

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207561Orig1s000

MEDICAL REVIEW(S)



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products**

Date: October 1, 2015
Drug Name: Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination tablet)
NDA: 207561
Applicant: Gilead Sciences, Inc.
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Myung-Joo Hong, Regulatory Project Manager, Division of Antiviral Products
Subject: Consult to review the labeling of renal safety findings for a single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

Background

Genvoya is a new four drug fixed-dose combination product with a proposed indication of treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. This product combines the approved drugs elvitegravir (integrase inhibitor; EVG; Vitekta), cobicistat (pharmacokinetic enhancer for EVG; COBI; Tybost), and emtricitabine (nucleoside reverse transcriptase inhibitor; FTC; Emtriva) along with a novel nucleotide reverse transcriptase inhibitor tenofovir alafenamide fumarate (TAF).

Tenofovir-containing products are known to cause renal toxicity including Fanconi Syndrome and acute renal failure. According to the applicant, TAF has better entry and concentration in HIV-target cells than tenofovir disoproxil fumarate (TDF), thereby allowing the administration of smaller doses and reducing systemic tenofovir exposure and renal toxicity. In addition, preclinical studies suggest that TAF is less likely to accumulate in renal proximal tubules in an OAT-dependent manner, supporting the potential for an improved renal safety profile.

With the current NDA, Gilead submitted a renal safety study (GS-US-292-0112) intended to support use of Genvoya in patients with an estimated creatinine clearance of $\geq 30\text{mL/min}$. The Division of Cardiovascular and Renal Products was previously consulted regarding the interpretation the study's findings and associated labeling (see review dated May 29, 2015). On August 7, 2015, the applicant submitted revised labeling. The Division of Antiviral Products requested input on the renal aspects of Sections 5.7 and 6.1. Our feedback is reflected in the draft label and comments provided to the applicant on September 17, 2015 (see document appended to this review). The rationale for the deletion (b) (4) in Section 6.1 of the label is not captured in the attached label; for purposes of documentation, we are providing our rationale below.

Rationale for the deletion (b) (4) in Section 6.1

1. (b) (4)

We recommended limiting the renal laboratory information presented in Section 6 to changes in serum creatinine and urine protein-to-creatinine ratio. In addition, we recommended

reporting absolute (b) (4) changes in protein-to-creatinine ratio. Because tenofovir containing products can cause increases in serum creatinine and tubular proteinuria, we think this information is important to include in Section 6 of the label. We did not think the other information was needed.

2. We recommended removal of (b) (4) because the purpose of Section 6 is to describe the safety findings, (b) (4).

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Attachments: [9.17.15.PI to Gilead.docx](#)
[9.17.15.PI to Gilead.pdf](#)

Hi Erik, please find attached the draft GENVOYA labeling proposal with comments from the review team embedded. Please provide your response by COB on **September 30, 2015**. Please let me know if you have any questions.

*Warm Regards,
Pat*

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51 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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Clinical Review
William B. Tauber, M.D.
NDA 207561
Generic Name Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide
Trade Name: Genvoya™

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	207561
Priority or Standard	Standard
Submit Date(s)	05 November 2014
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PDUFA Goal Date	04 November 2015
Division / Office	Division of Antiviral products/Office of Antimicrobial Products
Reviewer Name(s)	William Tauber, M.D. Peter Miele, M.D. Andres Alarcon, M.D.
Review Completion Date	13 July 2015
Established Name	elvitegravir/cobicistat /emtricitabine /tenofovir alafenamide (E/C/F/TAF)
Trade Name	Genvoya™
Therapeutic Class	Integrase inhibitor, Pharmacokinetic Enhancer, Nucleoside reverse transcriptase inhibitor, Nucleotide reverse transcriptase inhibitor
Applicant	Gilead Sciences, INC
Formulation(s)	Fixed Dose Combination (FDC) tablet EVG 150mg/ COBI 150mg / FTC 200mg/TAF 10mg
Dosing Regimen	One tablet taken once per day
Indication(s)	Treatment of chronic HIV-1 infect
Intended Population(s)	Adult and Adolescent patients (12 years and older) infected with HIV-1 infection all serotypes

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (E/C/F/TAF) fixed-dose combination (FDC) for use in three HIV-1 infected populations. The first is treatment naïve adults and adolescents (ages 12-17). The second are those adults currently stably virologically suppressed with no history or viral resistance or viral failure who desire to switch their antiretroviral regimen. The third are adults with mild renal impairment defined as having a creatinine clearance of at least 50mL/min. This recommendation is based on the data contained in this NDA submission 207561. In the two pivotal Phase 3 trials, GS-US-292-0104 and GS-US-292-0111, E/C/F/TAF was demonstrated to be non-inferior to Stribild®. In the Phase 3 study GS-US-292-0109, switching to E/C/F/TAF was demonstrated to be non-inferior to remaining on stable, virologically successful treatment with a regimen containing emtricitabine/tenofovir disoproxil fumarate and a third agent(s); either elvitegravir/cobicistat (Stribild®), efavirenz (Atripla®), atazanavir/cobicistat or atazanavir/ritonavir. In the Phase 3 study GS-US-292-0112, switching to E/C/F/TAF in HIV-1 infected individuals with a creatinine clearance equal or greater than 50mL/min from a stable, virologically successful antiretroviral regimen was demonstrated to be sufficiently safe. The safety profile of E/C/F/TAF in adults and adolescents with creatinine clearance equal to or greater than 50 mL/min was acceptable with no deficiencies to preclude approval.

1.2 Risk Benefit Assessment

Benefits

Single tablet, once daily regimens offer patient convenience, the potential for increased compliance and fewer patient related dosing errors. There are three such regimens currently approved; Atripla®, Complera® and Stribild®. Stribild® is of particular relevance to the benefit/risk assessment of E/C/F/TAF since the two are identical except for the tenofovir prodrug component, tenofovir disoproxil fumarate for Stribild® and tenofovir alafenamide for E/C/F/TAF. The antiviral efficacy of E/C/F/TAF has been demonstrated to be non-inferior to that of Stribild® for treatment naïve, and virologically suppressed adults without history of virologic failure who desire to switch regimens. Immunologic benefit in treatment naïve as gauged by improvements in CD4 counts are similar to those noted in the comparator groups.

It has been appreciated that tenofovir disoproxil fumarate containing antiviral regimens are associated with adverse impact on bone mineral density (BMD) and renal proximal tubular function. This adverse impact has been associated with tenofovir exposures. Like tenofovir disoproxil fumarate, tenofovir alafenamide is a prodrug of tenofovir. It

differs in its penetration into target cells permitting much reduced dosages. These reductions in tenofovir exposure could translate into lesser problems with BMD and renal function.

In the pivotal studies (GS-US-292-0104 and GS-US-292-0111) decreases in BMD as measured by DEXA scan were observed to be less in the E/C/F/TAF group compared to that of the Stribild® group. The clinical impact of these differences is not established. There were no clear instances of fragility fracture in these clinical trials. However it is presumed that smaller decreases in BMD over time may result in lowered risk for development of osteoporosis. Complicating this assessment is the stabilization of BMD measurements in most individuals taking tenofovir disoproxil fumarate after a year. The Applicant provided data regarding biomarkers which seem to indicate less bone turnover with E/C/F/TAF but none of these are validated (b) (4) DEXA scan results are relevant to the individual and are of less value comparing relative benefit between individuals.

The other issue where E/C/F/TAF use may offer a benefit over Stribild® is in renal proximal tubular function. In the pivotal studies, both E/C/F/TAF and Stribild® use were associated with increases in serum creatinine and decreases in creatinine clearance as estimated by Cockcroft-Gault methodology. The serum creatinine increases and creatinine clearance decreases were statistically lower in the E/C/F/TAF group compared to the Stribild group. Unvalidated biomarkers including retinol binding protein, beta-2 microglobulin and proteinuria by dipstick favored E/C/F/TAF. Quantitative proteinuria measurements such as Urine Albumin to Creatinine Ratio (UACR) and Urine Protein to Creatinine Ratio (UPCR) generally were favorable to E/C/F/TAF.

Study GS-US-292-0112 enrolled individuals with mild ($eGFR \geq 50\text{mL/min} < 70\text{mL/min}$) and moderate ($eGFR \geq 30\text{mL/min} < 50\text{mL/min}$) renal impairment who were virologically suppressed. Although the majority of these subjects were switched from tenofovir disoproxil fumarate containing regimens (180/242 75%) many were receiving renal dosing. The data from this study indicated that daily dosing with E/C/F/TAF in individuals with baseline creatinine clearances of at least 50 mL/min was well tolerated. The implications of this would be the expansion of indicated population to include those with creatinine clearances of at least 50mL/min as opposed to the lower limit of 70mL/min for Stribild®.

Risks

The initiation of E/C/F/TAF is associated with substantial increases in serum lipids which exceed increases observed with the initiation of Stribild®. In the treatment naïve population, median and mean increases in total cholesterol of 29mg/dL and 31 mg/dL were seen with E/C/F/TAF compared to 15 mg/dL and 23 mg/dL with Stribild®. For LDL cholesterol relative differences are even greater with increases of a median of 14 mg/dL and mean of 16 mg/dL with E/C/F/TAF compared to 3 mg/dL and 4 mg/dl respectively for Stribild®. Approximately 40% of E/C/F/TAF subjects compared to 20% of Stribild® subjects went from normal total cholesterol to Grade 1 or higher. In the treatment naïve

trials nine individuals taking E/C/F/TAF went from normal levels of LDL cholesterol to > 190mg/dL, a level at which treatment for hyperlipidemia is strongly advised. The treatment of hyperlipidemia is undergoing change from target numbers at this time. None the less, it is certain that E/C/F/TAF use if approved will prompt ongoing discussion between patients and their providers regarding the health impact of elevated lipids.

Ocular safety was a concern during the conduct of these trials. During the preclinical development of E/C/F/TAF posterior uveitis was detected in the dog toxicology studies at the highest doses at the 3 and 9 month time period. Because of this finding, the Applicant instituted increased vigilance for eye disorders including the institution of a substudy and investigator instruction and incorporation of specific language into the protocols and informed consents. This increased vigilance did not identify an increased incidence of any form of uveitis. None the less, there did appear to be some evidence of increased inflammation of E/C/F/TAF use compared with that of Stribild® with numerically higher levels of conjunctivitis, visual blurring, and photophobia. Continued heightened vigilance is recommended.

Emtricitabine, one of the components of both Stribild® and E/C/F/TAF is not recommended for daily use in individuals with creatinine clearance lower than 50 mL/min. Below 50 mL/min every other day renal dosing is recommended. Study GS-US-292-0112, studied the use of E/C/F/TAF in subjects with eGFR by Cockcroft-Gault methodology of > 30 mL/min to 69 mL/min. Pharmacokinetic testing has demonstrated increased emtricitabine exposure of 115% in subjects with creatinine clearances less than 50mL/min receiving a daily dose of 200mg. Increases in the incidence in symptoms of dizziness and Grade 3 amylase levels in individuals with creatinine clearance ≥ 30 mL/min but < 50mL/min remains concerning. This concern combined with the observed development of acute renal failure in two participants with moderate renal impairment in this study makes expansion of the indicated population to those with eGFR < 50mL/min potentially unsafe pending review of the final data from this study. The expansion of indicated population to include those with eGFR < 50mL/min is not recommended pending additional data.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this NDA submission.

1.4 Recommendations for Postmarket Requirements and Commitments

Considerations at this time include the following:

1. Submit the complete 48 week study report results of Study GS-US-292-0112
2. Submit complete study report for adolescent Study GS-US-292-0106
3. (b) (4)

2 Introduction and Regulatory Background

HIV-1 infection is a life threatening and serious disease with approximately 35 million people infected worldwide and more than 1.2 million infected in the United States. HIV-1 rapidly develops resistance to single agents and the coadministration of multiple agents is needed for effective treatment. The standard of care for treatment of HIV-1 infection utilizes combination antiretroviral (ARV) therapy targeting preferably different components of the viral life cycle. The evolution of ARV therapy has been notable for the development of simpler, easier regimens which enhance patient adherence, a major determinant of successful therapy. At this time there are several approved ARV regimens consisting of a single Fixed Dose Combination (FDC) containing at least three antiviral agents combined together in a single tablet as a complete regimen taken once per day.

The current application requests approval of Genvoya™, a new FDC which contains three of the four components at identical dosage of the approved FDC complete regimen Stribild®. The agents that differ between the two FDC are both prodrugs of tenofovir (TFV) a nucleotide that interferes with HIV-1 reverse transcriptase. In Stribild® the tenofovir prodrug is tenofovir disoproxil fumarate (TDF) and in Genvoya™ it is tenofovir alafenamide fumarate (TAF). The major difference between TDF and TAF relates to cellular uptake in target cells. TDF is not readily absorbed into target cells but rather delivers TFV across the digestive tract into the blood stream where TFV is generated from where it enters target cells. TAF is more readily absorbed in target cells where the active agent TFV-diphosphate is generated at higher concentration. This absorption differential permits TAF to be given at doses which are 90% lower than TDF.

Chronic TDF use is associated with adverse impact on renal function up to and including renal failure and Fanconi Syndrome and decreased bone mineral density measurements by DXA scan. TFV is presumed to be the putative cause of these adverse events. Gilead has hypothesized that the lowered serum TFV concentrations found with TAF will result in lowered incidence of these adverse events making TAF safer to use compared with TDF.

2.1 Product Information

Generic (trade) name:	E/C/F/TAF (GENVOYA™)
Pharmacological class:	Elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor (INSTI), Cobicistat (COBI), a CYP3A inhibitor and Emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs)
Proposed indication:	GENVOYA is indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Dosing regimens:	elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, tenofovir alafenamide 10mg once daily
Dosage form:	Fixed Dose Combination tablet

GENVOYA™ is a four drug fixed drug combination tablet which is intended to provide a complete HIV-1 treatment regimen for patients with susceptible virus. EVG is an INSTI that prevents the integration of HIV-1 genetic information into the host-cell genome. COBI is a structural analogue of ritonavir devoid of ARV activity. It is a mechanism based cytochrome P450 3A (CYP3A) inhibitor that enhances or “boosts” the exposure of CYP 3A substrates including EVG. FTC and TAF are nucleoside/nucleotide (NRTIs) that inhibit the function of HIV-1 reverse transcriptase. FTC has been approved and TAF is a new chemical entity under review for approval herein.

2.2 Tables of Currently Available Treatments for Proposed Indications

Excluding fixed drug combinations or different formulations there are 28 drugs approved for the treatment of HIV-1 infection. The standard of care practice involves the administration of multiple drugs targeting different events in the viral life cycle. Based on the mechanism of action on the life cycle of HIV-1, the drugs are classified into 6 HIV-1 drug classes: nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PIs) fusion/entry inhibitors, CCR5 inhibitors, and integrase inhibitors (INSTI). Table 1 summarizes the approved antiretroviral drugs. If approved, the NME TAF can be used as an alternative to several nucleosides/nucleotides if available in other formulations.

Table 1- Approved Antiretroviral Drugs

Drug Class	Generic Name	Trade Name	
NRTI	Zidovudine (AZT)	Retrovir®	
	Didanosine (ddl)	Videx®	
	Stavudine (d4T)	Zerit®	
	Lamivudine (3TC)	Epivir®	
	Abacavir	Ziagen®	
	Tenofovir (TDF)	Viread®	
	Emtricitabine (FTC)	Emtriva®	
NNRTI	Delavirdine	Rescriptor®	
	Nevirapine	Viramune®	
	Efavirenz	Sustiva®	
	Etravirine	Intelence®	
	Rilpivirine	Edurant®	
PI	Indinavir	Crixivan®	
	Ritonavir	Norvir®	
	Saquinavir, hard gel	Invirase®	
	Saquinavir, soft gel	Fortavase®	
	Nelfinavir	Viracept®	
	Amprenavir	Agenerase®	
	fos-amprenavir	Lexiva®	
	Atazanavir (ATV)	Reyataz®	
	Lopinavir/ritonavir (LPV/r)	Kaletra®	
	Tipranavir	Aptivus®	
	Darunavir (DRV)	Prezista®	
	Fusion/Entry inhibitor	Enfuvirtide (ENF)	Fuzeon®
	CCR5 receptor inhibitor	Maraviroc	Selzentry®
Integrase Inhibitor	Raltegravir	Isentress®	
	Elvitegravir	Vitekta®	
	Dolutegravir	Tivicay®	

2.3 Availability of Proposed Active Ingredient in the United States

Three of the 4 drugs combined in GENVOYA FDC (EVG, COBI, and FTC) are available as single drugs for administration in the United States. In addition, all three at the same dosage and frequency of administration are components of the approved FDC ARV Stribild® approved on 27 August 2012.

FTC was first approved for treatment of HIV-1 in the United States on 02 July 2003 and remains available for use.

Clinical Review
William B. Tauber, M.D.
NDA 207561
E/C/F/TAF (Genvoya)

EVG used in combination with ritonavir boosted protease inhibitors and other drugs was first approved for treatment of HIV-1 infection in the United States on 24 September 2014 and remains available for use.

COBI used in combination with atazanavir or darunavir in combination with other ARV was first approved for treatment of HIV-1 infection in the United States on 24 September 2014 and remains in use.

TAF has not been approved and is not marketed elsewhere in the world.

2.4 Important Safety Issues with Consideration to Related Drugs

Stribild® is a 4 drug FDC nearly identical to GENVOYA. It differs from GENVOYA only in the use of tenofovir prodrug tenofovir disoproxil fumarate (TDF) rather than tenofovir prodrug tenofovir alafenamide (TAF).

In licensing trials for Stribild®, the most common adverse events included gastrointestinal disorders (predominantly diarrhea and nausea) and infections and infestations (led by upper respiratory infections). Musculoskeletal adverse events were also more common in the Stribild® (21%) arms compared to comparators (16%). In addition, headache and abnormal dreams were noted in more than 5% of Stribild® recipients.

Adverse reactions from clinical trials of the components of Stribild®

EVG was compared with raltegravir in a single clinical trial. Overall, the type and frequency of adverse events were similar between the two products. The most common adverse event related to elvitegravir was diarrhea at 7% followed by nausea (4%) and headache (3%). Less common adverse reactions observed in treatment experienced subjects included psychiatric disorders including suicidal thoughts and attempts as well as rash. Laboratory abnormalities were generally similar to the comparator and included lipid abnormalities in 5% and increases in amylase, hematuria, and total bilirubin in 6%.

