhibitor |
| ISE | Integrated Summary of Efficacy |
| ISS | Integrated Summary of Safety |
| LDL | low-density lipoprotein |
| m | module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MH | Mantel-Haenszel |
| N | number of subjects in a population |
| Q1, Q3 | first quartile, third quartile |
| RMP | Risk Management Plan |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| SmPC | Summary of Product Characteristics |
| SMQ | standardised MedDRA query |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| UACR | urine albumin-to-creatinine ratio |
| UPCR | urine protein-to-creatinine ratio |
| US | United States |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

This submission supports proposed changes to the prescribing information for Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), an oral, once-daily fixed-dose combination that provides a potent and well-tolerated regimen for the long-term treatment of patients infected with human immunodeficiency virus type 1 (HIV-1).
This submission also fulfills interim milestones for 2 Category 3 additional pharmacovigilance activities (Week 96 reports for Studies GS-US-292-0104 and GS-US-292-0111) for GEN in line with the European Union Risk Management Plan (RMP) agreed during the original marketing authorization application.

GEN contains the HIV-1 integrase strand-transfer inhibitor (INSTI) elvitegravir (EVG), the pharmacoenhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF).

The success of potent and well-tolerated antiretroviral (ARV) therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-acquired immune deficiency syndrome-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {29705}. In addition, effective therapies must take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, and regimen simplification.

This clinical overview presents an updated evaluation of the benefits and risks of GEN for use in the treatment of HIV-1 infection. Information that supports the proposed GEN labeling includes updated clinical efficacy and safety data in ART-naive adults.

Throughout the text of this document, Genvoya is referred to as “GEN.” The designation “E/C/F/TAF” is used in preprogrammed tables, figures, and listings.

This submission provides efficacy and safety data for ART-naive adults (Studies GS-US-292-0104 and GS-US-292-0111) through 96 weeks of treatment (vs 48 weeks in the original application) (Table 1).

Pooling of the efficacy and safety data for the studies is appropriate due to their identical study design, including eligibility criteria. Both studies were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the respective protocols.

Details of subject disposition and analysis sets for these clinical studies are provided in m2.7.3, Section 3.1.

## Table 1. Studies Included in this Submission

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| **HIV-Infected, ART-Naive Adult Subjects** | | | | |
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GEN vs STB | GEN + placebo-to-match STB (N = 435)<br>STB + placebo-to-match GEN (N = 432) | Week 96 efficacy and safety | **CSR:** m5.3.5.1, GS-US-292-0104 Week 96<br>**Narrative:** m2.7.3, Section 2.1 |
| GS-US-292-0111 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GEN vs STB | GEN + placebo-to-match STB (N = 431)<br>STB + placebo-to-match GEN (N = 435) | Week 96 efficacy and safety | **CSR:** m5.3.5.1, GS-US-292-0111 Week 96<br>**Narrative:** m2.7.3, Section 2.2 |

CSR = clinical study report; GEN = Genvoya; STB = Stribild
a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

# 2. OVERVIEW OF BIOPHARMACEUTICS

No new biopharmaceutics information (eg, formulation or dissolution data) is included within this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Pharmacology/Virology

Updated clinical virology data from Studies GS-US-292-0104 and GS-US-292-0111 are presented in m2.7.2, Section 4 and incorporated with efficacy data in this overview (Section 4).

## 3.2. Clinical Pharmacokinetics

No new clinical pharmacokinetic data are included in this submission.

# 4. OVERVIEW OF EFFICACY

This section provides an overview of the pooled analysis of efficacy that was conducted for Studies GS-US-292-0104 and GS-US-292-0111 (Table 1; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Baseline demographics and disease characteristics for the study population are presented in m2.7.4, Sections 1.2.1 and 1.2.2, respectively. Generally, the studied population is representative of ART-naive HIV-1 infected subjects in the general population.

Details of the efficacy results are presented in m2.7.3, Section 3.2.

The noninferiority of GEN compared with Stribild® (STB; EVG/COBI/FTC/tenofovir disoproxil fumarate [TDF]) was confirmed when the primary efficacy endpoint (percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the Food and Drug Administration (FDA)-defined snapshot algorithm) was re-analyzed using the Week 96 dataset for each study. Results were as follows:

- In Study GS-US-292-0104, virologic success at Week 48 using the Week 96 full analysis set (FAS) was as follows: GEN 93.1%; STB 92.8%; difference in percentages: 0.5%, 95.002% confidence interval (CI): −3.0% to 4.0%.

- In Study GS-US-292-0111, virologic success at Week 48 using the Week 96 FAS was as follows: GEN 91.9%; STB 88.7%; difference in percentages: 3.1%, 95.002% CI: −0.9% to 7.1%.

Based on the pooled data, high virologic success (HIV-1 RNA < 50 copies/mL using the FDA-defined snapshot algorithm) was maintained through Week 96 in both treatment groups in the FAS. The percentages of subjects with virologic success were as follows (Table 2):

- GEN 86.6%

- STB 85.2%

Genvoya was determined to be noninferior to STB because the lower bound of the 2-sided CI of the difference in response (GEN – STB) was greater than the prespecified −12% margin (difference in percentages: 1.5%, 95% CI: −1.8% to 4.8%).

These pooled results confirmed those from the individual studies GS-US-292-0104 and GS-US-292-0111, where noninferiority of GEN versus STB was determined at Week 96 using the FAS (GS-US-292-0104 difference in percentages: 1.3%, 95% CI: −2.9% to 5.5%; GS-US-292-0111 difference in percentages: 1.7%, 95% CI −3.3% to 6.8%) and confirmed using the Week 96 Per-Protocol Analysis Sets.

**Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 96 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS)**

| | GEN (N = 866) | STB (N = 867) | GEN vs. STB | |
|---|---|---|---|---|
| | | | p-value[a] | Difference in Percentages (95% CI)[a] |
| Virologic Success at Week 96 | | | | |
| HIV-1 RNA < 50 copies/mL | 750 (86.6%) | 739 (85.2%) | 0.36 | 1.5% (−1.8% to 4.8%) |
| Virologic Failure at Week 96 | 39 (4.5%) | 35 (4.0%) | | |
| HIV-1 RNA ≥ 50 copies/mL | 16 (1.8%) | 15 (1.7%) | | |
| Discontinued Study Drug Due to Lack of Efficacy | 6 (0.7%) | 6 (0.7%) | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[b] | 15 (1.7%) | 13 (1.5%) | | |
| Added New ARV | 2 (0.2%) | 1 (0.1%) | | |
| No Virologic Data in Week 96 Window | 77 (8.9%) | 93 (10.7%) | | |
| Discontinued Study Drug Due to AE/Death | 11 (1.3%) | 21 (2.4%) | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b] | 52 (6.0%) | 64 (7.4%) | | |
| Missing Data During Window but on Study Drug | 14 (1.6%) | 8 (0.9%) | | |

Week 96 window is between Day 630 and 713 (inclusive).

a Difference in percentages of virologic success between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline HIV-1 RNA, region, and study stratum. P-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA, region and study stratum, baseline HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: United States (US) or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

b Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Programming Details: .../version1/prog/t-snapshot-pooled.sas v9.2 Output file: t-snapshot-50-wk96-pooled.out [redacted]
Source: m5.3.5.3, E/C/F/TAF Week 96 ISE, Table 2.1

Results for subgroup analyses and key secondary efficacy endpoints were similar between treatment groups, as summarized below:

- In the pooled subgroup analysis, the rates of virologic success at Week 96 for the subgroups age, sex, race, baseline HIV-1 RNA level, baseline cluster determinant 4 (CD4) cell count, region (United States [US] versus ex-US), or study drug adherence were similar for the GEN and STB groups (Table 3). The 95% CIs for differences in virologic success between treatment groups included zero for all subgroups evaluated, suggesting no differences between the treatments (m2.7.3, Section 3.3).

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using the missing = failure method for the pooled data was 87.5% for both the GEN and STB groups.

- The percentages of subjects with HIV-1 RNA < 20 copies/mL at Week 96 using the FDA-defined snapshot algorithm for the pooled data were as follows: GEN 81.5%; STB 80.2%; difference in percentages: 1.5%, 95% CI: −2.2% to 5.2% (m2.7.3, Section 3.2.2).

- The emergence of resistance mutations was rare across the GEN and STB groups. The emergence of resistance was similar for the GEN group (1.2%, 10 of 866 subjects) compared with the STB group (0.9%, 8 of 867 subjects) (integrated analysis of Studies GS-US-292-0104 and GS-US-292-0111; m2.7.2, Section 4.1.3). The cross resistance profiles for the virologic failure subjects with emergent resistance to EVG, FTC, and tenofovir (TFV) were consistent with historical data. No novel TAF resistance mutations were observed.

- The immunologic benefits of treatment with GEN were demonstrated by improvements in CD4 cell counts. The mean (standard deviation [SD]) increases from baseline in CD4 cell counts at Week 96 (observed data) using the pooled data were as follows: GEN 280 (194.0) cells/μL; STB 266 (194.6) cells/μL; difference in least-squares mean: 15 cells/μL, 95% CI: −5 to 34 cells/μL (p = 0.14; similar results were shown for the last observation carried forward analysis).

**Table 3. GS-US-292-0104 and GS-US-292-0111: Treatment Difference in Virologic Success by Subgroup at Week 96 Using FDA Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS)**

| | E/C/F/TAF (N = 866) | STB (N = 867) | E/C/F/TAF vs. STB Difference in Percentages (95% CI)[a] |
|---|---|---|---|
| Age (Years) | | | |
| < 50 | 668/777 (86.0%) | 639/753 (84.9%) | 1.2% (−2.3% to 4.8%) |
| ≥ 50 | 82/89 (92.1%) | 100/114 (87.7%) | 4.0% (−5.7% to 13.7%) |
| Sex | | | |
| Male | 635/733 (86.6%) | 631/740 (85.3%) | 1.6% (−2.0% to 5.2%) |
| Female | 115/133 (86.5%) | 108/127 (85.0%) | 1.5% (−7.3% to 10.4%) |
| Race | | | |
| Black | 173/223 (77.6%) | 168/213 (78.9%) | −1.6% (−9.6% to 6.4%) |
| Nonblack | 577/643 (89.7%) | 571/654 (87.3%) | 2.7% (−0.8% to 6.2%) |
| Baseline HIV-1 RNA (copies/mL) | | | |
| ≤ 100,000 | 587/670 (87.6%) | 573/672 (85.3%) | 2.4% (−1.3% to 6.0%) |
| > 100,000 | 163/196 (83.2%) | 166/195 (85.1%) | −1.4% (−8.7% to 5.9%) |
| Baseline CD4 Cell Count (/μL) | | | |
| < 200 | 93/112 (83.0%) | 97/117 (82.9%) | −0.9% (−11.1% to 9.2%) |
| ≥ 200 | 657/753 (87.3%) | 642/750 (85.6%) | 1.8% (−1.7% to 5.3%) |
| Region | | | |
| US | 452/532 (85.0%) | 446/532 (83.8%) | 1.4% (−3.0% to 5.8%) |
| ex-US | 298/334 (89.2%) | 293/335 (87.5%) | 1.7% (−3.2% to 6.7%) |
| Study Drug Adherence (%)[b] | | | |
| < 95 | 145/193 (75.1%) | 153/194 (78.9%) | −3.0% (−11.5% to 5.4%) |
| ≥ 95 | 605/669 (90.4%) | 586/667 (87.9%) | 2.6% (−0.8% to 6.0%) |

Week 96 window is between Day 630 and 713 (inclusive).

a Difference in response rates and its 95% CI were calculated based on the MH proportions adjusted by baseline HIV-1 RNA and region (if not the subgroup factor), and study (for pooled analysis) stratum.
Baseline HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

b Study drug adherence subgroups are based on the adherence up to the Week 96 visit for active study drug.

Source: m5.3.5.3, E/C/F/TAF ISE, Table 3

# 5. OVERVIEW OF SAFETY

This section provides an overview of the pooled analysis of safety that was conducted for Studies GS-US-292-0104 and GS-US-292-0111 (Table 1; detailed descriptions of safety data are provided in m2.7.4, Section 2).

## 5.1. Extent of Exposure

Median (first quartile, third quartile [Q1, Q3]) duration of exposure to study drugs for ART-naive adults (Studies GS-US-292-0104 and GS-US-292-0111) was similar between the 2 treatment groups, as follows: GEN 96.3 weeks (94.7, 108.1), STB 96.3 weeks (92.0, 108.1).

## 5.2. Overall Safety

Safety data continue to demonstrate that GEN is well tolerated. There was a preferential profile for GEN versus STB for multiple measures of renal and bone safety. The safety profile of GEN was similar to that reported in the original submission, and no new safety signal for GEN was detected in the studies through 96 weeks of treatment (m2.7.4, Section 2).

### Adverse Events

Pooled data from Studies GS-US-292-0104 and GS-US-292-0111 showed that the adverse event (AE) profile was unchanged from that in the original submission (Table 4). The most commonly reported AEs for GEN were diarrhea, headache, and upper respiratory tract infection.

Both GEN and STB were well tolerated with low rates of Grade 3 or 4 AEs, serious AEs (SAEs), SAEs considered related to study drugs, and AEs leading to drug discontinuations.

The majority of AEs considered related to study drug by the investigator were Grade 1 in severity; few subjects had Grade 3 or 4 AEs considered related to study drugs (GEN 1.5%, 13 subjects; STB 1.0%, 9 subjects).

Five subjects died (GEN 2 subjects [embolic stroke and alcohol poisoning]; STB 3 subjects [cardiac arrest, recreational drug and alcohol overdose, and acute myocardial infarction]). None of the SAEs that resulted in death were considered related to study drug by the investigator.

No cases of proximal renal tubulopathy (including Fanconi syndrome) or renal AEs leading to discontinuation of study drugs were reported in the GEN group. In contrast, 6 subjects in the STB group had proximal renal tubulopathy and/or other renal AEs that led to discontinuation; all events were considered related to study drugs by the investigator. Renal safety is further discussed in Section 5.5.

### Clinical Laboratory Evaluations

In Studies GS-US-292-0104 and GS-US-292-0111, there were no clinically relevant changes from baseline within groups, or differences between the treatment groups in median values for hematology or clinical chemistry parameters, and all median values were within normal ranges.

Most subjects had at least 1 laboratory abnormality, the majority of which were Grade 1 or 2. Similar percentages of subjects in each treatment group had Grade 3 or 4 laboratory abnormalities (GEN 27.6%, 238 subjects; STB 25.1%, 217 subjects). The most common Grade 3 or 4 laboratory abnormality was creatine kinase (GEN 9.4%, 81 subjects; STB 7.3%, 63 subjects). Creatine kinase abnormalities occurred at a variety of time points and were not consistently present for individual subjects. One subject in each treatment group in Study GS-US-292-0111 had an SAE of rhabdomyolysis; neither event was considered related to study drugs by the investigator.

**Table 4. GS-US-292-0104 and GS-US-292-0111: Overall Summary of Adverse Events (Week 96 Analysis, Safety Analysis Set)**

| | GS-US-292-0104 / GS-US-292-0111 | |
|---|---|---|
| **Subjects Experiencing Any** | **GEN (N = 866)** | **STB (N = 867)** |
| Treatment-Emergent Adverse Event | 807 (93.2%) | 823 (94.9%) |
| Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 507 (58.5%) | 478 (55.1%) |
| Grade 3 or 4 Treatment-Emergent Adverse Event | 106 (12.2%) | 101 (11.6%) |
| Treatment-Emergent Study-Drug-Related Adverse Event | 367 (42.4%) | 398 (45.9%) |
| Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 99 (11.4%) | 95 (11.0%) |
| Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 13 (1.5%) | 9 (1.0%) |
| Treatment-Emergent Serious Adverse Event | 97 (11.2%) | 87 (10.0%) |
| Treatment-Emergent Study-Drug-Related Serious Adverse Event | 5 (0.6%) | 2 (0.2%) |
| Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 10 (1.2%) | 20 (2.3%) |
| Treatment-Emergent Death | 2 (0.2%) | 3 (0.3%) |

Source: m2.7.4, Table 5

## 5.3. Analysis of Adverse Drug Reactions

The adverse drug reactions (ADRs) included in Section 4.8 of the GEN Summary of Product Characteristics (SmPC) were based on an assessment of safety data from across all Phase 2 and 3 studies in which 2396 patients received GEN for a median duration of 84 weeks. In addition, ADRs not observed in the Phase 3 clinical studies for GEN but identified from clinical studies or post-marketing experience for the FTC (anemia, angioedema) or EVG (depression) components when used with other ARVs were also included in Section 4.8 of the SmPC. No new ADRs for GEN were identified from the Week 96 pooled data from Studies GS-US-292-0104 and GS-US-292-0111.

The most frequently reported ADRs in clinical studies of GEN were nausea (10%), diarrhea (7%), and headache (6%) (pooled data from Phase 3 clinical studies GS-US-292-0104 and GS-US-292-0111 in treatment-naive adult patients through 48 weeks; there was no increase in the frequency of these ADRs through Week 96).

The frequency category of ADRs for GEN in Section 4.8 of the GEN SmPC was based on data from Studies GS-US-292-0104 and GS-US-292-0111 as these represent the most robust data source with respect to the number of subjects and design of the studies (randomized, double-blind, comparative studies). There was no change in frequency category for any of the ADRs for GEN through Week 96 compared to Week 48 (Table 5).

**Table 5. GS-US-292-0104 and GS-US-292-0111: Adverse Events (All Grades) Related to Study Drug for ADRs to Genvoya (Week 96 Analysis)**

| Adverse Events by System Organ Class and Preferred Term | Frequency Category based on Week 48 data[a] | GEN (N = 866) | STB (N = 867) |
|---|---|---|---|
| Psychiatric disorders | | | |
| Abnormal dreams | Common | 14 (1.6%) | 29 (3.3%) |
| Nervous system disorders | | | |
| Headache | Common | 53 (6.1%) | 47 (5.4%) |
| Dizziness | Common | 26 (3.0%) | 20 (2.3%) |
| Gastrointestinal disorders | | | |
| Nausea | Very common | 90 (10.4%) | 114 (13.1%) |
| Diarrhea | Common | 63 (7.3%) | 77 (8.9%) |
| Vomiting | Common | 16 (1.8%) | 28 (3.2%) |
| Abdominal pain | Common | 12 (1.4%) | 11 (1.3%) |
| Flatulence | Common | 20 (2.3%) | 26 (3.0%) |
| Dyspepsia | Uncommon | 4 (0.5%) | 8 (0.9%) |
| Skin and subcutaneous tissue disorders | | | |
| Rash | Common | 15 (1.7%) | 10 (1.2%) |
| Pruritus | Uncommon | 4 (0.5%) | 2 (0.2%) |
| General disorders and administration site conditions | | | |
| Fatigue | Common | 44 (5.1%) | 37 (4.3%) |

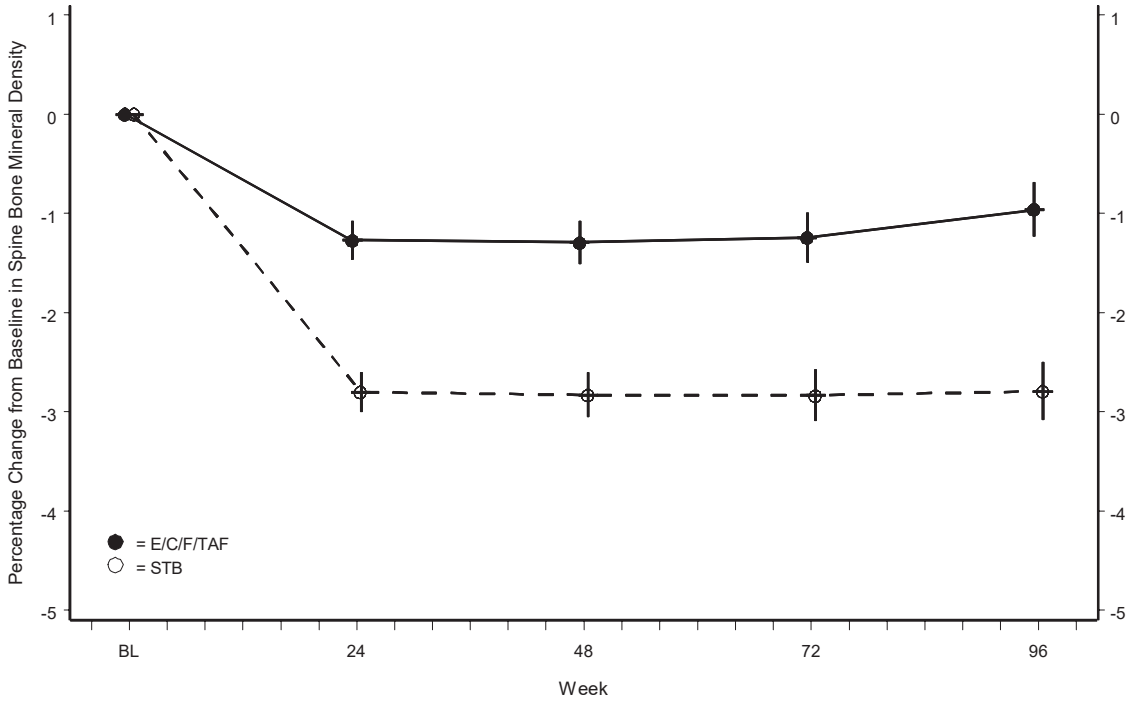
a Frequency categories defined as follows: very common (≥ 10%), common (≥ 1% to < 10%) and uncommon (≥ 0.1% to < 1%)

Source: m5.3.5.3, E/C/F/TAF Week 96 ISS, Table 11

## 5.4. Bone Safety

In the original submission, the totality of results from bone safety analyses in HIV-infected adults across the clinical development program demonstrated that treatment with GEN was associated with a preferential bone safety profile compared with STB or with other TDF-containing regimens, with statistically significant differences in multiple tests of bone metabolism. Data presented through 96 weeks of treatment in ART-naive adults from Studies GS-US-292-0104 and GS-US-292-0111 in the current submission are consistent with the findings in the original submission demonstrating a preferential bone safety profile in adults treated with GEN compared to STB (m2.7.4, Section 2.2.5.1). Significantly less bone mineral density (BMD) change from baseline at both the hip and spine were observed after treatment with GEN compared with STB through Week 96 (Table 6, Figure 1 [spine]). Compared with the STB group, fewer subjects in the GEN group had a decrease from baseline in hip and spine BMD, and more subjects in the GEN group had an increase from baseline in hip and spine BMD.

**Figure 1. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | | | |
|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 845 | 797 | 795 | 760 | 722 |
| STB (n=): | 850 | 816 | 790 | 751 | 714 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,Lab Data: 04AUG2015, DXA Data: 03AUG2015, s292-0111: CRF,DXA Data: 06AUG2015, Lab Data: 07AUG2015
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out 17AUG2015:14:33

Source: m5.3.5.3, E/C/F/TAF Week 96 ISS, Figure 3.2.2

**Table 6. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 96 Analysis)**

| | GEN | STB | GEN vs STB[a] | |
|---|---|---|---|---|
| | | | p-value | Difference in Least Square Mean (95% CI) |
| **Hip DXA Analysis** | **(N = 716)** | **(N = 711)** | | |
| Mean (SD) % Change in BMD | −0.672% (3.8887) | −3.275% (3.9668%) | p < 0.001 | 2.604% (2.196%, 3.012%) |
| Subjects with Categorical Change (%) | | | | |
| > 3% Decrease in BMD | 22.9% | 56.4% | — | — |
| No Decrease (≥ 0% Change) | 38.7% | 15.8% | | |
| > 3% Increase in BMD | 11.6% | 5.6% | | |
| **Lumbar Spine DXA Analysis** | **(N = 722)** | **(N = 714)** | | |
| Mean % Change in BMD | −0.960% (3.7227%) | −2.792% (3.9156%) | p < 0.001 | 1.832% (1.437%, 2.228%) |
| Subjects with Categorical Change (%) | | | | |
| > 3% Decrease in BMD | 26.2% | 48.0% | | |
| No Decrease (≥ 0% Change) | 37.4% | 21.0% | — | — |
| > 3% Increase in BMD | 11.2% | 5.9% | | |

a P-values, difference in least-squares means, and its 95% CI were from the analysis of variance model including treatment as fixed effect.
Source: m5.3.5.3, E/C/F/TAF Week 96 ISS, Tables 20.1.2, 20.2.2, 23.1, and 23.2

## 5.5. Renal Safety

In the original submission, the totality of results from both clinical and subclinical renal assessments in HIV-infected adults across the clinical development program demonstrated that treatment with GEN is associated with a preferential renal safety profile when compared with STB or other TDF-containing regimens, with statistically significant differences in multiple tests of renal function. Data presented through 96 weeks of treatment in ART-naive adults in the current submission are consistent with the findings in the original submission demonstrating a preferential renal safety profile in adults treated with GEN compared to STB (m2.7.4, Section 2.2.5.2). No cases of proximal renal tubulopathy (including Fanconi Syndrome) have been reported in subjects receiving GEN. In contrast, 2 cases of clinically evident proximal renal tubulopathy have been reported in the STB group after similar durations of exposure to study drug as in the GEN group.

At Week 96, treatment with GEN was associated with less change in serum creatinine and estimated glomerular filtration rate by Cockcroft-Gault method and less proteinuria (by dipstick) compared with treatment with STB (Table 7). For serum creatinine, mean (SD) changes from baseline in the GEN group were 0.06 (0.105) mg/dL at Week 2 and 0.04 (0.114) mg/dL at Week 96. At Week 96 the difference in least-squares mean between groups was −0.03 mg/dL,

p < 0.001. Decreases from baseline in proteinuria (as measured by urine protein-to-creatinine ratio [UPCR]) and albuminuria (as measured by urine albumin-to-creatinine ratio [UACR]) were seen with GEN that persisted through Week 96, while increases from baseline in UPCR and UACR were seen with STB.

**Table 7. GS-US-292-0104 and GS-US-292-0111: Key Renal Laboratory Parameters (Week 96 Analysis)**

| | GEN (N = 866) | STB (N = 867) | p-value |
|---|---|---|---|
| Serum Creatinine (mg/dL)[a] | 0.04 (0.114) | 0.07 (0.127) | < 0.001 |
| $eGFR_{CG}$ (mL/min)[b] | −2.0 (−12.4, 9.4) | −7.5 (−17.4, 2.9) | < 0.001 |
| Proteinuria by Urinalysis (Dipstick) (%)[c] | 35.6% | 40.9% | 0.034 |
| UPCR (mg/g) | | | |
| % Change from baseline at Week 96[d] | -9.1% (-39.6%, 36.0%) | 16.2% (-22.5%, 81.5%) | < 0.001 |
| UACR (mg/g) | | | |
| % Change from baseline at Week 96[d] | -5.2% (-35.7%, 30.1%) | 4.9% (-32.7%, 60.0%) | < 0.001 |
| Retinol-Binding Protein to Urine Creatinine ratio (µg/g)[d] | 13.8% (–18.8%, 66.1%) | 74.2% (10.4%, 192.2%) | < 0.001 |
| Beta-2-microglobulin to Urine Creatinine ratio (µg/g)[d] | −32.1% (–61.0%, 4.2%) | 33.5% (–27.8%, 230.7%) | < 0.001 |

$eGFR_{CG}$ = estimated glomerular filtration rate by Cockcroft–Gault method
a Mean (SD) change from baseline
b Median (Q1, Q3) change from baseline
c Treatment-emergent graded abnormalities
d Median (Q1, Q3) percent change from baseline
Source: m5.3.5.3, E/C/F/TAF Week 96 ISS, Tables 26.2, 27.1, 28, 29.2 to 29.5, 30.1, and 30.2

## 5.6. Suicidal Ideation and Suicide Attempt

Suicidal ideation and suicide attempt have been reported with the use of other INSTI-containing regimens. However, the current data do not support a causal association between suicidal ideation/suicide attempt and GEN.