Cobicistat causes increases in serum creatinine and decreases in estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function.

Adverse reactions in other clinical trials where FTC has been administered are diffuse and include peripheral neuropathy, anxiety, and depression. Skin discoloration has been reported with higher frequency among FTC treated subjects manifested by hyperpigmentation of the palms and soles which was generally mild and asymptomatic.

Laboratory

In the licensing trials, renal laboratory abnormalities (renal failure, Fanconi's syndrome, and increased blood creatinine) leading to discontinuation were more notable in the Stribild® arm. Overall there was a higher incidence of graded creatinine elevations and graded proteinuria in the Stribild® arm compared to its comparators. Of note, the incidence and severity of creatinine elevations were higher in the Stribild® arm than had been previously noted in clinical trials in which TDF was administered.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

This section will summarize those notable regulatory events which had a direct effect on the current submission for GENVOYA.

End of Phase 2 meeting (EOP2) for IND 111007: This Face-to-Face meeting occurred on 17 December 2012. Specific objectives of the meeting included: [REDACTED] (b) (4) and discussion as to whether the proposed Phase 3 clinical studies are adequate to support registration of E/C/F/TAF for the proposed indication.

The following issues relevant to the E/C/F/TAF development program were discussed with Gilead Sciences at the EOP2 meeting:

- Proposed study GS-US-292-0104 combined with another adequate and well controlled trial would be adequate to support approval and may proceed.
- Proposed study [REDACTED] (b) (4) was deemed unsuitable [REDACTED] (b) (4)
- GS-US-292-0111 differing only from 0104 only in geographic area of study was proposed and accepted as the second pivotal trial
- In both studies 0104 and 0111, Stribild® was the comparator.
- In studies 0104 and 0111 a non-inferiority margin of 12% was adequate to permit assessment of comparative efficacy contribution of TAF versus TDF.
- A proposed study of E/C/F/TAF in subjects with mild to moderate renal insufficiency (creatinine clearance of $\geq 30\text{mL/min}$) was acceptable to the Agency with the caveat that adequate safety data to support doses of FTC above those approved in its product label would be needed.
- Study GS-US-292-0109 switch study was acceptable to the Agency
- Study GS-US-292-0106 PK and safety study in adolescents could

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- support an indication for pediatric patients 12 to <18 years of age.
(b) (4)
- Gilead Sciences would submit PREA pediatric study plan within 60 days

Fast Track Designation

Fast Track Designation for E/C/F/TAF was granted on 23 January 2013.



Pre-NDA

On March 18, 2014, Gilead Sciences requested a pre-NDA meeting to discuss:

- The proposed clinical studies to be included in the E/C/F/TAF NDA to support the proposed indication
- The statistical analyses to be conducted for the Phase 3 clinical studies and content, format and proposed pooling strategy to generate Integrated Summaries of Efficacy and Safety
- The content and format of the E/C/F/TAF FDC NDA and NDA Safety Update

The following issues were discussed in correspondence between the Agency and

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Gilead Sciences related to the pre-NDA meeting:

- Gilead Sciences proposed submission of Studies GS-US-292-0104, 0111, 0109, 0106 and (b) (4). The Division indicated that the submission of (b) (4) was premature at the time of the NDA.
- The Applicant inquired as to whether a Type C safety meeting in November 2014 should be requested if not prompted by receipt of the Phase 3 data. The Agency indicated that the Applicant should provide a topline result summary of all pivotal trials as soon as those data are available. Additionally they should be prepared to schedule a Type C meeting/teleconference if the Agency has specific concerns related to the study results or recommendations for additional analyses.

A type C meeting scheduled for 30 October 2014 to discuss the Phase 3 clinical data supportive of the NDA submission was canceled after the Division was able to review top line clinical data from the Phase 3 program. The Division requested that as part of the NDA, in addition to deaths, SAEs, and all discontinuations, that narratives would be provided for all subjects who experienced a TEAE with symptoms consistent with posterior uveitis, myocardial infarction and stroke. In addition, the Division informed the Applicant that a consultation with DBRUP to assist in evaluating and labeling BMD/bone biomarker data was being considered.

2.6 Other Relevant Background Information

There is no other relevant background information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site audits by Division of Scientific Investigations (DSI) were conducted for this NDA. The site selection process involved the GENVOYA review team and Dr. Antoine El-Hage from DSI. Please refer to Dr. El-Hage's DSI review for further details. Eight sites were inspected, four domestic and four non-US.

The inspected sites and the Primary Investigators were:

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Table 2 Principle Investigators and Sites inspected by DSI

Primary Investigator	Location
Melanie Thompson, M.D.	Atlanta, Georgia, USA
Rachel Koening, M.D.	Santo Domingo, Dominican Republic
Gordon Crofoot, M.D.	Houston, Texas, USA
Ploenchan Chetchotisakd, M.D.	Khon Kaen, Thailand
Armin Reiger, M.D.	Vienna, Austria
Daniel P. Podzamczar, M.D.	Barcelona, Spain
Cynthia Brinson, M.D.	Austin, Texas, USA
Paul Benson, M.D.	Berkley, Michigan, USA

The data from these sites were deemed acceptable in support of Gilead Sciences NDA for GENVOYA™.

3.2 Compliance with Good Clinical Practices

The clinical trials were conducted in accordance with the ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of selected clinical sites by DSI found the data provided by the sites to be acceptable (refer to 3.1 for additional details).

3.3 Financial Disclosures

The Applicant examined financial data regarding significant payments and equity for all participating Phase 2 and 3 investigators per 21 CFR Part 54. During review of the financial disclosure forms (Form 3455) it was noted that a substantial number of site principal investigators (25-45%, varying by study) participating in Studies 292-0102, 292-0104, 292-0109, and 292-0112 were identified in the Applicant's financial certification and disclosure statements as having received significant payments of greater than \$25,000 beyond trial conduct costs and or had reported equity interests of greater than \$50,000. The table below was derived by the clinical reviewer.

Table 3 Comparison of Numbers and Categories of Investigators by study and requirement for Financial Disclosure

Numbers and Categories of Investigators participating per Study	Studies Submitted					
	0102	0104	0111	0106	0109	0112
Principal Investigators per study total	55	138	150	21	183	59
Principal Investigators No Financial Disclosure (FD) required	30 (55%)	93 (67%)	103 (69%)	21	136 (74%)	34 (58%)
Principal Investigators Financial Disclosure (FD) required	25 (45%)	45 (33%)	47 (31%)	0	47 (26%)	25 (42%)
Sub-investigators per study total	215	581	678	86	680	371
Sub-Investigators No FD required	210 (98%)	574 (98%)	669 (98%)	86	673 (99%)	367 (99%)
Sub-Investigators FD required	5 (2%)	7 (2%)	9 (2%)	0	7 (1%)	4 (1%)

A request for information was sent to the Applicant requesting additional analysis. The Applicant's responses are summarized below.

The Applicant corrected the reviewer derived table above. The percentage of sites with PIs/Sub-investigators with financial disclosures in Study 0102 was 57% and about 27-34% of the sites in Studies 0104, 0111, 0109 and 0112. The percentage of subjects enrolled at sites where PIs/Sub-investigators had financial disclosure ranged from 21% in Study 0112 to 63% in Study 0102. In their response to the review team inquiry, the Applicant provided the following table illustrating these points and comparing GENVOYA arms to STRIBILD arms.

TABLE 4 Applicant Provided Number and Percent of Subjects and Sites Staffed by PIs and Sub-Investigators with Financial Disclosures by Study

Table 1. Number and Percent of Subjects and Sites Staffed by PIs and Sub-Investigators with Financial Disclosures by Study

Study (Analysis Set)	Treatment Group	Number of Sites with Financial Disclosures / Total Number of Sites (%)	Number of Subjects at Sites with Financial Disclosures / Total Number of Subjects (%)
Study 292-0102 (Safety Analysis Set)	E/C/F/TAF	20/35 (57.1%)	71/112 (63.4%)
	STB	17/30 (56.7%)	35/58 (60.3%)
Study 292-0104 (Safety Analysis Set)	E/C/F/TAF	34/108 (31.5%)	143/435 (32.9%)
	STB	35/112 (31.3%)	145/432 (33.6%)
Study 292-0111 (Safety Analysis Set)	E/C/F/TAF	35/113 (31.0%)	131/431 (30.4%)
	STB	35/117 (29.9%)	150/435 (34.5%)
Study 292-0109 (Safety Analysis Set)	E/C/F/TAF	45/167 (26.9%)	332/959 (34.6%)
	FTC/TDF + 3 rd Agent	42/151 (27.8%)	176/477 (36.9%)
Study 292-0109 (Week 48 Full Analysis Set)	E/C/F/TAF	44/129 (34.1%)	326/799 (40.8%)
	FTC/TDF + 3 rd Agent	42/123 (34.1%)	176/397 (44.3%)
Study 292-0112 (Safety Analysis Set)	E/C/F/TAF Cohort 1	22/69 (31.9%)	51/242 (21.1%)
	E/C/F/TAF Cohort 2	1/6 (16.7%)	1/6 (16.7%)

Sources: Adhoc Tables 7396.1, 7397.1, 7398.1, 7399.1, and 7400.1

The Applicant provided a sensitivity analysis of virologic response at Week 48 (Studies 0102, 0104, 0109, 0111) and Week 24 (Study 0112) which excluded subjects enrolled from sites staffed by PIs/Sub-investigators with financial disclosures (FD). That sensitivity analysis demonstrated that except for Study 0102 where the E/C/F/TAF arm virologic response was 82.9% and Stribild® arm virologic response was 95.7%, the success rates seen with the Full Analysis Set (FAS) and the FAS excluding FD sites were similar. The reason Study 0102 was at variance from the others was not known but was theorized to be the result of its small size.

The Applicant also performed a sensitivity analysis of adverse events. The Applicant assessed the data generated in this analysis which considered proportions of subjects experiencing any TEAE, any Grade 2, 3, or 4 TEAEs, any Grade 3 or 4 TEAE, any study drug-related TEAE, Grade 2, 3, or 4 study drug related TEAE, Grade 3 or 4 study drug-related TEAE, serious TEAE, study drug-related TEAE, TEAE leading to premature study drug discontinuation, and treatment emergent death. In the final analysis, the Applicant determined that except for Study 0102, all the safety data in the remaining studies were comparable between the Safety Analysis Set (SAS) and the data generated by the sensitivity analysis.

The Applicant compared the proportion of adverse events considered to be drug related between sites with financial disclosure versus those without financial disclosure. The Applicant's analysis was that except for Study 0102 and the treatment naïve arm of Study 0112 (6 subjects total) there was no evidence of biased

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determination of adverse event study drug relatedness. The data results are represented in tabular form below from their response.

Table 5 Numbers and Percentage of Subjects with Treatment-Emergent Study Drug Related Adverse Events by Study

Table 3. Number and Percentage of Subjects with Treatment-Emergent Study-Drug-Related Adverse Events by Study

Study (Safety Analysis Set)	Treatment Group	Number of Subjects with Drug-Related AEs / Total Number of Subjects (%)	
		Enrolled at Sites with Financial Disclosure	Enrolled at Sites without Financial Disclosure
Study 292-0102	E/C/F/TAF	23/71 (32.4%)	20/41 (48.8%)
	STB	14/35 (40.0%)	5/23 (21.7%)
Study 292-0104	E/C/F/TAF	57/143 (39.9%)	125/292 (42.8%)
	STB	66/145 (45.5%)	130/287 (45.3%)
Study 292-0111	E/C/F/TAF	45/131 (34.4%)	115/300 (38.3%)
	STB	54/150 (36.0%)	114/285 (40.0%)
Study 292-0109	E/C/F/TAF	64/332 (19.3%)	121/627 (19.3%)
	FTC/TDF + 3 rd Agent	15/176 (8.5%)	46/301 (15.3%)
Study 292-0112	E/C/F/TAF Cohort 1	14/51 (27.5%)	48/191 (25.1%)
	E/C/F/TAF Cohort 2	0/1 (0%)	1/5 (20.0%)

The Applicant indicated that compared to their other recent approval applications, the numbers of principal investigators with financial disclosure requirements in this development program were higher. Their analysis indicated that 75 PIs (21.3% of total PI population) in the E/C/F/TAF development program had financial disclosure requirements compared to 13 (6.4% of total PI population) in the Stribild® development program.

The Applicant's analysis of this increase in proportion of PIs reporting Financial Disclosures in the E/C/F/TAF program is speculative. Factors possibly responsible included increased transparency in reporting Financial Disclosures in accordance with the Sunshine Act, the large size of the PI population needed for the E/C/F/TAF development program, the increased likelihood that individual investigators might be participating in multiple other Applicant studies and the numbers of investigators engaged by the Applicant to promote other Applicant products as well as provide HIV education in general. The Applicant was confident that their standard operating procedure (SOP CR-23010) and Minimization of Bias (MoB) process is able to mitigate any potential for bias among their investigators.

The clinical reviewer agrees with the Applicant that as demonstrated by the sensitivity analysis, efficacy data were largely unaffected by the presence of Financial Disclosure requirements. This probably derives from the double-blind, active comparator study

design of most of the submitted studies.

The overall proportional reporting of all AEs appears to be similar between the sites without Financial Disclosure and those sites with Financial Disclosure. The proportions of AEs rated as Grade 2 or higher are noted to be greater in sites without Financial Disclosure than those with Financial Disclosure. The overall incidence of greater intensity adverse events is noted to be higher in the non-Financial Disclosure sites. This difference ranges from 3% to 9%. Disparity between the two types of sites seems to be predominantly in the assessment of Grade 2 intensity. The relative ratios between study arms are maintained which lessens the likelihood of bias between study agents but the lessening of severity assessment potentially impacts upon the accuracy of the risk benefit ratio calculation.

Table 6 Comparison Adverse Events by Grade and Presence or Absence of FD PIs

	Studies 104/111		Study 102		Study 109		Study 112
	TAF	TDF	TAF	TDF	TAF	TDF	TAF all
NUMBER total	866	867	112	58	959	477	248
NUMBER w/o FD	592(68%)	572(66%)	41 (37%)	23 (40%)	627(65%)	301 (63%)	196 (79%)
NUMBER with FD	274(32%)	295(34%)	71 (63%)	35 (60%)	332(35%)	176(37%)	52 (21%)
AE total	778(90%)	782(90%)	107(96%)	57 (98%)	764(80%)	368 (77%)	214 (86%)
AE without FD	521(88%)	506(89%)	38 (93%)	22 (96%)	489(78%)	239 (79%)	165 (84%)
AE with FD	257(94%)	276(94%)	71(100%)	35(100%)	275(82%)	129 (73%)	49 (94%)
GRADE 2,3,4 total	419(48%)	380(44%)	72 (64%)	29 (50%)	389(41%)	177 (37%)	117 (47%)
Grade 2,3,4 w/o FD	300(51%)	261(46%)	27 (65%)	14 (66%)	275(44%)	121 (40%)	86 (44%)
Grade 2,3,4, w/FD	119(43%)	119(43%)	45 (63%)	15 (43%)	114(35%)	56 (32%)	31 (60%)
Grade 3,4 total	71 (8%)	75 (9%)	13 (12%)	3 (5%)	61 (6%)	32 (7%)	18 (7%)
Grade 3,4 w/o FD	55 (9%)	53 (9%)	7 (17%)	2 (9%)	45 (7%)	22 (7%)	15 (8%)
Grade 3,4 with FD	16 (6%)	22 (7%)	6 (8%)	1 (3%)	16 (5%)	10 (6%)	3 (6%)
SAE total	70 (8%)	59 (7%)	12 (11%)	3 (5%)	42 (4%)	21 (4%)	26 (11%)
SAE without FD	47 (8%)	39 (7%)	6 (15%)	2 (9%)	30 (5%)	14 (5%)	19 (10%)
SAE with FD	23 (8%)	20 (7%)	6 (8%)	1 (3%)	12 (4%)	7 (4%)	7 (13%)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The significant efficacy and safety issues noted in other review disciplines are summarized in this section. Please refer to the Primary Review for the particular discipline for detailed assessments.

4.1 Chemistry Manufacturing and Controls

Please refer to Dr. George Lunn and Dr. Jeffrey Medwid Chemistry review.

A thorough review of the Drug Substance Quality was conducted. The following assessments were made:

Properties/CQAs Relevant to Drug Product Quality

- The solid state form (b) (4) was selected over the (b) (4) (b) (4) which was used in Phase I. The (b) (4) was used in Phase 1 and not beyond. Based on current scientific knowledge, the drug substance may be (b) (4).
- The nomenclature of the name tenofovir alafenamide reflects the current USP practice of not including the salt in the name. Tenofovir alafenamide 10 mg would actually be a higher value if the fumarate were included.
- To ensure a consistent particle size for all future batches of drug substance going into the drug product, Gilead has agreed to incorporate the particle size acceptance limit of NMT (b) (4) μm at d_{90} into the final drug substance specification.
- Information Relevant to Impurity Control: Maximum Daily Dose of TAF fumarate is 10 mg/day for this indication. Acceptable Intake of Mutagenic Impurities: (b) (4) ug/day at 10 mg/day maximum dose = (b) (4) % for TAF fumarate. (w) (4)

The Product Quality reviewers are awaiting the results of a final re-inspection of a manufacturing site found to be non-compliant. It is expected that the results of this re-inspection will be favorable.

If the re-inspection is favorable, then evaluation of the quality aspects of Genvoya tablets supports approval without consideration of specific benefit/risk aspects. This is a solid-oral dosage form with conventional packaging and simple dosing recommendations.

4.2 Clinical Microbiology

Please refer to Dr. Lisa Naeger's Review for detailed assessment. Key findings are summarized below.

Nonclinical Virology

TAF and TDF have a similar resistance profile in cell culture and in clinical trials.

Clinical Virology

In treatment-naïve studies (Study 104 and 111) comparing the efficacy of elvitegravir, cobicistat, emtricitabine and tenofovir alafenamide fumarate (E/C/F/TAF) to elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate (STRIBILD[®]; STB), there were

a similar number of virologic failures in the E/C/F/TAF and STB arms with a similar resistance pattern. At Week 48, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide fumarate substitutions associated with resistance was observed in 7 of 14 subjects with evaluable genotypic data from paired baseline and E/C/F/TAF treatment-failure isolates compared with 6 of 17 treatment-failure isolates from subjects in the STB treatment group. Of the 7 subjects with resistance development in the E/C/F/TAF group, the substitutions that emerged were M184V/I (N = 7) and K65R (N = 1) in reverse transcriptase and T66T/A/I/V (N = 2), E92Q (N = 2), E138K (N = 1), Q148Q/R (N = 1) and N155H (N = 1) in integrase. Of the 6 subjects with resistance development in the STB group, the substitutions that emerged were M184V/I (N = 5) and K65R (N = 1) in reverse transcriptase and E92E/Q (N = 2), E138K (n = 3) and Q148R (N = 2) in integrase. In both treatment groups, most subjects who developed substitutions associated with resistance to elvitegravir also developed emtricitabine resistance-associated substitutions.

In a clinical study of virologically-suppressed subjects (Study 109, N = 799) who switched from a regimen containing emtricitabine/tenofovir disoproxil fumarate and a third agent to E/C/F/TAF, one subject had emergent emtricitabine resistance, with the emergence of M184M/I, out of 4 virologic failure subjects.

This product is approvable from a virology perspective for the treatment of HIV-1 infection in adults and pediatric patients 12 year of age and older who have antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed on a stable antiretroviral regimen for at least 6 months with no history of treatment failure.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Dr. Claudia Wrzesinski's Pharmacology Toxicology review for more details.

Per agreement with the FDA carcinogenicity studies and a perinatal and postnatal study have not been conducted for TAF registration due to the rapid conversion of TAF to TFV resulting in a lack of TAF exposure in rats and TgRasH2 mice.

In general, the toxicity profiles of the 4 agents involved different target organs with no significant overlapping toxicities.

EVG related changes in the cecum and upper small intestine in rats and dogs were due to high local concentrations and were not considered adverse or relevant to clinical use. Potential toxicities related to COBI observed in nonclinical toxicology studies have not

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been observed in clinical studies with E/C/F/TAF. The only toxicity observed in chronic animal studies with FTC was mild reversible anemia at large multiples of clinical exposure. Combination toxicity studies on these 3 agents conducted for Stribild® did not reveal any new or additive toxicity.

The principle target organs of toxicity in animals following oral administration of TAF were the kidney (karyomegaly, tubular degeneration/regeneration), bone (reduction in bone mineral density and mineral content, changes in bone turnover markers and in related hormones), and eye (posterior uveitis in dogs). Renal and bone toxicity findings correlate with the known clinical toxicities for TFV. Cobicistat, EVG, and FTC have not shown any potential for bone toxicity; thus, exacerbation of any TAF effects on bone is not expected.

Minimal to slight infiltration of mononuclear cells of the posterior uvea of dogs was seen in the high dose group with similar severity after 3 and 9 month administration of TAF. Reversibility of the uveitis was seen after a 3 month recovery period. Ocular findings were not seen with TAF in any other animal model (mouse, rat, monkey) and were not seen with Viread (TDF, prodrug of TFV). At the NOAEL for eye toxicity the systemic TAF exposure in dogs was lower than in humans, therefore no safety margins were established. The systemic exposure for TFV was 4 times higher than the exposures seen in humans after Genvoya administration. No ocular toxicities were described for EVG, COBI and FTC. In clinical trials monitoring for ocular symptoms was included and if necessary followed by an ophthalmological exam, no safety signals were reported.

COBI showed the potential for cardiotoxicity in isolated rabbit hearts, follow up data from clinical trials did not reveal clinically-significant changes in these parameters at the proposed dosage of COBI. Further, TAF reversibly reduced the heart rate with an associated mild QT interval prolongation in the week 39 chronic dog study in the high dose group. The potential for cardiovascular effects with the E/C/F/T tablet is considered low.

Of the E/C/F/TAF products, none had positive findings in genotoxicity studies. Since TAF is rapidly converted to TFV no carcinogenicity studies were conducted with TAF. However, carcinogenicity studies were conducted with TDF the results of which were negative. The E/C/F/TAF combination is not expected to have an altered reproductive toxicity profile compared with that of the individual agents

Chronic administration of TAF led to a dose dependent slight to moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog as well as renal

karyomegaly in the rat. Partial recovery was observed in the dog. Nonclinical data suggest that COBI reversibly blocks secretion of creatinine in humans. Since no pathological changes were observed in the kidney due to COBI, and the routes of excretion differ for TFV and COBI, and it is not anticipated that the combination of E/C/F/TAF could exacerbate the renal toxicity of TAF.

4.4 Clinical Pharmacology

This section provides a brief summary of the clinical pharmacology of E/C/F/TAF. Please refer to the FDA Clinical Pharmacology Reviews by Dr. Mario Sampson for additional information.

4.4.1 Mechanism of Action

This 4 drug FDC will interfere with the following life cycle steps of HIV-1: HIV integrase and HIV reverse transcriptase.

4.4.2 Pharmacokinetics

Absorption

After multiple dosing, the components of E/C/F/TAF FDC are absorbed in HIV-infected subjects with a median T_{max} of 1-4 hours. Below is the result of a 19 subject PK study.

Table 7 Multiple dose PK parameters of E/C/F/TAF

	AUC _{tau} (ng*h/mL)	C _{max} (ng/mL)	C _{min} (ng/mL)	T _{max} (h)	T _{1/2} (h)
EVG	22,797 (34.7)	2113 (33.7)	287.3 (61.7)	3.9 (2.0, 4.0)	6.6 (6.2, 7.6)
COBI	9,459 (33.9)	1,450 (28.4)	20.6 (85.2)	3.0 (2.0, 4.0)	3.0 (2.8, 3.4)
FTC	11,714 (16.6)	2,056 (20.2)	95.2 (46.7)	1.5 (1.1, 2.0)	6.4 (5.8, 7.0)
TAF	227 (47.3)*	233 (64.6)	Not detectable	1.0 (0.75, 1.5)	0.47 (0.4, 0.9)
TFV	362 (14.8)	18.2 (12.4)	11.4 (17.9)	3.0 (1.5, 4.0)	38 (33, 46)

*AUC_{last}. Source: study GS-US-292-0103.

Food Effect

EVG and COBI are recommended to be administered with food, while FTC may be taken without regard to food. In a food effect study where subjects were administered E/C/F/TAF, only TAF and TFV were measured; relative to the fasted state, TAF and

TFV exposures were not significantly altered by administration of E/C/F/TAF following low-fat or high-fat meals. In subjects administered E/C/F/TAF or its components as single agents with food in cross-over study 292-0103, PK was comparable for the components of E/C/F/TAF versus single agents, suggesting no difference in food effect for E/C/F/TAF versus single agents. The E/C/F/TAF label states that it is to be administered with food.

Table 8 TAF and TFV food effect in healthy subjects administered E/C/F/TAF

	TAF		TFV	
	AUCinf	Cmax	AUCinf	Cmax
Low-fat meal	↑15 (7, 24)	↓32 (21, 41)	↑14 (8, 19)	↓16 (7, 24)
High-fat meal	↑18 (9, 26)	↓37 (27, 45)	↑13 (7, 18)	↓16 (7, 25)

Distribution

It was determined that EVG and COBI are highly human plasma protein bound and TAF was about 80% bound. FTC and TFV were not protein bound.

Table 9 E/C/F/TAF distribution

	Fraction bound to human plasma proteins	Blood-to-plasma ratio
EVG	98-99%	0.73
COBI	97-98%	0.5
FTC	<4%	1
TAF	80%	0.6 (0.25 h postdose) 2.4 (216 h postdose)
TFV	<0.7%	Not reported

Drug Metabolism/Elimination

The metabolic and elimination pathways for E/C/F/TAF are presented in tabular form.

Table 10 E/C/F/TAF elimination

	Route of elimination	Metabolism
EVG	Hepatobiliary	CYP3A (major), UGT1A1/3 (minor)
COBI	Hepatobiliary	CYP3A (major) and CYP2D6 (minor)
FTC	Renal via glomerular filtration and active tubular secretion	Not significant
TAF	Conversion to TFV	Cathepsin A (PBMCs) and carboxylesterase 1 (hepatocytes)
TFV	Renal via glomerular filtration and active tubular secretion	Not a substrate of CYP enzymes

Renal Impairment Pharmacokinetics

One of the factors to be considered in this review is the expansion of indicated population to subjects with mild and moderate renal impairment. Both TAF and FTC have predominant renal elimination. Study GS-US-292-0112 is the first safety study in which FTC 200 mg daily was administered to subjects with renal impairment. In this study, FTC was only measured in intensive PK substudy participants; only TAF and TFV were measured in the single PK sample collected in all subjects. Thus FTC exposure-response relationships for safety have not been evaluated in subjects with renal impairment and the clinical significance of 2-fold increased FTC exposures is unclear.

Table 11 Comparison of E/C/F/TAF PK in renal normal and renal impaired

Analyte	PK parameter	Normal renal function*	Current study eGFR _{CG} ≥30- <50 mL/min	Current study eGFR _{CG} ≥50-69 mL/min
EVG	C _{min} (ng/mL)	287 (62)	425 (83)	332 (72)
COBI	AUC _{tau} (ng*h/mL)	9459 (34)	11,317 (49)	9394 (43)
FTC	AUC _{tau} (ng*h/mL)	11,714 (17)	25,140 (22)	19380 (23)
TAF	AUC _{clast} (ng*h/mL)	228 (47)	341 (60)	227 (44)
TFV	AUC _{tau} (ng*h/mL)	326 (15)	680 (29)	504 (29)

*Data from Phase 2 study GS-US-292-0102 (n=19). Values are mean (CV%).

Table 12 Percent changes in PK parameters renal normal and renal impaired

Analyte	PK parameter	Current study eGFR _{CG} 30-<50 mL/min	Current study eGFR _{CG} ≥50-69 mL/min
EVG	C _{min} (ng/mL)	↑48	↑16
COBI	AUC _{tau} (ng*h/mL)	↑20	↓1
FTC	AUC _{tau} (ng*h/mL)	↑115	↑65
TAF	AUC _{last} (ng*h/mL)	↑50	↔
TFV	AUC _{tau} (ng*h/mL)	↑109	↑55

Drug Interactions

A drug-drug interaction study with E/C/F/TAF and sertraline (study GS-US-292-1316) found exposure changes of <16% for each component of E/C/F/TAF and sertraline. Based on flat exposure-response relationships, no dose adjustment is recommended for based on a <16% exposure change.

Coadministration of EVG/COBI and carbamazepine in drug-drug interaction study GS-US-216-0137 resulted in EVG AUC decreased 69%, COBI AUC decreased 84%, carbamazepine AUC increased 43%, and carbamazepine-10,11-epoxide (CYP3A-mediated active metabolite of carbamazepine) AUC decreased 35%. Based on significant EVG exposure decreases, coadministration of E/C/F/TAF and carbamazepine is contraindicated.

Coadministration of TAF and COBI in drug-drug interaction study GS-US-311-0101 resulted in TAF AUC increased 2.7-fold and TFV AUC increased 3.3-fold. This drug interaction was addressed by a dose reduction of the TAF dose from 25 mg to 10 mg in the E/C/F/TAF tablet.

Within the E/C/F/TAF regimen, drug-drug interactions occur via COBI-mediated CYP3A and Pgp inhibition, resulting in increased exposures of EVG (CYP3A substrate) and TAF (Pgp substrate). EVG and TAF exposures may also be increased via inhibition of BCRP, OATP1B1, and OATP1B3 as EVG, TAF, and COBI are substrates of these transporters and COBI is an inhibitor of these transporters.

5 Sources of Clinical Data

The two pivotal phase 3 trials GS-US-292-0104 and GS-US-292-0111 combined with a single phase 2 trial, GS-US-292-0102 provided the primary data for the characterization of the tolerability, safety and effectiveness of E/C/F/TAF FDC formulation in HIV-1

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infected, treatment naïve subjects. All three studies were multi-centered, randomized (portion of 0102), double blinded, double-dummy studies in which the active comparator was Stribild®. GS-US-292-0102 differed from the two phase 3 studies by providing enrollment in an open-label treatment extension with E/C/F/TAF following the completion of the 48 week randomized, double blind portion. The two phase 3 trials were identical in design differing only in the geographic location of their respective sites with 292-0104 having more Asian sites and 292-0111 having more South American sites.

In addition to these 3 studies, a large phase 3 switch study (GS-US-292-0109), an open label uncontrolled phase 3 study of E/C/F/TAF FDC (GS-US-292-0112) in renally impaired patients and a small phase 2/3 study (GS-US-292-0106) of E/C/F/TAF in adolescent patients were submitted for review. The purpose of the switch study was to demonstrate the safety and efficacy of switching from a successful ARV regimen in virally suppressed individuals. The renal impairment study provides data on the safety and efficacy of E/C/F/TAF use in this special population. Data from GS-US-292-0106 is intended to inform the use of E/C/F/TAF in patients between the ages of 12 and less than 18 years of age.

5.1 Tables of Studies/Clinical Trials

The four pivotal phase 3 and two phase 2 or 2/3 studies discussed above form the primary basis of the E/C/F/TAF Clinical Review. In addition, a large number of phase 1 clinical pharmacology trials have been submitted by the Applicant. Please refer to the Clinical Pharmacology review for further details on these trials.

Table 13 Overview of Phase 2 and Pivotal Phase 3 E/C/F/TAF Trials

Trial Number	Trial Design	Population	Regimen and Duration	Number Enrolled	Primary Efficacy Endpoint
292-0102	Phase 2, randomized DB and OL, multicenter, active control	Randomized HIV naïve adults Open Label (OL) Switch prior DRV/COBI	Randomized: E/C/F/TAF vs Stribild OL E/C/F/TAF	Randomized 171 2:1 OL 158	HIV-1 RNA <50 copies/mL
292-0104	Phase 3, randomized, DB, active controlled, multicenter	HIV-1 infected treatment naïve adults	E/C/F/TAF 1/d vs Stribild 1/d Duration 96 wks	Randomized 872	HIV-1 RNA <50 copies/mL
292-0111	Phase 3, randomized, DB, active controlled, multicenter	HIV-1 infected treatment naïve adults	E/C/F/TAF 1/d vs Stribild 1/d Duration 96 wks	Randomized 872	HIV-1 RNA <50 copies/mL
292-0109	Phase 3, randomized, open label, switch study, active control, multicenter	HIV-1 infected fully suppressed while receiving ARV x 6 months, multicenter	Randomized stay on prior ARV or switch to E/C/F/TAF	Randomized 1443: 959 switch and 477 no switch	HIV-1 RNA < 50 copies/mL
292-0112	Phase 3, open label, multicenter, multi-cohort	HIV-1 infected with stable renal impairment eGFR 30-69mL/min	E/C/F/TAF 150mg/150mg/200mg/10mg X 96 weeks	Enrolled 252	HIV-1 RNA < 50 copies/mL
292-0106	Phase 2/3 open label, multicenter, 2 part single group	HIV-1 infected, ARV naïve adolescents (12- < 18 years)	E/C/F/TAF 150mg/150mg/200mg/10mg X 48 weeks	Enrolled 48	HIV-1 RNA < 50 copies/mL

5.2 Review Strategy

This reviewer, Dr. William Tauber, is the primary clinical reviewer for this application. This review was performed in collaboration with two other clinical reviewers. Dr. Peter Miele, Medical Officer, reviewed the data from the Phase 3 switch study 292-0109, and Dr. Andreas Alarcon reviewed the Adolescent Subject Trial 292-0106. The findings of Drs. Miele and Alarcon are incorporated throughout this review in the relevant sections. Dr. Miele's clinical review of GS-US-292-0109 is attached to this review as Appendix 1. Dr. Alarcon's clinical review of GE-US-292-0106 is attached to this review as Appendix 2. Additionally, the FDA clinical and statistical reviewers collaborated extensively during the review process, and a number of the efficacy

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analyses were performed by the FDA statistician (Please refer to Statistical Review by Dr. Thomas Hammerstrom). In addition, there were significant interactions with the FDA clinical pharmacology, clinical virology, toxicology, and product quality (CMC) evaluation groups. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

Consultation was requested from the Division of Bone, Reproductive and Urologic Products (DBRUP) to gain expert opinion and recommendations regarding interpretation of comparative bone mineral density imaging and bone marker laboratory values between GENVOYA and STRIBILD. The pertinent findings, comments and recommendations from the consult review are incorporated in this document. Please refer to the Consult Review by Dr. Stephen Voss dated March 25, 2015 for detailed assessment of their findings.

Consultation was also requested from the Division of Cardiovascular and Renal Products (DCRP) relating to the assessment of 292-0112, the trial which enrolled subjects with mild to moderate renal impairment. The major focus of this consultation was on the suitability of the population studied to inform the safety of expansion of dosing to subjects with this level of renal insufficiency as well as recommendations regarding subject monitoring. The key points are incorporated in this review. Please refer to the consult review by Dr. Kimberly Smith dated May 31, 2015 for details.

Consultation was also requested from the Division of Dermatology and Dental Products (DDDP) regarding an apparent increase in dental fractures, abscesses, and caries among recipients of GENVOYA compared to STRIBILD. The key points are incorporated into this review. Please refer to the Consult Review of John Kelsey, DDS dated May 22, 2015 for details.

5.3 Discussion of Individual Studies/Clinical Trials

This section describes the single phase 2 and the pivotal phase 3 or 2/3 trials. The study designs of the individual trials and the pertinent results from some of the early phase trials are discussed in this section.

Phase 2 Trials

GS-US-292-0102:

Title: A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate Single Tablet Regimen in HIV-1 Infected, Antiretroviral Treatment-Naive Adults

Study Centers: Patients were enrolled at 37 study sites; 36 in the U.S and 1 in Puerto

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Rico

Objectives: Demonstrate safety and efficacy of E/C/F/TAF versus E/C/F/TDF (Stribild®) in treatment naïve HIV infected subjects

Trial Design

This Phase 2, double blinded, active controlled trial in adult HIV-1 infected, treatment naïve was comprised of two parts. The first part was comprised of a randomized, double blind comparison of the safety and efficacy of single daily doses of fixed drug combination (FDC) E/C/F/TAF (GS-7340) (GENVOYA) tablet with that of single daily doses of approved FDC E/C/F/TDF (STRIBILD). Eligible subjects were initially randomized in a 2:1 ratio to one of the following arms:

- Treatment Group 1-E/C/F/TAF + STRIBILD placebo (100 subjects planned)
- Treatment Group 2 STRIBILD + E/C/F/TAF placebo (50 subjects planned)

Randomization was stratified by HIV-1 RNA level of $\leq 100,000$ copies/mL or $> 100,000$ copies/mL at screening. The dosages of the first three components of both competing drugs were identical; E (elvitegravir) 150mg, C (cobicistat) 150mg, F (emtricitabine) 200mg. The fourth components of both are prodrugs of the active nucleotide tenofovir (TFV). GENVOYA utilized tenofovir alafenamide fumarate (TAF) 10mg and STRIBILD's utilized tenofovir disoproxil fumarate (TDF), at the approved dose of 300mg.