Adverse events based on the suicide/self-injury standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) were infrequent in Studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks of treatment (GEN 1.2%, 10 subjects; STB 1.3%, 11 subjects; Table 8). None of these suicide/self-injury AEs was considered related to study drug by the investigator, and none was fatal.

**Table 8. GS-US-292-0104 and GS-US-292-0111: Summary of Suicide Events by Suicide/Self-Injury SMQ (Week 96 Analysis)**

| | GEN (N = 866) | STB (N = 867) |
|---|---|---|
| Suicide Events by Suicide/Self-Injury SMQ[a] | 10 (1.2%) | 11 (1.3%) |
| Depression Suicidal | 0 | 3 (0.3%) |
| Suicidal Ideation | 7 (0.8%) | 6 (0.7%) |
| Suicide Attempt | 3 (0.3%) | 3 (0.3%) |
| Intentional self-injury | 1 (0.1%) | 0 |

Adverse events were coded using MedDRA 18.0.
a Preferred terms from the suicide/self-injury SMQ reported for the same subject were only counted once.
Source: m5.3.5.3, E/C/F/TAF Week 96 ISS, Table 7

## 5.7. Fasting Glucose and Lipid Parameters

Data presented through 96 weeks of treatment in ART-naive adults in the current submission are consistent with the findings in the original submission and showed greater increases in the fasting lipid parameters total cholesterol, direct low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol to HDL ratio, triglycerides, and glucose in subjects treated with GEN compared with those treated with STB ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides; m2.7.4, Section 3.2). Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL ratio was 0.1 (-0.3, 0.7) in the GEN group and 0.0 (–0.4, 0.5) in the STB group ($p < 0.001$ for the difference between treatment groups). Similar percentages of subjects in each treatment group initiated lipid-modifying medications during the studies through 96 weeks (GEN 3.8%, 33 subjects; STB 4.4%, 38 subjects).

The TDF lipid effect is generally associated with the plasma level of TFV {27870}, {16173}, {29756}. Subjects who receive TAF have plasma TFV exposure that is > 90% lower than in subjects who receive TDF; the changes in fasting lipids reflect a reduction of this off-target TFV lipid effect. Therefore, the changes in fasting lipid levels are not an adverse effect of TAF but rather an effect of the markedly lower plasma TFV in subjects receiving GEN.

## 5.8. Safety in Special Groups and Situations

Safety information pertinent to the use of GEN in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the prescribing information.
Key findings for data presented through 96 weeks of treatment in ART-naive adults are consistent with the findings in the original submission demonstrating that the AE profile for subjects receiving GEN was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count.

# 6. BENEFITS AND RISKS CONCLUSIONS

Data are presented through 96 weeks of treatment in ART-naive adults in the current submission.

The updated evaluation of the benefits and risks of GEN for use in the treatment of HIV-1 infection supports the proposed updates to the prescribing information for GEN. The following considerations continue to demonstrate a favorable benefit:risk profile for GEN in the treatment of HIV-1 infected patients.

## 6.1. Benefits

In the original submission, GEN demonstrated potent and durable ARV activity and a favorable safety and tolerability profile in ART-naive adults. A preferential bone and renal safety profile was observed compared with STB. Data presented through 96 weeks of treatment in ART-naive adults in the current submission are consistent with the findings in the original submission and demonstrated GEN has many benefits as a chronic treatment for ART-naive subjects, including the following:

- GEN demonstrated potent and durable ARV activity. Using the FDA-defined snapshot methodology at Week 96, GEN was noninferior to STB. Results were supported by several sensitivity analyses, and immunologic benefits of treatment were demonstrated by increases in CD4 cell counts. The efficacy of GEN in subgroup analyses revealed no meaningful differences in virologic success, supporting GEN as an effective treatment for the treatment of HIV-1 infection regardless of demographics and disease baseline characteristics.

- The development of drug resistance and loss of regimen efficacy is a risk of ART. Generally, the risk of resistance development is dependent on the efficacy, tolerability, and adherence to an ART regimen. The frequency of resistance development in ART-naive subjects taking GEN was very low and comparable to that of the STB group through 96 weeks of treatment.

- Treatment with GEN continued to be well tolerated, as demonstrated by the low incidence of SAEs considered related to study drug, or study drug discontinuation due to AEs. No new ADRs were identified.

- Treatment with GEN is associated with a preferential bone safety profile, as compared with STB, with statistically significant differences in tests of bone metabolism. Specifically, GEN resulted in less change in BMD at both the hip and spine compared to STB.

- Treatment with GEN is associated with preferential renal safety profile, as compared with STB, with statistically significant differences in multiple tests of renal function. Specifically, GEN resulted in less change in serum creatinine, less proteinuria, and less renal tubular proteinuria compared with STB. In addition, no cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported for subjects who received GEN. In contrast, 2 cases of clinically evident proximal renal tubulopathy were reported for subjects who received STB.

## 6.2. Risks

Safety concerns for GEN are discussed in the current GEN RMP (version 1.0; eCTD 0007, m1.8.2) within which Studies GS-US-292-0104 and GS-US-292-0111 are pharmacovigilance activities for the following safety concerns:

- *Important potential risk of suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness:* AEs associated with suicidal ideation and suicide attempt continued to be infrequent in Studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks of treatment, with none considered related to study drug by the investigator (see Section 5.6).

- *Missing information on long-term safety:* Treatment with GEN was well tolerated in ART-naive adults with no new safety signals detected through 96 weeks of treatment (see Section 6.1). GEN continued to have a preferential renal safety profile with no reports of proximal renal tubulopathy, and resulted in less change in BMD at both the hip and spine compared to STB. There were no reports of posterior uveitis.

- *Missing information on development of drug resistance in long-term use:* The frequency of resistance development in ART-naive subjects taking GEN was very low and comparable to that of the STB group through 96 weeks of treatment.

Overall, there were no changes to these safety concerns or any of the other safety concerns included in the GEN RMP based on the Week 96 data from Studies GS-US-292-0104 and GS-US-292-0111.

No new warnings or precautions are warranted based on the data summarized in the current submission.

## 6.3. Conclusions

Genvoya has continued to demonstrate a positive benefit:risk ratio as shown by potent antiviral efficacy and a safety and tolerability profile that offer advantages over STB in ART-naive subjects. Virologic success with GEN was noninferior to STB and durable in ART-naive subjects through 96 weeks of treatment. Treatment with GEN is associated with a preferential renal and bone safety profile compared with STB.

# 7. REFERENCES

**16173** Tungsiripata M, Kitchb D, Glesbyc MJ, Guptad SK, Mellorse JW, Moranf L, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: A CTG5206. AIDS 2010;24 (1):1781-4.

**27870** Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. Antivir Ther 2012;17 (6):1011-20.

**29705** Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

**29756** Mulligan K, Glidden DV, Anderson PL, McMahan V, Guanira JV, Lama JR, et al. Decreases in cholesterol in HIV-seronegative men using emtricitabine/tenofovir pre-exposure prophylaxis: lipid results of iPrEx [Abstract O05]. 15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; 2013 October 15-17; Brussels, Belgium.

SECTION 2.5—CLINICAL OVERVIEW

# EMTRICITABINE/TENOFOVIR ALAFENAMIDE

## GS-US-311-1089 ADDENDUM

Gilead Sciences

29 March 2016

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 4
1. PRODUCT DEVELOPMENT RATIONALE ..... 5
1.1. Introduction ..... 5
1.2. Overview of Data Included in This Submission ..... 5
1.2.1. Regulatory Guidelines and Advice ..... 5
2. OVERVIEW OF BIOPHARMACEUTICS ..... 6
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 7
4. OVERVIEW OF EFFICACY ..... 8
4.1. Study Population for Evaluation of Efficacy ..... 8
4.2. Overview of Study Providing Clinical Efficacy Data ..... 8
4.3. Rationale for Primary Efficacy Endpoint ..... 8
4.4. Efficacy in Study GS-US-311-1089 ..... 8
4.5. Efficacy Discussion and Conclusions ..... 10
5. OVERVIEW OF SAFETY ..... 11
5.1. Introduction ..... 11
5.2. Summary of Safety Evaluation ..... 11
5.2.1. Extent of Exposure ..... 11
5.2.2. Subject Demographics ..... 11
5.2.3. Adverse Events ..... 11
5.2.4. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events ..... 13
5.2.5. Clinical Laboratory Abnormalities ..... 14
5.3. Bone Safety ..... 14
5.4. Renal Safety ..... 16
5.5. Safety in Special Groups and Situations ..... 18
5.6. Safety Discussion and Conclusions ..... 19
6. BENEFITS AND RISKS CONCLUSIONS ..... 21
6.1. Benefits ..... 21
6.2. Risks ..... 21
6.3. Conclusions ..... 22
7. REFERENCES ..... 23

# LIST OF IN-TEXT TABLES

Table 1. GS-US-311-1089: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Full Analysis Set) ..... 9
Table 2. GS-US-311-1089: Treatment-Emergent Adverse Events – Overall Summary (Safety Analysis Set) ..... 12
Table 3. GS-US-311-1089: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set) ..... 18

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| ARV | antiretroviral |
| BMD | bone mineral density |
| CI | confidence interval |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated according to the Cockcroft-Gault formula |
| $eGFR_{CKD\text{-}EPI,\ creatinine}$ | estimated glomerular filtration rate calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation |
| CSR | clinical study report |
| F | emtricitabine (Emtriva®) |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated) |
| FTC | emtricitabine (Emtriva®) |
| FTC/TDF | emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) |
| HDL | high-density lipoprotein |
| HIV-1 | human immunodeficiency virus, type 1 |
| LDL | low-density lipoprotein |
| Q1, Q3 | first quartile, third quartile |
| RBP | retinol binding protein |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| UACR | urine albumin to creatinine ratio |
| UPCR | urine protein to creatinine ratio |
| US FDA | United States Food and Drug Administration |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction

Emtricitabine/tenofovir alafenamide [F/TAF] is an oral, once-daily, fixed-dose combination that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients infected with HIV-1. F/TAF contains the nucleoside reverse transcriptase inhibitor emtricitabine (F, FTC) and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF).

Data in this clinical overview support the prescribing information for F/TAF.

## 1.2. Overview of Data Included in This Submission

This clinical overview provides additional efficacy and safety data for the following population:

- HIV-1 positive adult subjects virologically suppressed on regimens containing FTC/tenofovir disoproxil fumarate (TDF) who switch to a regimen containing F/TAF (Study GS-US-311-1089); results through 48 weeks of treatment are presented.

Study GS-US-311-1089 is an ongoing, Phase 3, randomized, double-blind study to evaluate the efficacy, safety, and tolerability of switching FTC/TDF to F/TAF in virologically suppressed, HIV-1 infected adult subjects.

Details of subject disposition and analysis sets for this study are provided in m2.7.3, Section 3.1.

### 1.2.1. Regulatory Guidelines and Advice

Study GS-US-311-1089 is being conducted in accordance with recognized international scientific and ethical standards, including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations Title 21, Part 312 and Directive 2001/20/EC in the European Union.

# 2. OVERVIEW OF BIOPHARMACEUTICS

No new information is submitted.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

Clinical virology data from Study GS-US-311-1089 is presented in m2.7.2, Section 4, and incorporated with efficacy data in this overview (Section 4).

# 4. OVERVIEW OF EFFICACY

This section provides an overview of efficacy results through Week 48 from the pivotal Phase 3 Study GS-US-311-1089. Detailed descriptions of efficacy data are provided in m2.7.2, Section 4 (virological resistance data) and m2.7.3, Section 3 (efficacy data).

## 4.1. Study Population for Evaluation of Efficacy

Study GS-US-311-1089 was conducted 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. Baseline demographics and disease characteristics of the study population are presented in m2.7.4, Section 1.3.

## 4.2. Overview of Study Providing Clinical Efficacy Data

Eligible subjects for Study GS-US-311-1089 were HIV-1 infected adults who had received an antiretroviral (ARV) regimen containing FTC/TDF in combination with a protocol-specified third agent for at least 6 consecutive months prior to the screening visit and maintained plasma HIV-1 RNA levels < 50 copies/mL. Subjects were randomized in a 1:1 ratio to switch to F/TAF or to continue FTC/TDF. In each group the third agent remained unchanged. 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.

## 4.3. Rationale for Primary Efficacy Endpoint

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 Food and Drug Administration (US FDA) snapshot algorithm.

## 4.4. Efficacy in Study GS-US-311-1089

High virologic success was maintained through Week 48 in both treatment groups in the Full Analysis Set, as assessed using the US FDA snapshot algorithm with HIV-1 RNA cut-off at 50 copies/mL. The percentages of subjects in each group with virologic success at Week 48 were as follows (Table 1):

- F/TAF+3rd Agent 94.3%
- FTC/TDF+3rd Agent 93.0%

Switching to F/TAF+3rd Agent was determined to be noninferior to maintaining FTC/TDF+3rd Agent at Week 48 because the lower band of the 2-sided 95.002% confidence interval (CI) of the difference in response rate was greater than the prespecified –10% margin (difference in percentages: 1.3%, 95.002% CI: –2.5% to 5.1%). This finding was confirmed using the Per Protocol Analysis Set.

**Table 1. GS-US-311-1089: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (Full Analysis Set)**

| | F/TAF+ 3rd Agent (N = 333) | FTC/TDF+ 3rd Agent (N = 330) | F/TAF vs. FTC/TDF | |
|---|---|---|---|---|
| | | | P-value[a] | Difference in Proportions (95.002% CI)[b] |
| Virologic Success at Week 48 | | | | |
| HIV-1 RNA < 50 copies/mL | 314 (94.3%) | 307 (93.0%) | 0.50 | 1.3% (−2.5% to 5.1%) |
| Virologic Failure at Week 48 | 1 (0.3%) | 5 (1.5%) | | |
| HIV-1 RNA ≥ 50 copies/mL | 0 | 5 (1.5%) | — | — |
| Discontinued Study Drug Due to Lack of Efficacy | 0 | 0 | — | — |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[c] | 1 (0.3%) | 0 | — | — |
| Added New Antiretroviral Agent | 0 | 0 | — | — |
| No Virologic Data in Week 48 Window | 18 (5.4%) | 18 (5.5%) | — | — |
| Discontinued Study Drug Due to AE/Death | 7 (2.1%) | 3 (0.9%) | — | — |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[c] | 10 (3.0%) | 15 (4.5%) | — | — |
| Missing Data During Window but on Study Drug | 1 (0.3%) | 0 | — | — |

AE = adverse event; Week 48 window was between Days 294 and 377 (inclusive).
a P-value for the superiority test comparing the percentages of virologic success was from the Cochran-Mantel-Haenszel test stratified by third agent (ritonavir-boosted protease inhibitors vs. others).
b Difference in percentages of virologic success between treatment groups and its 95.002% CI were calculated based on the Mantel-Haenszel proportions adjusted by the third agent stratum.
c Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.
Source: GS-US-311-1089 Week 48 CSR, Section 15.1, Table 10.1

Results for subgroup analyses and key secondary endpoints were similar between treatment groups, as summarized below:

- The rates of virologic success (HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm) at Week 48 for the subgroups age, sex, race, ethnicity, third agent stratum (boosted protease inhibitors versus others), region (US versus ex-US [Belgium, Canada, France, Italy, and United Kingdom]), and study drug adherence were similar in the F/TAF+3rd Agent and FTC/TDF+3rd Agent groups. The 95% CIs for differences in response rates included 0 for all subgroups, suggesting no differences between treatment groups.

- The percentages of subjects with plasma HIV-1 RNA < 20 copies/mL at Week 48 using the US FDA-defined snapshot algorithm were as follows: F/TAF+3rd Agent 91.6%, FTC/TDF+3rd Agent 90.9%.

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the Missing = Failure method was 95.8% for the F/TAF+3rd Agent group and 95.2% for the FTC/TDF+3rd Agent group.

- The emergence of resistance mutations in the F/TAF+3rd Agent and FTC/TDF+3rd Agent groups was rare (1 subject in the F/TAF+3rd Agent group).

- Mean (SD) increases from baseline at Week 48 in CD4 cell count (observed data) were as follows: F/TAF+3rd Agent group 20 (161.8) cells/μL; FTC/TDF+3rd Agent group 21 (152.7) cells/μL; (similar results were obtained using last-observation-carried-forward analysis).

## 4.5. Efficacy Discussion and Conclusions

It was demonstrated in Study GS-US-311-1089 that for HIV-1 infected adults virologically suppressed on an FTC/TDF-containing ARV regimen, switching to F/TAF plus a protocol-specified third agent was noninferior to remaining on their current FTC/TDF plus third agent regimen, through 48 weeks of treatment (virologic success at Week 48: F/TAF+3rd Agent 94.3%, FTC/TDF+3rd Agent 93.0%). There was no difference in efficacy across the different subpopulations evaluated.

Analysis of the secondary HIV-1 RNA endpoints supported the primary efficacy analyses. Additionally, the immunologic benefits of treatment with an FTC/TDF-containing regimen were maintained in subjects who switched to F/TAF plus a third agent, as demonstrated by the maintenance of, and slight increases from baseline in, CD4 cell counts in both groups at Week 48.

The incidence of treatment-emergent resistance mutations in subjects experiencing virologic failure was restricted to 1 subject in the F/TAF+3rd Agent group, in whom a known resistance mutation was demonstrated.

# 5. OVERVIEW OF SAFETY

## 5.1. Introduction

This section provides an overview of safety findings in Study GS-US-311-1089. A detailed description of safety data is provided in m2.7.4.

## 5.2. Summary of Safety Evaluation

### 5.2.1. Extent of Exposure

The duration of exposure to study drug was similar in the 2 treatment groups. Median (Q1, Q3) exposure was as follows: F/TAF+3rd Agent 48.3 (47.9, 59.9) weeks; FTC/TDF+3rd Agent 48.2 (47.9, 59.9) weeks.

### 5.2.2. Subject Demographics

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 white (75.0%) or black (20.5%), and most were not Hispanic/Latino (81.0%). Demographic and general baseline characteristics (height, weight, body mass index) were similar in the 2 treatment groups, except that a statistically significantly higher percentage of subjects in the FTC/TDF+3rd Agent group were Hispanic or Latino (23.6%) than in the F/TAF+3rd Agent group (14.4%).

Baseline disease characteristics were similar in the 2 groups. Because the study enrolled a virologically suppressed, HIV-1 infected population, 98.8% of subjects in the Safety Analysis Set had a baseline HIV-1 RNA level < 50 copies/mL. The median (Q1, Q3) baseline CD4 cell count was 646 (491, 835) cells/µL, and approximately 75% of subjects had a baseline CD4 cell count ≥ 500 cells/µL.

Most subjects (91.1%) had no proteinuria (Grade 0 by dipstick) on urinalysis, and mean (SD) values for estimated glomerular filtration rate (eGFR) calculated according to the Cockcroft-Gault formula ($eGFR_{CG}$) were similar in the 2 groups (F/TAF+3rd Agent 104.7 [31.07] mL/min; FTC/TDF+3rd Agent 105.3 [30.22] L/min).

### 5.2.3. Adverse Events

Similar percentages of subjects in each group had at least 1 adverse event (AE) reported (F/TAF+3rd Agent 84.4%, 281 of 333 subjects; FTC/TDF+3rd Agent 79.4%, 262 of 330 subjects) or any Grade 2, 3, or 4 AE (F/TAF+3rd Agent 39.0%, 130 subjects; FTC/TDF+3rd Agent 36.4%, 120 subjects) (Table 2).

A similar percentage of subjects in each group had any Grade 3 or Grade 4 AE (F/TAF+3rd Agent 5.1%, 17 subjects; FTC/TDF+3rd Agent 3.6%, 12 subjects) or serious AE (SAE; F/TAF+3rd Agent 5.4%, 18 subjects; FTC/TDF+3rd Agent 4.2%, 14 subjects).

A similar percentage of subjects in each group had any AE considered by the investigator as related to study drug (F/TAF+3rd Agent 9.3%, 31 subjects; FTC/TDF+3rd Agent 12.1%, 40 subjects). Most of the AEs considered related to study drug were Grade 1. Few subjects in either group had study drug-related Grade 3 or 4 AEs (F/TAF+3rd Agent 0.6%, 2 subjects; FTC/TDF+3rd Agent 0.3%, 1 subject) or study drug-related SAEs (F/TAF+3rd Agent 0 subject; FTC/TDF+3rd Agent 0.3%, 1 subject).

Adverse events that led to study drug discontinuation were uncommon in both groups (F/TAF+3rd Agent 2.1%, 7 subjects; FTC/TDF+3rd Agent 0.9%, 3 subjects). One subject, in the F/TAF+3rd Agent group, died during the study.

**Table 2. GS-US-311-1089: Treatment-Emergent Adverse Events – Overall Summary (Safety Analysis Set)**

| Adverse Event Category, n(%) | F/TAF+3rd Agent (N = 333) | FTC/TDF+3rd Agent (N = 330) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 281 (84.4%) | 262 (79.4%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 130 (39.0%) | 120 (36.4%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 17 (5.1%) | 12 (3.6%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 31 (9.3%) | 40 (12.1%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 5 (1.5%) | 7 (2.1%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study Drug–Related Adverse Event | 2 (0.6%) | 1 (0.3%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 18 (5.4%) | 14 (4.2%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 0 | 1 (0.3%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 7 (2.1%) | 3 (0.9%) |
| Subjects who had Treatment-Emergent Death[a] | 1 (0.3%) | 0 |

a Treatment-emergent death refers to a death occurring between the first dose date and the last dose date plus 30 days (inclusive).
Source: GS-US-311-1089 Week 48 CSR, Section 15.1, Table 20

The most common AEs by treatment group were as follows:

- F/TAF+3rd Agent: diarrhea and upper respiratory tract infection (each 9.0%, 30 of 333 subjects); headache (8.1%, 27 of 333 subjects); and nasopharyngitis (7.5%, 25 of 333 subjects)

- FTC/TDF+3rd Agent: upper respiratory tract infection (13.6%, 45 of 330 subjects); diarrhea (10.0%, 33 of 330 subjects); and sinusitis (6.7%, 22 of 330 subjects)

The rates and types of common AE were similar in the 2 treatment groups and consistent with those expected in the study population. No AE was reported with a ≥ 5% difference in incidence between treatment groups.

Most AEs reported in each treatment group were Grade 1 or 2 in severity. Similar percentages of subjects in each group had any Grade 3 or 4 AE reported (F/TAF+3rd Agent 5.1%, 17 subjects; FTC/TDF+3rd Agent 3.6%, 12 subjects).

Similar percentages of subjects in each group had any AE considered as related to study drug by the investigator (F/TAF+3rd Agent 9.3%, 31 subjects; FTC/TDF+3rd Agent 12.1%, 40 subjects). The most common AEs considered by the investigator as related to study drug, reported for ≥ 1% of subjects in either group, were as follows:

- F/TAF+3rd Agent: nausea and diarrhea (each 1.2%, 4 subjects)
- FTC/TDF+3rd Agent: nausea (3.0%, 10 subjects) and diarrhea (2.7%, 9 subjects)

Among the common study drug-related AEs, there were no notable differences between treatment groups.

### 5.2.4. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

One subject in the F/TAF+3rd Agent group died during the study as a result of the SAEs lymphoma and increased lipase, which were considered by the investigator as not related to study drug.

Serious AEs were reported for similar percentages of subjects in the 2 groups (F/TAF+3rd Agent 5.4%, 18 subjects; FTC/TDF+3rd Agent 4.2%, 14 subjects). The only SAE occurring in > 1 subject in either treatment group was intervertebral disc protrusion, reported in 2 subjects (0.6%) in the F/TAF+3rd Agent group (0 subjects in the FTC/TDF+3rd Agent group).

No study drug related SAEs were reported in the F/TAF+3rd Agent group. One study drug related SAE (nephrolithiasis) occurred in 1 subject, in the FTC/TDF+3rd Agent group (raltegravir).

Few subjects in either group discontinued study drug due to AEs (F/TAF+3rd Agent 2.1%, 7 subjects; FTC/TDF+3rd Agent 0.9%, 3 subjects). No AE led to study drug discontinuation for more than 1 subject in either group.

Two subjects in the F/TAF+3rd Agent group and 3 subjects in the FTC/TDF+3rd Agent group had study drug-related AEs leading to study drug discontinuation as follows:

- F/TAF+3rd Agent: diarrhea (Subject [redacted]), peripheral edema (Subject [redacted])
- FTC/TDF+3rd Agent: feeling abnormal and headache (Subject [redacted]), rectal tenesmus (Subject [redacted]), blood creatinine increased (Subject [redacted])

### 5.2.5. Clinical Laboratory Abnormalities

Most subjects in each group had at least 1 laboratory abnormality reported during the study (F/TAF+3rd Agent 90.0%, 298 subjects; FTC/TDF+3rd Agent 84.5%, 278 subjects). The majority of abnormalities were Grade 1 or 2 in severity.

The incidence of laboratory abnormalities of any grade was balanced in both treatment groups for most chemistry, hematology, and urinalysis parameters. Grade 3 or 4 laboratory abnormalities were reported for similar percentages of subjects in the 2 treatment groups (F/TAF+3rd Agent 21.5%, FTC/TDF+3rd Agent 18.8%). A higher percentage of subjects in the F/TAF+3rd Agent group had hyperuricemia than in the FTC/TDF+3rd Agent group (F/TAF+3rd Agent 11.2%, 37 of 331 subjects; FTC/TDF+3rd Agent 4.6%, 15 of 329 subjects); however, no Grade 3 or Grade 4 hyperuricemia was reported, and no AEs related to uric acid (eg, gout) were reported in either group.

## 5.3. Bone Safety

Improvements in bone mineral density (BMD) were seen at both the hip and the spine at Weeks 24 and 48 in virologically suppressed, HIV-1 infected subjects in Study GS-US-311-1089 who switched to F/TAF plus a protocol-specified third agent, compared with minimal changes at each site in subjects who remained on their current FTC/TDF plus third agent regimen (Figure 1 and Figure 2). The incidence of fracture events (based on the Medical Dictionary for Regulatory Activities Standardised Medical Query for osteoporosis/osteopenia fractures, excluding fractures of fingers and toes) was low, and comparable in each group (F/TAF+3rd Agent 0.3%, 1 subject; FTC/TDF+3rd Agent 0.6%, 2 subjects; $p = 0.62$). Each reported fracture AE was the result of trauma, and not considered related to study drug by the investigator.