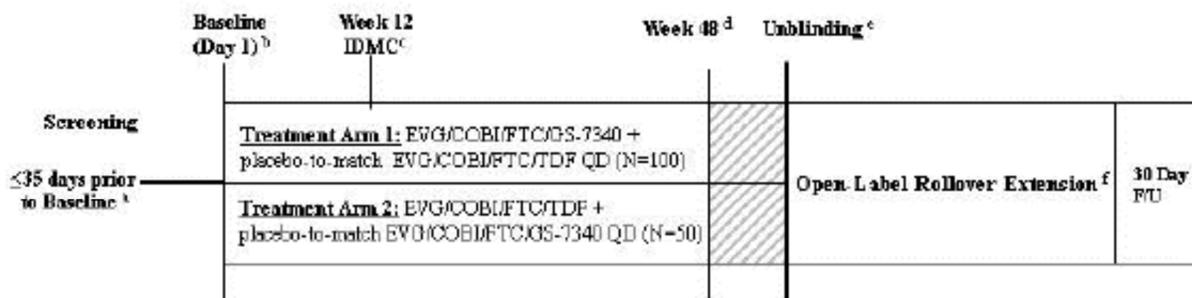
The GENVOYA dose was based on previous Phase 1 study GS-US-120-0104 which determined an exposure of 25mg TAF was optimal. When given with cobicistat, TAF 10mg achieves a PK exposure similar to TAF 25mg given without cobicistat.

The study duration for part 1 was 48 weeks during which time laboratory testing to include HIV-1 viral titers, CD4 counts, bone and renal biomarkers, DXA scans were conducted on all subjects. An intensive pharmacokinetic (PK) substudy was performed on a subset of 24 evaluable subjects.

After 48 weeks subjects were continued on blinded study medication through the unblinding visit at which time they were offered participation in Part 2 the open-label rollover extension. In addition to subjects from GS-US-292-0102 additional subjects from Gilead sponsored GS-US-299-0102 (DRV+COBI+ Truvada) were recruited to participate in the open label extension. The open label extension could enroll up to 300 subjects but was not comparative for efficacy.

Study 292-0102 Study Design

Figure 7-1. GS-US-292-0102: Study Schema



Source Clinical Study Report GS-US-292-0102 page 34

Efficacy in this study was only obtained on the double blinded, randomized portion of the study (part 1). The primary objective of the study was to evaluate the comparative safety and efficacy of the E/C/F/TAF (GENVOYA) versus E/C/F/TDF (STRIBILD).

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at week 24 as determined by the FDA-defined snapshot analysis.

The secondary efficacy endpoints included:

- The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as determined by the FDA-defined snapshot analysis
- The change from baseline in log₁₀ HIV-1 RNA and in CD4+ cell count at Weeks 24 and 48
- CD4+ counts and resistance testing

The study population consisted of HIV-1 infected adults with HIV-1 RNA levels ≥ 5,000 copies/mL, no prior ARV, and eGFR (Cockcroft-Gault formula) of ≥ 70mL/min.

A total of 170 HIV-1 infected treatment naïve subjects were randomized and treated in the double-blind portion of the study; 112 received E/C/F/TAF and 58 subjects received E/C/F/TDF. A total of 266 subjects entered the extension phase and received E/C/F/TAF including 158 subjects from this study and 108 subjects who switched from Study GS-US-299-0102. Of these 108, 38 had been receiving DRV+COBI+TVD and 70 had received D/C/F/TAF in Study GS-US-299-0102. Of the 266 entering the Open Label extension, 264 continue to receive treatment.

In the randomized, double-blind portion of this study, similar rates of virologic suppression were achieved and maintained in the 2 treatment groups at 24 and 48 weeks. At 24 weeks virologic success rates were E/C/F/TAF 88.4% and STRIBILD 89.7%. The rate of virologic success for subgroups of age, sex, race, baseline HIV-1

RNA level baseline CD4+ count and study adherence rate were similar. At 48 weeks virologic suppression was achieved in 90.2% of E/C/F/TAF and 89.7% of STRIBILD recipients. The remainder of the data at 48 weeks was consistent with the results at week 24.

There were 6 subjects who experienced confirmed virologic rebound during the randomized double blind period. There were 3 in the E/C/F/TAF arm (2.7%) and 3 (5.2%) of the STRIBILD subjects.

Safety

No deaths or Grade 4 AEs occurred during the conduct of the randomized portion of the trial. The only related Grade 3 AE was a Grade 3 AE of diarrhea in an E/C/F/TAF recipient. Overall the frequency and severity of AEs were similar between the two study arms during the randomized period as demonstrated below.

Table 14 Summary of Adverse Events during randomized phase Study 292-0102

Subjects experiencing any of the following during blinded phase	E/C/F/TAF N=112	STB N=58
Numbers experiencing any TEAE	109 (97%)	57 (98%)
Grade 2 or Higher AE	74 (66%)	35 (60%)
Grade 3 or Higher AE	15 (13%)	7 (12%)
Study Drug Related AE	44 (39%)	19 (33%)
Serious Adverse Events	15 (13%)	5 (9%)
Discontinuations due to AEs	4 (4%)	0

Some subjects experienced more than one different SAE. When actual SAE events are considered, except for infections, there was balance across the study arms. With infections there was a trend toward higher incidence in E/C/F/TAF subjects.

Table 15 Serious Adverse Events Study 292-0102

Serious Adverse Events* 292-0102 SOC Blinded Phase	E/C/F/TAF N=112	STB N=58
Totals	18 (16%)	7 (12%)
Psychiatric	2 (2%)	2 (3%)
Bacteria/Viral Infections	6 (5%)	2 (3%)
Cardiovascular	2 (2%)	1(2%)
Surgery/Trauma	3 (3%)	0
Gastrointestinal	1 (1%)	1 (2%)
Respiratory	1 (1%)	0
Neoplasms	1 (1%)	1 (2%)
Immune Reconstitution Syndrome	1 (1%)	0
Hematology	1 (1%)	0

*One subject could experience multiple SAEs

There were an additional 4 SAEs occurring in three individuals receiving E/C/F/TAF during the extension phase. One individual suffered a myocardial infarction with resultant heart failure, one suffered a non-pathologic ankle fracture and one experienced colitis.

There were a total of 4 discontinuations due to adverse events, all occurring in the E/C/F/TAF arm. Three were assessed as SAEs: promyelocytic leukemia, Coxsackie colitis, and disseminated Mycobacterium avium in an individual with baseline CD4+ of 140. The remaining discontinuation was due to a non-serious adverse event of facial flushing/photosensitivity.

The most common AEs in both treatment groups were nausea, diarrhea, and URTI. Of note, nausea, fatigue, depression, rash, conjunctivitis, and abnormal dreams were more prevalent in the E/C/F/TAF arm. Please see the table below.

Table 16 Common Adverse Events Study 292-0102

Subjects experiencing any of the following during blinded phase	E/C/F/TAF N=112	STB N=58
Nausea	25 (22%)	7 (12%)
Diarrhea	19 (17%)	9 (16%)
Fatigue	18 (16%)	5 (9%)
URTI	18 (16%)	12 (21%)
Headache	11 (10%)	8 (14%)
Depression	12 (11%)	3 (5%)
Rash	11 (10%)	3 (5%)
Conjunctivitis	9 (8%)	0
Abnormal Dreams	8 (7%)	1 (2%)

Eye AEs

Eye abnormalities were seen in a non-clinical study in dogs. As a result, eye AEs were designated a special interest area during the conduct of the Phase 2 and 3 studies. In this study a total of 8 Eye Disorders were observed among E/C/F/TAF recipients compared to none among the STB recipients. The single case of photophobia was assessed as drug related, the remainder were assessed as not related to study drug. Except for visual blurring, the eye AEs were all single reports.

Table 17 Eye Adverse Events Study 292-0102

Subjects experiencing any of the following during blinded phase	E/C/F/TAF N=112	STB N=58
Eye Disorders	8 (7%)	0
Vision Blurred	2 (2%)	0
Conjunctival hemorrhage	1 (1%)	0
Diplopia	1 (1%)	0
Increased Lacrimation	1 (1%)	0
Photophobia	1 (1%)	0
Retinal Detachment	1 (1%)	0
Visual Impairment	1 (1%)	0

Laboratory AEs

More subjects in the E/C/F/TAF group had Grade 3 or 4 laboratory abnormalities, 28% E/C/F/TAF versus 19% STB. The most common Grade 3 or 4 laboratory abnormality was fasting LDL; 9% E/C/F/TAF vs 5% in STB recipients. Grade 3 or 4 abnormalities of creatine kinase and neutrophils were reported in 6% of E/C/F/TAF recipients versus 3% of STB recipients.

Protocol GS-US-292-0106

This study conducted in an adolescent population was reviewed by Dr. Andres Alarcon. This study is an ongoing, open label, PK, safety, tolerability and antiviral activity of E/C/F/TAF in antiretroviral treatment naïve adolescents ages 12 years to less than 18 years of age. The study design provided for two phases, one an intensive PK evaluation with safety and efficacy data reviewed by an independent data monitoring committee and the second long term evaluation of the safety, efficacy and tolerability through week 48. A complete discussion of the trial design and safety results is available in his review which can be found in Appendix 2.

Pivotal Phase 3 E/C/F/TAF Trials

The trial designs and the safety results for the four Phase 3 pivotal trials are described in this section. The notable safety events and the integrated safety analyses are discussed in detail in Section 7.3.

Protocols GS-US-292-0104 and GS-US-292-0111

The trial design of these 2 Phase 3 studies is identical, the only difference relates to the geographic distribution of study sites. Both studies had a preponderance of study sites in North America, and Europe. Compared to each other Study 292-0104 had more Asian sites and Study 292-0111 had more sites in central and South America. The study design compared E/C/F/TAF with Stribild® (1:1) which

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permitted the comparison of the safety and efficacy of TAF versus TDF since the two FDCs are otherwise identical.

Title(s): A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide versus Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Positive, Antiretroviral Treatment- Naïve Adults

Study Centers:

- GS-US-292-0104: 120 study sites: 82 US, 9 Spain, 8 Canada, 6 Thailand, 5 Australia, 3 Switzerland, 2 Austria, 2 Belgium, 1 Italy, 1 Japan, 1 U.K.
- GS-US-292-0111: 121 study sites: 82 US, 10 U.K., 9 France, 5 Canada, 4 Italy, 4 Portugal, 2 Mexico, 2 Netherlands, 2 Sweden, 1 Dominican Republic.

Trial Design: These ongoing phase 3, randomized, double-blind, multicenter, active-controlled studies were designed to evaluate the safety and efficacy of a regimen containing elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF administered as a FDC) compared to the approved FDC elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF administered as a FDC, STRIBILD) in HIV-1 positive, antiretroviral treatment naïve adult subjects at 48 weeks of treatment.

Subjects will be randomized in a 1:1 ratio to one of the following two treatment arms:

- **Treatment Arm 1:** FDC of elvitegravir 150 mg/cobicistat/150 mg/emtricitabine 200 mg/ tenofovir alafenamide 10 mg (E/C/F/TAF) QD + Placebo to match FDC of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg (E/C/F/TDF) QD (n = 420)
- **Treatment Arm 2:** FDC of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/ tenofovir disoproxil fumarate 300 mg (E/C/F/TDF) QD + Placebo to match FDC of elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg (E/C/F/TAF) QD (n = 420).

Randomization was stratified by HIV-1 RNA level ($\leq 100,000$ copies/mL, $>100,000$ to $\leq 400,000$ copies/mL or $> 400,000$ copies/mL), CD4 count (< 50 cells/ μ L, $50 - 199$ cells/ μ L, or ≥ 200 cells/ μ L), and region (US vs. Ex-US) at screening.

The primary efficacy determination took place at 48 weeks but the total planned duration of treatment is 96 weeks. After Week 96, subjects will continue to take their blinded study drug and attend visits every 12 weeks until treatment assignments are unblinded, at which point all subjects will return for an Unblinding Visit and will be given the option to participate in an open-label rollover study to receive the E/C/F/TAF FDC until it becomes commercially available, or until Gilead Sciences terminates development of the E/C/F/TAF FDC.

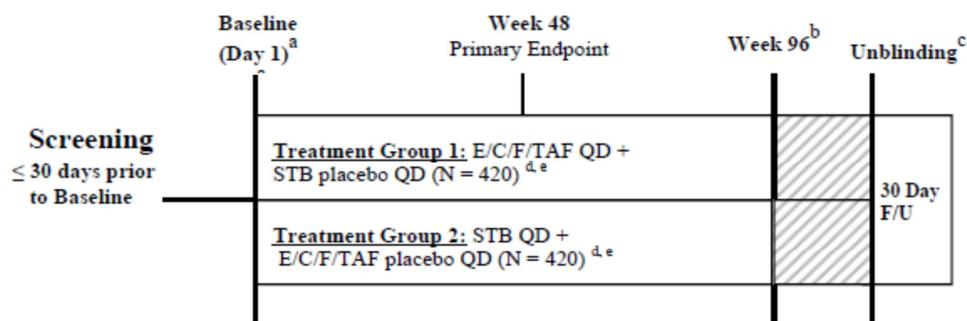
- The target population is HIV-1 infected adults who are antiretroviral treatment-naïve (except for PREP, PEP, or treatment during pregnancy) with ≥ 1000 copies/mL and a screening genotype showing sensitivity to EVG, FTC, TDF and an estimated glomerular filtration rate (eGFR) by Cockcroft-Gault formula of ≥ 50 mL/min (except in France and Sweden where a eGFR ≥ 70 mL/min was required).
- For all subjects, dual energy x-ray absorptiometry (DEXA) scans will be performed prior to study drug administration at Baseline (Day 1), and then every 24 weeks throughout the study and at the Unblinding Visit or early study discontinuation date (ESDD), if > 12 weeks since last scan. DEXA scan results will be provided to study sites when available.
- Blood and urine for selected renal and bone biomarkers were collected at Baseline (Day 1), Weeks 2, 4, 12, 24, 48 and ESDD (if applicable).
- The primary efficacy endpoint is the proportion of subjects that achieve HIV-1 RNA < 50 copies/mL at Week 48 as defined by the Food and Drug Administration (FDA) snapshot analysis.

The secondary efficacy endpoints are:

- The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA Time to Loss of Virologic Response (TLOVR) analysis
- The proportion of subjects with HIV-1 RNA < 20 copies/mL and < 200 copies/mL at Weeks 48 and 96 as defined by the FDA snapshot analysis
 - The proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 96 as defined by the FDA snapshot analysis and TLOVR analysis
 - The change from Baseline in CD4+ cell count at Weeks 48 and 96

Study Design 292-0104 and 292-0111

Figure 7-1. GS-US-292-0111: Study Design



The primary analysis of the results of the HIV-1 RNA was planned to be a non-inferiority test of E/C/F/TAF versus E/C/F/TDF, with respect to the proportion of subjects with HIV-

1 RNA less than 50 copies/mL at Week 48 as defined by the FDA snapshot analysis. It would be concluded that E/C/F/TAF is not inferior to E/C/F/TDF if the lower bound of the two-sided 95% confidence interval of the difference (E/C/F/TAF arm – E/C/F/TDF arm) in the response rate (HIV-1 RNA < 50 copies/mL as defined by the FDA snapshot analysis) is greater than -12%; i.e., a margin of 12% is applied to noninferiority assessment. The 95% confidence interval will be constructed using normal approximation method stratified by baseline HIV-1 RNA level ($\leq 100,000$ copies/mL, $>100,000$ to $\leq 400,000$ copies/mL or $> 400,000$ copies/mL) and region (US vs. Ex-US).

In Study 292-0104 a total of 1105 subjects were screened, 872 were randomized and 867 subjects received at least 1 dose of study drug. Baseline demographic and disease characteristics between study groups were similar. The median age of E/C/F/TAF participants was 33 years and STB 35 years. The racial composition was white 58%, black 20%, and Asian 18%. Median baseline CD4+ count for both groups was 404 cells/ μ L and 2.5 % and 10% had < 50 cells and >50 cells < 200 cells/ μ L respectively. Baseline eGFRs (Cockcroft-Gault formula) were higher in the E/C/F/TAF arm 119mL/min compared to STB 113mL/min.

As of the week 48 cut-off a total of 813 subjects (413 (94.9%) E/C/F/TAF and 400 (93%) STB) were continuing study drugs. A total of 54 subjects (6.2%) discontinued study drug prior to week 48 (22 (5.1%) E/C/F/TAF and 32 (7.4%) STB). Forty-eight subjects discontinued participation in the study prior to week 48 (21 (4.8%) E/C/F/TAF and 27 (6.3%) STB). The reasons for discontinuation were similar. Subjects' discontinuations for AEs were 0.9% with E/C/F/TAF and 1.4% for STB.

In Study 292-0111, a total of 1070 subjects were screened, 872 were randomized and 866 subjects received at least 1 dose of study drug (E/C/F/TAF 431, STB 435). Four subjects randomized to E/C/F/TAF and 2 randomized to STB did not receive study drug. Baseline demographic and disease characteristics between the two study groups were similar. The median age of E/C/F/TAF participants was 33 years and STB 34 years. The racial composition was white 55%, black 30%, Asian 11%. Median baseline CD4+ count for both groups was 406 cells/ μ L and 2.5 % and 10% had < 50 cells and >50 cells < 200 cells/ μ L respectively. Baseline eGFRs (Cockcroft-Gault formula) were similar with the E/C/F/TAF arm 116mL/min compared to STB 115mL/min.

As of the week 48 cut-off date 804 subjects were continuing (E/C/F/TAF 408 (95%) and STB 396 (91%)). Of the 866 treated, 62 (7.2%) discontinued study drugs and 46 (5.3%) discontinued participation in the study (E/C/F/TAF 18 (4.2%), STB 28 (6.4%)). The reasons for discontinuation were balanced across groups. Ten subjects discontinued because of AEs (4 (0.9%) E/C/F/TAF and 6 (1.4%) were STB).

The virologic outcomes at week 48 were similar in both studies as summarized below. These results were interpreted to demonstrate E/C/F/TAF is non-inferior to STB in this treatment naïve population.

Table 18 Virologic Success Studies 292-0104 and 292-0111

Virologic Success at 48 weeks	Study 292-0104			Study 292-0111		
	E/C/F/TAF	STB	CI	E/C/F/TAF	STB	CI
Virologic Success VL < 50 copies/mL	93.1%	92.4%	-2.6% - 4.5%	91.6%	88.5%	-1.0% - 7.1%
Virologic Success VL < 20 copies/mL	86.4%	87.3%	-5.1% - 3.8%	82.4%	80.7%	-3.7% - 6.5%

Safety:

Both E/C/F/TAF and STB were well tolerated in these studies. The median duration of exposure for study 292-0104 which was begun first was approximately 60 weeks. For study 292-0111 the median duration of exposure is approximately 48 weeks. The 12 week difference in median exposure durations is not considered to be consequential and the safety data for these two studies are considered together.

In the combined safety database the numbers of subjects experiencing any TEAE were very similar between the two study drugs. In the 120 day safety update, each arm reported an additional 10 SAEs. The numbers of individuals experiencing Grade 2 adverse events were higher with E/C/F/TAF and discontinuations were numerically higher in the STB arm. Otherwise, as shown below, the major categories had similar incidences between the study arms.

Table 19 Summary of Adverse Events Studies 292-0104 and 292-0111

Subjects enrolled in 0104 or 0111	E/C/F/TAF N=866	STB N=867
Numbers experiencing any TEAE	795 (92%)	800 (92%)
Grade 2 or Higher AE	493 (57%)	455 (52%)
Grade 3 or Higher AE	77 (9%)	84 (10%)
Study Drug Related AE	342 (39%)	367 (42%)
Serious Adverse Events	80 (9%)	69 (8%)
Discontinuations due to AEs	8 (1%)	16 (2%)
Deaths	2 (<1%)	4 (<1%)

A total of 5 deaths in studies 292-0104 and 292-0111 were reported with NDA submission. An additional death (7714-4583) occurring in the Stribild® arm of 292-0104 was reported in the 120 day safety update. This death was the result of non-small cell carcinoma of the lung. None of the 6 deaths were assessed as related to study drug. All six deaths are reported in tabular form below:

Table 20 Deaths Studies 292-0104 and 292-0111

Subject ID number	Study Drug	Cause of Death/Study number	Investigator Related
4127-4587	E/C/F/TAF	Large hemorrhagic CVA in patient with chronic atrial fibrillation (0104)	No
5129-5794	E/C/F/TAF	Alcohol Poisoning (0111)	No
1543-4364	Stribild®	Post-extubation anoxic brain injury cardiac arrest (0104)	No
1624-5009	Stribild®	Multiple Drug Overdose (0111)	No
2348-5663	Stribild®	<i>Neisseria meningitidis</i> sepsis precipitating Acute Myocardial Infarction	No
7714-4583	Stribild®	Non-small cell Lung Cancer (0104)	No

The overall numbers of SAEs were similar between the two treatment arms. The safety update reported 8 additional infection SAEs. After considering the safety update, it appears there may be imbalance in incidence of infection SAEs. Otherwise, there were slight imbalances in the system organ systems involved with more respiratory and gastrointestinal disorder SAEs in E/C/F/TAF and more neoplastic and cardiovascular in STB. Of note, as previously stated, non-clinical data had suggested the possibility of uveitis as a consequence of E/C/F/TAF usage. The eye disorder SAEs were low and similar between the two arms in these studies.

Table 21 Serious Adverse Events Studies 292-0104 and 292-0111

292-0104 and 292-0111 Serious Adverse Events includes update	E/C/F/TAF N=80 (9%)	STB N=69 (8%)
Psychiatry/Substance Abuse	10	10
Surgery Trauma	7	10
Bacterial /Viral Infections	36	22
Muscular-Skeletal	3	1
Cardiovascular Conditions	2	4
Neurologic Disorders	6	7
Respiratory Disorders	5	2
Gastrointestinal Disorders	7	9
Eye Problems	2	2
Neoplastic Disorders	4	8

Adverse event related discontinuations were infrequent in these two studies. After

the safety update data are included there were 8 discontinuations among the E/C/F/TAF recipients and 16 among STB recipients. The safety update included three new discontinuations all in the Stribild arm. Two of these discontinuations involved cancers; Hodgkin's Lymphoma and the patient with non-small cell lung cancer already discussed in deaths. The third individual was asymptomatic but was found to meet criteria for osteoporosis on DEXA scan resulting in study drug discontinuation. The only possible imbalance among the categories of adverse event leading to discontinuation appears to be renal in STB recipients.\

Table 22 Discontinuations Studies 292-0104 and 292-0111

292-0104 and 292-0111 Discontinuations due to Adverse Events	E/C/F/TAF N=8 (0.9%)	STB N=16 (1.8%)
Psychiatry/Substance Abuse	0	1
Surgery Trauma	0	1
Infections	0	1
Drug Administration	2	0
Cardiovascular Conditions	0	1
Neurologic Disorders	2	0
Rash	1	3
Metabolic	1	0
Eye Problems	1	1
Renal Problems	0	4
Gastrointestinal Disorders	1	1
Neoplastic Disorders	0	2
Bone Disorders	0	1

Common Adverse Events

Ninety-two percent of participants in both study arms experienced a TEAE. Gastrointestinal disorders predominantly nausea and diarrhea were most common followed by headache, URTI, fatigue. Further down the list were insomnia, rash, dizziness and depression. The incidence and type of common adverse events were similar between study arms. The only exception was the higher incidence of arthralgias in the E/C/F/TAF arms.

Table 23 Common Adverse Events Studies 292-0104 and 292-0111

Subjects enrolled in 0104 or 0111 experiencing any of the following:	E/C/F/TAF N=866	STB N=867
Nausea	132 (15%)	151 (17%)
Diarrhea	147 (17%)	164 (19%)
Headache	132 (15%)	121 (14%)
URTI	99 (11%)	109 (13%)
Fatigue	71 (8%)	70 (8%)
Arthralgias	71 (8%)	49 (6%)
Insomnia	57 (7%)	48 (6%)
Rash	55 (6%)	46 (5%)
Dizziness	44 (5%)	37 (4%)
Depression	32 (4%)	32 (4%)

The overall incidence of TEAEs per organ system was similar between the two study drugs. This overall balance was mostly maintained even when Grade 2 and higher severity adverse events were considered. There were instances of higher severity differences in uncommon categories that merit mention. The small numbers of total events and differences between them preclude conclusions but their relevance to other related data may be important.

The first of these is Eye Disorders. On the basis of non-clinical data demonstrating posterior uveitis in the dog, ophthalmologic adverse events were actively sought in the execution of these trials. It is acknowledged that HIV-1 infected individuals are more likely to experience eye conditions making interpretation more difficult. No specific instances of posterior uveitis were detected but it is noted that numerically more *Any Grade* and *Grade 2 or Higher* instances of eye disorders were detected in E/C/F/TAF recipients (see Table 24 below). It remains reasonable to continue to focus on this organ system in future data generation.

During review of the safety data it was noted that there were numerous instances of dental disorders. Terms such as dental necrosis, tooth fracture, gingivitis, tooth abscess some with toxicity grades of 3 called into question a possible safety signal. Although these were encountered in both study arms, there were numerically more *Grades 2 or Higher* dental AEs in E/C/F/TAF recipients (please see Table 24 below). In response, consultation with the division of Dermatology and Dental Products (DDDP) was requested. Dr. John Kelsey DDS reviewed the relevant data but was unable to substantiate a safety signal due to the small numbers of subjects involved.

Arthralgias and other rheumatologic adverse events of all grades were numerically

greater in E/C/F/TAF recipients. It is also noted that recrudescence herpes virus manifestations were more numerous and more severe in E/C/F/TAF recipients. In combination with the numerically higher incidence of Infection SAEs, this may portend an immunologic AE attendant to E/C/F/TAF use. Although these findings are likely due to chance alone it is valuable to be sensitized to the possibility of an immunologic impact of E/C/F/TAF that may become more apparent in the future.

Table 24 Selected Adverse Events Studies 292-0104 and 292-0111

292-0104 and 292-0111 Selected AEs	E/C/F/TAF N=866	STB N=867
Eye Disorders		
All Grades	37 (4%)	26 (3%)
Grade 2 or higher	9 (1%)	3 (<1%)
Dental Disorders		
All Grades	84 (10%)	74 (9%)
Grade 2 or higher	41 (5%)	23 (3%)
Joint Discomfort Inflammation		
All Grades	71 (8%)	49 (6%)
Grade 2 or higher	18 (2%)	7 (<1%)
Herpes Infections		
All Grades	74 (9%)	48 (6%)
Grade 2 or higher	21 (2.4%)	14 (1.6%)

Laboratory AEs

Data from three laboratory AEs demonstrated important differences between the two study drugs in Studies 292-0104 and 292-0111. These were differences in Bone Mineral Density (BMD), renal function and lipids. These will be discussed in section 7 as part of the pooled safety analysis (Please see Section 7.3.5)

GS-US-292-0109

Title: A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects

This study was reviewed by Dr. Peter Miele. For information on the design, demographics, and safety data from this study please see his review in Appendix 1.

GS-US-292-0112:

Title: A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single-Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment

Study Centers: Patients were enrolled at 70 study sites; 51 in the U.S, 4 in Thailand, 4 in the United Kingdom, 3 in Australia, 3 in Spain, 2 in France, 1 in the Netherlands, 1 in the Dominican Republic and 1 in Mexico.

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Objectives: to evaluate safety, efficacy, and tolerability of EVG/ COBI/ FTC/TAF (E/C/F/TAF) fixed-dose combination (FDC) in in HIV-infected adult patients with stable, mild to moderate renal function (subjects with baseline estimated glomerular filtration rate [eGFR] measured by the Cockcroft-Gault formula [eGFR_{CG}] 30 to 69 mL/min, inclusive).

Trial Design This Phase 3, open label, multicenter, multi-cohort uncontrolled trial in adult HIV-1 infected individuals whose baseline eGFR performed by Cockcroft-Gault formula was measured as being between 30 and 69 mL/min for at least 3 months prior to enrollment.

Enrollment of up to 260 subjects was planned and 2 cohorts were designated; cohort 1 virally suppressed (HIV-1 RNA < 50 copies/mL x 6 months) adults switched from a successful baseline regimen to E/C/F/TAF and cohort 2, individuals who were treatment naïve (HIV-1 RNA ≥ 1000 copies/mL). Although any subject with a stable eGFR between the values above could be enrolled, the design called for a minimum of 30 individuals who had a stable eGFR of ≥ 30mL/min and < 50 mL/min. It should be noted that the product label for emtricitabine (FTC) recommends increased dosage intervals of 48 hours for recipients with eGFRs of less than 50 mL/min.

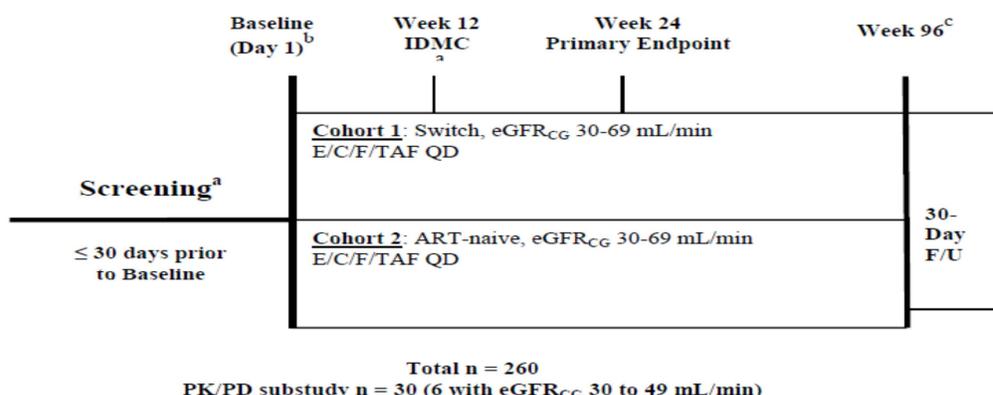
The study duration was planned for 96 weeks although primary efficacy endpoint was at 24 weeks. Ongoing routine laboratory monitoring including renal testing was conducted at weeks 1, 2, 4, 8, 12, 16, 24, 36, 48, 60, 72, 84, 96. Blood and urine biomarkers were collected less frequently at weeks 1, 2, 4, 12, 24 and 48. DEXA scans were performed at baseline and again at 24 weeks and at 24 week intervals thereafter.

An intensive pharmacokinetics (PK)/pharmacodynamics (PD) substudy was performed between the baseline and Week 24 visits in a subset of subjects at study sites able to conduct this testing.

The actual glomerular filtration rate (aGFR) (PD) was measured by iohexol clearance (CL_{iohexol}) at baseline, at Week 24, and at a time-matched intensive PK day during Week 2, 4, or 8 in a 32 subject pre-selected subset.

Study Design 292-0112

Table 7-1. GS-US92-0112: Study Schema



Source Clinical Study Report GS-US-292-0112 page 38

The primary efficacy endpoint was the percentage of subjects who achieved (maintained) HIV-1 RNA < 50 copies/mL at week 24 by FDA snapshot algorithm. Secondary endpoints included percentages HIV-1 RNA < 20 copies/mL at 24, 48 and 96 weeks, HIV-1 RNA < 50 copies/mL at 48 and 96, and by differing imputation methods.

A total of 246 HIV-1 infected switch treatment and 6 treatment naïve subjects were enrolled and treated with E/C/F/TAF. The switch treatment subjects were predominantly male (79%) with a median age of 58 years. When segregated by renal function, the subjects with eGFRs < 50mL/min were slightly older with a median age of 58.5 compared to a median age of 57 for subjects with eGFRs of ≥ 50mL/min. A total of 63 subjects (26%) were ≥ 65 years of age. The most common races were white (63%), black (18%) and Asian (14%). There were 80 subjects with eGFR of ≥ 30 < 50mL/min and 162 had eGFR of ≥ 50 < 70mL/min. At baseline 42% had significant proteinuria (UPCP >200mg/g), 10% had Grade 2 proteinuria by dipstick and the median eGFR was 56mL/min. All 6 treatment naïve subjects were male, median age 54 years, 3 blacks, 2 whites and 1 Asian. The median eGFR was 60.2 mL/min and one of the subjects had Grade 2 proteinuria.

Drug Exposure

Through the data cut point including the 120 day safety update 56% of subjects in the switch treatment group and 67% of the treatment naïve had received at least 48 weeks of treatment and 93% switch treatment and 100% of treatment naïve remained on study drugs.

Efficacy Results

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Although there were 2 cohorts that varied by treatment history, the virologic success rates were reported in relationship to baseline renal function. The virologic success rate reported by baseline eGFR was identical at 95%. Three switch subjects with mild renal impairment were classified as treatment failures. Two of the three were noted to have HIV-1 RNA \geq 50 copies/mL and one added a new ARV. At 24 weeks the virologic success rate using the HIV-1 RNA cut off of $<$ 20 copies/mL was 93% for both groups.

Reviewer comments: This study population was virologically suppressed at baseline. Virologic success rates are anticipated to be higher than in treatment naïve. There was no evidence that more severe renal impairment impacted efficacy.

Five of six of the treatment naïve population had HIV-1 RNA $<$ 50 copies/mL at week 24. The remaining subject was noted to be a virologic failure at 24 weeks but was observed to have HIV-1 RNA $<$ 50 copies/mL at 48 weeks.

Reviewer comments: The small number of treatment naïve individuals participating in this study precludes definitive conclusions regarding the efficacy of E/C/F/TAF in this patient population.

Safety

A single death and 2 Grade 4 AEs occurred during the conduct of the randomized portion of the trial. These will be discussed below:

Deaths:

One death occurred during the conduct of this trial and was reported in the 120 day safety update. This individual (b) (6) a 74 year old African American man with baseline eGFR of 52 mL/min reported to an ER with complaints of chest pain and constipation. Shortly after arrival he experienced a cardiopulmonary arrest and was not successfully resuscitated. No autopsy was performed. Concomitant to his HIV-1 infection he had a history of coronary artery disease, previous myocardial infarction, and hyperlipidemia for which he was prescribed rosuvastatin. After beginning E/C/F/TAF his total cholesterol rose 30 mg/dL and his LDL rose minimally. The subject's last laboratory samples obtained within a month of his demise indicated reduction in total cholesterol toward baseline.

Grade 4 AEs

There were 2 subjects who experienced Grade 4 AEs. The first experienced major depression with suicidal attempt.

The second individual experienced an acute myocardial infarction. This 70 year old man with baseline eGFR of 54 mL/min had past medical history of coronary artery disease, coronary artery stents and dyslipidemia on atorvastatin. After enrollment, lipid profile remained unchanged but unfavorable with total cholesterol of 260mg/dL. The Grade 4 event occurred during his participation in study 292-0112. He successfully had

additional coronary artery stents placed with resolution of his cardiac ischemia. Overall, approximately 90% of all participants experienced a TEAE during participation. The incidence and types of mild severity adverse events were balanced across renal function levels. There was higher incidence of AEs in all categories among subjects with greater levels of renal impairment.