- Mean (SD) percentage changes from baseline in BMD at Week 48 (observed data) were as follows for the F/TAF+3rd Agent group vs FTC/TDF+3rd Agent group:

  — Hip: 1.135% (2.7526) vs −0.152% (2.5317); $p < 0.001$

  — Spine: 1.527% (3.1816) vs −0.206% (3.2233); $p < 0.001$

- A greater number of subjects in the F/TAF+3rd Agent group than in the FTC/TDF+3rd Agent group had a ≥ 3% increase from baseline in BMD at both hip and spine:

  — Hip: Week 24, 8.4% versus 5.6%; Week 48, 16.7% versus 8.6%

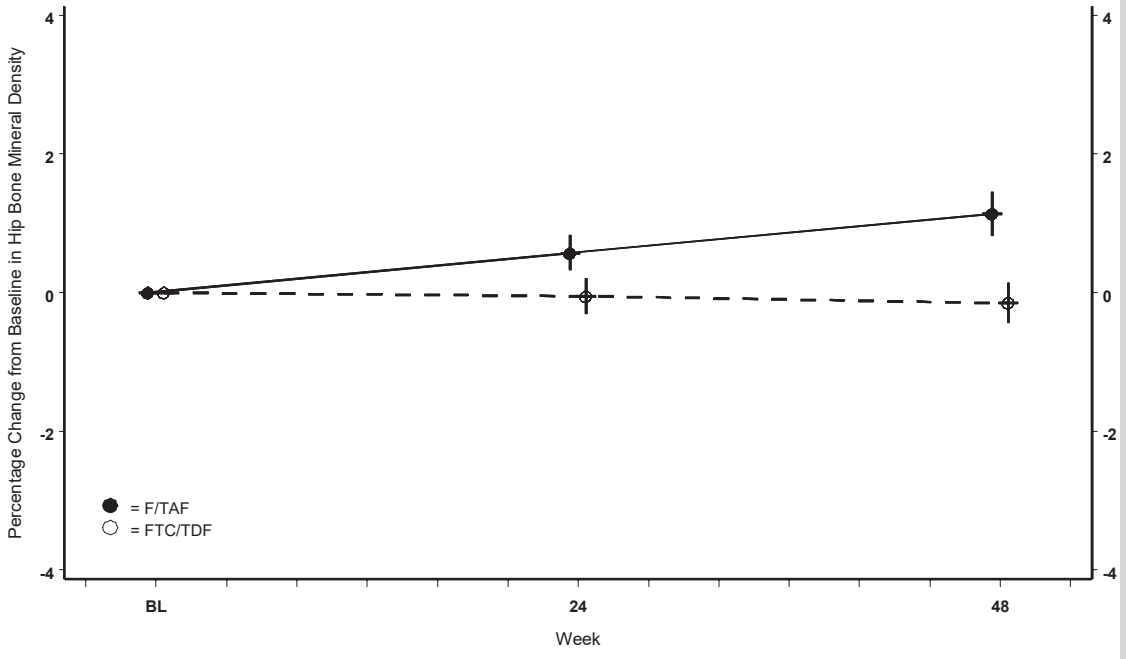
  — Spine: Week 24, 20.6% versus 9.4%; Week 48, 30.3% versus 13.7%

- Fewer subjects in the F/TAF+3rd Agent group than in the FTC/TDF+3rd Agent group had a ≥ 3% decrease from baseline in BMD at both hip and spine:

  — Hip: Week 24, 6.1% versus 6.9%; Week 48 4.7% versus 13.2%

  — Spine: Week 24, 7.7% versus 15.5%; Week 48, 5.7% versus 16.7%

**Figure 1.** **GS-US-311-1089: Mean (95% CI) of Percentage Change from Baseline in Hip Bone Mineral Density by Visit (Observed Data; Hip DXA Analysis Set)**



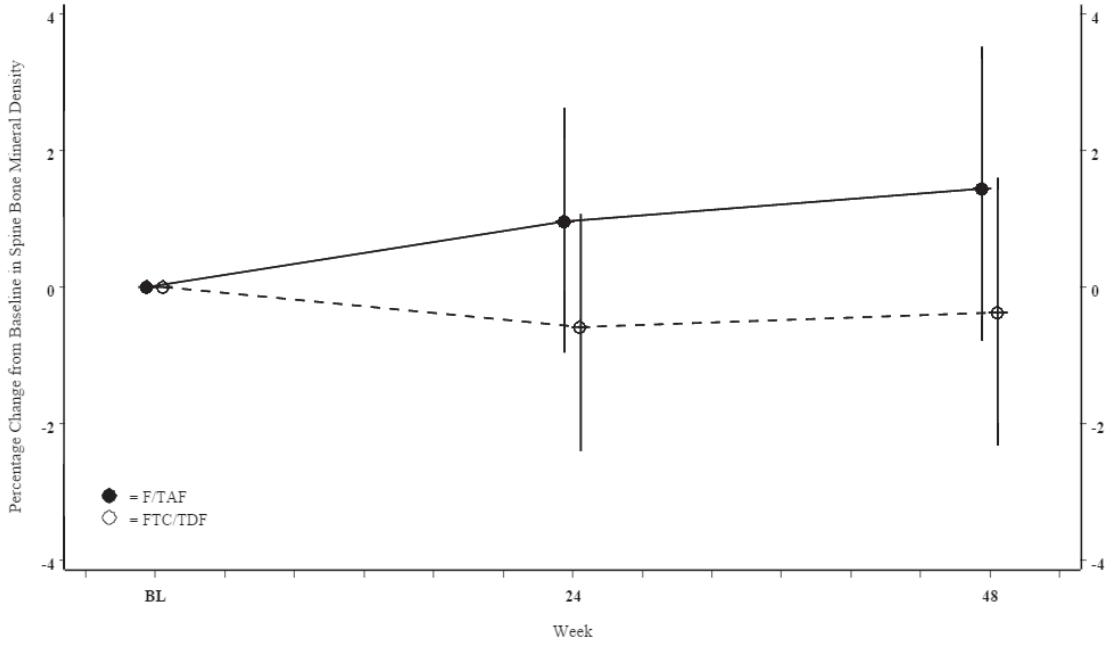

| | | | |
|---|---|---|---|
| F/TAF (n=): | 321 | 309 | 300 |
| FTC/TDF (n=): | 317 | 305 | 303 |

BL = Baseline.
Only subjects with nonmissing hip BMD for the baseline visit were included in hip DXA analysis set.

Data Extracted: CRF Data: 21AUG2015, Lab Data: 24AUG2015, DXA Data: 21AUG2015, PK Data: 27MAY2015
Source: .../s3111089/wk_48/version1/prog/t-dexa.sas v9.2 Output file: g-dexa-hip-bmd-mn.out 25AUG2015:17:08

Source: GS-US-311-1089 Week 48 CSR, Section 15.1, Figure 8.2.1

**Figure 2. GS-US-311-1089: Mean (95% CI) of Percentage Change from Baseline in Spine Bone Mineral Density by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | |
|---|---|---|---|
| F/TAF (n=): | 321 | 310 | 300 |
| FTC/TDF (n=): | 320 | 310 | 306 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: CRF Data: 21AUG2015, Lab Data: 24AUG2015, DXA Data: 21AUG2015, PK Data: 27MAY2015
Source: .../s3111089/wk_48/version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd.out 25AUG2015:17:08

Source: GS-US-311-1089 Week 48 CSR, Figure 8.1.2

## 5.4. Renal Safety

Among the virologically suppressed, HIV-1 infected subjects enrolled in Study GS-US-311-1089:

- No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported through 48 weeks of treatment with F/TAF+3rd Agent or FTC/TDF+3rd Agent.

- At Week 48 there were decreases from baseline in mean (SD) serum creatinine values and increases from baseline in median (Q1, Q3) $eGFR_{CG}$ and eGFR calculated according to the Chronic Kidney Disease Epidemiology Collaboration creatinine equation ($eGFR_{CKD\text{-}EPI,\ creatinine}$) values in the F/TAF+3rd Agent group, compared with minimal changes from baseline in each in the FTC/TDF+3rd Agent group:

  — Serum creatinine: –0.08 (0.238) vs –0.04 (0.126) mg/dL; p = 0.005

  — $eGFR_{CG}$: 8.4 (0.2, 15.6) vs 2.8 (–5.1, 10.9) mL/min; $p < 0.001$

  — $eGFR_{CKD\text{-}EPI,\ creatinine}$: 5.5 (–1.3, 11.4) vs 2.4 (–2.6, 8.8) mL/min/1.73 $m^2$; $p < 0.001$

- The majority of subjects in each group had no proteinuria (Grade 0) by dipstick at baseline and through Week 48. There were decreases from baseline in urine protein to creatinine (UPCR) and urine albumin to creatinine (UACR) ratios at Week 48 in the F/TAF+3rd Agent group compared with increases from baseline in each in the FTC/TDF+3rd Agent group. Median (Q1, Q3) percentage changes from baseline in UPCR and UACR values at Week 48 were as follows (F/TAF+3rd Agent group vs FTC/TDF+3rd Agent group):

  — UPCR: –14.6% (–39.1%, 17.3%) vs 7.7% (–21.6%, 43.4%); $p < 0.001$

  — UACR: –7.7% (–40.2%, 37.3%) vs 12.3% (–22.3%, 53.8%); $p < 0.001$

- There were decreases from baseline in urine retinol binding protein (RBP) to creatinine and beta-2-microglobulin to creatinine ratios in the F/TAF+3rd Agent group at Week 48 compared with increases from baseline in both parameters in the FTC/TDF+3rd Agent group. Median (Q1, Q3) percentage changes from baseline in RBP to creatinine and beta-2-microglobulin ratios at Week 48 were as follows (F/TAF+3rd Agent group vs FTC/TDF+3rd Agent group):

  — RBP to creatinine ratio: –16.3% (–48.7%, 17.9%) vs 18.2% (–19.0%, 87.5%); $p < 0.001$

  — Beta-2-microglobulin to creatinine ratio: –39.6% (–70.7%, 9.2%) vs 22.0% (–24.9%, 135.8%); $p < 0.001$

- No renal AEs leading to discontinuation of study drug were reported in the F/TAF+3rd Agent group compared with 1 event in the FTC/TDF+3rd Agent group (increased creatinine, considered related to study drug by the investigator).

**Fasting Glucose and Lipid Parameters**

In Study GS-US-311-1089, there were increases from baseline in fasting values of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in the F/TAF+3rd Agent group, while these parameters were relatively unchanged in the FTC/TDF+3rd Agent group (Table 3). Median changes from baseline at Week 48 were not considered clinically relevant for any fasting lipid parameter or for fasting glucose. Similar percentages of subjects in each treatment group were taking lipid-modifying agents at study entry (F/TAF+3rd Agent: 21.3%, 71 subjects; FTC/TDF+3rd Agent: 19.1%, 63 subjects) and initiated treatment with lipid-modifying agents during the study (F/TAF+3rd Agent: 3.9%, 13 subjects; FTC/TDF+3rd Agent: 3.6%, 12 subjects).

**Table 3. GS-US-311-1089: Summary of Fasting Metabolic Assessments Change from Baseline at Weeks 24 and 48 (Safety Analysis Set)**

| | F/TAF+3rd Agent (N = 333) | | FTC/TDF+3rd Agent (N = 330) | | |
|---|---|---|---|---|---|
| Metabolic Assessment[a] | N | Median (Q1, Q3) | N | Median (Q1, Q3) | P-Value[b] |
| Fasting Total Cholesterol (mg/dL) | | | | | |
| Baseline | 329 | 187 (157, 213) | 329 | 182 (157, 206) | 0.21 |
| Change at Week 24 | 309 | 17 (1, 37) | 312 | 1 (−14, 17) | < 0.001 |
| Change at Week 48 | 307 | 14 (−2, 33) | 310 | 1 (−17, 15) | < 0.001 |
| Fasting Direct LDL Cholesterol (mg/dL) | | | | | |
| Baseline | 329 | 112 (92, 134) | 329 | 110 (88, 133) | 0.25 |
| Change at Week 24 | 308 | 12 (−2, 30) | 314 | 2 (−12, 12) | < 0.001 |
| Change at Week 48 | 308 | 13 (−1, 28) | 309 | 4 (−9, 16) | < 0.001 |
| Fasting HDL Cholesterol (mg/dL) | | | | | |
| Baseline | 329 | 49 (40, 62) | 329 | 50 (42, 58) | 0.61 |
| Change at Week 24 | 309 | 4 (−3, 9) | 312 | −1 (−7, 4) | < 0.001 |
| Change at Week 48 | 307 | 2 (−4, 8) | 310 | −1 (−6, 5) | < 0.001 |
| Fasting Total Cholesterol to HDL Ratio | | | | | |
| Baseline | 329 | 3.6 (3.0, 4.5) | 329 | 3.6 (2.9, 4.4) | 0.33 |
| Change at Week 24 | 309 | 0.1 (−0.3, 0.6) | 312 | 0.1 (−0.3, 0.5) | 0.27 |
| Change at Week 48 | 307 | 0.1 (−0.3, 0.6) | 310 | 0.0 (−0.4, 0.4) | 0.073 |
| Fasting Triglycerides (mg/dL) | | | | | |
| Baseline | 329 | 118 (84, 174) | 329 | 112 (82, 168) | 0.31 |
| Change at Week 24 | 309 | 9 (−27, 48) | 312 | 0 (−28, 29) | 0.016 |
| Change at Week 48 | 307 | 10 (−22, 46) | 310 | −2 (−30, 31) | 0.002 |
| Fasting Glucose (mg/dL) | | | | | |
| Baseline | 329 | 93 (86, 100) | 329 | 93 (87, 100) | 0.31 |
| Change at Week 24 | 309 | 1 (−6, 8) | 314 | 0 (−7, 7) | 0.13 |
| Change at Week 48 | 310 | 1 (−5, 8) | 312 | 0 (−8, 5) | 0.003 |

a Only laboratory measurements under fasting status were summarized.
b P-values comparing the 2 treatment groups were from the 2-sided Wilcoxon rank sum test.
Source: GS-US-311-1089 Week 48 CSR, Section 15.1, Tables 35.1.1, 35.2.1, 35.3.1, 35.4, 35.5.1, and 35.6

## 5.5. Safety in Special Groups and Situations

No safety analyses of intrinsic (eg, sex, age, race) or extrinsic (eg, region) factor subgroups were performed for Study GS-US-311-1089.

## 5.6. Safety Discussion and Conclusions

Study GS-US-311-1089 demonstrated that in virologically suppressed, HIV-1 infected adult subjects who switched from their FTC/TDF-containing baseline regimen, F/TAF plus a protocol-specified third agent was generally well tolerated through a median of 48.3 weeks exposure, as evidenced by the low incidence of discontinuations due to AEs, and the absence of study drug-related SAEs. The most commonly reported AEs in the F/TAF+3rd Agent group were diarrhea, upper respiratory tract infection, headache, and nasopharyngitis. In subjects who stayed on their baseline FTC/TDF+3rd Agent regimen, study drug was generally well tolerated through a median of 48.2 weeks of exposure. The most commonly reported AEs in the FTC/TDF+3rd Agent group were upper respiratory tract infection, diarrhea, and sinusitis.

Statistically significant differences favoring F/TAF+3rd Agent over FTC/TDF+3rd Agent were observed in change from baseline in hip and spine BMD at Week 48. Mean (SD) percentage changes from baseline in hip and spine BMD at Week 48 (F/TAF+3rd Agent vs FTC/TDF+3rd Agent) were as follows:

- Hip: 1.135% (2.7526) vs –0.152% (2.5317); p 0.001
- Spine: 1.527% (3.1816) vs –0.206% (3.2233); $p < 0.001$

The differences between the 2 treatment groups in each of these safety endpoints may be associated with the markedly lower plasma concentrations of TFV in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent group.

Comparing the F/TAF+3rd Agent group with the FTC/TDF+3rd Agent group, a higher percentage of subjects had ≥ 3% increases from baseline in hip and spine BMD, and a lower percentage of subjects had ≥ 3% decreases from baseline in hip and spine BMD.

Statistically significant differences favoring F/TAF+3rd Agent over FTC/TDF+3rd Agent were observed in prespecified renal parameters. At Week 48 there were decreases from baseline in mean serum creatinine values and increases from baseline in median eGFR values in the F/TAF+3rd agent group, compared with minimal changes from baseline in each in the FTC/TDF+3rd Agent group. There were also decreases from baseline in UPCR, UACR, and urine RBP to creatinine and beta-2-microglobulin to creatinine ratios at Week 48 in the F/TAF+3rd Agent group compared with increases in each of these parameters in the FTC/TDF+3rd Agent group. No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported in either group during the study.

There were greater increases in the fasting lipid parameters total cholesterol, direct LDL cholesterol, HDL cholesterol, and triglycerides in the F/TAF+3rd Agent group compared with the FTC/TDF+3rd Agent group. These differences are consistent with findings in the Genvoya (elvitegravir/cobicistat/F/TAF) Studies GS-US-292-0104 and GS-US-292-0111, and are considered to be associated with the lipid-lowering effect of tenofovir (TFV), plasma levels of which were markedly lower in the F/TAF+3rd Agent group than in the FTC/TDF+3rd Agent group.

In conclusion, an acceptable safety profile was demonstrated over 48 weeks of treatment in virologically suppressed, HIV-1 infected adults who switched from an FTC/TDF-containing regimen to F/TAF plus a protocol-specified third agent, along with a tolerability profile that offers renal and bone advantages compared with TDF-based regimens.

# 6. BENEFITS AND RISKS CONCLUSIONS

The results of Study GS-US-311-1089 support a positive benefit:risk profile for F/TAF in virologically suppressed, HIV-1 infected adults switching from an FTC/TDF-containing regimen to F/TAF plus a protocol-specified third agent regimen, over a 48-week treatment period. Subjects received a TAF dose of 10 or 25 mg per day 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.

## 6.1. Benefits

F/TAF demonstrated a potent and durable ARV activity and a favorable safety and tolerability profile, showing a lack of evidence of TFV-related bone and renal effects, through Week 48 in virologically suppressed, HIV-1 infected adults who switched to F/TAF plus a third agent, including the following:

- **F/TAF is Highly Effective in Virologically Suppressed, HIV-1 Infected Adults**

At Week 48, the primary endpoint time point, switching to F/TAF plus a protocol-specified third agent was noninferior to continuing FTC/TDF with an unchanged third agent in maintaining a high virologic success rate in virologically suppressed, HIV-1 infected adults. The emergence of resistance development was rare in both groups.

- **F/TAF is Well Tolerated**

In virologically suppressed, HIV-1 infected adults who switched from their baseline FTC/TDF-containing regimen, F/TAF plus a protocol-specified third agent was generally well tolerated, as evidenced by the low incidence of discontinuations due to AEs, and the absence of study drug-related SAEs. The most commonly reported AEs were diarrhea, upper respiratory tract infection, headache, and nasopharyngitis. No new adverse drug reactions were identified.

- **F/TAF Shows No Evidence of TFV-Related Bone or Renal Toxicity**

There were improvements in bone and renal parameters at Week 48 in virologically suppressed, HIV-1 infected adults who switched to F/TAF plus a protocol-specified third agent from an FTC/TDF-containing regimen. There was no evidence of TFV-related bone or renal effects with F/TAF.

## 6.2. Risks

Treatment with F/TAF was well tolerated by virologically suppressed, HIV-1 infected adults who switched from an FTC/TDF-containing regimen. No new safety signal for F/TAF was detected.

No new warnings or precautions are warranted based on Week 48 data from Study GS-US-311-1089.

## 6.3. Conclusions

In virologically suppressed, HIV-1 infected adults, switching to F/TAF was noninferior to continuing an existing FTC/TDF-containing regimen in maintaining a high virologic success rate, and was associated with an improved bone and renal safety profile, with no evidence of TFV-related bone and renal effects.

# 7. REFERENCES

Not applicable.

# SECTION 2.5—CLINICAL OVERVIEW

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

Gilead Sciences

29 February 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 3
1. PRODUCT DEVELOPMENT RATIONALE ..... 4
1.1. Introduction and Background ..... 4
2. OVERVIEW OF BIOPHARMACEUTICS ..... 6
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 7
3.1. Pharmacology/Virology ..... 7
3.2. Clinical Pharmacokinetics ..... 7
3.2.1. Pediatrics ..... 7
4. OVERVIEW OF EFFICACY ..... 8
5. OVERVIEW OF SAFETY ..... 9
5.1. Extent of Exposure ..... 9
5.2. Overall Safety ..... 9
5.3. Bone Safety ..... 10
5.4. Renal Safety ..... 10
5.5. Fasting Lipid Parameters ..... 11
5.6. Safety Discussion and Conclusions ..... 11
6. BENEFITS AND RISKS CONCLUSIONS ..... 12
6.1. Benefits ..... 12
6.2. Risks ..... 12
6.3. Conclusions ..... 12
7. REFERENCES ..... 13

# LIST OF IN-TEXT TABLES

Table 1. Study Included in this Submission ..... 5
Table 2. GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set) ..... 10

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ART | antiretroviral treatment or therapy |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| COBI or C | cobicistat (Tybost®) |
| CSR | clinical study report |
| DXA | dual-energy x-ray absorptiometry |
| EVG or E | elvitegravir (Vitekta®) |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FTC | emtricitabine (Emtriva®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated; Genvoya® (previously referred to as E/C/F/TAF) |
| $eGFR_{CG}$ | glomerular filtration rate, estimated, by Cockcroft-Gault method |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| HDL | high-density lipoprotein |
| INSTI | integrase strand-transfer inhibitor |
| LDL | low-density lipoprotein |
| m | module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | number of subjects in a population |
| Q1, Q3 | first quartile, third quartile |
| RMP | Risk Management Plan |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| TAF | tenofovir alafenamide |
| TFV | tenofovir |
| UACR | urine albumin-to-creatinine ratio |
| UPCR | urine protein-to-creatinine ratio |
| US | United States |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

The success of potent and well-tolerated antiretroviral (ARV) therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-acquired immune deficiency syndrome-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}.

Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]) is an oral, once-daily, fixed-dose combination (FDC) that provides a potent and well-tolerated regimen for the long-term treatment of patients infected with HIV-1. Genvoya contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG), the pharmacoenhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States on 05 November 2015 and in the European Union on 19 November 2015.

This submission supports proposed changes to the prescribing information for GEN and also fulfills the milestone for a Category 4 additional pharmacovigilance activity (Week 48 report for Study GS-US-292-0106) for GEN in line with the European Union Risk Management Plan (RMP) agreed during the original marketing authorization application. In addition, Study GS-US-292-0106 is being conducted in accordance with the agreed Genvoya Pediatric Investigation Plan (EMEA-001460-PIP01-13-M01).

This clinical overview presents an updated evaluation of the benefits and risks of GEN for use in the treatment of HIV-1 infection in adolescents (12 to < 18 years of age). Information that supports the proposed GEN labeling includes updated clinical efficacy and safety data in ART-naive adolescents evaluated in Study GS-US-292-0106 through 48 weeks (N = 50 subjects vs 24 weeks for N = 23 subjects through Week 24 in the original submission) (Table 1). Details of subject disposition and analysis sets for this clinical study are provided in m2.7.3, Section 3.1 and m2.7.4, Section 1.2.

Results of an additional pharmacokinetic (PK) analysis (intracellular PK from a peripheral blood mononuclear cell [PBMC] substudy) are also presented for Study GS-US-292-0106.

Study GS-US-292-0106 was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the respective protocol.

Throughout the text of this document, Genvoya is referred to as “GEN.” The designation “E/C/F/TAF” is used in preprogrammed tables, figures, and listings.

**Table 1. Study Included in this Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented[b] | CSR and Narrative Locations |
|---|---|---|---|---|
| GS-US-292-0106 | Phase 2/3, open-label, multicenter, multicohort, 2-part, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of GEN | GEN (N = 50) | Week 48 efficacy and safety, PBMC PK | **CSR:** m5.3.5.2, GS-US-292-0106 Interim 2 and Amendment 1 **Narrative:** m2.7.4, Section 1.1.2 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b Study GS-US-292-0106 was amended to include virologically suppressed children (6 to < 12 years of age [Cohort 2]); only data for ART-naive adolescent subjects (12 to < 18 years of age [Cohort 1, N = 50]) are included in this submission.

# 2. OVERVIEW OF BIOPHARMACEUTICS

No new biopharmaceutics information (eg, formulation or dissolution data) is submitted.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Pharmacology/Virology

No new information for in vitro or nonclinical pharmacology data is submitted.

Updated clinical virology data from Study GS-US-292-0106 are presented in m2.7.2, Section 4 and incorporated with efficacy data in this overview (Section 4).

## 3.2. Clinical Pharmacokinetics

### 3.2.1. Pediatrics

PBMC PK in HIV-infected, ART-naive adolescent subjects 12 to < 18 years of age from Study GS-US-292-0106 are summarized in m2.7.2, Section 3. The main plasma PK data for adolescents from this study were described in the original submission.

Intracellular tenofovir diphosphate (TFV-DP) trough concentration was measured in PBMC samples collected predose at the Week 32 visit from 12 adolescent subjects. These concentrations are in the range of those observed in studies of HIV-infected, ART-naive adults (GS-US-292-0104 and GS-US-292-0111), where the mean (%CV) trough TFV-DP concentration in PBMC was 0.0566 (56) ng/million cells.

No other new PK information is submitted.

# 4. OVERVIEW OF EFFICACY

This section provides an overview of the efficacy results of GEN in ART-naive adolescent subjects (detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Baseline demographics and disease characteristics for the study populations are presented in m2.7.4, Section 1.3. Generally, the studied population is representative of HIV-1 infected, ART-naive adolescent patients in the general population.

The percentages of subjects with virologic success based on the FAS (plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48 using Untied States [US] FDA-defined snapshot algorithm) were 90.0% (45 of 50 subjects) and 92.0% (46 of 50 subjects), respectively.

Two subjects at Week 48 had HIV-1 RNA ≥ 50 copies/mL; all achieved virologic suppression (HIV-1 RNA < 50 copies/mL) prior to the specified week analysis window, remained on study drug, and had HIV-1 RNA < 50 copies/mL at later study visits.

Results for the secondary endpoints are shown below:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL through Week 48 using the Missing = Failure method was 92.0%.
- No virologic resistance was detected in any subject.
- The mean (SD) increase from baseline in CD4 cell count at Week 48 was 224 (170.3) cells/μL.

# 5. OVERVIEW OF SAFETY

## 5.1. Extent of Exposure

Additional exposure data is available from 50 ART-naive adolescents at the commercial dose of GEN, with a median (Q1, Q3) duration of exposure of 60.6 (48.1, 84.1) weeks (vs 12.1 [4.1, 32.1] weeks in 48 subjects described in the original application).

## 5.2. Overall Safety

No unique safety signal for TAF or GEN was detected in ART-naive adolescents (m2.7.4, Section 2).

### Adverse Events

Genvoya was well tolerated in ART-naive adolescents through 48 weeks of exposure to GEN. Most adolescents had at least 1 adverse event (AE) (Table 2); the most commonly reported AEs were respiratory tract infection, diarrhea, and upper respiratory tract infection. Common AEs were consistent with those expected in the subject population, the known safety profile of GEN, and with previous clinical study experience with GEN.

Treatment with GEN was associated with low rates of Grade 3 or 4 AEs, and serious adverse events (SAEs) considered related to GEN. No deaths or AEs leading to study drug discontinuation was reported. Adverse events considered related to GEN were reported for 18 subjects (36.0%).

No AEs of proximal renal tubulopathy (including Fanconi syndrome) were reported.

### Clinical Laboratory Evaluations

No clinically relevant changes from baseline in median values for clinical chemistry parameters were observed through Week 48. Median values were within normal ranges.

Most subjects had at least 1 laboratory abnormality reported during the study (98.0%, 49 of 50 subjects). The majority of abnormalities reported were Grade 1 or 2 in severity. Grade 3 or 4 laboratory abnormalities were reported for 14.0%, 7 subjects; most were isolated and transient occurrences. Grade 3 low neutrophil count was reported for 3 subjects, Grade 3 hematuria by quantitative assessment was reported for 3 subjects, and Grade 3 high aspartate aminotransferase (AST) and Grade 4 creatine kinase were each reported for 1 subject.

**Table 2. GS-US-292-0106: Overall Summary of Adverse Events (Safety Analysis Set)**

| Adverse Event Category, n (%) | GEN (N = 50) |
|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 42 (84.0%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event | 22 (44.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 6 (12.0%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Related to Study Drug | 18 (36.0%) |
| Subjects Experiencing Any Grade 2, 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 2 (4.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event Related to Study Drug | 1 (2.0%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 6 (12.0%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event Related to Study Drug | 1 (2.0%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 0 |
| Subjects who had Treatment-Emergent Death | 0 |

Source: m2.7.4, Table 5

## 5.3. Bone Safety

Detailed results from bone safety analyses conducted in Study GS-US-292-0106 are discussed in m2.7.4, Section 2.1.5.1. Consistent with results presented in the original submission, treatment with GEN resulted in minimal changes from baseline in bone mineral density (BMD) Z-scores at Week 48 in ART-naive adolescent subjects, as follows:

- Mean (SD) change in height-age adjusted spine: 0.00 (0.403)
- Mean (SD) change in height-age adjusted total body less head (TBLH): −0.15 (0.310)

The results suggest no impact on bone mineralization relative to the reference population.

## 5.4. Renal Safety

Detailed results from renal safety analyses conducted in Study GS-US-292-0106 are discussed in m2.7.4, Section 2.1.5.2. Consistent with results presented in the original submission, changes in serum creatinine and eGFR calculated using the Schwartz formula were seen as early as Week 1 and subsequently stabilized and were nonprogressive through Week 48 in ART-naive adolescent subjects. These changes are consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion, which results in an increase in serum creatinine and a decrease in eGFR without an effect on aGFR. No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported.