Table 25 Summary of Adverse Events Study 292-0112

Subjects 292-0112	eGFR Creatinine Clearance ≥ 30 < 50 mL/min N=82	eGFR Creatinine Clearance ≥ 50 < 70 mL/min N=165
Numbers experiencing any TEAE	73 (89%)	150 (91%)
Grade 2 or Higher AE	54 (66%)	88 (53%)
Grade 3 or Higher AE	9 (11%)	11 (7%)
Study Drug Related AE	33 (40%)	40 (24%)
Serious Adverse Events	10 (12%)	18 (11%)
Discontinuations due to AEs	6 (7%)	2 (1%)

The total percentages of SAEs were similar across renal function levels. With the exception of cardiovascular and neoplastic disorders, SAEs were similar across study arms. Cardiovascular disorders were increased in the moderate renal impairment compared to the mild renal impairment group. The number of myocardial infarctions was 2 in both groups, with one instance of syncope each. There were an additional 3 cardiovascular SAEs in the moderate impairment group which included ventricular tachycardia, worsening congestive heart failure and bilateral avascular necrosis of the femoral head. There were 3 neoplastic disorders all in the mild renal impairment group. Both groups were older at median of 58 years, the age difference between the two renal impairment groups is approximately one year.

Table 26 Serious Adverse Events Study 292-0112

292-0112 Serious Adverse Events	eGFR Creatinine Clearance ≥ 30 < 50 mL/min N=82	eGFR Creatinine Clearance ≥ 50 < 70 mL/min N=165
Totals	10 (12%)	19 (12%)
Psychiatric	0	2 (1%)
Bacteria/Viral Infections	1 (1%)	3 (2%)
Cardiovascular	6 (7%)	3 (2%)
Surgery/Trauma	1 (1%)	4 (2%)
Gastrointestinal	1 (1%)	2 (1%)
Neurological	0	2 (1%)
Neoplasms	0	3 (2%)
Metabolic	1 (1%)	0

There were a total of 9 discontinuations due to adverse events, 6 occurring among the subjects with baseline creatinine clearances less than 50 mL/min and 3 occurring in subjects with creatinine clearances greater than 50mL/min. The 6 discontinuations among the < 50 mL/min group were as follows. There were 2 instances of acute renal failure, and one instance each of infectious diarrhea, generalized fatigue, generalized arthralgias with multiple joint swelling, worsening of chronic sleep disorder due to abnormal dreams/anxiety. The adverse events leading to discontinuation on the ≥ 50mL/min group were the death previously discussed as well as one instance of administration disorders characterized by choking and one instance of urologic neoplasm discovered.

Common Adverse Events

The most common AEs in both treatment groups were nausea, diarrhea, and URTI. Please see the table below. Arthralgias were prominent and balanced across renal function as were fatigue, bronchitis and abdominal pain. There were imbalances noted between the two renal impairment groups. Headache was more prominent in subjects with mild renal impairment. Syncope/disturbances of mental functioning were more prevalent in subjects with moderate renal impairment. Dizziness was more than twice as frequently reported in subjects with moderate renal impairment. Dizziness is a non-specific symptom but it is specifically mentioned in the Emtriva® label. Finding increased percentages of dizziness and syncope/change mental status (a symptom which may overlap) may be a consequence of elevated emtricitabine levels in subjects whose baseline eGFR is less than 50mL/min.

Table 27 Common Adverse Events Study 292-0112

Subjects with TEAE all grades	eGFR Creatinine Clearance ≥ 30 < 50 mL/min N=82	eGFR Creatinine Clearance ≥ 50 < 70 mL/min N=165
Nausea	6 (7%)	12 (7%)
Diarrhea	9 (11%)	14 (8%)
URTI	12 (15%)	23 (14%)
Arthralgias	8 (10%)	15 (9%)
Bronchitis	7 (9%)	14 (8%)
Fatigue	5 (6%)	14 (8%)
Headache	2 (2%)	13 (8%)
Dizziness	9 (11%)	7 (4%)
Syncope/mental status change	6 (7%)	8 (5%)
Abdominal pain	5 (6%)	8 (5%)

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Laboratory AEs

Laboratory data from 292-0112 will be combined with the other studies as part of the pooled safety analysis of differences between E/C/F/TAF and Stribild® in bone mineral density, renal function and lipids. (Please see Section 7.3.5).

There are, however, specific laboratory data issues regarding 292-0112 that will be discussed herein:

Discrepancy between baseline eGFR measurements:

During the review it was noted that the baseline eGFR values calculated using the three eGFR methodologies were discordant. The three methodologies utilized for the baseline eGFR were: Cockcroft-Gault Formula (creatinine based), EKD-EPI-creatinine, and the CKD-Epi Cystatin C methods. The two creatinine based methodologies arrived at similar mean values of approximately 55 mL/min whereas the mean value of the Cystatin C eGFRs were reported as approximately 70mL/min.

By the Cockcroft-Gault method 222 (90%) subjects met the inclusion criteria of eGFR of 30 and 69 mL/min. From this pool there would be 80 subjects having moderate renal impairment ($\geq 30 < 50$ mL/min). In contrast, by the Cystatin C methodology 119 (50%) met inclusion criteria and only 35 (14%) would have baseline moderate renal impairment. If the Cystatin C eGFR values were correct the data became difficult to interpret. If only 14% of the study population actually had moderate renal impairment, the data generated indicating safety in this population would be inadequate. Since the Applicant intended to expand the indicated population to include moderate renal impairment, this issue needed resolution.

An information request was sent on April 1, 2015 to Gilead regarding the discrepancy between the methodologies for calculation of eGFRs and its impact on interpretation of the data. In their response, Gilead acknowledged the discrepancy between the serum creatinine based eGFR methods; Cockcroft-Gault, CKD-EPI creatinine and the serum cystatin C method. Gilead recommended that the cystatin C methodology results should be ignored.

The bases for this recommendation were as follows:

- The results from the iohexol substudy of 32 individuals demonstrated closer correspondence between the iohexol aGFR and the Cockcroft-Gault and CKD-EPI creatinine results compared to the cystatin C results.

Table 28 Iohexol aGFR compared to eGFRs Cockcroft-Gault, CKD-EPI and Cystatin C

	aGFR (mL/min)	eGFR, Cockcroft-Gault (mL/min)	eGFR, CKD-EPI Creatinine (mL/min/1.73m ²)	eGFR, CKD-EPI Cystatin C (mL/min/1.73m ²)
N	32	32	32	32
Mean (SD)	60.1 (19.06)	56.7 (11.82)	57.8 (16.97)	69.7 (20.98)
Median	59.6	57.6	54.7	72.6
Q1, Q3	46.2, 71.4	48.3, 64.4	48.3, 65.0	56.6, 79.9
Min, Max	26.4, 107.3	33.3, 88.6	33.8, 103.3	26.5, 113.2

Source: Table req7252.1 (r-req-7252-summary)

- Cystatin C is a general marker of inflammation and the difference between cystatin C results and the creatinine based eGFRs may relate to non-renal causes including inflammation, obesity and smoking.
- The use of eGFR CKD-EPI cystatin C is not the clinical standard of care. Various groups were quoted as recommending eGFR cystatin C only as a second step to confirm serum creatinine if there are extremes in muscle mass or diet.
- The HIV Medical Association of the Infectious Disease Society of America recommends use of serum creatinine based eGFR for patient management.
- The cystatin C based eGFR has not been shown to be more accurate or precise than the creatinine based equations in the general population or in HIV infected individuals.

An unanswered aspect of the discrepancy issue was data documented in the Stribild® product label that indicates cobicistat has been shown to increase serum creatinine and decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. This effect also occurs when ritonavir is given. Since 46% of the switch treatment patients had been receiving one of these two agents, and 64% had been receiving TDF, it remained plausible that the creatinine based eGFR measurements were artificially lower than they would have been if the switch treatment population had been instead treatment naïve. Although the iohexol aGFR values were assessed as potentially helpful they had been performed on 35 subjects at 12 investigative sites and may not generalize for the whole population.

Consultation was requested from the Division of Cardiovascular and Renal Products (DCRP). Consultative advice was requested regarding the discrepancies between the eGFR methodologies, the adequacy of the data from 292-0112 to support expansion of use to individuals with moderate renal impairment and advice on optimal renal monitoring.

The consultation was answered by Dr. Kimberly Smith, Medical Officer with DCRP. Summarizing, Dr. Smith indicated that she retained confidence that the creatinine based eGFRs were sufficiently accurate to agree with the Applicant that the enrolled

population was mildly and moderately renally impaired. She could not explain the reason that the cystatin C eGFR methodology was 15 points higher than the creatinine based methodologies but did not assess the cystatin C as more likely to be accurate. Her analysis found that mean values and differences between the eGFR methodologies were the same regardless of prior use of pharmaco-boosters. She pointed out the limitations of the data supporting the safety of E/C/F/TAF use in the moderately renally impaired. The median duration of exposure was 43 weeks. Only 50 individuals with a baseline eGFR of < 50 mL/min reached ≥ 36 weeks of exposure. Nephrotoxicity with Stribild® occurred at low incidence with discontinuation of the tenofovir disoproxil fumarate portion occurring at approximately 1% incidence. Sometimes the development of nephrotoxicity may take months or years to develop. Prior to switch, 180/246 (73%) subjects in Study 292-0112 were taking tenofovir disoproxil fumarate (TDF) which may imply that at least some of the study participants might be TDF tolerant and may not be representative of all subjects with mild to moderate renal impairment. Please see Dr. Smith's consult for more information.

6 Review of Efficacy

Efficacy Summary

In two pivotal Phase 3 trials conducted in HIV-1 infected, treatment naïve subjects E/C/F/TAF was shown to be non-inferior to Stribild® with respect to efficacy in treatment naïve individuals. In trial 292-0104, 93% of E/C/F/TAF subjects had virologic success compared to 92% of Stribild® subjects. In trial 292-0111, 92% of E/C/F/TAF subjects had virologic success compared to 89% of Stribild® subjects. In both studies the E/C/F/TAF group met the pre-specified NI margin of 12%. In both studies, the rates of virologic failure were low in the E/C/F/TAF group and similar to those observed with Stribild®.

A Phase 2 clinical trial 292-0102 provides support for the non-inferiority of E/C/F/TAF compared to Stribild®. At 48 weeks of treatment, subjects in this trial taking E/C/F/TAF had virologic success of 88% compared to 88% in Stribild® subjects. This study was not pre-specified to demonstrate non-inferiority, however.

In addition, in a trial conducted in HIV-1 infected individuals whose virus was stably suppressed (<50 copies/mL) for a period of at least six months, E/C/F/TAF was shown to be non-inferior to their baseline antiretroviral regimen containing tenofovir disoproxil. In trial 292-0109, 96% of individuals switched to E/C/F/TAF from a virally suppressive regimen which contained tenofovir disoproxil fumarate maintained their viral success compared to 93% of individuals who continued their baseline virally suppressive regimen. Because the lower bound of the 2 sided 95% CI was greater than the prespecified -12% margin, it was concluded that switching to E/C/F/TAF was non-inferior to maintaining baseline regimen (FTC +TDF +3rd agent) at Week 48.

In addition in 292-0112, an open label, uncontrolled trial conducted in HIV-1 infected

individuals with documented renal impairment (baseline eGFR by Cockcroft-Gault of > 30mL/min < 70mL/min) whose virus was stably suppressed (< 50 copies/mL) who were switched to E/C/F/TAF, 95% maintained their virologic success. Three subjects were classified as virologic failures at Week 24. Of these three, two had HIV-1 RNA > 50 copies/mL and one added a new ARV. These data were from the 246 subjects who were virologically suppressed and participated in this switch study. There were six treatment naïve subjects also enrolled and as of data submission; two of these six had made the 48 week cutoff and both were suppressed.

6.1 Indication

The indication proposed by the Applicant is the following:

[TRADENAME] is a four-drug combination of elvitegravir, an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat, a CYP3A inhibitor, and emtricitabine and tenofovir alafenamide, both HIV nucleoside analog reverse transcriptase inhibitors (NRTIs) and is indicated for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. (1)

Reviewer's comment: This indication statement does not accurately represent the populations studied. This indication statement implies that treatment experienced as well as treatment naïve have been studied. Study 292-0109 studied patients who were switched from a successful regimen. There is no requirement that the patient has a history of viral resistance which would be the Division's concept of treatment experienced.

6.1.1 Methods

The efficacy data for five Phase 2 or 3 trials were reviewed in support of the proposed indication. These trials are: 292-0102, a Phase 2 trial of E/C/F/TAF versus Stribild®; 292-0104 and 292-0111 two Phase 3 pivotal trials in treatment naïve HIV-1 infected adults; 292-0109, a Phase 3 study enrolling subjects who were virally suppressed for at least 6 months prior to switch; 292-0112, a Phase 3 uncontrolled study in subjects with mild and moderate renal impairment. In addition, a sixth non-controlled trial in adolescents 292-0106 was conducted to explore pharmacokinetics and safety of E/C/F/TAF.

6.1.2 Demographics

A total of 3587 treatment naïve and ARV switched subjects were randomized and received at least one dose of study drugs in these studies. A total of 1201 subjects stably virally suppressed were switched to E/C/F/TAF from another ARV regimen, 477 retained their original ARV as comparator. The study population was mostly men (87%) and the majority were white (62%). The mean ages varied according to population with

treatment naïve having a mean age of 34 years. The mean age of the switched treatment normal renal function study population was 41 years. The mean age of the switched treatment mild to moderate renal impairment population was 58 years. Across studies, a total of 87 subjects were ≥ 65 years of age. The median age of adolescent subjects in Study GS-US-292-0106 was 15 years (range, 12 to 17).

Women comprised approximately 15% of the ART-naïve population in the pivotal studies (292-0104 and 292-0111), approximately 10% of the virologically suppressed population in Study GS-US-292-0109, and approximately 20% of the population with mild to moderate renal impairment in Study 292-0112. The adolescent study (292-0106) included 28 female subjects (58.3%). Across studies of adult subjects, 55%-70% were white, 20 to 30% were black and approximately 15% to 25% subjects were Hispanic or Latino. Of the adolescent subjects (Study 292-0106), 87.5% were black and 12.5% were Asian, and none were Hispanic or Latino.

A majority of subjects (78%) had a HIV-1 viral load $\leq 100,000$ copies/mL. Baseline disease characteristics were generally similar between treatment groups and within each randomized study. The median baseline HIV-1 RNA value in treatment naïve subjects was approximately $4.5 \log_{10}$ copies/mL and approximately 25% had baseline HIV-1 RNA $> 100,000$ copies/mL. Of virologically suppressed subjects in Studies 292-0109 and 292-0112, approximately 98% had baseline HIV-1 RNA < 50 copies/mL, and most subjects in the switch groups of Study GS-US-292-0102 also had baseline HIV-1 RNA values < 50 copies/mL.

Median baseline CD4 cell count was approximately 425 cells/ μ L in ART-naïve subjects (across all 5 studies) and approximately 675 cells/ μ L in virologically suppressed subjects (Studies 292-0109 and 292-0112). The most common HIV risk factor was homosexual sex (approximately 75% to 90%) across subjects who were ART-naïve (Studies 292-0104, 292-0111, and 292-0102) or virologically suppressed (Study 292-0109). Heterosexual sex and homosexual sex were approximately equal risk factors (approximately 50% each) for subjects with mild to moderate renal impairment (Study 292-0112), and vertical transmission was the most common HIV risk factor (83.3%) for adolescent subjects (Study 292-0106). Most subjects in each study had asymptomatic HIV-1 infection (approximately 75% to 90%; status was not collected at baseline in Study 292-0109).

The median baseline eGFR values of subjects who were ART-naïve (Studies 292-0104, 292-0111, 292-0102, and 292-0106) or virologically suppressed (Study 292-0109) ranged from 105.7 to 117.0 mL/min (eGFR_{CG} in adult subjects or calculated using the modified Schwartz formula in adolescent subjects), and proteinuria by urinalysis (dipstick) of any grade was observed in approximately 10% or less of these subjects.

In contrast, the median (Q1, Q3) baseline eGFR_{CG} value in Study 292-0112 was 55.6 mL/min (45.7, 62.4) among subjects who were ART-experienced and 60.2 mL/min

(45.0, 63.2) among subjects who were ART-naive. Overall, 33.1% of ART-experienced subjects (80 of 242 subjects) had eGFR_{CG} < 50 mL/min, 42.3% (101 of 239 subjects) had clinically significant proteinuria (UPCR > 200 mg/g), and 48.9% (115 of 235 subjects) had clinically significant albuminuria (UACR ≥ 30 mg/g). At baseline, 9.5% of ART-experienced subjects had Grade 2 proteinuria by urinalysis (dipstick) and 23.1% had Grade 1 proteinuria.

Table 29 Demographics Baseline Disease Characteristics Studies 0104.0111, 0102, 0109, 0112

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects	
	GS-US-292-0104/ GS-US-292-0111		GS-US-292-0102 ^a		GS-US-292-0109		GS-US-292-0112	
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)
HIV-1 RNA (log₁₀ copies/mL)								
N	866	867	112	58	NC	NC	242	6
Mean (SD)	4.54 (0.665)	4.53 (0.682)	4.63 (0.572)	4.69 (0.577)	NC	NC	1.32 (0.318)	4.66 (0.675)
Median	4.58	4.58	4.55	4.58	NC	NC	1.28	4.72
Q1, Q3	4.14, 4.95	4.15, 4.96	4.30, 4.89	4.35, 5.08	NC	NC	1.28, 1.28	4.01, 5.35
Min, Max	2.57, 6.89	1.28, 6.98	3.11, 6.94	3.50, 6.44	NC	NC	1.28, 4.88	3.76, 5.39
HIV-1 RNA categories (copies/mL)								
< 50	—	—	—	—	943 (98.3%)	466 (97.7%)	236 (97.5%)	0
≤ 100,000	670 (77.4%)	672 (77.5%)	93 (83.0%)	42 (72.4%)	959 (100%)	477 (100%)	242 (100%)	4 (66.7%)
> 100,000 to ≤ 400,000	147 (17.0%)	154 (17.8%)	14 (12.5%)	13 (22.4%)	—	—	0	2 (33.3%)
> 400,000	49 (5.7%)	41 (4.7%)	5 (4.5%)	3 (5.2%)	—	—	0	0
CD4 cell count (cells/μL)								
N	865	867	112	58	959	477	242	6
Mean (SD)	426 (215.6)	429 (219.6)	404 (181.6)	394 (209.6)	701 (261.8)	689 (248.0)	664 (286.4)	412 (244.0)
Median	404	406	385	397	675	662	632	397
Q1, Q3	283, 550	291, 542	283, 528	232, 535	520, 833	525, 831	456, 811	184, 673
Min, Max	0, 1311	1, 1360	30, 897	2, 866	89, 1951	79, 1739	126, 1813	115, 708
CD4 cell count categories (cells/μL)								
< 50	24 (2.8%)	27 (3.1%)	2 (1.8%)	1 (1.7%)	0	0	0	0
≥ 50 to < 200	88 (10.2%)	90 (10.4%)	12 (10.7%)	10 (17.2%)	5 (0.5%)	4 (0.8%)	5 (2.1%)	2 (33.3%)
≥ 200 to < 350	218 (25.2%)	200 (23.1%)	32 (28.6%)	14 (24.1%)	54 (5.6%)	25 (5.2%)	19 (7.9%)	0
≥ 350 to < 500	256 (29.6%)	284 (32.8%)	33 (29.5%)	17 (29.3%)	151 (15.7%)	70 (14.7%)	53 (21.9%)	2 (33.3%)
≥ 500	279 (32.3%)	266 (30.7%)	33 (29.5%)	16 (27.6%)	749 (78.1%)	378 (79.2%)	165 (68.2%)	2 (33.3%)
Missing	1	0	0	0	0	0	0	0

HIV disease status									
Asymptomatic	780 (90.4%)	802 (92.9%)	99 (88.4%)	52 (89.7%)	— ^e	— ^e	180 (74.4%)	5 (83.3%)	
Symptomatic HIV infection	53 (6.1%)	35 (4.1%)	9 (8.0%)	5 (8.6%)	— ^e	— ^e	28 (11.6%)	1 (16.7%)	
AIDS	30 (3.5%)	26 (3.0%)	4 (3.6%)	1 (1.7%)	— ^e	— ^e	34 (14.0%)	0	
Unknown	3	4	0	0	— ^e	— ^e	0	0	
eGFR _{CG} (mL/min)									
N	866	867	112	58	959	477	242	6	
Mean (SD)	120.8 (30.87)	118.7 (30.73)	120.4 (30.77)	114.8 (23.72)	111.9 (33.39)	112.1 (32.70)	54.8 (11.64)	55.1 (11.73)	
Median	117.0	113.9	115.2	113.3	105.7	107.7	55.6	60.2	
Q1, Q3	99.6, 135.6	99.0, 133.6	100.8, 131.7	97.7, 129.4	89.4, 126.0	88.7, 128.2	45.7, 62.4	45.0, 63.2	
Min, Max	33.7, 287.2	55.3, 320.2	72.6, 239.5	73.5, 176.8	48.0, 344.1	53.7, 304.8	26.2, 89.7	36.3, 65.5	
Proteinuria by urinalysis									
Grade 1	80 (9.2%)	67 (7.7%)	10 (8.9%)	2 (3.4%)	81 (8.5%)	44 (9.2%)	56 (23.1%)	0	
Grade 2	8 (0.9%)	18 (2.1%)	1 (0.9%)	1 (1.7%)	4 (0.4%)	3 (0.6%)	23 (9.5%)	1 (16.7%)	
Grade 3	0	1 (0.1%)	0	0	0	0	0	0	
Missing	0	1	0	0	1	0	0	0	

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects	
	GS-US-292-0104/ GS-US-292-0111		GS-US-292-0102 ^a		GS-US-292-0109		GS-US-292-0112	
	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)	ART-Experienced E/C/F/TAF (N=242)	ART-Naive E/C/F/TAF (N=6)
Diabetes mellitus [‡]								
Yes	25 (2.9%)	40 (4.6%)	5 (4.5%)	1 (1.7%)	— ^e	— ^e	33 (13.6%)	0
Hypertension [‡]								
Yes	118 (13.6%)	146 (16.8%)	14 (12.5%)	6 (10.3%)	— ^e	— ^e	95 (39.3%)	3 (50%)
Cardiovascular disease [‡]								
Yes	11 (1.3%)	14 (1.6%)	4 (3.6%)	1 (1.7%)	— ^e	— ^e	—	—
Hyperlipidemia [‡]								
Yes	92 (10.6%)	100 (11.5%)	15 (13.4%)	6 (10.3%)	— ^e	— ^e	—	—

Source Adapted from ISE p 61-62

6.1.3 Subject Disposition

Across the 6 clinical studies summarized in this document, 2394 subjects were randomized or enrolled and received at least 1 dose of E/C/F/TAF. For E/C/F/TAF overall, 2306 subjects (96.3%) were still on study treatment up to the applicable data cut date for each study. The percentages of subjects who discontinued study drug prematurely were comparable across studies; and were comparable between treatment groups in randomized studies. Across all 6 studies, 88 subjects (3.7%) prematurely discontinued E/C/F/TAF. The reasons for premature discontinuation of study drug were generally comparable across studies and between treatment groups in randomized studies. The most common reasons (across all 6 studies) for discontinuation of E/C/F/TAF were AE (1.2%, 29 subjects), lost to follow-up (0.9%, 22 subjects), and withdrawal of consent (0.8%, 19 subjects).

A total of 1032 ART-naive subjects across 5 studies were randomized or enrolled and received at least 1 dose of E/C/F/TAF as follows: 866 adult subjects in the pivotal Phase 3 studies (GS-US-292-0104 and GS-US-292-0111); 112 adult subjects in the Phase 2 study (GS-US-292-0102); 6 adult subjects with mild to moderate renal impairment in the Phase 3 study GS-US-292-0112; and 48 adolescent subjects in the Phase 2/3 study GS-US-292-0106.

A total of 1362 virologically suppressed, ART-experienced adult subjects across 3 studies were randomized or enrolled and received at least 1 dose of E/C/F/TAF as follows: 959 subjects in the Phase 3 study GS-US-292-0109, 161 subjects in the extension phase of the Phase 2 study GS-US-292-0102, and 242 subjects with mild to moderate renal impairment in the Phase 3 study GS-US-292-0112.

Table 30 Disposition Subjects Studies 0104, 0111, 0101, 0109 and 0112

	ART-Naive Adult Subjects				Virologically Suppressed Subjects		Renally Impaired Subjects		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
	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 + 3 rd Agent (N = 477)	ART- Experienced E/C/F/TAF (N = 242)	ART-Naive E/C/F/TAF (N = 6)	E/C/F/TAF (N = 48)
Subjects in Safety Analysis Set	866	867	112	58	959	477	242	6	48
Subjects in FAS	866 (100%)	867 (100%)	112 (100%)	58 (100%)	799 (83.3%)	397 (83.2%)	242 (100%)	6 (100%)	48 (100%)
Subjects still on study treatment up to the data cut date	821 (94.8%)	796 (91.8%)	105 (93.8%)	53 (91.4%)	939 (97.9%)	447 (93.7%)	226 (93.4%)	6 (100%)	48 (100%)
Subjects prematurely discontinuing study treatment prior to the data cut date	45 (5.2%)	71 (8.2%)	7 (6.3%)	5 (8.6%)	20 (2.1%)	30 (6.3%)	16 (6.6%)	0	0
Reasons for prematurely discontinuing study treatment									
Adverse event	8 (0.9%)	13 (1.5%)	4 (3.6%)	0	9 (0.9%)	7 (1.5%)	8 (3.3%)	0	0
Death	1 (0.1%)	2 (0.2%)	0	0	2 (0.2%)	0	0	0	0
Pregnancy	0	5 (0.6%)	0	0	0	0	0	0	0
Lack of efficacy	2 (0.2%)	3 (0.3%)	0	1 (1.7%)	1 (0.1%)	0	1 (0.4%)	0	0
Investigator's discretion	0	7 (0.8%)	0	0	1 (0.1%)	4 (0.8%)	1 (0.4%)	0	0
Non-compliance with study drug	2 (0.2%)	1 (0.1%)	1 (0.9%)	1 (1.7%)	0	2 (0.4%)	0	0	0
Protocol violation	5 (0.6%)	6 (0.7%)	0	0	0	0	1 (0.4%)	0	0
Withdrew consent	12 (1.4%)	16 (1.8%)	0	1 (1.7%)	4 (0.4%)	12 (2.5%)	3 (1.2%)	0	0
Lost to follow-up	15 (1.7%)	18 (2.1%)	2 (1.8%)	2 (3.4%)	3 (0.3%)	5 (1.0%)	2 (0.8%)	0	0
Subjects still in study up to the data cut date	827 (95.5%)	812 (93.7%)	105 (93.8%)	53 (91.4%)	942 (98.2%)	455 (95.4%)	232 (95.9%)	6 (100%)	48 (100%)
Subjects prematurely discontinuing from study prior to the data cut date	39 (4.5%)	55 (6.3%)	5 (4.5%) ^c	5 (8.6%)	17 (1.8%)	22 (4.6%)	10 (4.1%)	0	0

Source Adapted from ISE p 55-56

6.1.4 Analysis of Primary Endpoint(s)

Studies 292-0104 and 292-0111

The primary endpoint for the pivotal Phase 3 trials was the percentage of subjects with virologic success (HIV-1 RNA < 50 copies/mL at Week 48) using the FDA-defined snapshot analysis algorithm. In trial 292-0104 the Agency biostatistician calculated 93 % of E/C/F/TAF subjects had virologic success compared to 92 % of subjects in the Stribild® arm. In trial 292-0111, the Agency biostatistician calculated 92% of E/C/F/TAF subjects had virologic success compared to 89% of Stribild® recipients.

The E/C/F/TAF group met the pre-specified non-inferiority margins of 12%. In both studies, both the Applicant and the Agency were in agreement. Please see Applicant's table below for details.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups; Study 292-0104 (E/C/F/TAF 3.0%; STB 2.5%) and Study 292-0111 (E/C/F/TAF 4.2%; STB 5.5%).

Table 31 Efficacy Results Studies 292-0104 and 292-0111

	292-0104		292-0111	
	E/C/F/TAF (N=435)	STB (N=432)	E/C/F/TAF (N=431)	STB (N=435)
Virologic success at Week 48 ^a				
HIV-1 RNA < 50 copies/mL	405 (93.1%)	399 (92.4%)	395 (91.6%)	385 (88.5%)
Difference in percentages (95.002% CI) ^b	1.0% (-2.6% to 4.5%)		3.1% (-1.0% to 7.1%)	
p-value ^c	0.58		0.13	
Virologic failure at Week 48 ^a	13 (3.0%)	11 (2.5%)	18 (4.2%)	24 (5.5%)
HIV-1 RNA ≥ 50 copies/mL	9 (2.1%)	6 (1.4%)	11 (2.6%)	17 (3.9%)
Discontinued study drug due to lack of efficacy	0	2 (0.5%)	2 (0.5%)	1 (0.2%)
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL ^d	3 (0.7%)	3 (0.7%)	5 (1.2%)	5 (1.1%)
Added new ARV	1 (0.2%)	0	0	1 (0.2%)
No virologic data in Week 48 window ^a	17 (3.9%)	22 (5.1%)	18 (4.2%)	26 (6.0%)
Discontinued study drug due to AE/death	4 (0.9%)	5 (1.2%)	4 (0.9%)	9 (2.1%)
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL ^d	11 (2.5%)	15 (3.5%)	10 (2.3%)	16 (3.7%)
Missing data during window but on study drug	2 (0.5%)	2 (0.5%)	4 (0.9%)	1 (0.2%)

Source Adapted from ISE p 66

Study 292-0102

In Study GS-US-292-0102, virologic outcomes at Week 48 were similar between the 2 treatment groups for the primary endpoint analysis based on the FAS (Full Analysis Set). Virologic success rates calculated by the Agency biostatistician were as follows: E/C/F/TAF 88%, STB 88%; difference in percentages: -1.0%, 95% CI -12.1% to 10.0%. The Applicant and the Agency were in agreement.

Percentages of subjects with virologic failure at Week 48 (and reasons for failure) were similar for the 2 treatment groups (E/C/F/TAF 6.3%; STB 10.3%).

Table 32 Efficacy Results Study 292-0102

	E/C/F/TAF (N=112)	STB (N=58)	E/C/F/TAF vs. STB	
			p-value ^a	Difference in Percentages (95% CI) ^b
Virologic Success at Week 48^c				
HIV-1 RNA < 50 copies/mL	99 (88.4%)	51 (87.9%)	0.84	-1.0% (-12.1% to 10.0%)
Virologic Failure at Week 48^c	7 (6.3%)	6 (10.3%)		
HIV-1 RNA ≥ 50 copies/mL	6 (5.4%)	4 (6.9%)		
Discontinued Study Drug Due to Lack of Efficacy	0	1 (1.7%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL ^d	1 (0.9%)	1 (1.7%)		
No Virologic Data in Week 48 Window^c	6 (5.4%)	1 (1.7%)		
Discontinued Study Drug Due to AE	4 (3.6%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL ^d	2 (1.8%)	1 (1.7%)		

Source Adapted from ISE p 68

292-0109

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA snapshot algorithm. The rates of maintained virologic suppression in Study GS-US-292-0109 at Week 48 were high in both groups. As calculated by the Agency biostatistician at Week 48 E/C/F/TAF had a virologic success rate of 96%; FTC/TDF+3rd Agent 93%; difference in percentages: 2.7%, 95.01% CI: -0.3% to 5.6%). Because the lower bound of the 2-sided 95.01% CI of the difference in response rate was greater than the prespecified -12% margin, switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48.

The rates of maintained virologic suppression were also similar between treatment groups using the Week 48 Per Protocol (PP) Analysis Set (E/C/F/TAF 99.1%, 748 of 755 subjects; FTC/TDF+3rd Agent 98.9%, 363 of 367 subjects; difference in percentages: 0.2%, 95.01% CI: -1.3% to 1.6%), confirming that switching to E/C/F/TAF was noninferior to maintaining FTC/TDF+3rd Agent at Week 48. For more details regarding the primary efficacy endpoint calculation please see Dr. Miele’s review in Appendix 1.

Table 33 Efficacy Results Study 292-0109

			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 ^c	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%)		

Source Adapted from ISE p 79

292-0112

The primary efficacy endpoint was the percentage of subjects with HIV 1 RNA < 50 copies/mL at Week 24 using the FDA snapshot algorithm. The Applicant calculated the virologic success rate among virologically suppressed subjects with mild to moderate renal impairment who switched treatment to E/C/F/TAF in Study GS-US-292-0112 was 95.0% (baseline eGFRCG < 50 mL/min 95.0%; baseline eGFRCG ≥ 50 mL/min 95.1%). Three subjects (1.2%) were classified as virologic failures at Week 24. Of those 3 subjects, 2 had HIV-1 RNA ≥ 50 copies/mL at Week 24, and 1 added a new ARV

Table 34 Efficacy Results Study 292-0112

	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 24^a				
HIV-1 RNA < 50 copies/mL	76 (95.0%)	154 (95.1%)	230 (95.0%)	5 (83.3%)
95% CI ^b	87.7% to 98.6%	90.5% to 97.8%	91.5% to 97.4%	35.9% to 99.6%
Virologic failure at Week 24^a	0	3 (1.9%)	3 (1.2%)	1 (16.7%)
HIV-1 RNA ≥ 50 copies/mL	0	2 (1.2%)	2 (0.8%)	1 (16.7%)
Added new ARV	0	1 (0.6%)	1 (0.4%)	0
No virologic data in Week 24 window ^a	4 (5.0%)	5 (3.1%)	9 (3.7%)	0
Discontinued study drug due to AE/death	4 (5.0%)	2 (1.2%)	6 (2.5%)	0
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL ^c	0	3 (1.9%)	3 (1.2%)	0
Missing data during window but on study drug	0	0	0	0

Source Adapted from ISE p 81

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for pivotal studies 292-0104 and 292-0111 as well as switch study 292-0109 were: 1) percent changes from baseline in hip bone mineral density at Week 48 and 2) change from baseline in serum creatinine at Week 48. Since these are safety endpoints they will be discussed in Section 7. The secondary efficacy endpoints for 292-0102 included percentage of subjects with HIV-1 RNA < 50 copies/mL at week 48, and change from baseline in HIV-1 RNA and CD4+ cell count at Weeks 24 and 48. The virologic success and failure at Week 48 were previously discussed. Study 292-0112 had 7 secondary endpoints. These included the following: change from baseline in eGFR performed by three methods (Cockcroft-Gault, CKD-EPI and cystatin C), change in aGFR performed by iohexol GFR, change in bone biomarkers and renal biomarkers, incidence of adverse events, PK parameters, and proportion of subjects achieving virologic success at 24, 48 and 96 Weeks. The 24 week virologic success is discussed in the previous section. The remainder of these secondary endpoints will be discussed elsewhere.

Please refer to FDA Statistical Review for details of other analyses performed.

6.1.6 Other Endpoints

No other efficacy endpoints were explored by the clinical reviewer.

6.1.7 Subpopulations

Pivotal Studies 292-0104 and 292-0111 provide the most information regarding the efficacy findings with regard to age, sex, race, baseline CD4+ count, baseline HIV-1 viral load, region, and study drug adherence. The data pooled from both studies is

presented below. In general, high baseline viral load, low baseline CD4+, black race, low study drug adherences were unfavorable factors. The virologic success rate for E/C/F/TAF and Stribild® were similar for each subgroup except for women and blacks taking Stribild®. The numbers of women in both treatment arms are balanced but small. The discrepancy may be related to these small numbers. This will need to be followed closely however.

Table 35 Efficacy in Demographic Subgroups

Subgroup		E/C/F/TAF N=866	STB N=867
Age	<50 yrs	716/777 (92%)	680/753 (90%)
	≥ 50 yrs	84/89 (94%)	104/114 (91%)
Gender	Male	674/733 (92%)	673/740 (91%)
	Female	126/133 (95%)	111/127 (87%)
Race	Black	197/223 (88%)	177/213 (83%)
	Non-Black	603/643 (94%)	607/654 (93%)
Baseline HIV RNA	≤ 100K	629/670 (94%)	610/672 (91%)
	> 100K	171/196 (87%)	174/195 (89%)
Baseline CD4+	< 200	96/112 (86%)	104/117 (89%)
	≥ 200	703/753 (94%)	680/750 (91%)
Region	U.S.	484/532 (91%)	474/532 (89%)
	Not –U.S.	316/334 (95%)	310/335 (93%)
Adherence	< 95%	136/159 (86%)	143/165 (87%)
	≥ 95%	664/703 (95%)	641/696 (92%)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant used 2 Phase 1 trial data to develop the dosage recommendation for the TAF component of E/C/F/TAF.