## 5.5. Fasting Lipid Parameters

Detailed results from fasting lipid parameter safety analyses conducted in Study GS-US-292-0106 are discussed in m2.7.4, Section 3.2. Consistent with results presented in the original submission, there were increases from baseline through Week 48 in the following fasting lipid parameters: total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides; however, there was a decrease from baseline in the total cholesterol to HDL cholesterol ratio.

## 5.6. Safety Discussion and Conclusions

The expanded safety database in ART-naive adolescents reflected in the current submission continues to demonstrate the favorable safety and tolerability profile of the GEN FDC in this population.

Based on data reflecting longer exposure and additional subjects, treatment with GEN continued to be well tolerated in ART-naive adolescents, as demonstrated by the low overall incidences of SAEs considered related to drug or study drug discontinuation due to AEs. The most commonly reported AEs for GEN were respiratory tract infection, diarrhea, and upper respiratory tract infection. Common AEs were consistent with those expected in the subject population, the known safety profile of GEN, and with previous clinical study experience with GEN.

Treatment with GEN resulted in minimal changes from baseline in height-age adjusted spine and TBLH BMD Z-scores at Week 48, demonstrating that GEN had no impact on bone mineralization.

Treatment with GEN also resulted in non-progressive changes in serum creatinine and eGFR that were consistent with the known inhibitory effect of COBI on renal tubular creatinine secretion. No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported.

Increases from baseline through Week 48 were observed in the following fasting lipid parameters: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. However, there was a decrease from baseline in the total cholesterol to HDL cholesterol ratio. Treatment with GEN is not considered to have a clinically relevant effect on fasting lipid parameters.

In conclusion, GEN continued to demonstrate an acceptable safety profile in HIV-1 infected, ART-naive adolescent subjects, along with a tolerability profile that shows minimal impact of GEN on renal and bone safety.

# 6. BENEFITS AND RISKS CONCLUSIONS

This submission provides additional PBMC PK, efficacy, and safety in ART-naive adolescents (12 to < 18 years of age) evaluated in Study GS-US-292-0106 through 48 weeks of treatment (N = 50) (vs N=23 through 24 weeks of treatment for the original application).

These data collectively support the proposed changes to the approved prescribing information. The following considerations continue to demonstrate a favorable benefit:risk profile for GEN for the treatment of HIV-1 infected adolescents.

## 6.1. Benefits

Similar to results from studies in ART-naive adults, treatment with GEN demonstrated potent efficacy, robust immunological response, and tolerability through 48 weeks of treatment. Changes from baseline in serum creatinine and eGFR were consistent with the inhibitory effect of COBI on renal tubular secretion of creatinine, and the lack of notable changes from baseline in height-age adjusted spine and TBLH BMD Z scores indicates that subjects mineralized bone at rates consistent with those of the reference population.

## 6.2. Risks

No new safety signal for TAF or GEN was detected with additional safety data from this ongoing Phase 2/3 study. All precautionary language included in the current approved prescribing information remains unchanged.

## 6.3. Conclusions

GEN has demonstrated potent efficacy in HIV-1 infected, ART-naive adolescents, with a renal safety profile consistent with that in adults, and no impact on bone mineralization relative to a reference population. No new precautionary language is proposed for the prescribing information.

# 7. REFERENCES

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

# SECTION 2.5—CLINICAL OVERVIEW

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# DESCOVY®
# (EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/ TENOFOVIR ALAFENAMIDE)

Gilead Sciences

24 June 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 3
1. PRODUCT DEVELOPMENT RATIONALE ..... 4
1.1. Introduction and Background ..... 4
1.2. Overview of Data Included in this Submission ..... 5
2. OVERVIEW OF BIOPHARMACEUTICS ..... 7
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 8
3.1. Pharmacology/Virology ..... 8
3.2. Clinical Pharmacokinetics ..... 8
4. OVERVIEW OF EFFICACY ..... 9
4.1. Efficacy in HIV-Infected Adults with Mild to Moderate Renal Impairment ..... 9
5. OVERVIEW OF SAFETY ..... 10
5.1. Extent of Exposure ..... 10
5.2. Overall Safety ..... 10
5.3. Analysis of Adverse Drug Reactions ..... 12
5.4. Bone Safety ..... 12
5.5. Renal Safety ..... 13
5.6. Safety in Special Groups and Situations ..... 14
5.7. Postmarketing Experience ..... 14
6. BENEFITS AND RISKS CONCLUSIONS ..... 15
6.1. Benefits ..... 15
6.2. Risks ..... 16
6.3. Conclusions ..... 16
7. REFERENCES ..... 17

# LIST OF IN-TEXT TABLES

Table 1. Study Included in this Submission ..... 6
Table 2. GS-US-292-0112: Overall Summary of Adverse Events (Week 96 Analysis, Cohort 1, Safety Analysis Set) ..... 11
Table 3. GS-US-292-0112: Key Renal Laboratory Parameters (Week 96 Analysis) ..... 14

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| B2MG | beta-2-microglobulin |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| /co | boosted with cobicistat |
| COBI; C | cobicistat |
| CSR | clinical study report |
| DVY | emtricitabine/tenofofovir alafenamide (coformulated; Descovy®) |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| eGFR | estimated glomerular filtration rate |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| EVG; E | elvitegravir |
| F/TAF | emtricitabine/tenofofovir alafenamide (coformulated; Descovy®) |
| F/R/TAF | emtricitabine/rilpivirine/tenofofovir alafenamide (coformulated; Odefsey®) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| FTC; F | emtricitabine |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| m | module |
| M = F | missing = failure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | number of subjects in a population (N) |
| ODE | emtricitabine/rilpivirine/tenofofovir alafenamide (coformulated; Odefsey®) |
| RMP | risk management plan |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| SMQ | Standardized MedDRA Query |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| TFV-DP | tenofovir diphosphate |
| TVD | emtricitabine/tenofovir disoproxil fumarate (coformulated; Truvada®) |
| UACR | urine albumin to creatinine ratio |
| UPCR | urine protein to creatinine ratio |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

This submission supports proposed changes to prescribing informations for Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), Descovy (DVY; emtricitabine/tenofovir alafenamide [F/TAF]), and Odefsey (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [F/R/TAF]. The provision of the Week 96 clinical study report (CSR) for Study GS-US-292-0112 is an additional pharmacovigilance activity (Category 4) in the GEN, DVY and ODE Risk Management Plans (RMPs) agreed during the original marketing authorisation applications.

Morbidity and mortality in the HIV-infected population is increasingly driven by non-acquired immune deficiency syndrome-associated comorbidities, and the development of novel therapeutics has become more focused on the optimization of tolerability, long-term safety, and adherence of potent antiretroviral (ARV) therapy (ART) regimens {Costagliola 2014}. In addition, new therapies must take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, regimen simplification, and durable efficacy.

Genvoya is an oral, once daily fixed-dose combination (FDC) that provides an effective and well-tolerated regimen for the long term treatment of patients infected with human immunodeficiency virus type 1 (HIV-1). GEN contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG; E), the pharmacoenhancer cobicistat (COBI; C), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC; F), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 05 November 2015 and in the European Union on 19 November 2015.

Descovy is an oral, once-daily, FDC that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients with HIV-1. DVY contains the nucleoside reverse transcriptase inhibitor FTC and the nucleotide reverse transcriptase inhibitor TAF. Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the US on 04 April 2016 and in the European Union on 21 April 2016.

Odefsey is once daily FDC that provides an effective and well-tolerated regimen for the long term treatment of patients infected with HIV-1. ODE contains the nucleoside reverse transcriptase inhibitor FTC, the non-nucleoside reverse transcriptase inhibitor rilpivirine (R, RPV) and the nucleotide reverse transcriptase inhibitor TAF. Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the European Union on 21 June 2016.

## 1.2. Overview of Data Included in this Submission

This submission provides efficacy and safety data for HIV-virologically suppressed adults with estimated glomerular filtration rate (eGFR) measured by the Cockcroft-Gault formula ($eGFR_{CG}$) 30 to 69 mL/min (Table 1) in Study GS-US-292-0112 through 96 weeks of treatment with GEN (primary endpoint at Week 24).

Details of subject disposition and analysis sets are provided in m2.7.3, Section 3.1.

This study was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the study protocol.

**Table 1. Study Included in this Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| HIV-Infected Adults with Mild to Moderate Renal Impairment ($eGFR_{CG}$ 30 to 69 mL/min) | | | | |
| GS-US-292-0112 | Phase 3, open-label, multicenter, multicohort study to evaluate the safety, efficacy, and tolerability of GEN | **GEN:**<br>Virologically Suppressed (N = 242)<br>ART Naive (N = 6)[b] | Week 96 efficacy and safety | **CSR:**<br>GS-US-292-0112 Week 96<br>**Narrative:**<br>m2.7.4, Section 1.1.3 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of TAF containing regimen).
b Because only 6 ART-naive subjects were enrolled in Study GS-US-292-0112, data for these subject are not summarized; however, these data are presented in the CSR.

# 2. OVERVIEW OF BIOPHARMACEUTICS

No new biopharmaceutics information (eg, formulation or dissolution data) is included within this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Pharmacology/Virology

Updated clinical virology data from Study GS-US-292-0112 are presented in m2.7.2, Section 4 and incorporated with efficacy data in this overview (Section 4).

## 3.2. Clinical Pharmacokinetics

No new clinical pharmacokinetic data are included in this submission.

# 4. OVERVIEW OF EFFICACY

This section provides an overview of the efficacy results of GEN in HIV-infected adults with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) (as described in Table 1; a detailed description of efficacy data are provided in m2.7.3, Section 3.2).

Baseline demographics and disease characteristics for the study populations are presented in m2.7.4, Section 1.3.

## 4.1. Efficacy in HIV-Infected Adults with Mild to Moderate Renal Impairment

In virologic suppressed subjects with $eGFR_{CG}$ of 30 to 69 mL/min who switched to treatment with GEN (Cohort 1, N = 242), efficacy results were as follows:

- Virologic success (HIV-1 RNA < 50 copies/mL using the Food and Drug Administration [FDA] snapshot algorithm) was maintained at Week 96 using the Full Analysis Set (FAS): 88.4%.

- There were no clinically relevant differences in virologic success at Week 96 (FDA snapshot algorithm, HIV-1 RNA < 50 copies/mL) between subgroups (age, sex, race, region, or study drug adherence rate; m2.7.3, Section 3.3).

- The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 96 using the missing = failure (M = F) method was 91.7%.

- The percentage of subjects with virologic success (plasma HIV-1 RNA < 20 copies/mL using the FDA snapshot algorithm) at Week 96 using the FAS was 86.4%.

- The emergence of resistance mutations was rare in virologic suppressed subjects who switched to treatment with GEN (0.4%, 1 of 242 subjects; analysis of Study GS-US-292-0112; m2.7.2, Section 4.2).

- Cluster determinant 4 (CD4) cell counts remained stable during treatment with GEN; mean (standard deviation, SD) change from baseline in CD4 cell counts at Week 96 using the FAS (observed data) was 12 (174.0) cells/µL.

# 5. OVERVIEW OF SAFETY

This section provides an overview of the safety results of GEN in HIV-infected adults with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) (as described in Table 1; a detailed description of safety data are provided in m2.7.4, Sections 2 to 4).

## 5.1. Extent of Exposure

Median (first quartile, third quartile [Q1, Q3]) duration of exposure to GEN in Cohort 1 switch subjects was as follows: overall 108.1 (107.3, 111.3) weeks; baseline $eGFR_{CG} < 50$ mL/min 107.7 (92.4, 108.8) weeks; baseline $eGFR_{CG} \geq 50$ mL/min 108.3 (107.9, 119.7) weeks.

## 5.2. Overall Safety

Clinical safety data continue to demonstrate that GEN has no evidence of tenofovir (TFV)-related bone or renal toxicity. The safety profile of GEN was consistent across all populations and maintained for the full duration of exposure. No unique safety signal for TAF or GEN was detected. Common adverse events (AEs) were consistent with those expected in the subject population, the known safety profiles of the study drugs, and with previous clinical study experience with GEN.

**Adverse Events**

Most subjects in Study GS-US-292-0112 reported at least 1 AE (Table 2). The most commonly reported AEs in Cohort 1 switch subjects were upper respiratory tract infection, diarrhea, and arthralgia.

GEN was well tolerated with low rates of Grade 3 or 4 AEs, serious adverse events (SAEs), and AEs leading to drug discontinuations. No subject had an SAE considered related to study drugs.

The majority of AEs considered related to study drug by the investigator were Grade 1 or 2; 3 subjects each had a single nonserious Grade 3 AE considered related to study drug.

One treatment-emergent death was reported (cardiopulmonary arrest). The event leading to death was considered unrelated to study drug by the investigator.

No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported. Five subjects had renal AEs that led to discontinuation of study drug; events for 2 of these subjects were considered to be related to study drug by the investigator. Renal safety is further discussed in Section 5.5.

## Clinical Laboratory Evaluations

In Study GS-US-292-0112, there were no clinically significant changes from baseline in median values for hematology or clinical chemistry parameters through Week 96. Median values were generally within normal ranges.

Most subjects had at least 1 laboratory abnormality reported. The majority of reported laboratory abnormalities were Grade 1 or 2 for Cohort 1 switch subjects. The most commonly observed Grade 3 or 4 laboratory abnormalities were low-density lipoprotein (fasting) (28 subjects), total cholesterol (fasting, hypercholesterolemia) (18 subjects), and serum glucose (nonfasting, hyperglycemia) (13 subjects).

**Table 2. GS-US-292-0112: Overall Summary of Adverse Events (Week 96 Analysis, Cohort 1, Safety Analysis Set)**

| | Cohort 1: Switch | | |
|---|---|---|---|
| **Subjects Experiencing Any** | **Baseline $eGFR_{CG}$ < 50 mL/min (N = 80)** | **Baseline $eGFR_{CG}$ ≥ 50 mL/min (N = 162)** | **Total (N = 242)** |
| Treatment-Emergent Adverse Event | 76 (95.0%) | 152 (93.8%) | 228 (94.2%) |
| Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 56 (70.0%) | 107 (66.0%) | 163 (67.4%) |
| Grade 3 or 4 Treatment-Emergent Adverse Event | 10 (12.5%) | 26 (16.0%) | 36 (14.9%) |
| Treatment-Emergent Study Drug-Related Adverse Event | 27 (33.8%) | 45 (27.8%) | 72 (29.8%) |
| Grade 2, 3, or 4 Treatment-Emergent Study Drug-Related Adverse Event | 13 (16.3%) | 18 (11.1%) | 31 (12.8%) |
| Grade 3 or 4 Treatment-Emergent Study Drug-Related Adverse Event | 1 (1.3%) | 2 (1.2%) | 3 (1.2%) |
| Treatment-Emergent Serious Adverse Event | 12 (15.0%) | 28 (17.3%) | 40 (16.5%) |
| Treatment-Emergent Study Drug-Related Serious Adverse Event | 0 | 0 | 0 |
| Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 8 (10.0%) | 4 (2.5%) | 12 (5.0%) |
| Treatment-Emergent Death | 0 | 1 (0.6%) | 1 (0.4%) |

Source: m2.7.4, Table 18

## 5.3. Analysis of Adverse Drug Reactions

No additional adverse drug reactions (ADRs) to GEN were identified through Week 96 in HIV-infected, virologically suppressed subjects with renal impairment (Study GS-US-292-0112). Five subjects in Study GS-US-292-0112 (3 with baseline $eGFR_{CG} < 50$ mL/min, 2 with baseline $eGFR_{CG} \geq 50$ mL/min) who switched to GEN had renal AEs that led to discontinuation of study drug; events for 2 of these subjects were considered to be related to study drug by the investigator. Otherwise, the safety profile of GEN in subjects in this study was similar to that of subjects with normal renal function.

## 5.4. Bone Safety

In the original submissions, the totality of results from bone safety analyses in HIV-infected adults across the clinical development program demonstrated that treatment with GEN, DVY, and ODE was associated with a preferential bone safety profile compared with STB or with other tenofovir disoproxil fumarate (TDF)-containing regimens, with statistically significant differences in multiple tests of bone metabolism. Data presented in the current submission are for 96 weeks of exposure to GEN (primary endpoint at Week 24). Current results are consistent with the original findings and provide additional evidence that GEN, DVY, and ODE do not have the TFV-related bone effects observed with TDF (m2.7.4, Section 2.1.5.1), as shown by the following:

- Improvements in bone mineral density (BMD) were seen through Week 96 in virologically suppressed suppressed with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) who switched to GEN from a TDF-based regimen; mean (SD) percentage BMD increase from baseline at Week 96 was 2.037% (4.2877%) at the hip and 2.261% (4.9061%) at the spine.
  The incidence of fracture events (based on the Medical Dictionary for Regulatory Activities [MedDRA] Standardized MedDRA Query [SMQ] for osteoporosis/osteopenia, excluding fingers and toes) was low (1.7%, 4 subjects; 3 were subjects with preswitch TDF use [1.9%] and 1 was a subject without preswitch TDF use [1.2%]). Based on a threshold of > 3% in change from baseline, more subjects had increases versus decreases in BMD at both hip and spine.

- Small increases in BMD were observed in virologically suppressed subjects with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) who switched to GEN from a non-TDF based regimen; mean (SD) percentage BMD increase from baseline at Week 96 was 0.939% (3.7338%) at the hip and 0.763% (4.4844%) at the spine. This demonstrated the absence of a drug-related effect of GEN on BMD.

## 5.5. Renal Safety

In the original submissions, the totality of results from both clinical and subclinical renal assessments in HIV-infected adults across the clinical development program demonstrated that treatment with GEN, DVY, and ODE is not associated with nephrotoxicity when compared with STB or other TDF-containing regimens. Data presented in the current submission are for 96 weeks of exposure to GEN (primary endpoint at Week 24). Current results are consistent with the original findings and provide additional evidence that GEN, DVY, and ODE do not have the TFV-related effect on renal function observed with TDF (m2.7.4, Section 2.1.5.2), as shown by the following:

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) have been reported in subjects receiving GEN.

- In HIV-infected, virologically suppressed adults with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) who switched to GEN, there were minimal changes from baseline in serum creatinine and eGFR through 96 weeks (Table 3). Decreases from baseline in proteinuria (urine protein to creatinine ratio; UPCR), albuminuria (urine albumin to creatinine ratio; UACR), and tubular proteinuria (urine retinol binding protein [RBP] to creatinine ratio and urine B2MG to creatinine ratio) were observed at Week 96. Renally impaired subjects who switched to GEN from a TDF-containing regimen had clinically significant improvements in UPCR, UACR, and tubular proteinuria. These decreases from baseline occurred as soon as 1 week after switch to GEN, strongly suggesting a reversal of TFV-associated toxicity. The levels decreased to around or below those of subjects on a non-TDF regimen at baseline.

- HIV-infected, virologically suppressed adults with renal impairment ($eGFR_{CG}$ 30 to 69 mL/min) who switched to GEN from a non-TDF-based regimen also had improvements or minimal changes in UPCR, UACR, and tubular proteinuria, demonstrating that GEN is not associated with TFV-related renal toxicity.

**Table 3. GS-US-292-0112: Key Renal Laboratory Parameters (Week 96 Analysis)**

| | Cohort 1: Switch (N = 242) | | |
|---|---|---|---|
| | With Pre-Switch TDF Use (N = 158) | Without Pre-Switch TDF Use (N = 84) | Total (N = 242) |
| Serum Creatinine (mg/dL) | | | |
| Change from baseline at Week 96 | | | |
| Mean (SD) | −0.05 (0.289) | 0.00 (0.256) | −0.03 (0.279) |
| eGFRCG (mL/min) Change from Baseline at Week 96a | 1.7 (−3.9, 9.0) | −0.9 (−5.3, 3.6) | 0.6 (−4.6, 7.2) |
| Improvement in Proteinuria by Urinalysis (Dipstick) (%)b | 92.5% | 61.1% | 84.5% |
| UPCR (mg/g) | | | |
| % Change from Baseline at Week 96a | −47.4% (−72.2, −12.2) | −7.2% (−40.8, 59.8) | −37.7% (−65.1, 7.5) |
| UACR (mg/g) | | | |
| % Change from Baseline at Week 96a | −63.2% (−82.1, 0.5) | −14.6% (-51.6, 36.4) | −45.5% (−77.3, 13.6) |
| RBP to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 96a | −84.8% (−95.9, −42.8) | 10.0% (−51.6, 110.2) | −64.1% (−91.4, 9.8) |
| Beta-2-microglobulin to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 96a | −91.4% (−97.6, −61.8) | −35.3% (−82.6, 47.1) | −83.6% (−96.4, −31.1) |

a Median (Q1, Q3)
b Graded abnormality at baseline and decrease of at least 1 grade from baseline
Source: m5.3.5.2, GS-US-292-0112 Week 96 CSR, Section 15.1, Tables 10.2.1, 10.2.4, 10.2.7 to 10.2.9, 10.2.10.1 to 10.2.10.3, and 10.2.11.1 to 10.2.11.3

## 5.6. Safety in Special Groups and Situations

Subgroup analyses of AE incidence were not conducted in Studies GS-US-292-0112.

## 5.7. Postmarketing Experience

No postmarketing data are included in this submission.

# 6. BENEFITS AND RISKS CONCLUSIONS

Data are presented through 96 weeks of treatment in HIV-infected, renally impaired adults in the current submission.

The updated evaluation of the benefits and risks of GEN in Study GS-US-292-0112 for use in the treatment of HIV-1 infection supports the proposed updates to the prescribing information for GEN, DVY, and ODE. The following considerations continue to demonstrate a favorable benefit:risk profile for GEN, DVY, and ODE in the treatment of HIV-1 infected patients.

## 6.1. Benefits

In the original submissions for GEN, DVY, and ODE, GEN maintained efficacy and demonstrated a favorable safety and tolerability profile in HIV-infected, renally impaired adults through 48 weeks. Data presented through 96 weeks of treatment in the current submission are consistent with the findings in the original submissions and demonstrate GEN has many benefits as a chronic treatment for HIV-infected, renally impaired adults, including the following:

- Treatment with GEN is associated with a preferential renal and bone safety profile in HIV-infected, virologically suppressed subjects with renal impairment who switched to GEN from a TDF-based regimen. Subjects with mild to moderate renal impairment who switched to GEN had no clinically significant change in eGFR, while proteinuria, albuminuria, proximal renal tubular function, and BMD significantly improved.

  — No change in actual GFR was observed through 24 weeks in Cohort 1 switch subjects, regardless of baseline $eGFR_{CG}$ or pre-switch TDF use.

  — Multiple assessments of renal function indicate significant improvements as soon as 1 week after switching to GEN and persisting through 96 weeks, including significant improvements in proteinuria, albuminuria, and tubular proteinuria in Cohort 1 switch subjects overall, with significant improvements in urine FEUA in subjects who switched from a TDF-containing regimen. Overall, no notable trends in changes from baseline through Week 96 were observed for TmP/GFR, $FEPO_4$, urine FEUA, or urine creatinine.

  — There were decreases in clinically significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) through Week 96 in the majority of subjects.

  — Switch to GEN generally resulted in improvements in BMD over 96 weeks. No fragility fractures were reported.

- The subset of subjects with $eGFR_{CG}$ < 50 mL/min, who currently require dose adjustment for both TDF and FTC, had stable eGFR and significant improvements in tubular function through 96 weeks after switching to once daily GEN without dose-limiting AEs.

  — Despite higher FTC exposures compared with historical data from HIV-infected subjects with normal renal function, AEs potentially associated with FTC use were similar in grade and frequency to subjects with $eGFR_{CG} \geq 50$ mL/min, indicating no untoward effects from higher FTC exposure.

- Treatment with GEN continued to be well tolerated. The incidence of discontinuations due to renal AEs was low, and no AEs of proximal renal tubulopathy (or Fanconi Syndrome) were reported.

- GEN demonstrated durable efficacy. In Cohort 1 subjects who switched treatment to GEN, 88.4% maintained virologic suppression (HIV-1 RNA< 50 copies/mL) and had stable CD4 cell counts through Week 96.

## 6.2. Risks

Overall, there are no changes to the GEN, DVY, or ODE safety profile based on the Week 96 data from Study GS-US-292-0112.No new ADRs were identified and no new warnings or precautions are warranted based on the data summarized in the current submission.

## 6.3. Conclusions

Overall, the clinical data from Study GS-US-292-0112 continue to support a favorable benefit-risk profile for GEN, DVY and ODE in patients with mild to moderate renal impairment and are consistent with data from previous studies. In this study, GEN maintained efficacy though 96 weeks, and a safety and tolerability profile that offers advantages over TDF-containing regimens in HIV-infected, virologically suppressed adults with mild to moderate renal impairment ($eGFR_{CG}$ 30 to 69 mL/min). Virologic success with GEN was maintained in HIV-infected, virologicaly suppressed adults through 96 weeks of treatment. Treatment with GEN is associated with a preferential renal and bone safety profile compared with TDF-containing regimens.

# 7. REFERENCES

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

SECTION 2.5—CLINICAL OVERVIEW

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

25 July 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 3
1. PRODUCT DEVELOPMENT RATIONALE ..... 4
1.1. Introduction and Background ..... 4
1.2. Overview of Data Included in this Submission ..... 4
2. OVERVIEW OF BIOPHARMACEUTICS ..... 6
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 7
3.1. Pharmacology/Virology ..... 7
3.2. Clinical Pharmacokinetics ..... 7
4. OVERVIEW OF EFFICACY ..... 8
5. OVERVIEW OF SAFETY ..... 9
5.1. Overall Safety ..... 9
5.2. Postmarketing Experience ..... 9
6. BENEFITS AND RISKS CONCLUSIONS ..... 10
7. REFERENCES ..... 11

# LIST OF IN-TEXT TABLES

Table 1. Study Included in this Submission ..... 5

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| COBI; C | cobicistat |
| CPT | Child-Pugh-Turcotte |
| CSR | clinical study report |
| DVY | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| EU | European Union |
| EVG; E | elvitegravir |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| FDC | fixed-dose combination |
| FTC; F | emtricitabine |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| HIV-1 | human immunodeficiency virus, human immunodeficiency virus type 1 |
| m | Module |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| PK | pharmacokinetic(s) |
| RPV; R | rilpivirine |
| TAF | tenofovir alafenamide |
| TFV | tenofovir |
| US | United States (of America) |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

This submission supports proposed changes to the prescribing information for Descovy® (DVY; emtricitabine/tenofovir alafenamide [F/TAF]), Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]), based on new clinical pharmacology data from Study GS-US-320-1615, a Phase 1, open-label, single-dose study that evaluated the pharmacokinetics (PK) of tenofovir alafenamide (TAF) and its metabolite, tenofovir (TFV), in subjects with normal hepatic function and subjects with severe hepatic impairment.

Descovy is an oral, once-daily, fixed-dose combination (FDC) that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients with HIV-1. Descovy contains the nucleoside reverse transcriptase inhibitor emtricitabine (FTC; F) and the nucleotide reverse transcriptase inhibitor TAF. Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the United States (US) on 04 April 2016 (F/TAF 200/25 mg FDC) and in the European Union (EU) on 21 April 2016 (F/TAF 200/10 mg and 200/25 mg FDCs).

Genvoya is an oral, once-daily, FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, GEN contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG; E) and the pharmacoenhancer cobicistat (COBI; C). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 05 November 2015 and in the EU on 19 November 2015 (E/C/F/TAF 150/150/200/10 mg FDC in both regions).

Odefsey is another oral, once-daily, FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, ODE contains the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV; R). Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the EU on 21 June 2016 (FTC/RPV/TAF 200/25/25 mg FDC in both regions).

## 1.2. Overview of Data Included in this Submission

One Phase 1 clinical pharmacology study is included (Study GS-US-320-1615) as summarized in Table 1. The PK of TAF and TFV was assessed in subjects who were hepatitis B surface antigen negative, with normal hepatic function or with severe hepatic impairment.

Study GS-US-320-1615 was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, applicable governmental regulatory requirements, and the study protocol.

**Table 1. Study Included in this Submission**

| Study | Study Design | Number of Subjects[a] | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| **Phase 1 Study** | | | | |
| GS-US-320-1615 | Phase 1 study to evaluate the PK and safety of TAF in subjects with or without severe hepatic impairment | TAF (N = 20) | TAF and TFV PK | **CSR:** GS-US-320-1615<br><br>**Narrative:** m2.7.2, Section 2.1 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

# 2. OVERVIEW OF BIOPHARMACEUTICS

Analytical methods for Study GS-US-320-1615 are provided in m2.7.1. No new biopharmaceutics information (eg, formulation or dissolution data) is included within this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Pharmacology/Virology

No new information is submitted.

## 3.2. Clinical Pharmacokinetics

This section provides an overview of the PK of TAF and TFV in subjects with or without severe hepatic impairment from Study GS-US-320-1615. A description of the study is provided in Table 1; detailed descriptions of the PK data are provided in m2.7.2, Section 3.

The PK of TAF and its metabolite TFV was evaluated in subjects with severe hepatic impairment (Child-Pugh-Turcotte [CPT] Class C) and control subjects with normal hepatic function each matched for age (± 10 years), sex, and body mass index (± 15%, and ≥ 18 and ≤ 38 $kg/m^2$) following a single dose of TAF in Study GS-US-320-1615. Results are summarized in m2.7.2, Section 3.

Free TAF exposure in subjects with severe hepatic impairment was comparable with that observed in matched control subjects with normal hepatic function. As the free TAF moiety is associated with therapeutic effect, no change in TAF efficacy is expected in patients with severe hepatic impairment.

# 4. OVERVIEW OF EFFICACY

No new information is submitted.

# 5. OVERVIEW OF SAFETY

This section provides an overview of safety from Study GS-US-320-1615 (Table 1); further descriptions of safety data are provided in m2.7.4, Section 2 and in the clinical study report (CSR) (GS-US-320-1615, Section 11).

## 5.1. Overall Safety

Data from Study GS-US-320-1615 showed that TAF (administered as TAF 25-mg tablets) was safe and generally well tolerated when administered in subjects with normal or severely impaired hepatic function.

## 5.2. Postmarketing Experience

No new information is submitted.

# 6. BENEFITS AND RISKS CONCLUSIONS

No change in TAF efficacy is anticipated in subjects with mild to moderate hepatic impairment based on previous data. Free TAF exposure in subjects with severe hepatic impairment was comparable in age- and sex- matched subjects with normal hepatic function. As the free TAF moiety is associated with therapeutic effect, no change in TAF efficacy is expected in patients with severe hepatic impairment. Overall, the data from Study GS-US-320-1615 do not affect the positive benefit-risk balance of the use of DVY, GEN, or ODE in HIV-1 infected patients.
No new warnings or precautions are warranted based on the data summarized in the current submission. However, the posology for DVY has been updated to allow dosing in patients with severe hepatic impairment. In addition, Section 5.1 of the summaries of product characteristics for DVY, GEN, and ODE have been updated with these data.

# 7. REFERENCES

No references are included.

SECTION 2.5—CLINICAL OVERVIEW

# DESCOVY®
# (EMTRICITABINE/TENOFOVIR ALAFENAMIDE)

# GENVOYA®
# (ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/ TENOFOVIR ALAFENAMIDE)

# ODEFSEY®
# (EMTICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

01 August 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 2
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 3
PHARMACOKINETIC ABBREVIATIONS ..... 5
1. PRODUCT DEVELOPMENT RATIONALE ..... 6
1.1. Introduction and Background ..... 6
1.2. Overview of Data Included in this Submission ..... 7
2. OVERVIEW OF BIOPHARMACEUTICS ..... 8
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 9
3.1. Pharmacology/Virology ..... 9
3.2. Clinical Pharmacokinetics and Potential for Drug Interactions ..... 9
3.3. Clinical Pharmacokinetics/Pharmacodynamics ..... 10
3.4. Clinical Pharmacology Conclusions ..... 10
4. OVERVIEW OF EFFICACY ..... 11
5. OVERVIEW OF SAFETY ..... 12
5.1. Overall Safety ..... 12
5.2. Postmarketing Experience ..... 12
6. BENEFITS AND RISKS CONCLUSIONS ..... 13
7. REFERENCES ..... 14

# LIST OF IN-TEXT TABLES

Table 1. Overview of Study Included in this Submission ..... 7
Table 2. GS-US-311-1790: Statistical Comparisons of Norelgestromin, Norgestrel, and Ethinyl Estradiol Pharmacokinetic Parameters for Test (DVY+NGM/EE) Versus Reference (NGM/EE Only) (Norelgestromin, Norgestrel, and Ethinyl Estradiol PK Analysis Sets, Respectively) ..... 9
Table 3. GS-US-311-1790: Summary of Progesterone, LH, and FSH Concentrations Following Administration of NGM/EE Alone and with DVY (Progesterone, LH, and FSH PD Analysis Sets, Respectively) ..... 10

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| AE | adverse event |
| AIDS | acquired immunodeficiency syndrome |
| ANOVA | analysis of variance |
| ART | antiretroviral therapy |
| ARV | antiretroviral |
| CI | confidence interval |
| COBI, C | cobicistat |
| CSR | clinical study report |
| DVY | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| ECG | electrocardiogram |
| EE | ethinyl estradiol |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault method |
| EU | European Union |
| EVG, E | elvitegravir |
| EVG/COBI/FTC/TDF | elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate (coformulated; Stribild®) |
| FDC | fixed-dose combination |
| FSH | follicle stimulating hormone |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated; Descovy®) |
| FTC, F | emtricitabine |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated; Genvoya®) |
| GLSM | geometric least-squares mean |
| HIV, HIV-1 | human immunodeficiency virus; human immunodeficiency virus, type 1 |
| LH | luteinizing hormone |
| m | module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | number of subjects in a population (N) |
| NG | norgestrel |
| NGM | norgestimate |
| NGMN | norelgestromin (17-desacetyl norgestimate) |
| ODE | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated; Odefsey®) |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| RMP | risk management plan |
| RPV | rilpivirine |
| SAE | serious adverse event |

| | |
|---|---|
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |
| TFV | tenofovir |
| US | United States |

## PHARMACOKINETIC ABBREVIATIONS

| | |
|---|---|
| $AUC_{tau}$ | area under the plasma concentration versus time curve over the dosing interval |
| $C_{max}$ | maximum observed plasma/serum concentration of drug |
| $C_{tau}$ | observed drug concentration at the end of the dosing interval |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

This submission supports proposed changes to the prescribing information for Descovy® (DVY, emtricitabine/tenofovir alafenamide [F/TAF]), Genvoya® (GEN, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), and Odefsey® (ODE, emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]), based on new clinical pharmacology data from Study GS-US-311-1790, a Phase 1, open-label study that evaluated the potential drug interaction between DVY and a representative oral contraceptive medication, in healthy female adult subjects. The provision of the final clinical study report (CSR) for Study GS-US-311-1790 is also an additional pharmacovigilance activity (Category 3) in the DVY Risk Management Plan (RMP) agreed during the original marketing authorization application.

The success of potent and well-tolerated antiretroviral (ARV) therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-AIDS-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence to potent ART regimens {Costagliola 2014}. In addition, effective therapies must take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, regimen simplification, and durable efficacy.

Descovy is an oral, once-daily, fixed-dose combination (FDC) that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients infected with HIV-1. Descovy contains the nucleoside reverse transcriptase inhibitor emtricitabine (FTC, F) and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Descovy was first approved for the treatment of HIV-1 infection in combination with other ARV agents in adults and adolescents (aged 12 years and older) in the United States (US) on 04 April 2016 and in the European Union (EU) on 21 April 2016.

Genvoya is an oral, once-daily FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, GEN contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG, E) and the pharmacoenhancer cobicistat (COBI, C). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 05 November 2015 and in the EU on 19 November 2015.

Odefsey is another oral, once-daily FDC that provides an effective and well-tolerated complete regimen for the long-term treatment of patients infected with HIV-1. In addition to FTC and TAF, ODE contains the nonnucleoside reverse transcriptase inhibitor rilpivirine (RPV, R). Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the EU on 21 June 2016.

## 1.2. Overview of Data Included in this Submission

Study GS-US-311-1790 was a Phase 1, randomized, open-label study that evaluated the potential drug interaction between DVY (administered as the F/TAF 200/25 mg FDC) and a representative oral contraceptive medication, norgestimate (NGM)/ethinyl estradiol (EE), in healthy female adult subjects (Table 1). The primary objective of the study was to determine the effect of FTC and TAF on the pharmacokinetics (PK) of NGM/EE (Cohort 1).

**Table 1. Overview of Study Included in this Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| GS-US-311-1790 | Phase 1, randomized, open-label study to evaluate the effect of DVY (F/TAF 200/25 mg FDC) on the PK of the hormonal contraceptive medication NGM/EE in healthy female adult subjects | DVY+NGM/EE (N = 16[b]) | DVY and NGM/EE PK, PD, and safety | **CSR:** GS-US-311-1790 **Narrative:** m2.7.2, Section 2.1 |

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).
b Sixteen subjects were enrolled in Cohort 1 (DVY+NGM/EE); however only 15 subjects received DVY.

This study was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the study protocol.

# 2. OVERVIEW OF BIOPHARMACEUTICS

Analytical methods for Study GS-US-311-1790 are provided in m2.7.1. No other new biopharmaceutics information (eg, formulation or dissolution data) is included in this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Pharmacology/Virology

No new information is submitted.

## 3.2. Clinical Pharmacokinetics and Potential for Drug Interactions

Drug interaction information and descriptions of PK data in Study GS-US-311-1790 are provided in m2.7.2, Section 3.1, and in the CSR (GS-US-311-1790, Section 10.1).

Comparisons of NGNM, NG, and EE PK parameters for DVY+NGM/EE versus NGM/EE administered alone are summarized in Table 2. Coadministration of DVY with NGM/EE did not change plasma exposure to NGNM, NG, or EE compared with NGM/EE administered alone. When NGM/EE and DVY were administered together, FTC, TAF, and TFV exposures were similar to historical data for DVY administered alone.

**Table 2. GS-US-311-1790: Statistical Comparisons of Norelgestromin, Norgestrel, and Ethinyl Estradiol Pharmacokinetic Parameters for Test (DVY+NGM/EE) Versus Reference (NGM/EE Only) (Norelgestromin, Norgestrel, and Ethinyl Estradiol PK Analysis Sets, Respectively)**

| | GLSM | | | |
|---|---|---|---|---|
| | DVY+NGM/EE (Test) (N = 14) | NGM/EE Only (Reference) (N = 15) | GLSM Ratio Test/Reference (%) | 90% CI[a] |
| **Norelgestromin (NGNM) PK Parameter** | | | | |
| $AUC_{tau}$ (h•pg/mL) | 16,875.43 | 15,103.01 | 111.74 | 106.72, 116.99 |
| $C_{max}$ (pg/mL) | 1717.26 | 1473.50 | 116.54 | 107.43, 126.42 |
| $C_{tau}$ (pg/mL) | 469.67 | 406.17 | 115.64 | 108.19, 123.59 |
| **Norgestrel (NG) PK Parameter** | | | | |
| $AUC_{tau}$ (h•pg/mL) | 54,829.36 | 50,276.33 | 109.06 | 101.09, 117.66 |
| $C_{max}$ (pg/mL) | 2850.03 | 2590.13 | 110.03 | 102.22, 118.44 |
| $C_{tau}$ (pg/mL) | 2130.07 | 1919.56 | 110.97 | 103.01, 119.54 |
| **Ethinyl Estradiol (EE) PK Parameter** | | | | |
| $AUC_{tau}$ (h•pg/mL) | 847.57 | 761.98 | 111.23 | 106.62, 116.04 |
| $C_{max}$ (pg/mL) | 90.55 | 74.38 | 121.75 | 114.61, 129.33 |
| $C_{tau}$ (pg/mL) | 17.72 | 17.42 | 101.74 | 92.46, 111.95 |

GLSM = geometric least-squares mean
Analysis of variance (ANOVA) model including treatment as a fixed effect was used for the comparison.
a The prespecified no-effects boundary was 70% to 143%.
Source: GS-US-311-1790 CSR, Section 15.1, Table 5.1

## 3.3. Clinical Pharmacokinetics/Pharmacodynamics

Pharmacodynamic (PD) results from Study GS-US-311-1790 are provided in m2.7.2, Section 3.2, and in the CSR (GS-US-311-1790, Section 10.2).

Results for LH, FSH, and progesterone following administration of NGM/EE alone or in combination with DVY are summarized in Table 3. Median concentrations for LH, FSH, and progesterone were generally comparable across all treatment cycles.

**Table 3. GS-US-311-1790: Summary of Progesterone, LH, and FSH Concentrations Following Administration of NGM/EE Alone and with DVY (Progesterone, LH, and FSH PD Analysis Sets, Respectively)**

| PD Parameter | DVY+NGM/EE (Cycle 2) (Test) (N = 15) | NGM/EE Only (Cycle 1) (Reference) (N = 15) |
|---|---|---|
| Progesterone (ng/mL) | 0.4 (0.4, 0.4) | 0.4 (0.4, 0.4) |
| LH (mIU/mL) | 3.9 (2.7, 7.0) | 3.1 (1.6, 8.1) |
| FSH (mIU/mL) | 3.4 (2.5, 4.4) | 1.7 (0.9, 3.8) |

Data presented as median (Q1, Q3).
Source: GS-US-311-1790 CSR, Section 15.1, Tables 19.1, 19.2, and 19.3

## 3.4. Clinical Pharmacology Conclusions

No clinically significant drug interactions were observed between DVY and NGM/EE. No dose adjustment of FTC or TAF is necessary when coadministered with NGM/EE. No loss of contraceptive efficacy is expected with coadministration of NGM/EE with FTC and TAF.

# 4. OVERVIEW OF EFFICACY

No efficacy information is included in this submission.

# 5. OVERVIEW OF SAFETY

Detailed descriptions of safety data from Study GS-US-311-1790 are provided in m2.7.4 and in the CSR (GS-US-311-1790, Section 11).

## 5.1. Overall Safety

Concurrent administration of FTC and TAF with NGM/EE was safe and generally well tolerated in the healthy female adult subjects in Study GS-US-311-1790.

## 5.2. Postmarketing Experience

No new information is submitted.

# 6. BENEFITS AND RISKS CONCLUSIONS

No clinically significant drug interactions between FTC and TAF, and NGM/EE were observed in Study GS-US-311-1790, or are expected. Overall, the data from Study GS-US-311-1790 do not affect the positive benefit-risk balance of the use of DVY, GEN, or ODE in HIV-1 infected patients. No new warnings or precautions for DVY, GEN, or ODE are warranted based on the data summarized in the current submission.

# 7. REFERENCES

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

# SECTION 2.5—CLINICAL OVERVIEW

# ODEFSEY®
# (EMTRICITABINE/RILPIVIRINE/TENOFOVIR ALAFENAMIDE)

Gilead Sciences

20 October 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

SECTION 2.5—CLINICAL OVERVIEW ..... 1
TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 4
PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS ..... 6
1. PRODUCT DEVELOPMENT RATIONALE ..... 7
1.1. Introduction and Background ..... 7
1.2. Overview of Data Included in this Submission ..... 7
2. OVERVIEW OF BIOPHARMACEUTICS ..... 9
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 10
3.1. Virology ..... 10
3.2. Clinical Pharmacokinetics ..... 10
3.2.1. Potential for Drug Interactions ..... 10
4. OVERVIEW OF EFFICACY ..... 11
4.1. Study GS-US-366-1216: CPA Switch ..... 11
4.2. Study GS-US-366-1160: ATR Switch ..... 13
4.3. Efficacy Discussion and Conclusions ..... 15
5. OVERVIEW OF SAFETY ..... 16
5.1. Extent of Exposure ..... 16
5.2. Overall Safety ..... 16
5.2.1. Study GS-US-366-1216: CPA Switch ..... 16
5.2.2. Study GS-US-366-1160: ATR Switch ..... 18
5.3. Analysis of Adverse Drug Reactions ..... 20
5.4. Bone Safety ..... 20
5.5. Renal Safety ..... 23
5.6. Safety in Special Groups and Situations ..... 25
5.7. Postmarketing Experience ..... 26
5.8. Discussion and Conclusions on Safety Experience ..... 26
6. BENEFITS AND RISKS CONCLUSIONS ..... 27
6.1. Benefits ..... 27
6.2. Risks ..... 28
6.3. Conclusions ..... 28
7. REFERENCES ..... 29

# LIST OF IN-TEXT TABLES

Table 1. Overview of Key Studies Included in Submission ..... 8
Table 2. GS-US-366-1216: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) ..... 12
Table 3. GS-US-366-1160: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS) ..... 14
Table 4. GS-US-366-1216: Overall Summary of Adverse Events (Safety Analysis Set) ..... 18
Table 5. GS-US-366-1160: Overall Summary of Adverse Events (Safety Analysis Set) ..... 20
Table 6. GS-US-366-1216: Key Measures of BMD at Week 48 (Observed Data; Hip or Spine DXA Substudy Analysis Set) ..... 21
Table 7. GS-US-366-1160: Key Measures of BMD at Week 48 (Observed Data; Hip or Spine DXA Analysis Set) ..... 22
Table 8. GS-US-366-1216: Key Renal Laboratory Parameters at Week 48 (Safety Analysis Set) ..... 24
Table 9. GS-US-366-1160: Key Renal Laboratory Parameters at Week 48 (Safety Analysis Set) ..... 25

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| β2M | beta-2-microglobulin |
| AE | adverse event |
| ANOVA | analysis of variance |
| ARV | antiretroviral |
| ART | antiretroviral therapy |
| ATR | Atripla® (efavirenz/rilpivirine/tenofovir disoproxil fumarate) |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| COBI; C | cobicistat |
| CPA | Complera®/Eviplera® (emtricitabine/rilpivirine/ tenofovir disoproxil fumarate) |
| CSR | clinical study report |
| CTx | C-telopeptide; C-terminal telopeptide of Type I collagen |
| DXA | dual-energy x-ray absorptiometry |
| E/C/F/TAF | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (coformulated, Genvoya®) |
| EFV | efavirenz |
| EFV/FTC/TDF | efavirenz/rilpivirine/tenofovir disoproxil fumarate (coformulated, Atripla®) |
| $eGFR_{CG}$ | estimated glomerular filtration rate calculated using the Cockcroft-Gault equation |
| EVG, E | elvitegravir |
| F/TAF | emtricitabine/tenofovir alafenamide (coformulated, Descovy®) |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| FDC | fixed-dose combination |
| FTC; F | emtricitabine |
| FTC/RPV/TAF | emtricitabine/rilpivirine/tenofovir alafenamide (coformulated, Odefsey®) |
| FTC/RPV/TDF | emtricitabine/rilpivirine/ tenofovir disoproxil fumarate (coformulated, Complera®/Eviplera®) |
| GEN | Genvoya® (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide) |
| GFR | glomerular filtration rate |
| GLSM | geometric least-squares mean |
| HDL | high-density lipoprotein |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| HLGT | High Level Group Term |
| LDL | low-density lipoprotein |
| LSM | least-squares mean |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N or n | number of subjects in a population (N) or subset (n) |
| ODE | Odefsey® (emtricitabine/rilpivirine/tenofovir alafenamide) |
| P1NP | procollagen type 1-N-terminal propeptide |
| PK | pharmacokinetic(s) |

| | |
|---|---|
| PP | Per-Protocol |
| PTH | parathyroid hormone |
| Q1, Q3 | first quartile, third quartile |
| RAP | resistance analysis population |
| RBP | urine retinol binding protein |
| RNA | ribonucleic acid |
| RPV | rilpivirine |
| RT | reverse transcriptase |
| SAE | serious adverse event |
| SD | standard deviation |
| SMQ | Standardized MedDRA Query |
| SOF | sofosbuvir |
| SOF/VEL | sofosbuvir/velpatasvir (coformulated; Epclusa®) |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate |
| TFV | tenofovir |
| UACR | urine albumin to creatinine ratio |
| UPCR | urine protein to creatinine ratio |
| US | United States, United States of America |
| VEL | velpatasvir |

## PHARMACOKINETIC ABBREVIATIONS AND DEFINITIONS

| | |
|---|---|
| $AUC_{tau}$ | area under the plasma/serum/PBMC concentration versus time curve over the dosing interval |
| $C_{max}$ | maximum observed plasma/serum concentration of drug |
| $C_{tau}$ | observed drug concentration at the end of the dosing interval |

# 1. PRODUCT DEVELOPMENT RATIONALE

## 1.1. Introduction and Background

This submission provides Phase 3 efficacy and safety data for the fixed-dose combination (FDC) Odefsey® (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [FTC/RPV/TAF]) in patients infected with human immunodeficiency virus type 1 (HIV-1) who were virologically suppressed on a stable antiretroviral (ARV) regimen. New clinical pharmacology data are also included.

ODE is an oral, once-daily FDC that provides an effective and complete option for the long-term treatment of patients infected with HIV-1. ODE contains the nucleoside reverse transcriptase inhibitor emtricitabine (FTC; F), the non-nucleoside reverse transcriptase inhibitor rilpivirine (RPV), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Odefsey was approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 01 March 2016 and in the European Union on 21 June 2016.

The efficacy and safety of ODE were established via a bioequivalence approach, with the pivotal study (GS-US-366-1159) demonstrating bioequivalence between the exposures of the FTC and TAF components of ODE to those of the FTC + TAF-containing regimen elvitegravir (EVG; E)/cobicistat (COBI;C)/F/TAF (E/C/F/TAF; Genvoya® [GEN]), and exposures of the RPV component of ODE to those of single-agent RPV (Edurant®). The clinical efficacy and safety of GEN and RPV-containing regimens thus support the efficacy and safety of ODE in a broad range of populations.

## 1.2. Overview of Data Included in this Submission

Data are provided through 48 weeks of treatment (primary endpoint) for subjects who switched to ODE from the tenofovir disoproxil fumarate (TDF)-based regimens FTC/RPV/TDF (Complera®/Eviplera® [CPA]) or efavirenz (EFV)/FTC/TDF (Atripla® [ATR]) from the following Phase 3 studies (Table 1):

- Switch to ODE from CPA (Study GS-US-366-1216)
- Switch to ODE from ATR (Study GS-US-366-1160)

Data were not pooled across studies due to the different prior treatment regimens evaluated.

One Phase 1 clinical pharmacology study is included (Table 1) that evaluated the potential drug interaction between FTC/RPV/TDF (which includes the FTC and RPV components of ODE) and the hepatitis C virus treatment, sofosbuvir/velpatasvir (SOF/VEL; Epclusa®) (Study GS-US-342-1167).

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the respective protocols.

**Table 1. Overview of Key Studies Included in Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| **Drug–Drug Interaction** | | | | |
| GS-US-342-1167 | Phase 1, open-label, multiple-dose, 4-cohort, PK study to evaluate the drug interaction potential between FTC/RPV/TDF and SOF/VEL | Cohort 2 (N = 24) | Drug interaction data from Cohort 2 (FTC/RPV/TDF, SOF/VEL) | **CSR:** GS-US-342-1167 **Narrative:** m2.7.2, Section 2.1 |
| **HIV-Infected, Virologically Suppressed Adults** | | | | |
| GS-US-366-1216 | Phase 3b, randomized, double-blind, multicenter study to evaluate the efficacy, safety, and tolerability of switching to ODE from CPA | Switch to ODE (N = 316) Stay on CPA (N = 314) | Week 48 efficacy and safety | **CSR:** GS-US-366-1216 **Narrative:** m2.7.3, Section 2.1 |
| GS-US-366-1160 | Phase 3b, randomized, double-blind, multicenter study to evaluate the efficacy, safety, and tolerability of switching to ODE from ATR | Switch to ODE (N = 438) Stay on ATR (N = 437) | Week 48 efficacy and safety | **CSR:** GS-US-366-1160 **Narrative:** m2.7.3, Section 2.2 |

CSR = clinical study report; PK = pharmacokinetic
a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug).

# 2. OVERVIEW OF BIOPHARMACEUTICS

Analytical methods are provided in m2.7.1. No other new biopharmaceutics information (eg, formulation or dissolution data) is included within this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

## 3.1. Virology

Clinical virology data from Studies GS-US-366-1160 and GS-US-366-1216 are presented in m2.7.2, Section 4 and incorporated with efficacy data in this overview (Section 4).

## 3.2. Clinical Pharmacokinetics

This section provides an overview of the results of drug interaction data for the FTC and RPV components of ODE with concomitant SOF/VEL. The study is described in Table 1; detailed descriptions of pharmacokinetic (PK) data are provided in m2.7.2, Section 3.

### 3.2.1. Potential for Drug Interactions

Drug interaction data for the FTC and RPV components of ODE (as FTC/RPV/TDF) with concomitant SOF/VEL are provided in m2.7.2, Section 3.1.

No alteration in the overall exposure of SOF, GS-566500, GS-331007, or VEL was observed following coadministration of SOF/VEL with FTC/RPV/TDF. The 90% confidence intervals (CIs) for the geometric least-squares mean (GLSM) ratios for all primary PK parameters ($AUC_{tau}$, $C_{max}$, and $C_{tau}$) were within the predetermined lack of alteration boundaries of 70% to 143%, confirming a lack of an effect on the PK of SOF, SOF metabolites, and VEL by FTC/RPV/TDF.

The PK of RPV and FTC were not altered following coadministration of FTC/RPV/TDF with SOF/VEL. The 90% CIs for the GLSM ratios for RPV and FTC ($AUC_{tau}$, $C_{max}$, and $C_{tau}$) remained within the predetermined lack of PK alteration boundaries of 70% to 143%.

No clinically significant drug interactions have been observed or are expected between the components of ODE and SOF/VEL.

# 4. OVERVIEW OF EFFICACY

This section provides an overview of the efficacy results of ODE in HIV-infected, virologically suppressed adults. Studies GS-US-366-1216 and GS-US-366-1160 are described in Table 1; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Baseline demographics and disease characteristics for the studies are presented in m2.7.4, Sections 1.3.1 and 1.3.2, respectively.

The primary efficacy endpoint in Studies GS-US-366-1216 and GS-US-366-1160 was the percentage of subjects with HIV-1 ribonucleic acid (RNA) < 50 copies/mL at Week 48, as determined by the US Food and Drug Administration (FDA)-defined snapshot algorithm.

## 4.1. Study GS-US-366-1216: CPA Switch

In Study GS-US-366-1216, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were high and comparable in both treatment groups using the Full Analysis Set (FAS) (Table 2):

- ODE 93.7%
- CPA 93.9%

Switching to ODE was determined to be noninferior to maintaining treatment with CPA at Week 48. The lower bound of the 2-sided 95.001% CI of the difference in response (ODE − CPA) was greater than the prespecified −8% margin difference in percentages: −0.3%, 95.001% CI: −4.2% to 3.7%.

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were also high and similar between treatment groups at Week 48 using the Week 48 Per Protocol (PP) Analysis Set, confirming noninferiority of switching to ODE versus maintaining CPA (ODE 99.3%, 287 of 289 subjects; CPA 100.0%, 280 of 280 subjects; difference in percentages: −0.7%, 95.001% CI: −2.5% to 0.7%).

**Table 2. GS-US-366-1216: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**

| | ODE (N = 316) | CPA (N = 313) | ODE vs CPA | |
|---|---|---|---|---|
| | | | P-Value | Difference in Percentages (95.001% CI) |
| HIV-1 RNA < 50 copies/mL | 296 (93.7%) | 294 (93.9%) | 1.00 | −0.3% (−4.2% to 3.7%) |
| HIV-1 RNA ≥ 50 copies/mL | 2 (0.6%) | 0 | 0.50 | 0.6% (−0.6% to 2.3%) |
| HIV-1 RNA ≥ 50 copies/mL in Week 48 Window | 2 (0.6%) | 0 | | |
| Discontinued Study Drug Due to Lack of Efficacy | 0 | 0 | | |
| Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL | 0 | 0 | | |
| Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL | 0 | 0 | | |
| No Virologic Data in Week 48 Window | 18 (5.7%) | 19 (6.1%) | | |
| Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL | 5 (1.6%) | 4 (1.3%) | | |
| Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL | 12 (3.8%) | 11 (3.5%) | | |
| Missing Data During Window but on Study Drug | 1 (0.3%) | 4 (1.3%) | | |

AE = adverse event
a Other reasons include subjects who discontinued study drug due to investigator's discretion, withdrawal of consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
Week 48 window is between Day 295 and 378 (inclusive).
P-Values for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 or ≥ 50 copies/mL were from the Fisher exact test.
Differences in percentages of subjects with HIV-1 RNA < 50 or ≥ 50 copies/mL between treatment groups and their 95.001% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Source: m2.7.3, Table 6

Results for subgroup analyses and key secondary efficacy endpoints in Study GS-US-366-1216 are summarized below:

- The percentages of subjects in Study GS-US-366-1216 with HIV-1 RNA ≥ 50 copies/mL (US FDA-defined snapshot algorithm) at Week 48 were low using the FAS (ODE 0.6%, 2 of 316 subjects; CPA 0 subjects; difference in percentages: 0.6%, 95.001% CI: −0.6% to 2.3%). The upper bound of the 2-sided 95.001% CI of the difference in between treatment groups (ODE – CPA) was less than the prespecified 4% margin, indicating that switching to ODE was noninferior to maintaining CPA.

- The percentage of subjects who maintained HIV-1 RNA < 50 copies/mL was high in both groups through 48 weeks, as assessed using the missing = failure (M = F) method in the FAS (ODE 95.3%, 301 of 316 subjects; CPA 94.9%, 297 of 313 subjects; difference 0.4%, 95% CI: −3.2% to 4.0%).

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm was comparable between treatment groups across subgroups for age, sex, race, region, and study drug adherence. The 95% CIs for the differences in response rates included 0 for all subgroups, suggesting no differences between treatments (m2.7.3, Section 3.3.1).

- None of the subjects in the ODE or CPA group had emergent resistance to study drugs (m2.7.2, Section 4.2.2). The resistance analysis population (RAP) comprised 2 subjects with data through Week 48, as follows: 1 of 316 subjects (0.3%) in the ODE group and 1 of 313 subjects (0.3%) in the CPA group. The subject in the CPA group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs. The subject in the ODE group had reemergence of archived resistance (M41L, E44D, D67N, V118I, L210W, and T215Y) and did not resuppress HIV-1 RNA to < 50 copies/mL.

- Cluster determinant 4 (CD4) cell counts were maintained in both groups; mean (standard deviation [SD]) changes from baseline at Week 48 (FAS, observed data) were as follows: ODE 9 (159.7) cells/µL; CPA −1 (152.7) cells/µL (difference in least-squares mean [LSM]: 11 cells/µL, 95% CI: −15 to 36 cells/µL).

## 4.2. Study GS-US-366-1160: ATR Switch

In Study GS-US-366-1160, the percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were high and comparable in both treatment groups using the FAS (Table 3):

- ODE 90.0%

- ATR 92.0%

Switching to ODE was determined to be noninferior to maintaining treatment with ATR at Week 48. The lower bound of the 2-sided 95.001% CI of the difference in response (ODE − ATR) was greater than the prespecified −8% margin difference in percentages: −2.0%, 95.001% CI: −5.9% to 1.8%.

The percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 were also high and similar between treatment groups at Week 48 using the Week 48 PP Analysis Set (ODE 99.2%, 377 of 380 subjects; ATR 99.3%, 397 of 400 subjects; difference in percentages: −0.0%, 95.001% CI: −1.7% to 1.5%).

**Table 3. GS-US-366-1160: Virologic Outcome at Week 48 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL (FAS)**

| | ODE (N = 438) | ATR (N = 437) | ODE vs ATR | |
|---|---|---|---|---|
| | | | P-Value | Difference in Percentages (95.001% CI) |
| HIV-1 RNA < 50 copies/mL | 394 (90.0%) | 402 (92.0%) | 0.35 | −2.0% (−5.9% to 1.8%) |
| HIV-1 RNA ≥ 50 copies/mL | 5 (1.1%) | 4 (0.9%) | 1.00 | 0.2% (−1.4% to 1.8%) |
| HIV-1 RNA ≥ 50 copies/mL in Week 48 Window | 2 (0.5%) | 3 (0.7%) | | |
| Discontinued Study Drug Due to Lack of Efficacy | 2 (0.5%) | 0 | | |
| Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 copies/mL | 0 | 0 | | |
| Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA ≥ 50 copies/mL | 1 (0.2%) | 1 (0.2%) | | |
| No Virologic Data in Week 48 Window | 39 (8.9%) | 31 (7.1%) | | |
| Discontinued Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 copies/mL | 12 (2.7%) | 6 (1.4%) | | |
| Discontinued Study Drug Due to Other Reasons[a] and Last Available HIV-1 RNA < 50 copies/mL | 23 (5.3%) | 20 (4.6%) | | |
| Missing Data During Window but on Study Drug | 4 (0.9%) | 5 (1.1%) | | |

AE = adverse event
a Other reasons include subjects who discontinued study drug due to investigator's discretion, withdrawal of consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.
Week 48 window is between Day 295 and 378 (inclusive).
P-Values for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 or ≥ 50 copies/mL were from the Fisher exact test.
Differences in percentages of subjects with HIV-1 RNA < 50 or ≥ 50 copies/mL between treatment groups and their 95.001% CIs were calculated based on an unconditional exact method using 2 inverted 1-sided tests.
Source: m2.7.3, Table 8

Results for subgroup analyses and key secondary efficacy endpoints in Study GS-US-366-1160 are summarized below:

- The percentages of subjects in Study GS-US-366-1160 with HIV-1 RNA ≥ 50 copies/mL (US FDA-defined snapshot algorithm) at Week 48 were low using the FAS (ODE 1.1%, 5 of 438 subjects; ATR 0.9%, 4 of 437 subjects; difference in percentages: 0.2%, 95.001% CI: −1.4% to 1.8%) (Table 3). The upper bound of the 2-sided 95.001% CI of the difference in between treatment groups (ODE – ATR) was less than the prespecified 4% margin, indicating that switching to ODE was noninferior to maintaining ATR.

- The percentage of subjects who maintained HIV-1 RNA < 50 copies/mL was high in both groups through 48 weeks, as assessed using the M = F method in the FAS (ODE 92.0%, 403 of 438 subjects; ATR 93.1%, 407 of 437 subjects; difference −1.1%, 95% CI: −4.7% to 2.4%).

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm was comparable between treatment groups across subgroups for age, sex, race, and region. The 95% CIs for the differences in response rates included 0 for all subgroups except study drug adherence, suggesting no differences between treatments. In the study drug adherence ≥ 95% subgroup, there was a lower percentage of subjects with HIV-1 RNA < 50 copies/mL in the ODE group compared with the ATR group, driven by the higher rate of discontinuations due to non-virologic reasons in the ODE group compared with the ATR group (m2.7.3, Section 3.3.2).

- No subject in the ODE group had emergent resistance to study drugs compared with 1 subject in the ATR group (m2.7.2, Section 4.2.1). The RAP comprised 8 subjects with data through Week 48 as follows: 6 of 438 subjects (1.4%) in the ODE group and 2 of 437 subjects (0.5%) in the ATR group. Four subjects in the ODE group and no subject in the ATR group resuppressed HIV-1 RNA to < 50 copies/mL while maintaining study drugs. No subject in the ODE group developed resistance to study drugs. Two subjects in the ODE group had re-emergence of archived resistance (1 subject with K219K/R and K103N in reverse transcriptase [RT] who resuppressed while on study drugs; 1 subject with V90V/I, K103K/N, E138E/A in RT who did not resuppress). One subject (0.2%) in the ATR group developed resistance to study drugs (M184V, V106I/L, and Y188L in RT).

- CD4 cell counts were maintained in both groups; mean (SD) changes from baseline at Week 48 (FAS, observed data) were as follows: ODE 23 (156.4) cells/μL; ATR 12 (153.3) cells/μL (difference in LSM: 11 cells/μL, 95% CI: −11 to 33 cells/μL).

### 4.3. Efficacy Discussion and Conclusions

The Phase 3 efficacy data in this submission represent the first available for ODE and demonstrate that ODE maintained virologic and immunologic control in HIV-infected, virologically suppressed adults switching to ODE from other ARV regimens.

In Studies GS-US-366-1216 and GS-US-366-1160 there were high and comparable percentages of subjects with HIV-1 RNA < 50 copies/mL at Week 48 when switching to ODE from CPA in Study GS-US-366-1216 (ODE 93.7%; CPA 93.9%) or from ATR in Study GS-US-366-1160 (ODE 90.0%; ATR 92.0%).

Analyses of the secondary HIV-1 RNA endpoints supported the primary efficacy endpoint data. In addition, the immunologic benefits of treatment with ODE were demonstrated by maintenance of CD4 cell counts in HIV-infected, virologically suppressed subjects. In general, there was no difference in efficacy across the different subpopulations evaluated, demonstrating that ODE is efficacious in populations without regard to demographic characteristics.

None of the subjects who received ODE in the Phase 3 studies had emergent resistance to study drug.

# 5. OVERVIEW OF SAFETY

This section provides an overview of safety of studies in HIV-infected, virologically suppressed adults (as described in Table 1; detailed descriptions of safety data are provided in m2.7.4, Sections 2 to 4).

Supportive safety data from the Phase 1 DDI Study GS-US-342-1167 are provided in m2.7.4. Data from this study showed that 2 components of ODE, FTC and RPV, in addition to TDF were safe and generally well tolerated when administered in combination with SOF/VEL, with no deaths, serious adverse events (SAEs), or discontinuations due to adverse events (AEs).

## 5.1. Extent of Exposure

In HIV-infected, virologically suppressed adults, the median (first quartile [Q1], third quartile [Q3]) duration of exposure was similar between subjects receiving ODE and subjects receiving CPA (Study GS-US-366-1216) or ATR (Study GS-US-366-1160), as follows (m2.7.4, Section 1.2):

- Study GS-US-366-1216: ODE 47.9 (43.7, 59.1) weeks, CPA 48.0 (43.7, 50.1) weeks
- Study GS-US-366-1160: ODE 47.9 (43.4, 59.1) weeks, ATR 48.0 (43.4, 59.9) weeks

## 5.2. Overall Safety

Clinical safety data demonstrate that bone and renal laboratory parameters improved upon switching to ODE from a TDF-based regimen. No unique safety signal for TAF or ODE was detected. Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs.

### 5.2.1. Study GS-US-366-1216: CPA Switch

**Adverse Events**

Most subjects in Study GS-US-366-1216 reported at least 1 AE (Table 4). The most commonly reported AEs in both treatment groups were upper respiratory tract infection, diarrhea, and nasopharyngitis.

Both ODE and CPA were well tolerated with low rates of SAEs, AEs leading to study drug discontinuation, and an absence of SAEs considered related to study drug.

Most AEs reported in either treatment group were Grade 1 or 2 in severity. Grade 3 or Grade 4 AEs were reported for 5.4% (17 subjects) in the ODE group and 3.2% (10 subjects) in the CPA group. No pattern was observed in the type of Grade 3 or 4 events.

The incidence of SAEs was low in the study (ODE 5.7%, 18 subjects; CPA 3.8%, 12 subjects). No SAE was considered related to study drug by the investigator.

One subject in each treatment group died (cardiac arrest, which was later amended to acute methamphetamine intoxication, in the ODE group and carbon monoxide poisoning in the CPA group). None of the events leading to death was considered related to study drug by the investigator.

No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported. One subject who switched to ODE from CPA had a renal SAE (acute kidney injury, reported as acute renal failure, in the context of pneumonia and sepsis) that was not considered related to study drug by the investigator. No discontinuations due to renal AEs occurred during the study. Renal safety is further discussed in Section 5.5.

**Clinical Laboratory Evaluations**

In Study GS-US-366-1216, there were no clinically relevant changes from baseline or differences between the treatment groups in median values for hematology or clinical chemistry parameters. Median values were within normal ranges throughout the studies.

The majority of subjects had at least 1 laboratory abnormality reported during the study. The incidence of laboratory abnormalities of any grade was similar between treatment groups for most chemistry, hematology, and urinalysis parameters. Overall, a higher percentage of subjects in the ODE group than the CPA group had Grade 3 or 4 abnormalities (ODE 12.7%, CPA 6.1%).

There were increases from baseline in fasting values of total cholesterol, direct low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides in the ODE group, and no clinically relevant changes from baseline in median fasting values for total cholesterol to HDL ratio or glucose in either treatment group. Data are consistent with those observed previously for TAF. The preferential effect of TFV on lipids following administration of TDF is not seen with ODE due to the lower levels of circulating TFV following administration of TAF. Metabolic laboratory parameter results are provided in m2.7.4, Section 3.3.

**Table 4. GS-US-366-1216: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 254 (80.4%) | 254 (80.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 124 (39.2%) | 110 (35.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 17 (5.4%) | 10 (3.2%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 20 (6.3%) | 37 (11.8%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 7 (2.2%) | 10 (3.2%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 1 (0.3%) | 0 |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 18 (5.7%) | 12 (3.8%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 0 | 0 |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 4 (1.3%) | 3 (1.0%) |
| Subjects who had Treatment-Emergent Death | 1 (0.3%) | 1 (0.3%) |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Treatment-emergent death refers to a death which occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: m2.7.4, Table 9

### 5.2.2. Study GS-US-366-1160: ATR Switch

#### Adverse Events

Most subjects in Study GS-US-366-1160 reported at least 1 AE (Table 5). The most commonly reported AEs were upper respiratory tract infection, nasopharyngitis, and cough in the ODE group and upper respiratory tract infection, diarrhea, and arthralgia in the ATR group.

Both ODE and ATR were well tolerated with low rates of AEs leading to study drug discontinuation, SAEs, and SAEs considered related to study drug.

Most AEs reported in either treatment group were Grade 1 or 2 in severity. Grade 3 or Grade 4 AEs were reported for 6.2% (27 subjects) in the ODE group and 5.7% (25 subjects) in the ATR group. No pattern was observed in the type of Grade 3 or 4 events.

Similar percentages of subjects in each group had an SAE (ODE 5.5%, 24 subjects; ATR 5.7%, 25 subjects). No SAE in the ODE group was considered related to study drug by the investigator.

One subject in the ODE group died during the study (methamphetamine/cocaine drug overdose). None of the events leading to death were considered related to study drug by the investigator. No deaths occurred in the ATR group.

No cases of proximal renal tubulopathy (including Fanconi syndrome) were reported.
One subject who switched to ODE from ATR discontinued study drug due to a nonserious renal AE (glomerular filtration rate [GFR] decreased) that was considered to be related to study drug by the investigator. No renal SAEs occurred during the study. Renal safety is further discussed in Section 5.5.

**Clinical Laboratory Evaluations**

In Study GS-US-366-1160, there were no clinically relevant changes from baseline or differences between the treatment groups in median values for hematology or clinical chemistry parameters. Median values were within normal ranges throughout the studies.

The majority of subjects had at least 1 laboratory abnormality reported during the study. The incidence of laboratory abnormalities of any grade was similar between treatment groups for most chemistry, hematology, and urinalysis parameters. Overall, similar percentages of subjects in each group had a Grade 3 or 4 laboratory abnormality (ODE 9.8%, 43 subjects; ATR 9.0%, 39 subjects). Metabolic laboratory parameter results are provided in m2.7.4, Section 3.3.

There were decreases from baseline in the fasting lipid parameters 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, direct LDL cholesterol, triglycerides, or glucose in either treatment group. Switching from EFV-based therapy to an RPV-based regimen has demonstrated improved lipid profiles in HIV-infected, virologically suppressed patients {Thamrongwonglert et al 2016}.

**Table 5. GS-US-366-1160: Overall Summary of Adverse Events (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 351 (80.1%) | 323 (73.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 155 (35.4%) | 147 (33.6%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 27 (6.2%) | 25 (5.7%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 56 (12.8%) | 45 (10.3%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 11 (2.5%) | 19 (4.3%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 0 | 2 (0.5%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 24 (5.5%) | 25 (5.7%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 0 | 1 (0.2%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 11 (2.5%) | 8 (1.8%) |
| Subjects who had Treatment-Emergent Death | 1 (0.2%) | 0 |

Adverse events were coded using MedDRA version 19.0.
Treatment-emergent events began on or after the study drug start date up to 30 days after permanent discontinuation of study drug, or led to premature study drug discontinuation.
Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities.
Treatment-emergent death refers to a death which occurred between the first dose date and the last dose date plus 30 days (inclusive).
Source: m2.7.4, Table 10

## 5.3. Analysis of Adverse Drug Reactions

The key data source supporting the Adverse Reactions section of the ODE prescribing information is the pooled 48-week data from the pivotal Phase 3 studies of FTC + TAF with EVG + COBI in HIV-infected, antiretroviral therapy (ART)-naive adults (GEN Studies GS-US-292-0104 and GS-US-292-0111) and the pooled 96-week data from the pivotal Phase 3 studies of RPV + FTC/TDF in HIV-infected, ART-naive adults (RPV Studies C209 and C215).

No new adverse drug reactions to ODE were identified through 48 weeks of treatment in the 2 clinical trials of HIV-infected, virologically suppressed subjects who switch to ODE from CPA or ATR.

## 5.4. Bone Safety

In the original submission, the totality of results from bone safety analyses in HIV-infected adults across the TAF program demonstrated that treatment with a regimen containing FTC + TAF (E/C/F/TAF; GEN) was associated with a preferential bone safety profile compared with TDF-containing regimens, with statistically significant differences in multiple tests of bone metabolism. Data in the current submission are the first available for ODE and are consistent with the original findings, providing additional evidence that ODE has an improved bone safety profile compared with TDF (m2.7.4, Section 2.1.5.1).

### Study GS-US-366-1216: CPA Switch

For HIV-infected, virologically suppressed adults who switched to ODE from CPA, improvements in both hip and spine bone mineral density (BMD) were observed through Week 48, compared with minimal changes from baseline at both sites in the CPA group (Table 6). Compared with the CPA group, lower percentages of subjects in the ODE group had decreases from baseline in hip and spine BMD, and higher percentages of subjects in the ODE group had increases from baseline in hip and spine BMD. The incidence of fracture events (based on the Medical Dictionary for Regulatory Activities [MedDRA] Standardized MedDRA Query [SMQ] for osteoporosis/osteopenia and High Level Group Term [HLGT] of fractures, excluding fingers and toes) was low (ODE 1.3%, 4 subjects; CPA 1.6%, 5 subjects). The incidence of clinically relevant decreases in BMD was lower in the ODE group, as follows:

- ≥ 7% decrease from baseline in femoral neck BMD: ODE 0.0%, CPA 1.2%
- ≥ 5% decrease from baseline in spine BMD: ODE 1.7%, CPA 3.0%

Results for prespecified bone laboratory parameters corroborated the changes in hip and spine BMD, with a decrease in bone turnover for subjects who switched to ODE. There were decreases from baseline in median percent changes of parathyroid hormone (PTH; a hormone involved in bone formation and resorption), C-telopeptide (CTx; a bone resorption biomarker), and procollagen type 1-N-terminal propeptide (P1NP; a bone formation biomarker) for subjects who switched to ODE.

**Table 6. GS-US-366-1216: Key Measures of BMD at Week 48 (Observed Data; Hip or Spine DXA Substudy Analysis Set)**

| | | | ODE vs CPA | |
|---|---|---|---|---|
| | ODE | CPA | p-value | Difference in Least Square Mean (95% CI) |
| **Hip DXA Analysis** | **(N = 168)** | **(N = 165)** | | |
| Mean (SD) % Change in BMD[a] | 1.040 (1.9404) | −0.245 (2.0805) | < 0.001 | 1.285 (0.851, 1.718) |
| Subjects with Categorical Change (%) | | | | |
| ≥ 3% Decrease in BMD | 3.0 | 6.7 | — | — |
| No Decrease (≥ 0% Change) | 70.8 | 46.1 | | |
| ≥ 3% Increase in BMD | 16.1 | 4.2 | | |
| **Spine DXA Analysis** | **(N = 172)** | **(N = 168)** | | |
| Mean (SD) % Change in BMD[a] | 1.613 (3.4346) | 0.075 (2.9605) | < 0.001 | 1.538 (0.853, 2.222) |
| Subjects with Categorical Change (%) | | | | |
| ≥ 3% Decrease in BMD | 6.4 | 13.1 | — | — |
| No Decrease (≥ 0% Change) | 66.9 | 51.8 | | |
| ≥ 3% Increase in BMD | 27.3 | 11.3 | | |

DXA = dual-energy x-ray absorptiometry
a % Change = Change from baseline at a postbaseline visit / baseline × 100%
P-values, difference in LSMs, and its 95% CI were from the ANOVA model including treatment as a fixed effect.
Source: m2.7.4, Tables 13 and 14

### Study GS-US-366-1160: ATR Switch

For HIV-infected, virologically suppressed adults who switched to ODE from ATR, improvements in both hip and spine BMD were observed through Week 48, compared with minimal changes from baseline at both sites in the ATR group (Table 7). Compared with the ATR group, lower percentages of subjects in the ODE group had decreases from baseline in hip and spine BMD, and higher percentages of subjects in the ODE group had increases from baseline in hip and spine BMD. The incidence of fracture events (based on the MedDRA SMQ for osteoporosis/osteopenia and HLGT of fractures) was low (ODE 1.8%, 8 subjects; ATR 0.9%, 4 subjects). The incidence of clinically relevant decreases in BMD was lower in the ODE group, as follows:

- ≥ 7% decrease from baseline in femoral neck BMD: ODE 1.4%, ATR 3.3%
- ≥ 5% decrease from baseline in spine BMD: ODE 2.3%, ATR 4.9%

There were decreases from baseline in median percent changes in PTH (a hormone involved in bone formation and resorption) and P1NP (a bone formation biomarker) for subjects who switched to ODE.

**Table 7. GS-US-366-1160: Key Measures of BMD at Week 48 (Observed Data; Hip or Spine DXA Analysis Set)**

| | ODE | ATR | ODE vs ATR | |
|---|---|---|---|---|
| | | | p-value | Difference in Least Square Mean (95% CI) |
| **Hip DXA Analysis** | **(N = 347)** | **(N = 367)** | | |
| Mean (SD) % Change in BMD[a] | 1.279 (2.3800) | −0.134 (2.4930) | < 0.001 | 1.413 (1.054, 1.771) |
| Subjects with Categorical Change (%) | | | | |
| ≥ 3% Decrease in BMD | 2.3 | 10.1 | — | — |
| No Decrease (≥ 0% Change) | 71.5 | 48.5 | | |
| ≥ 3% Increase in BMD | 18.7 | 6.3 | | |
| **Spine DXA Analysis** | **(N = 351)** | **(N = 369)** | | |
| Mean (SD) % Change in BMD[a] | 1.645 (3.3198) | −0.045 (2.9087) | < 0.001 | 1.690 (1.234, 2.146) |
| Subjects with Categorical Change (%) | | | | |
| ≥ 3% Decrease in BMD | 6.6 | 13.8 | — | — |
| No Decrease (≥ 0% Change) | 71.5 | 49.3 | | |
| ≥ 3% Increase in BMD | 29.1 | 12.7 | | |

a % Change = Change from baseline at a postbaseline visit / baseline × 100%
P-values, difference in LSMs, and its 95% CI were from the ANOVA model including treatment as a fixed effect.
Source: m2.7.4, Tables 15 and 16

## 5.5. Renal Safety

In the original submission, the totality of results from both clinical and subclinical renal assessments in HIV-infected adults across the TAF program demonstrated that treatment with a regimen containing FTC + TAF (E/C/F/TAF; GEN) is associated with an improved renal safety profile compared with TDF-containing regimens. Data presented in the current submission are consistent with the original findings (m2.7.4, Section 2.1.5.2).

### Study GS-US-366-1216: CPA Switch

There were no cases of proximal renal tubulopathy (including Fanconi Syndrome) reported in subjects receiving ODE in Study GS-US-366-1216. One subject who switched to ODE from CPA had a renal SAE (acute kidney injury, reported as acute renal failure, in the context of pneumonia and sepsis) that was not considered related to study drug by the investigator. No discontinuations due to renal AEs occurred during the study.

In HIV-infected, virologically suppressed adults who switched to ODE from CPA, there were minimal changes in serum creatinine and estimated glomerular filtration rate calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) (Table 8). In subjects with graded proteinuria, more subjects in the ODE group compared with the CPA group had an improvement from baseline in proteinuria toxicity grade at Week 48, and fewer subjects in the ODE group compared with the CPA group had a worsening of proteinuria toxicity grade from baseline at Week 48. Decreases from baseline in proteinuria (urine protein to creatinine ratio [UPCR]) and albuminuria (urine albumin to creatinine ratio [UACR]) were seen with ODE, while mostly increases from baseline in UPCR and UACR were seen with CPA. Decreases in renal tubular proteinuria (urine retinol binding protein [RBP] to creatinine ratio and urine beta-2-microglobulin [β2M] to creatinine ratio) occurred in subjects who switched to ODE from CPA at Week 48, versus increases in subjects who continued their baseline CPA regimen.

**Table 8. GS-US-366-1216: Key Renal Laboratory Parameters at Week 48 (Safety Analysis Set)**

| | ODE (N = 316) | CPA (N = 314) | p-value |
|---|---|---|---|
| Serum Creatinine (mg/dL) | −0.02 (0.108)[a]<br>−0.02 (−0.09, 0.05)[b] | −0.02 (0.112)[a]<br>−0.01 (−0.08, 0.05)[b] | 0.67 |
| $eGFR_{CG}$ (mL/min)[b] | 4.5 (−4.1, 12.3) | 0.7 (−6.6, 8.1) | 0.002 |
| Improvement in Proteinuria by Urinalysis (Dipstick) (%)[c] | 89.3 | 75.0 | - |
| UPCR (mg/g) | | | |
| Baseline[d] | 53.2 (35.5, 88.7) | 50.0 (36.4, 80.6) | 0.69 |
| Week 48[d] | 41.9 (28.7, 65.0) | 50.7 (34.5, 88.2) | - |
| % Change from baseline at Week 48[e] | −18.8 (−47.4, 26.8) | 7.3 (−31.4, 63.0) | < 0.001 |
| UACR (mg/g) | | | |
| Baseline[d] | 5.5 (3.7, 10.0) | 5.4 (3.8, 9.2) | 0.98 |
| Week 48[d] | 5.1 (3.7, 8.5) | 6.3 (4.2, 9.7) | - |
| % Change from baseline at Week 48[e] | −7.8 (−34.2, 27.6) | 16.8 (−19.6, 64.0) | < 0.001 |
| RBP to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 48[e] | −18.0 (−43.7, 19.6) | 21.5 (−17.3, 84.2) | < 0.001 |
| Beta-2-microglobulin to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 48[e] | −29.0 (−63.8, 10.8) | 12.0 (−40.6, 119.4) | < 0.001 |

a Mean (SD) change from baseline
b Median (Q1, Q3) change from baseline
c Toxicity grade decreased at least 1 grade from baseline.
d Median (Q1, Q3)
e Median (Q1, Q3) percent change from baseline
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: m2.7.4 Tables 17, 18, 19, and 20

### Study GS-US-366-1160: ATR Switch

There were no cases of proximal renal tubulopathy (including Fanconi Syndrome) reported in subjects receiving ODE in Study GS-US-366-1160. One subject who switched to ODE from ATR discontinued study drug due to a nonserious renal AE (GFR decreased) that was considered to be related to study drug by the investigator. The subject had an $eGFR_{CG}$ at screening of 54.2 mL/min. After study drug discontinuation the subject initiated GEN; subsequent $eGFR_{CG}$ was 51.7mL/min. No renal SAEs occurred during the study.

In HIV-infected, virologically suppressed adults who switched to ODE from ATR, there was an increase at Week 4 followed by stabilization Weeks 12 through 48 in serum creatinine, and a decrease in $eGFR_{CG}$ (Table 9). The changes are consistent with the known effects of RPV on tubular secretion of creatinine and do not represent a true change in renal function. In subjects with graded proteinuria, more subjects in the ODE group compared with the ATR group had an improvement from baseline in proteinuria toxicity grade at Week 48. Decreases from baseline in

proteinuria (UPCR) and albuminuria (UACR) were seen with ODE, while mostly increases from baseline in UPCR and UACR were seen with ATR. Decreases in renal tubular proteinuria (urine RBP to creatinine ratio and urine β2M to creatinine ratio) occurred in subjects who switched to ODE from ATR at Week 48, versus increases in subjects who continued their baseline ATR regimen.

**Table 9. GS-US-366-1160: Key Renal Laboratory Parameters at Week 48 (Safety Analysis Set)**

| | ODE (N = 438) | ATR (N = 437) | p-value |
|---|---|---|---|
| Serum Creatinine (mg/dL) | 0.06 (0.102)[a]<br>0.07 (0.00, 0.13)[b] | 0.01 (0.105)[a]<br>0.00 (-0.06, 0.06)[b] | < 0.001 |
| $eGFR_{CG}$ (mL/min)[b] | −4.1 (−12.7, 4.6) | −0.6 (−7.8, 6.7) | < 0.001 |
| Improvement in Proteinuria by Urinalysis (Dipstick) (%)[c] | 80.0 | 65.6 | - |
| UPCR (mg/g) | | | |
| Baseline[d] | 63.3 (40.8, 105.4) | 62.2 (40.7, 108.7) | 0.91 |
| Week 48[d] | 45.3 (30.6, 78.6) | 60.9 (38.6, 108.7) | - |
| % Change from baseline at Week 48[e] | −30.0 (−54.4, 18.9) | −2.0 (−35.6, 42.0) | < 0.001 |
| UACR (mg/g) | | | |
| Baseline[d] | 6.9 (4.2, 13.6) | 6.4 (4.3, 11.8) | 0.40 |
| Week 48[d] | 5.6 (3.8, 10.3) | 7.0 (4.7, 13.9) | - |
| % Change from baseline at Week 48[e] | −13.5 (−47.5, 25.3) | 12.2 (−20.0, 55.6) | < 0.001 |
| RBP to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 48[e] | −27.6 (−58.8, 4.2) | 29.1 (−13.4, 96.8) | < 0.001 |
| Beta-2-microglobulin to Urine Creatinine ratio (µg/g) | | | |
| % Change from Baseline at Week 48[e] | −41.0 (−74.5, 0.8) | 17.1 (−34.1, 135.7) | < 0.001 |

a Mean (SD) change from baseline
b Median (Q1, Q3) change from baseline
c Toxicity grade decreased at least 1 grade from baseline.
d Median (Q1, Q3)
e Median (Q1, Q3) percent change from baseline
P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups.
Source: m2.7.4 Tables 21, 22, 23, and 24

## 5.6. Safety in Special Groups and Situations

Safety information pertinent to the use of ODE in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the prescribing information. The safety of ODE, as assessed by the incidence of AEs, was analyzed by sex, age, race, and region. While there were differences between some subgroups, they were not considered clinically relevant overall.

## 5.7. Postmarketing Experience

Postmarketing safety data for ODE and its individual components are carefully evaluated on an ongoing basis for any new safety issues, and labeling changes are submitted to regulatory authorities when new adverse reactions are identified. There have been no newly identified adverse reactions for ODE based on the postmarketing data available to date.

## 5.8. Discussion and Conclusions on Safety Experience

Treatment with ODE was well tolerated in HIV-infected, virologically suppressed subjects who switched to ODE from CPA and ATR, as demonstrated by the low overall incidence of study drug discontinuation due to AEs, SAEs, and the absence of SAEs considered related to study drug.

Safety results from the ODE Phase 3 studies demonstrate that ODE has an improved bone safety profile compared with CPA and ATR in HIV-infected, virologically suppressed subjects, as follows:

- In both studies, ODE was associated with improvements in hip and spine BMD through Week 48, compared with minimal changes from baseline at both sites in the CPA and ATR groups. Compared with the CPA and ATR groups, lower percentages of subjects in the ODE groups in both studies had decreases from baseline in hip and spine BMD, and higher percentages of subjects in the ODE group had increases from baseline in hip and spine BMD.

Safety results from the ODE Phase 3 studies also demonstrate that ODE has an improved renal safety profile compared with CPA and ATR. Specific findings are as follows:

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported for subjects who received ODE.

- Subjects who switched to ODE had decreases from baseline in proteinuria by quantitative assessment (UACR and UPCR) and tubular proteinuria (RBP and β2M to creatinine ratios) at Week 48 compared with minimal changes or increases from baseline in these measures for subjects who remained on treatment with CPA or ATR.

The preferential bone and renal safety profiles with ODE are consistent to those seen in HIV-infected subjects on other F/TAF-containing regimens, ie, GEN and Descovy® (F/TAF).

In conclusion, ODE was well tolerated and demonstrated an improved bone and renal safety profile in HIV-infected, virologically suppressed subjects switching from the TDF-based regimens CPA and ATR.

# 6. BENEFITS AND RISKS CONCLUSIONS

The information presented in the current submission provides the first clinical data for the fixed-dose combination Odefsey, and further support for the use of ODE in HIV-infected, virologically suppressed patients who wish to switch from their existing ARV regimen.

The updated evaluation of the benefits and risks of ODE for use in the treatment of HIV-1 infection supports the proposed updates to the prescribing information for ODE. Data presented from Studies GS-US-366-1216 and GS-US-366-1160 further support the use of ODE in HIV-infected, virologically suppressed adults. The following considerations in the sections below continue to demonstrate a favorable benefit:risk profile for ODE in the treatment of HIV-infected patients.

## 6.1. Benefits

ODE is efficacious and has a favorable safety and tolerability profile. ODE has several benefits as an alternative to TDF-based treatments, including an improved bone and renal safety profile for patients living with HIV infection. The benefits of ODE include the following:

- **ODE is Highly Efficacious in HIV-Infected, Virologically Suppressed Adults**

In HIV-infected, virologically suppressed adults, ODE was noninferior to continuing treatment with CPA or ATR at the Week 48 primary endpoint. These results demonstrate that ODE maintains efficacy in suppressed subjects switching regimens.

There was no resistance development in subjects taking ODE.

- **ODE is Well Tolerated**

Treatment with ODE was well tolerated in HIV-infected, virologically suppressed adults as demonstrated by the low overall incidence of SAEs and study drug discontinuation due to AEs, and the absence of SAEs considered related to study drug. No new ADRs were identified.

- **ODE Has an Improved Bone and Renal Profile Compared with TDF-Based Regimens**

Results summarized in the current submission are for HIV-infected, virologically suppressed adults who completed 48 weeks of treatment after switching to ODE from a TDF-based regimen. These data are consistent with those in the original submission and show that treatment with ODE demonstrated a preferential bone and renal safety profile, as compared with TDF-based regimens (CPA and ATR), with statistically significant differences in multiple tests of bone and renal function. Specifically, the following results were noted:

- ODE was associated with improvements in hip and spine BMD through Week 48, compared with minimal changes from baseline at both sites in the CPA and ATR groups. Compared with the CPA and ATR groups, lower percentages of subjects in the ODE groups in both studies had decreases from baseline in hip and spine BMD, and higher percentages of subjects in the ODE group had increases from baseline in hip and spine BMD.

- No cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported for subjects who received ODE.

- Subjects who switched to ODE had decreases from baseline in proteinuria by quantitative assessment (UACR and UPCR) and tubular proteinuria (RBP and β2M to creatinine ratios) at Week 48 compared with minimal changes or increases from baseline in these measures for subjects who remained on treatment with CPA or ATR.

The totality of the data demonstrate the efficacy and safety of ODE in HIV-infected, virologically suppressed patients switching to ODE from their existing ARV regimen.

## 6.2. Risks

Treatment with ODE was well tolerated in HIV-infected, virologically suppressed patients. No new safety signal for TAF or ODE was detected with safety data from these Phase 3 studies.

No new warnings or precautions are warranted based on the data summarized in the current submission.

Results from a drug interaction study of FTC/RPV/TDF (which include the FTC and RPV components of ODE) and SOF/VEL demonstrated that no clinically significant drug interactions have been observed or are expected between the components of ODE and SOF/VEL.

## 6.3. Conclusions

Odefsey is efficacious and has a favorable safety and tolerability profile that offers advantages over existing ARV regimens. ODE maintained virologic and immunologic control in HIV-infected, virologically suppressed adults switching from TDF-based ARV regimens. ODE demonstrated an improved bone and renal safety profile in subjects who switched from TDF-based regimens. Overall, the data demonstrate that ODE is an efficacious and safe option for HIV-infected patients.

# 7. REFERENCES

Thamrongwonglert P, Chetchotisakd P, Anunnatsiri S, Mootsikapun P. Improvement of lipid profiles when switching from efavirenz to rilpivirine in HIV-infected patients with dyslipidemia. HIV Clin Trials 2016;17 (1):12-6.

# SECTION 2.5—CLINICAL OVERVIEW

**GENVOYA®**
**(ELVITEGRAVIR/COBICISTAT/EMTRICITABINE/**
**TENOFOVIR ALAFENAMIDE)**

**DESCOVY®**
**(EMTRICITABINE/**
**TENOFOVIR ALAFENAMIDE)**

**ODEFSEY®**
**(EMTRICITABINE/RILPIVIRINE/**
**TENOFOVIR ALAFENAMIDE)**

Gilead Sciences

04 November 2016

CONFIDENTIAL AND PROPRIETARY INFORMATION

# TABLE OF CONTENTS

TABLE OF CONTENTS ..... 2
LIST OF IN-TEXT TABLES ..... 2
LIST OF IN-TEXT FIGURES ..... 3
GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS ..... 4
1. PRODUCT DEVELOPMENT RATIONALE ..... 5
1.1. Overview of Data Included in This Submission ..... 6
2. OVERVIEW OF BIOPHARMACEUTICS ..... 8
3. OVERVIEW OF CLINICAL PHARMACOLOGY ..... 9
4. OVERVIEW OF EFFICACY ..... 10
5. OVERVIEW OF SAFETY ..... 13
5.1. Extent of Exposure ..... 13
5.2. Overall Safety ..... 13
5.3. Analysis of Adverse Drug Reactions ..... 15
5.4. Bone Safety ..... 16
5.5. Renal Safety ..... 18
5.6. Suicidal Ideation and Suicide Attempt ..... 20
5.7. Fasting Lipid Parameters ..... 21
5.8. Safety in Special Groups and Situations ..... 21
5.9. Postmarketing Experience ..... 22
6. BENEFITS AND RISKS CONCLUSIONS ..... 23
6.1. Benefits ..... 23
6.2. Risks ..... 24
6.3. Conclusions ..... 25
7. REFERENCES ..... 26

# LIST OF IN-TEXT TABLES

Table 1. Studies Included in this Submission ..... 7
Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 144 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS) ..... 11
Table 3. GS-US-292-0104 and GS-US-292-0111: Overall Summary of Adverse Events (Week 144 Analysis, Safety Analysis Set) ..... 14
Table 4. GS-US-292-0104 and GS-US-292-0111: Adverse Events (All Grades) Related to Study Drug for ADRs Applicable to GEN, DVY, and ODE (Week 144 Analysis, Safety Analysis Set) ..... 15
Table 5. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 144 Analysis, Hip and Spine DXA Analysis Sets) ..... 18
Table 6. GS-US-292-0104 and GS-US-292-0111: Treatment-Emergent Renal Adverse Events Leading to Premature Study Drug Discontinuation (Week 144 Analysis, Safety Analysis Set) ..... 19
Table 7. GS-US-292-0104 and GS-US-292-0111: Key Renal Laboratory Parameters (Week 144 Analysis, Safety Analysis Set) ..... 20

Table 8. GS-US-292-0104 and GS-US-292-0111: Summary of Suicide Events by Suicide/Self-Injury SMQ (Week 144 Analysis, Safety Analysis Set) ..... 21

## LIST OF IN-TEXT FIGURES

Figure 1. GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set) ..... 17

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| ADR | adverse drug reaction |
| AE | adverse event |
| ART | antiretroviral treatment or therapy |
| ARV | antiretroviral |
| BL | baseline |
| BMD | bone mineral density |
| CD4 | cluster determinant 4 |
| CI | confidence interval |
| COBI or C | cobicistat (Tybost®) |
| CSR | clinical study report |
| DXA | dual-energy x-ray absorptiometry |
| EVG or E | elvitegravir (Vitekta®) |
| FAS | full analysis set |
| FDA | Food and Drug Administration |
| FTC | emtricitabine (Emtriva®) |
| GEN | elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated; Genvoya® (previously referred to as E/C/F/TAF) |
| $eGFR_{CG}$ | glomerular filtration rate, estimated, by Cockcroft-Gault method |
| HIV, HIV-1 | human immunodeficiency virus, type 1 |
| HDL | high-density lipoprotein |
| INSTI | integrase strand-transfer inhibitor |
| ISE | Integrated Summary of Efficacy |
| ISS | Integrated Summary of Safety |
| LDL | low-density lipoprotein |
| m | module |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MH | Mantel-Haenszel |
| N | number of subjects in a population |
| Q1, Q3 | first quartile, third quartile |
| RMP | Risk Management Plan |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SD | standard deviation |
| SmPC | Summary of Product Characteristics |
| SMQ | standardised MedDRA query |
| STB | elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®) |
| TAF | tenofovir alafenamide |
| TDF | tenofovir disoproxil fumarate (Viread®) |
| TFV | tenofovir |
| UACR | urine albumin-to-creatinine ratio |
| UPCR | urine protein-to-creatinine ratio |
| US | United States |

# 1. PRODUCT DEVELOPMENT RATIONALE

This submission supports proposed changes to the prescribing information for Genvoya® (GEN; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide [E/C/F/TAF]), Descovy (DVY; emtricitabine/tenofovir alafenamide [F/TAF]), and Odefsey (ODE; emtricitabine/rilpivirine/tenofovir alafenamide [F/R/TAF]. This submission also fulfills 2 Category 3 additional pharmacovigilance activities for GEN in line with the European Union Risk Management Plan (RMP) agreed during the original marketing authorization application.

Genvoya is an oral, once-daily, fixed-dose combination (FDC) that provides a potent and well-tolerated regimen for the long-term treatment of patients infected with HIV-1. Genvoya contains the HIV-1 integrase strand-transfer inhibitor elvitegravir (EVG), the pharmacoenhancer cobicistat (COBI), the nucleoside reverse transcriptase inhibitor emtricitabine (FTC), and the nucleotide reverse transcriptase inhibitor tenofovir alafenamide (TAF). Genvoya was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the United States (US) on 05 November 2015 and in the European Union on 19 November 2015.

Descovy is an oral, once-daily, FDC that provides a nucleo(s/t)ide reverse transcriptase inhibitor backbone that can be combined with different third agents in the long-term treatment of patients with HIV-1. DVY contains the nucleoside reverse transcriptase inhibitor FTC and the nucleotide reverse transcriptase inhibitor TAF. Descovy was first approved for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents (aged 12 years and older) in the US on 04 April 2016 and in the European Union on 21 April 2016.

Odefsey is an oral once daily FDC that provides an effective and well-tolerated regimen for the long term treatment of patients infected with HIV-1. ODE contains the nucleoside reverse transcriptase inhibitor FTC, the non-nucleoside reverse transcriptase inhibitor rilpivirine (R, RPV) and the nucleotide reverse transcriptase inhibitor TAF. Odefsey was first approved for the treatment of HIV-1 infection in adults and adolescents (aged 12 years and older) in the US on 01 March 2016 and in the European Union on 21 June 2016.

The success of potent and well-tolerated antiretroviral (ARV) therapy (ART) means that morbidity and mortality in the HIV-infected population is increasingly driven by non-acquired immune deficiency syndrome (AIDS)-associated comorbidities. Clinical attention has become more focused on the optimization of tolerability, long-term safety, and adherence of potent ART regimens {Costagliola 2014}. In addition, effective therapies must take into consideration HIV genetic variability, the aging HIV-infected population, ARV resistance, regimen simplification, and durable efficacy.

This clinical overview presents an updated evaluation of the benefits and risks of GEN, DVY, and ODE for use in the treatment of HIV-1 infection. Information that supports the proposed labeling includes updated clinical efficacy and safety data in ART-naive adults receiving GEN.

Throughout the text of this document, Genvoya is referred to as “GEN.” The designation “E/C/F/TAF” is used in preprogrammed tables, figures, and listings.

## 1.1. Overview of Data Included in This Submission

This submission provides additional long-term efficacy and safety data for HIV-infected, antiretroviral therapy (ART)-naive adults in Studies GS-US-292-0104 and GS-US-292-0111 with results through 144 weeks of treatment with GEN (Table 1).

The pooling of data was prespecified in the protocol for each of the 2 pivotal Phase 3 studies GS-US-292-0104 and GS-US-292-0111, because the study designs and populations were identical, differing only in geography. For the integrated analysis, data were pooled by treatment group (GEN versus E/C/F/tenofovir disoproxil fumarate [TDF], coformulated; Stribild® [STB]) according to the randomized treatment (efficacy) or the treatment received (safety).

Both studies were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization Good Clinical Practice guidelines, applicable governmental regulatory requirements, and in compliance with the respective protocols.

Details of subject disposition and analysis sets for these clinical studies are provided in m2.7.3, Section 3.1.

**Table 1. Studies Included in this Submission**

| Study | Study Design | Number of Subjects[a] by Treatment Regimen | Data Presented | CSR and Narrative Locations |
|---|---|---|---|---|
| GS-US-292-0104 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GEN vs STB | GEN + placebo-to-match STB (N = 435)<br>STB + placebo-to-match GEN (N = 432) | Week 144 efficacy and safety | **CSR:** GS-US-292-0104 Week 144<br>**Narrative:** m2.7.3, Section 2.1 |
| GS-US-292-0111 | Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of GEN vs STB | GEN + placebo-to-match STB (N = 431)<br>STB + placebo-to-match GEN (N = 435) | Week 144 efficacy and safety | **CSR:** GS-US-292-0111 Week 144<br>**Narrative:** m2.7.3, Section 2.2 |

CSR = clinical study report; GEN = elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, coformulated; Genvoya® (previously referred to as E/C/F/TAF); STB = elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (coformulated; Stribild®)

a Subjects included in the Safety Analysis Set (subjects who received at least 1 dose of study drug)

# 2. OVERVIEW OF BIOPHARMACEUTICS

No new biopharmaceutics information (eg, formulation or dissolution data) is included within this submission.

# 3. OVERVIEW OF CLINICAL PHARMACOLOGY

Updated clinical virology data from Studies GS-US-292-0104 and GS-US-292-0111 are presented in m2.7.2, Section 4 and incorporated with efficacy data in this overview (Section 4).

No new clinical pharmacology data are included in this submission.

# 4. OVERVIEW OF EFFICACY

This section provides an overview of the pooled analysis of efficacy that was conducted for the pivotal Phase 3 studies in ART-naive adults (GS-US-292-0104 and GS-US-292-0111) (studies are described in Table 1; detailed descriptions of efficacy data are provided in m2.7.3, Section 3.2).

Baseline demographics and disease characteristics for the study populations are presented in m2.7.4, Sections 1.3.1 and 1.3.2, respectively. The studied population is considered representative of ART-naive HIV-1 infected subjects in the general population.

The primary efficacy endpoint for Studies GS-US-292-0104 and GS-US-292-0111 was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the US FDA-defined snapshot algorithm. Results from the primary efficacy analysis demonstrated that GEN once daily was noninferior to STB once daily when administered through 48 weeks of treatment.

Treatment with GEN was noninferior and statistically superior to treatment with STB in the Week 144 pooled analysis based on the percentage of subjects with virologic suppression, defined as HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm (difference in percentages: 4.2%, 95% CI: 0.6% to 7.8%; p = 0.021; Table 2). GEN demonstrated potent and durable virologic efficacy; the percentage of subjects with HIV-1 RNA < 50 copies/mL in each group were as follows:

- GEN 84.2%
- STB 80.0%

The percentage of subjects with no virology data in the Week 144 window was lower in the GEN group compared with the STB group (GEN 11.2%, STB 16.0%). Fewer subjects in the GEN group compared with the STB group had no virology data in the Week 144 window due to AE/death leading to discontinuation of study drugs (GEN 1.5%, 13 subjects; STB 3.3%, 29 subjects), discontinuation of study drugs due to other reasons and last available HIV-1 RNA < 50 copies/mL (GEN 9.1%, 79 subjects; STB 11.4%, 99 subjects), and missing data during window but on study drug (GEN 0.6%, 5 subjects; STB 1.3%, 11 subjects).

These pooled results confirmed those from the individual studies GS-US-292-0104 and GS-US-292-0111, where the percentage of subjects with virologic suppression was higher in the GEN group compared with the STB group at Week 144 for the FAS in each study (GS-US-292-0104 difference in percentages: 4.0%, 95% CI: −0.8% to 8.8%; GS-US-292-0111 difference in percentages: 4.5%, 95% CI: −0.9% to 9.9%; p = 0.10 in each study). Noninferiority was confirmed using the Week 144 per protocol (PP) Analysis Set in each study.

**Table 2. GS-US-292-0104 and GS-US-292-0111: Virologic Outcome at Week 144 Using the US FDA-Defined Snapshot Algorithm and HIV-1 RNA < 50 copies/mL − Pooled Data (FAS)**

| | GEN (N = 866) | STB (N = 867) | GEN vs. STB | |
|---|---|---|---|---|
| | | | p-value[a] | Difference in Percentages (95% CI)[a] |
| HIV-1 RNA < 50 copies/mL | 729 (84.2%) | 694 (80.0%) | 0.021 | 4.2% (0.6% to 7.8%) |
| HIV-1 RNA ≥ 50 copies/mL | 40 (4.6%) | 34 (3.9%) | | |
| HIV-1 RNA ≥ 50 copies/mL in Week 144 Window | 10 (1.2%) | 9 (1.0%) | | |
| Discontinued Study Drug Due to Lack of Efficacy | 7 (0.8%) | 8 (0.9%) | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[b] | 21 (2.4%) | 15 (1.7%) | | |
| Added New ARV | 2 (0.2%) | 2 (0.2%) | | |
| No Virologic Data in Week 144 Window | 97 (11.2%) | 139 (16.0%) | | |
| Discontinued Study Drug Due to AE/Death | 13 (1.5%) | 29 (3.3%) | | |
| Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[b] | 79 (9.1%) | 99 (11.4%) | | |
| Missing Data During Window but on Study Drug | 5 (0.6%) | 11 (1.3%) | | |

Week 144 window is between Day 966 and 1049 (inclusive).

a Difference in percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel (MH) proportions adjusted by baseline (BL) HIV-1 RNA, region, and study stratum. P-value for the superiority test comparing the percentages of subjects with HIV-1 RNA < 50 copies/mL between treatment groups was from the Cochran-Mantel-Haenszel (CMH) test stratified by BL HIV-1 RNA, region and study stratum. BL HIV-1 RNA stratum: ≤ 100,000 or > 100,000 copies/mL; region stratum: US or ex-US; study stratum: GS-US-292-0104 or GS-US-292-0111.

b Discontinuation due to other reasons included subjects who prematurely discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, noncompliance with study drug, protocol violation, pregnancy, and study termination by sponsor.

Programming Details: .../version1/prog/t-snapshot-pooled.sas v9.2 Output file: t-snapshot-50-wk144-pooled.out [redacted]

Source: GEN Week 144 ISE, Table 2.1

The percentage of subjects with virologic suppression, defined as HIV-1 RNA < 20 copies/mL using the US FDA-defined snapshot algorithm, was higher in the GEN group compared with the STB group at Week 144, as follows: GEN 81.1%, 702 of 866 subjects; STB 75.8%, 657 of 867 subjects; difference in percentages: 5.4%, 95% CI: 1.5% to 9.2% (p = 0.006).

Analyses of other secondary HIV-1 RNA endpoints supported the primary efficacy analyses in favoring treatment with GEN over treatment with STB at Week 144, as summarized below:

- In the pooled subgroup analysis, the rates of virologic suppression at Week 144, defined as HIV-1 RNA < 50 copies/mL using the US FDA-defined snapshot algorithm, for the subgroups age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count, region (United States [US] versus ex-US), or study drug adherence favored treatment with GEN over treatment with STB in the age ≥ 50 years, female sex, nonblack race, baseline HIV-1 RNA ≤ 100,000 copies/mL, baseline CD4 cell count ≥ 200 cells/µL, and study drug adherence ≥ 95% subgroups. Homogeneity tests of the treatment effects between subgroups did not show a significant difference in treatment effects between subgroups (m2.7.3, Section 3.3).

- High rates of virologic suppression at Week 144 were maintained in the 2 treatment groups, as assessed using the missing = failure (M = F) method for the pooled data. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 144 (M = F) were as follows: GEN 85.0%, 736 of 866 subjects; STB 83.0%, 720 of 867 subjects; difference in percentages: 2.0%, 95% CI: −1.4% to 5.5%.

The emergence of resistance mutations was rare across the GEN and STB groups (GEN 1.4%, 12 of 866 subjects; STB 1.4%, 12 of 867 subjects) (integrated analysis of Studies GS-US-292-0104 and GS-US-292-0111; m2.7.2, Section 4.1.1). The cross resistance profiles for the virologic failure subjects with emergent resistance to EVG, FTC, and tenofovir (TFV) were consistent with historical data. No novel TAF resistance mutations were observed.

The immunologic benefits of treatment with GEN were demonstrated by improvements in CD4 cell counts. The mean (standard deviation [SD]) increases from baseline in CD4 cell counts at Week 144 (observed data) using the pooled data were as follows: GEN 326 (215.3) cells/µL, STB 305 (204.5) cells/µL; difference in LSM: 20 cells/µL, 95% CI: −1 to 42 cells/µL (similar trends were seen for the last observation carried forward [LOCF] analysis).

Overall, these results continue to demonstrate that GEN is efficacious in ART-naive adults without regard to demographic characteristics, or baseline viral load, with superior efficacy seen for both the HIV-1 RNA < 50 copies/mL and < 20 copies/mL (using the US FDA-defined snapshot algorithm) endpoints compared to STB over 144 weeks of treatment.

# 5. OVERVIEW OF SAFETY

This section provides an overview of safety for the pooled analysis conducted for the pivotal Phase 3 studies in ART-naive adults (GS-US-292-0104 and GS-US-292-0111) (studies are described in Table 1; detailed descriptions of safety data are provided in m2.7.4).

## 5.1. Extent of Exposure

The duration of exposure to study drugs for ART-naive subjects in Studies GS-US-292-0104 and GS-US-292-0111 was similar in the 2 treatment groups. Median (first quartile [Q1], third quartile [Q3]) exposure was as follows: GEN 144.9 (143.0, 156.6) weeks; STB 144.4 (140.9, 156.4) weeks

## 5.2. Overall Safety

Safety data from Studies GS-US-292-0104 and GS-US-292-0111 continue to demonstrate that GEN is well tolerated, with a preferential bone and renal safety profile versus STB over a longer-term exposure of 144 weeks. The safety profile of GEN was similar to that reported through Week 96, and no new safety signal for GEN, DVY, or ODE was detected.

### Adverse Events

Pooled data from Studies GS-US-292-0104 and GS-US-292-0111 showed that the adverse event (AE) profile was consistent with the data submitted previously (Table 3). The most commonly reported AEs for GEN were diarrhea, upper respiratory tract infection, and headache.

At Week 144, fewer subjects in the GEN group than the STB group had AEs that resulted in discontinuation of study drugs (GEN 1.3%, 11 of 866 subjects; STB 3.3%, 29 of 867 subjects). The difference was driven primarily by study drugs discontinuation due to bone and renal events in the STB group, as follows: GEN 0 subjects; STB 17 subjects (of which 1 subject had both bone and renal events).

No subject discontinued GEN due to a renal and urinary disorder or associated investigation AE, compared with 12 subjects who discontinued STB ($p < 0.001$). No subject in the GEN group had a renal event indicative of renal tubular disorder (including Fanconi syndrome), compared to 4 subjects in the STB group, including 1 event of acquired Fanconi syndrome. All but 1 of the 14 renal events in 12 subjects that led to discontinuation of STB were considered related to study drug by the investigator. The subject with the unrelated event of blood creatinine increased discontinued STB and had a bone density decreased AE that was considered related to study drug by the investigator. Bone and renal safety are discussed further in Sections 5.4 and 5.5, respectively.

Fewer subjects in the GEN group than the STB group had AEs considered related to study drugs by the investigator (GEN 44.1%, 382 of 866 subjects; STB 48.9%, 424 of 867 subjects). Similar percentages of subjects in each treatment group had AEs in other categories.
Nine treatment-emergent deaths were reported (GEN 4 subjects; STB 5 subjects). None of the SAEs that resulted in death were considered related to study drug by the investigator.

**Table 3. GS-US-292-0104 and GS-US-292-0111: Overall Summary of Adverse Events (Week 144 Analysis, Safety Analysis Set)**

| | GEN (N=866) | STB (N=867) |
|---|---|---|
| Subjects Experiencing Any Treatment-Emergent Adverse Event | 817 (94.3%) | 833 (96.1%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event | 559 (64.5%) | 552 (63.7%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Adverse Event | 140 (16.2%) | 137 (15.8%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Adverse Event | 382 (44.1%) | 424 (48.9%) |
| Subjects Experiencing Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 109 (12.6%) | 113 (13.0%) |
| Subjects Experiencing Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event | 15 (1.7%) | 15 (1.7%) |
| Subjects Experiencing Any Treatment-Emergent Serious Adverse Event | 121 (14.0%) | 124 (14.3%) |
| Subjects Experiencing Any Treatment-Emergent Study-Drug-Related Serious Adverse Event | 5 (0.6%) | 6 (0.7%) |
| Subjects Experiencing Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation | 11 (1.3%) | 29 (3.3%) |
| Subjects who had Treatment-Emergent Death | 4 (0.5%) | 5 (0.6%) |

Source: m2.7.4, Table 5

## Clinical Laboratory Evaluations

In Studies GS-US-292-0104 and GS-US-292-0111, most subjects had at least 1 laboratory abnormality, the majority of which were Grade 1 or 2. Grade 3 or 4 laboratory abnormalities were reported for similar percentages of subjects in the 2 treatment groups (GEN 32.9%, 284 subjects; STB 30.8%, 266 subjects). The most common Grade 3 or 4 laboratory abnormality was creatine kinase (GEN 11.5%, 99 subjects; STB 10.1%, 87 subjects). Creatine kinase abnormalities occurred at a variety of time points and were not consistently present for individual subjects. Clinical rhabdomyolysis was reported as an SAE for 3 subjects; 2 subjects in the GEN group and 1 subject in the STB group, all events were considered unrelated to study drugs and had alternative explanations (methamphetamine abuse, rigorous exercise, or vaccination).

## 5.3. Analysis of Adverse Drug Reactions

The adverse drug reactions (ADRs) included in Section 4.8 of the GEN Summary of Product Characteristics (SmPC) were based on an assessment of safety data from across all Phase 2 and 3 studies in which 2396 patients received GEN. In addition, ADRs not observed in the Phase 3 clinical studies for GEN but identified from clinical studies or post-marketing experience for the FTC (anemia, angioedema; applicable to GEN, DVY, and ODE) or EVG (depression; applicable to GEN) components when used with other ARVs were also included in Section 4.8 of the SmPCs. In addition to the GEN clinical study data, ADRs included in Section 4.8 of the DVY SmPC were also taken from DVY study GS-US-311-1089, and ADRs for ODE also included clinical study data for FTC/RPV/TDF and RPV. No new ADRs for GEN, DVY, or ODE were identified from the Week 144 pooled data from Studies GS-US-292-0104 and GS-US-292-0111.

The most frequently reported ADRs in clinical studies of GEN were nausea (11%), diarrhea (7%), and headache (6%) (Table 4). The frequency category of ADRs for GEN, DVY, and ODE in Section 4.8 of the GEN, DVY, and ODE SmPCs was based on data from Studies GS-US-292-0104 and GS-US-292-0111 as these represent the most robust data source with respect to the number of subjects and design of the studies (randomized, double-blind, comparative studies). There was no change in frequency category for any of the ADRs for GEN, DVY, or ODE through Week 144 compared to Week 96.

**Table 4. GS-US-292-0104 and GS-US-292-0111: Adverse Events (All Grades) Related to Study Drug for ADRs Applicable to GEN, DVY, and ODE (Week 144 Analysis, Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | Frequency Category based on Week 96 data[a] | GEN (N = 866) | STB (N = 867) |
|---|---|---|---|
| Psychiatric disorders | | | |
| Abnormal dreams | Common | 13 ( 1.5%) | 29 ( 3.3%) |
| Nervous system disorders | | | |
| Headache | Common | 53 ( 6.1%) | 47 ( 5.4%) |
| Dizziness | Common | 26 ( 3.0%) | 20 ( 2.3%) |
| Gastrointestinal disorders | | | |
| Nausea | Very common | 91 ( 10.5%) | 115 ( 13.3%) |
| Diarrhea | Common | 63 ( 7.3%) | 77 ( 8.9%) |
| Vomiting | Common | 16 ( 1.8%) | 29 ( 3.3%) |
| Abdominal pain | Common | 12 ( 1.4%) | 11 ( 1.3%) |
| Flatulence | Common | 23 ( 2.7%) | 29 ( 3.3%) |
| Dyspepsia | Uncommon | 5 ( 0.6%) | 8 (0.9%) |

| Adverse Events by System Organ Class and Preferred Term | Frequency Category based on Week 96 data[a] | GEN (N = 866) | STB (N = 867) |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | |
| Rash | Common | 15 ( 1.7%) | 9 ( 1.0%) |
| Pruritus | Uncommon | 4 (0.5%) | 2 (0.2%) |
| General disorders and administration site conditions | | | |
| Fatigue | Common | 44 ( 5.1%) | 38 ( 4.4%) |

a Frequency categories defined as follows: very common (≥ 10%), common (≥ 1% to < 10%) and uncommon (≥ 0.1% to < 1%)
Source: GEN Week 144 ISS, Table 11

## 5.4. Bone Safety

The totality of results from bone safety analyses in HIV-infected adults across the clinical development program submitted previously demonstrated that treatment with GEN, DVY, and ODE were associated with a preferential bone safety profile compared with STB, with statistically significant differences in multiple tests of bone metabolism. Data presented through 144 weeks of treatment in ART-naive adults from Studies GS-US-292-0104 and GS-US-292-0111 in the current submission are for longer term exposure (approximately 2 years of additional exposure compared with data presented in the original submissions), and are consistent with results submitted previously (m2.7.4, Section 2.1.5.1).

Significantly less bone mineral density (BMD) changes from baseline at both the hip and spine were observed after treatment with GEN compared with STB through Week 144 (Table 5, Figure 1 [spine]). Compared with the STB group, fewer subjects in the GEN group had a decrease from baseline in hip and spine BMD, and more subjects in the GEN group had an increase from baseline in hip and spine BMD. The percentages of subjects with a > 3% decrease from baseline in BMD at Week 144 were as follows:

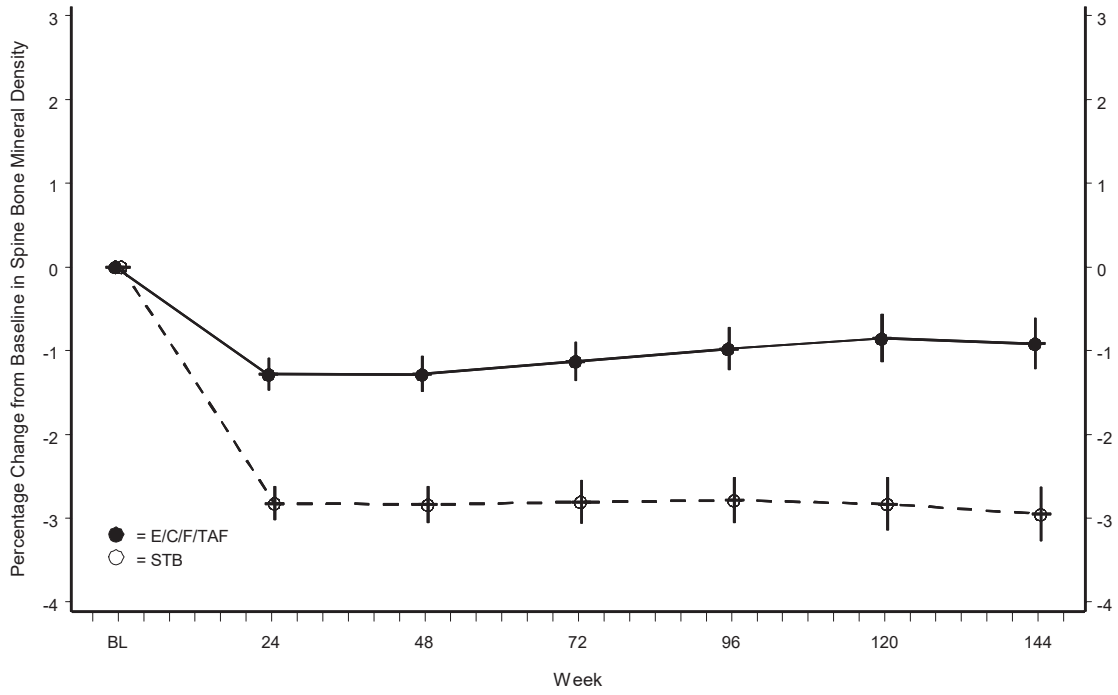
- Hip BMD: GEN 28.0%, STB 55.5%
- Spine BMD: GEN 30.2%, STB 49.0%

The percentages of subjects with a > 3% increase from baseline in BMD at Week 144 were as follows:

- Hip BMD: GEN 13.2%, STB 6.3%
- Spine BMD: GEN 13.4%, STB 6.9%

The incidence of reported fracture events (as defined by the SMQ for osteoporosis/osteopenia and fractures HLGT) was similar in both groups (GEN 3.6%, 31 of 866 subjects; STB 4.5%, 39 of 867 subjects). No subject discontinued GEN due to a bone AE; however, 6 subjects discontinued STB due to bone AEs.

**Figure 1.** **GS-US-292-0104 and GS-US-292-0111: Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Observed Data; Spine DXA Analysis Set)**




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| E/C/F/TAF (n=): | 845 | 797 | 795 | 760 | 744 | 706 | 702 |
| STB (n=): | 850 | 816 | 790 | 751 | 745 | 707 | 686 |

BL = Baseline.
Only subjects with nonmissing spine BMD for the baseline visit were included in spine DXA analysis set.

Data Extracted: s292-0104: CRF,DXA Data: 22JUL2016, Lab Data: 25JUL2016, s292-0111: CRF Data: 28JUL2016, Lab Data: 29JUL2016, DXA Data: 26JUL2016
Source: .../version1/prog/t-dexa.sas v9.2 Output file: g-dexa-spine-bmd-mn.out 09AUG2016:12:06

Source: m2.7.4, Figure 2

**Table 5. GS-US-292-0104 and GS-US-292-0111: Key Measures of BMD (Week 144 Analysis, Hip and Spine DXA Analysis Sets)**

| | GEN | STB | GEN vs STB[a] | |
|---|---|---|---|---|
| | | | p-value | Difference in Least Square Mean (95% CI) |
| **Hip DXA Analysis** | **(N = 690)** | **(N = 683)** | | |
| Mean (SD) % Change in BMD | −0.750% (4.4478%) | −3.364% (4.3292%) | p < 0.001 | 2.615% (2.150% , 3.079%) |
| Subjects with Categorical Change (%) | | | | |
| > 3% Decrease in BMD | 28.0% | 55.5% | | |
| No Decrease (≥ 0% Change) | 39.9% | 18.7% | — | — |
| > 3% Increase in BMD | 13.2% | 6.3% | | |
| **Lumbar Spine DXA Analysis** | **(N = 702)** | **(N = 686)** | | |
| Mean % Change in BMD | −0.916% (4.1186%) | −2.952% (4.2938%) | p < 0.001 | 2.036% (1.593% , 2.479%) |
| Subjects with Categorical Change (%) | | | | |
| > 3% Decrease in BMD | 30.2% | 49.0% | | |
| No Decrease (≥ 0% Change) | 38.9% | 21.7% | — | — |
| > 3% Increase in BMD | 13.4% | 6.9% | | |

a P-values, difference in least squares means, and its 95% CI were from the analysis of variance model including treatment as fixed effect.
Source: GEN Week 144 ISS, Tables 20.1.2, 20.2.2, 23.1 and 23.2

## 5.5. Renal Safety

The totality of results from both clinical and subclinical renal assessments in HIV-infected adults across the clinical development program submitted previously demonstrated that treatment with GEN is associated with a preferential renal safety profile when compared with STB or other TDF-containing regimens, with statistically significant differences in multiple tests of renal function. Data presented in the current submission are for longer term exposure (approximately 2 years of additional exposure) compared with data presented in the original submissions. Current results are consistent with the data submitted previously, demonstrating a preferential renal safety profile in adults treated with GEN compared to STB.

No subject discontinued GEN due to a renal and urinary disorder or associated investigation AE, compared with 12 subjects who discontinued STB (p < 0.001; Table 6). No subject in the GEN group had a renal event indicative of renal tubular disorder (including Fanconi syndrome), compared to 4 subjects in the STB group, as follows: renal tubular disorder, 3 subjects (one of the renal tubular disorders was reported as injury level renal tubule and 2 of the subjects also had proteinuria, normoglycemic glycosuria, and elevated serum creatinine); and acquired Fanconi syndrome, 1 subject (this subject also had proteinuria, elevated serum creatinine,

hypophosphatemia, and a concurrent AE of glycosuria). All but 1 of the 14 renal events in 12 subjects that led to discontinuation of STB were considered related to study drug by the investigator. The subject with the unrelated event of blood creatinine increased discontinued STB and had a bone density decreased AE that was considered related to study drug by the investigator.

Treatment with GEN was associated with less change in serum creatinine and eGFR compared with treatment with STB (Table 7). Importantly, treatment with GEN was associated with less proteinuria (by dipstick) compared with STB. Decreases from baseline in proteinuria (as measured by urine protein-to-creatinine ratio [UPCR]) were seen with GEN that persisted through Week 144, while increases from baseline were seen with STB.

**Table 6. GS-US-292-0104 and GS-US-292-0111: Treatment-Emergent Renal Adverse Events Leading to Premature Study Drug Discontinuation (Week 144 Analysis, Safety Analysis Set)**

| Adverse Events by System Organ Class and Preferred Term | GEN (N = 866) | STB (n = 867) | p-value[a] |
|---|---|---|---|
| Number of Subjects Experiencing Any Treatment-Emergent Renal Adverse Event Leading to Premature Study Drug Discontinuation | 0 | 12 (1.4%) | <0.001 |
| Investigations | 0 | 3 (0.3%) | |
| Blood creatinine increased | 0 | 2 (0.2%) | |
| Glomerular filtration rate decreased | 0 | 2 (0.2%) | |
| Renal and urinary disorders | 0 | 9 (1.0%) | |
| Renal tubular disorder | 0 | 3 (0.3%) | |
| Renal failure | 0 | 2 (0.2%) | |
| Bladder spasm[b] | 0 | 1 (0.1%) | |
| Fanconi syndrome acquired | 0 | 1 (0.1%) | |
| Glycosuria | 0 | 1 (0.1%) | |
| Nephropathy | 0 | 1 (0.1%) | |
| Proteinuria | 0 | 1 (0.1%) | |

a P-value was from the Fisher's exact test.
b The AE of bladder spasm was not considered to be an intrinsic kidney disorder.
Adverse events were coded using MedDRA 19.0.
System organ class (SOC) was presented alphabetically and preferred term was presented by descending order of the total frequencies.
Multiple AEs were counted only once per subject for each SOC and preferred term (PT), respectively.
Renal adverse events included SOC="Renal and urinary disorders" or PT="Blood creatinine increased" or PT="Glomerular filtration rate decreased".
Source: m2.7.4, Table 9

**Table 7. GS-US-292-0104 and GS-US-292-0111: Key Renal Laboratory Parameters (Week 144 Analysis, Safety Analysis Set)**

| | GEN (N = 845) | STB (N = 850) | p-value |
|---|---|---|---|
| Serum Creatinine (mg/dL)[a] | 0.04 (0.116) | 0.07 (0.131) | < 0.001 |
| $eGFR_{CG}$ (mL/min)[b] | −1.6 (−11.4, 9.4) | −7.7 (−18.4, 4.2) | < 0.001 |
| Proteinuria by Urinalysis (Dipstick) (%)[c] | 39.6% | 45.4% | 0.027 |
| UPCR (mg/g)[e] | −10.5% (−43.9%, 38.0%) | 25.2% (−23.8%, 95.2%) | < 0.001 |
| UACR (mg/g)[e,g] | −5.2% (-35.6%, 29.7%) | 5.2% (-32.6%, 59.1%) | < 0.001 |
| Urine RBP to Urine Creatinine ratio (µg/g)[e] | 34.8% (−4.6%, 83.3%) | 111.0% (38.4%, 264.9%) | < 0.001 |
| Urine beta-2-microglobulin to Urine Creatinine ratio (µg/g)[e] | −25.7% (−58.2%, 13.7%) | 53.8% (−26.0%, 305.1%) | < 0.001 |

a Mean (SD) change from baseline
b Median (Q1, Q3) change from baseline
c Treatment-emergent graded abnormalities
d Median (Q1, Q3)
e Median (Q1, Q3) percent change from baseline
f Based on subjects who had normal UPCR (≤ 200 mg/g) or UACR(< 30 mg/g) at baseline
g Only 46 subjects in the GEN group and 59 subjects in the STB group had UACR assessments after Week 96 therefore week 96 data are presented
Source: GEN Week 144 ISS, Table 26.2, 27.1, 28, 29.2 to 29.5, 30.1, and 30.2

## 5.6. Suicidal Ideation and Suicide Attempt

Suicidal ideation and suicide attempt have been reported with the use of INSTI-containing regimens. However, the current data do not support a causal association between suicidal ideation/suicide attempt and GEN.

Adverse events based on the suicide/self injury standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) were infrequent in Studies GS-US-292-0104 and GS-US-292-0111 through 144 weeks of treatment (GEN 1.6%, 14 subjects; STB 1.7%, 15 subjects; Table 8). One resulted in discontinuation of study drugs (suicide attempt), and 1 was fatal (completed suicide). Both events were reported for subjects who received GEN and in both cases acute psychosocial stressors and prior history of mental health problems were reported. None of the suicide/self-injury AEs was considered related to study drug by the investigator.

**Table 8. GS-US-292-0104 and GS-US-292-0111: Summary of Suicide Events by Suicide/Self-Injury SMQ (Week 144 Analysis, Safety Analysis Set)**

| | GEN (N = 866) | STB (N = 867) |
|---|---|---|
| Suicide Events by Suicide/Self-Injury SMQ[a] | | |
| Depression Suicidal | 0 (0.0%) | 3 ( 0.3%) |
| Suicidal Ideation | 9 ( 1.0%) | 8 ( 0.9%) |
| Suicide Attempt | 3 ( 0.3%) | 4 ( 0.5%) |
| Completed suicide | 1 ( 0.1%) | 0 (0.0%) |
| Intentional self-injury | 1 ( 0.1%) | 0 (0.0%) |

Adverse events were coded using MedDRA 19.0.
a Preferred terms from the suicide/self-injury SMQ reported for the same subject were only counted once.
Source: GEN Week 144 ISS, Table 7

## 5.7. Fasting Lipid Parameters

Consistent with results submitted previously, data through 144 weeks of treatment for ART-naive subjects in the current submission showed greater increases in the fasting lipid parameters total cholesterol, direct LDL, high-density lipoprotein (HDL), total cholesterol to HDL ratio, and triglycerides in subjects treated with GEN compared with those treated with STB ($p < 0.001$ for the difference between treatment groups for fasting total cholesterol, direct LDL, HDL, and triglycerides; m2.7.4, Section 3.2). The median (Q1, Q3) change from baseline at Week 144 in the total cholesterol to HDL cholesterol ratio was 0.2 (−0.3, 0.7) in the GEN group and 0.1 (−0.4, 0.6) in the STB group ($p = 0.006$ for the difference between groups).

Similar percentages of subjects in each treatment group initiated lipid-modifying medications during the studies (GEN 5.5%, 48 subjects; STB 5.8%, 50 subjects).

The effect of TDF on the level of plasma lipids has generally been associated with the higher TFV plasma levels reported in subjects who receive TDF {Behrens et al 2012}, {Tungsiripata et al 2010}, {Mulligan et al 2013}. Subjects who receive TAF have plasma TFV exposure that is > 90% lower than in subjects who receive TDF; the changes in fasting lipids reflect a reduction of this off-target TFV lipid effect. Based on available evidence, the higher levels of specific plasma lipids are not an adverse effect of TAF but rather an effect of the markedly lower plasma TFV in subjects receiving GEN.

## 5.8. Safety in Special Groups and Situations

Safety information pertinent to the use of GEN, DVY, and ODE in special groups and situations is described in m2.7.4, Section 5, with appropriate information included in the respective prescribing information. Key findings for data presented through 144 weeks of treatment in ART-naive adults are consistent with the findings in the original submissions demonstrating that the AE profile for subjects receiving GEN was not affected by sex, age, race, region, HIV-1 RNA level, or CD4 count.

## 5.9. Postmarketing Experience

Postmarketing safety data for GEN, DVY, and ODE and the individual components are carefully evaluated on an ongoing basis for any new safety issues, and labeling changes are submitted to regulatory authorities when new adverse reactions are identified. There have been no newly identified adverse reactions for GEN, DVY, or ODE based on the postmarketing data available to date.

# 6. BENEFITS AND RISKS CONCLUSIONS

## 6.1. Benefits

Data for GEN, DVY, and ODE submitted previously have demonstrated potent and durable ARV activity and a favorable safety and tolerability profile with a preferential bone and renal safety profile compared with STB. Data presented through 144 weeks of treatment in ART-naive adults in the current submission demonstrate the superior efficacy of GEN compared to STB over 144 weeks of treatment. Superiority of GEN over STB at 144 weeks was primarily driven by fewer subjects in the GEN group having no virology data in the Week 144 window than subjects in the STB group. The main reasons for the difference were a higher rate of AE/deaths leading to discontinuation of study drugs, including discontinuations due to bone and renal events, and a higher rate of discontinuations due to other reasons in the STB group. Data presented through 144 weeks of treatment continue to support an acceptable safety and tolerability profile with bone and renal advantages compared with STB. In summary, GEN, DVY, and ODE have many benefits as a chronic treatment, including the following:

- **GEN, DVY, and ODE are Highly Efficacious with a Low Incidence of Resistance Development**

GEN demonstrated potent and durable ARV activity which was noninferior and statistically superior to treatment with STB following 144 weeks of treatment based on the percentage of subjects with virologic suppression using both HIV-1 RNA thresholds for the US FDA-defined snapshot algorithm (defined as HIV-1 RNA < 50 copies/mL and < 20 copies/mL). Results were supported by several sensitivity analyses, and immunologic benefits of treatment were demonstrated by increases in CD4 cell counts. Results of subgroup analyses support GEN, DVY, and ODE as effective treatments for HIV-1 infection regardless of demographics and disease baseline characteristics.

The development of drug resistance and loss of regimen efficacy is a risk of ART. Generally, the risk of resistance development is dependent on the efficacy, tolerability, and adherence to an ART regimen. The frequency of resistance development in ART-naive subjects taking GEN was very low and comparable to that of the STB group through 144 weeks of treatment.

- **GEN, DVY, and ODE are Well Tolerated and Longer Term Treatment Offers Advantages Over STB**

Treatment with GEN continued to be well tolerated and offers advantages over STB in ART-naive subjects through 144 weeks of treatment. Fewer subjects in the GEN group than the STB group had AEs that resulted in discontinuation of study drugs, primarily driven by study drug discontinuation due to bone and renal events in the STB group. Additionally, fewer subjects in the GEN group than the STB group had AEs considered related to study drugs by the investigator. No new ADRs were identified.

- **GEN, DVY, and ODE have a Preferential Bone and Renal Safety Profile Compared with STB**

Treatment with GEN, DVY, and ODE is associated with a preferential bone safety profile, as compared with STB, with statistically significant differences in tests of bone metabolism. Specifically, GEN resulted in less change in BMD at both the hip and spine compared to STB.

Treatment with GEN is associated with preferential renal safety profile, as compared with STB, with statistically significant differences in multiple tests of renal function. Specifically, GEN resulted in less change in serum creatinine, less proteinuria, and less renal tubular proteinuria compared with STB. In addition, no cases of proximal renal tubulopathy (including Fanconi Syndrome) were reported for subjects who received GEN. In contrast, 4 cases of clinically evident proximal renal tubulopathy were reported for subjects who received STB and a total of 12 subjects discontinued study drugs due to a renal and urinary disorder or associated investigation AE compared to none for subjects who received GEN ($p < 0.001$).

## 6.2. Risks

Safety concerns for GEN, DVY, and ODE are discussed in the respective RMPs (GEN version 2.0; DVY version 1.0, ODE version 1.0) within which Studies GS-US-292-0104 and GS-US-292-0111 are pharmacovigilance activities for the following safety concerns:

- *Important potential risk of suicidal ideation/suicide attempt in patients with a pre-existing history of depression or psychiatric illness (applicable to GEN only):* AEs associated with suicidal ideation and suicide attempt continued to be infrequent in Studies GS-US-292-0104 and GS-US-292-0111 through 144 weeks of treatment, with none considered related to study drug by the investigator (see Section 5.6).

- *Missing information on long-term safety:* Treatment with GEN was well tolerated in ART-naive adults with no new safety signals detected through 144 weeks of treatment. GEN continued to have a preferential bone and renal safety profile with no reports of proximal renal tubulopathy, and resulted in less change in BMD at both the hip and spine compared to STB. There were no reports of posterior uveitis.

- *Missing information on development of drug resistance in long-term use:* The frequency of resistance development in ART-naive subjects taking GEN was very low and comparable to that of the STB group through 144 weeks of treatment.

Overall, there were no changes to these safety concerns or any of the other safety concerns included in the respective RMPs based on the Week 144 data from Studies GS-US-292-0104 and GS-US-292-0111.

No new warnings or precautions are warranted based on the data summarized in the current submission.

## 6.3. Conclusions

Genvoya, DVY, and ODE continue to demonstrate a positive benefit:risk ratio over a longer-term exposure of 144 weeks. GEN demonstrated superior antiviral efficacy and a safety profile that offers advantages over STB in ART-naive subjects through 144 weeks of treatment. GEN, DVY, and ODE are well tolerated and associated with a preferential bone and renal safety profile compared with STB.

# 7. REFERENCES

Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. Antivir Ther 2012;17 (6):1011-20.

Costagliola D. Demographics of HIV and aging. Curr Opin HIV AIDS 2014;9 (4):294-301.

Mulligan K, Glidden DV, Anderson PL, McMahan V, Guanira JV, Lama JR, et al. Decreases in cholesterol in HIV-seronegative men using emtricitabine/tenofovir pre-exposure prophylaxis: lipid results of iPrEx [Abstract O05]. 15th International Workshop on Co-morbidities and Adverse Drug Reactions in HIV; 2013 October 15-17; Brussels, Belgium.

Tungsiripata M, Kitchb D, Glesbyc MJ, Guptad SK, Mellorse JW, Moranf L, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: A CTG5206. AIDS 2010;24 (1):1781-4.