GS-US-120-0104

The primary objective of this 40 subject Phase 1 trial was to evaluate the short term antiviral potency of GS-7340 (tenofovir alafenamide fumarate). The anti-viral activities against HIV-1 of three doses of GS-7340 (8mg, 25mg, and 40mg) were compared with TDF (tenofovir disoproxil fumarate) 300mg (approved dose). Each participant received study drug daily as monotherapy for a period of 10 days. Nine subjects received GS-7340 8mg, 8 received GS-7340 at 25 mg, 8 subjects received 40mg, 6 subjects received TDF 300mg and 7 subjects received placebo. The efficacy outcome of this study was to demonstrate the decrease in HIV-1 RNA levels was significantly greater for groups receiving GS-7340 25mg (p=0.024) and 40mg (p=.003) than for the TDF 300mg qd. There was a statistically significant difference between GS-7340 8mg and 40mg. The safety profile of all three TAF doses were favorable. On the basis of

these data, the target dosage of 25 mg TAF was selected.

GS-US-292-0103

The primary objective of this 34 subject healthy volunteer study was to evaluate the pharmacokinetics and relative bioavailability of EVG, COBI, FTC and GS 7340 FDC relative to the administration of the individual components. The dose of TAF in the FDC was 10mg and the individual component of TAF was 25mg. In this study it was determined that in the presence of COBI, 10 mg of TAF had a similar exposure as TAF 25mg given in the absence of COBI. This increased exposure was attributed to inhibition by COBI of the P-glycoprotein mediated intestinal secretion of GS-7340. For this reason, the final dosage of TAF in the FDC was selected as 10mg.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Studies 292-0104, 292-0111, 292-0102, 292-0109 and 292-0112 are all designed to continue through 96 weeks. As such, additional efficacy and safety data will be generated by the Applicant and reviewed by the Division.

6.1.10 Additional Efficacy Issues/Analyses

No additional efficacy issues or analyses were addressed or performed.

7 Review of Safety

Safety Summary

The most common adverse events identified in adults participating in these five studies were gastrointestinal disorders (predominantly diarrhea and nausea) and infections and infestations (led by upper respiratory infections). In the pivotal studies in treatment naïve (Studies 292-0104 and 292-0111) the incidences of both were similar for E/C/F/TAF and Stribild® groups. For other MedDRA system organ classes, including musculoskeletal, nervous system disorders, psychiatric disorders, respiratory system and skin and subcutaneous tissues, the incidences between E/C/F/TAF and Stribild® are also similar in these treatment naïve subjects.

In the virally suppressed participants of Study 292-0109 the most common TEAEs were Infections and Infestations (predominantly upper respiratory infections) and gastrointestinal system (predominantly nausea and diarrhea). Among those switched to E/C/F/TAF there was a higher incidence of any AEs considered related to the study drug by the investigator (19% versus 11% in comparator). This discrepancy was attributed to the open label aspect of this trial. No differences were identified that appeared to warrant further investigation.

In Study 292-0112, the gastrointestinal system and upper respiratory infections are prominent. The incidences of arthralgias and dizziness are higher than what was seen

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in the other clinical trials. The reason for these findings is not known.

The incidence of deaths, nonfatal Serious Adverse Events and discontinuations for AEs were low and balanced across study arms in all five adult clinical trials.

Differences in Bone Safety and Bone mineral density (BMD) findings with use were a major safety concern of these studies. Tenofovir alafenamide was believed to have lower impact on BMD than tenofovir disoproxil fumarate. It was postulated by the Applicant that this feature would translate to lower loss of BMD with its use compared to Stribild® a product otherwise identical except for the use of tenofovir disoproxil. There were no fragility fractures clearly identified during the conduct of these trials. BMD differences favoring E/C/F/TAF by DEXA scans were observed. [REDACTED] (b) (4)

[REDACTED] Discussions with the Applicant regarding the product label are in progress.

Differences in Renal safety between E/C/F/TAF and Stribild® were also a major safety concern of these studies. Tenofovir alafenamide was believed to have lower impact on the renal proximal tubules due to its attendant lowered tenofovir exposures. Tenofovir (TFV) exposures are thought to be related to the development of renal injury. Differences in serum creatinine and eGFR creatinine clearances favoring E/C/F/TAF over Stribild have been demonstrated in the data submitted. Beyond the small but statistically significant changes in serum creatinine and eGFR by Cockcroft Gault the evidence for benefit is based upon non validated laboratory testing results. Discussions with the Applicant regarding this aspect of the product label are in progress at this time.

An allied issue concerning renal safety is the expansion of the indicated population for E/C/F/TAF to include individuals with mild to moderate renal impairment. Currently, Stribild® use is not recommended for use in individuals with a creatinine clearance lower than 70 mL/min. Emtricitabine, one of the components of both Stribild® and E/C/F/TAF is not recommended for daily use in individuals with creatinine clearance lower than 50 mL/min. Below 50 mL/min every other day renal dosing is recommended. Study 292-0112, studied the use of E/C/F/TAF in subjects with eGFR by Cockcroft-Gault methodology of > 30 mL/min to 69 mL/min. Pharmacokinetic testing has demonstrated increased emtricitabine exposure of 115% in subjects with creatinine clearances less than 50mL/min receiving a daily dose of 200mg. No discreet toxicity associated with the administration of E/C/F/TAF to this population was identified in this submission. Increases in the incidence of dizziness and Grade 3 amylase levels (mentioned in the Emtriva® label) in the more severely renally compromised remains concerning.

The initiation of E/C/F/TAF is associated with substantial increases in serum lipids which exceed increases observed with the initiation of Stribild®. In the treatment naïve population, median and mean increases in total cholesterol of 29mg/dL and 31 mg/dL were seen with E/C/F/TAF compared to 15 mg/dL and 23 mg/dL with Stribild®. For LDL

cholesterol changes are even greater with increases of a median of 14 mg/dL and mean of 16 mg/dL with E/C/F/TAF compared to 3 mg/dL and 4 mg/dl respectively for Stribild®. Approximately 40% of E/C/F/TAF subjects compared to 20% of Stribild® subjects went from normal total cholesterol to Grade 1 or higher. The height of these elevations is idiosyncratic. In the treatment naïve trials nine individuals went from normal levels of LDL cholesterol to > 190mg/dL. In the pivotal trials at Week 48, 27 (3.1%) of E/C/F/TAF recipients versus 13 (1.5%) of Stribild® recipients met that level of hyperlipidemia.

Ocular safety was a concern during the conduct of these trials. During the preclinical development of E/C/F/TAF posterior uveitis was detected in the dog model at the highest doses at the 3 and 9 month time period. Because of this finding, the Applicant instituted increased vigilance for eye disorders including the institution of a substudy and investigator instruction and incorporation of specific language into the protocols and informed consents. This increased vigilance did not identify an increased incidence of any form of uveitis. None the less, there did appear to be some evidence of increased inflammation compared with Stribild® with numerically higher levels of conjunctivitis, visual blurring, and photophobia. Continued heightened vigilance is recommended.

Dental Safety was a concern during the review. During the assessment of types and severities of adverse events, it was noted that terms such as dental necrosis and jaw necrosis were encountered. Although the overall numbers of dental disorders in the pivotal studies were similar at approximately 10% each, there were nearly twice as many Grade 2 or higher dental TEAEs in the E/C/F/TAF groups compared to the Stribild® groups. For this reason a consultation with Division of Dermatology and Dental Products was undertaken. The outcome of that consultation was that the numbers were too small to support any conclusion.

Graded hyperuricemia imbalance was detected in Study 292-0109 between subjects switching to E/C/F/TAF and those remaining on their baseline regimen (FTC/TDF and a 3rd agent). Thirteen percent of those who switched to E/C/F/TAF compared to 5% of those who remained on their baseline regimen were noted to have these abnormalities. When the pivotal trials 292-0104 and 292-0111 were examined, the percentage in the E/C/F/TAF group was similar at 12%. The percentage with Stribild® was 9%. When the same analysis was applied to the renally impaired population, the percentage was higher at 19%. The significance of this finding is unknown since the incidence of gout was low in all the clinical trials.

7.1 Methods

Safety data for this NDA was submitted by the Applicant as final study reports, clinical safety summary, an integrated summary of safety and electronic datasets. Narrative summaries were provided for all subjects who died, developed a serious adverse event (SAE), developed an adverse event of special interest or discontinued from the study because of an adverse event (AE).

Summary results of the integrated safety analysis are presented in the following sections. Minor differences between the Applicant's results and FDA's results can be attributed to the differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms are used in the analyses of the adverse event tables in this review; however American English spelling is used in the tables and text of this review instead of British English spelling. The Applicant's categorization of closely related events and coding of adverse event verbatim terms to preferred terms was assessed and was found to be appropriate.

Each AE is listed only once in summary tables, regardless of the number of times it occurred for the subject. A subject may report more than one AE; therefore, the total number of AEs reported may be greater than the number of subjects in the study. Adverse events and laboratory abnormalities were graded using the modified WHO grading scale.

Data tables in this section were generated by the primary clinical reviewer from the ISS datasets using JMP 11 unless otherwise specified.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant's primary bases for their analysis of clinical safety in treatment naïve adults are the safety data from the pivotal studies 292-0104 and 292-0111 combined with that of the Phase 2 study 292-0102. The Applicant's bases for their analysis of clinical safety in fully suppressed subjects who switched to E/C/F/TAF are the safety data of studies 292-0109 and 292-0112. The latter study also provides safety data on subjects with mild to moderate renal impairment. The Applicant's basis for their analysis of clinical safety in treatment naïve adolescents comes from the safety data from 292-0106.

This safety review will focus predominantly on the safety data from the Phase 3 pivotal studies 292-0104 and 292-0111 with periodic use of additional data from the two fully suppressed switch studies, especially the renal impairment study 292-0112. Safety data from both non-clinical studies and Phase 1 through 3 clinical trials were considered for identification of specific adverse events of interest.

7.1.2 Categorization of Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA), version 17.0 was used for AE coding. Adverse events were summarized by MedDRA System Organ Class and Preferred Term. A treatment-emergent AE was defined as any AE that began on or after the treatment start date up to 30 days after the treatment stop date.

A serious adverse event (SAE) is any event that results in any one of the following

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outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The two Phase 3 pivotal trials 292-0104 and 292-0111 were identical and their safety data were pooled. The study design of the randomized, blinded portion of Phase 2 study 292-0102 was similar to the pivotal trials and was pooled where appropriate. Where appropriate, the safety data from the fully virally suppressed switch study 292-0109 were integrated. The safety data from the other virally suppressed switch study 292-0112 was unique from the others and was considered individually where it provided insight into renal impairment issues.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The dose and formulation selected for marketing is the E/C/F/TAF (150/150/200/10mg) tablet. This was the dose and formulation used in the two Phase 3 pivotal studies (292-01104, 292-0111) and one Phase 2 (292-0102) supportive study in treatment naïve; the Phase 3 switch study (292-0109) in virally suppressed; the Phase 3 switch study in renally impaired (292-0112) and the Phase 2/3 study in HIV-1 infected adolescents (292-0106). Therefore, the use of these studies to assess the safety of the proposed dose and formulation intended for marketing is appropriate.

A total of 2573 subjects received at least 1 dose of E/C/F/TAF in the to be marketed doses and formulation in the E/C/F/TAF clinical program including 2121 subjects in the Phase 3 program, 272 in the phase 2 study (including both randomized and open-label extension) and 179 subjects in the Phase 1 studies. Across the Phase 2 and Phase 3 studies, a total of 2394 subjects have received E/C/F/TAF with a median (Q1, Q3) exposure of 48.1 weeks (42.3, 60.0). The median exposure was similar in subjects who were ART-naïve (Studies 292-0104 and 292-0111), subjects who were virologically suppressed (Study 292-0109), and subjects with mild to moderate renal impairment (Study 292-0112).

The median (Q1, Q3) exposure was shorter in adolescent subjects in Study 292-0106 compared with the studies in adults (12.1 [4.1, 32.1] weeks); however, approximately half of the subjects in the study received E/C/F/TAF for ≥ 24 weeks. In studies with comparators, exposure between groups was similar within each study.

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In the open-label extension phase of Study 292-0102, the median (Q1, Q3) duration of exposure for the E/C/F/TAF group in the All E/C/F/TAF analysis was 105.3 (98.0, 108.1) weeks, with the majority of subjects completing 96 weeks of treatment (92.0%, 103 subjects).

Please refer to Section 6.1.2 for demographic information.

7.2.2 Explorations for Dose Response

Please see Section 6.1.8

7.2.3 Special Animal and/or In Vitro Testing

Appropriate preclinical testing was performed. Please refer to Section 4.3 and Dr. Claudia Wrzesinski's review for details of the preclinical program.

7.2.4 Routine Clinical Testing

The routine clinical monitoring was performed at pre-specified regular intervals during the trials and was agreed upon by the review team when the protocols were initially reviewed. Safety assessments included, but were not limited to, the following; physical examinations, measurement of vital signs, and clinical laboratory tests. Additional testing was performed as indicated during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate. Please refer to Section 4.4 and to Dr. Mario Sampson's review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profiles of the NRTIs (including the FTC component of this FDC) and elvitegravir, cobicistat were taken into consideration in the safety evaluation.

7.3 Major Safety Results

7.3.1 Deaths

In the pooled Phase 3 analyses, there were a total of 10 deaths occurring during study participation. Three of these deaths were reported in the 120 day safety update, one each in the treatment naïve adults, virally suppressed adults and renal impairment. With this update there were 6 deaths in the E/C/F/TAF treatment group and 4 in the Stribild®

treatment group. Causes of death were myocardial infarction/cardiovascular disease in 3, advanced malignancy in 2, substance abuse in 2, cerebrovascular accident in an Asian individual with chronic atrial fibrillation, septic shock and an instance of unobserved, unexplained death with toxicology pending. Of the ten, five occurred in white individuals, four occurred in African Americans and there was a single Asian death. Two of the deaths added during review of the 120 day safety update were African American deaths which occurred unobserved; one had an unsuccessful cardiac resuscitation and the cause of the other remains unknown. The remaining newly reported death occurred in a 61 year old man who apparently had leg soft tissue infection which led to a septic shock death.

Table 36 Deaths Studies 292-0104, 292-0111, 292-0102, 292-0109, 292-0112

Subject ID	Treatment Group	Age	Sex	Race	Study Date	Cause of Death
Treatment Naïve Studies 292-0104 and 292-0111						
1543-4364	STB	45	M	AA	85	Myocardial Infarction
4127-4587	E/C/F/TAF	49	M	Asian	235	Stroke Hx A fibrillation
7714-4583	STB	47	M	White	468	Non-small cell Lung Ca
1624-5009	STB	26	M	White	62	ETOH/Drug Overdose
2348-5663	STB	47	M	White	110	Myocardial Infarction
5129-5794	E/C/F/TAF	29	M	White	90	ETOH Poisoning
Virally Suppressed at Baseline 292-0109						
(b) (6)	E/C/F/TAF	61	M	White	148	Septic Shock
(b) (6)	E/C/F/TAF	55	M	AA	391	Advanced Cancer
(b) (6)	E/C/F/TAF	63	F	AA	391	Sudden Death
Renal Impairment at Baseline 292-0112						
(b) (6)	E/C/F/TAF	74	M	AA	343	Cardiopulmonary Arrest History of CAD

No deaths were reported in studies 292-0102 (neither randomized nor open label extension) or in 292-0106 (adolescents).

Reviewer's comments:

The total number of deaths in these trials is small and the causes of death are varied. It seems unlikely that the cancer deaths are related to the study drug due to the short interval of time between beginning study drug and the advanced cancer death. The substance abuse deaths might be expected in a patient population historically known to have a high incidence of such deaths. It is not known if these individuals were substance abusers prior to enrollment. Alternatively, these could have been suicides although there is nothing in the narratives to signal depression. There were a total of 3 diagnosed or presumed cardiovascular deaths, 2 occurring in the African American (AA) subjects. It is possible that the unobserved unexplained death also in an African American might be due to undiagnosed cardiovascular disease. The other new death was sepsis presumably due to a gram positive organism.

7.3.2 Nonfatal Serious Adverse Events

In the pooled Phase 3 analysis of adult subjects a total of 169/2185 (9%) subjects in the E/C/F/TAF containing arms and 97/1402 (7%) subjects in the control arms had SAEs reported, regardless of causality. It is noted that the incidence of SAEs in open label study 292-0109 was 4% and 15% in Phase 2 study 292-0102 compared to 8% in the pivotal studies.

The most common SAE by System Organ Class (SOCs) was infection and infestation which was 4% in the E/C/F/TAF containing arms and 3% in the comparator arms of the treatment naïve subject studies. The remainder of the SOC categories were balanced between E/C/F/TAF and its comparator arms.

Table 37 Non-Fatal Serious Adverse Events

	ART Naive				Viral Suppress		Renal Impaired
	292-0104/0111		292-0102		292-0109		292-0112
	TAF N=866	TDF N=867	TAF N=112	TDF N=58	TAF N=959	Control N=477	TAF N=268
ANY SAE	80 (9%)	69 (8%)	18 (16%)	7 (12%)	42 (4%)	21 (4%)	29(11%)
Infection	36 (4%)	22 (3%)	6 (5%)	2 (3%)	18 (2%)	9 (2%)	5 (2%)
Psychiatry	10 (1%)	10 (1%)	2 (2%)	2 (3%)	4 (<1%)	1 (<1%)	2(<1%)
Surgery/Trauma	7 (<1%)	10 (1%)	3 (3%)	0	3 (<1%)	0	1 (<1%)
GI disorders	7 (<1%)	9 (1%)	1 (<1%)	1 (2%)	7 (<1%)	3 (<1%)	2 (<1%)
Respiratory	5 (<1%)	2 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)	0
Cardiovascular	2 (<1%)	4 (<1%)	2 (<1%)	1 (2%)	3 (<1%)	2 (<1%)	5 (2%)
Neurologic	6 (<1%)	7 (<1%)	0	0	1 (<1%)	1 (<1%)	4(1%)
Neoplastic	4 (<1%)	8 (1%)	1 (<1%)	1 (2%)	3 (<1%)	1 (<1%)	3(<1%)
Eye disorders	2 (<1%)	2 (<1%)	0	0	1(<1%)	0	0
Musculoskeletal	3 (<1%)	1 (<1%)	0	0	2 (<1%)	0	2 (<1%)
Hematologic	0	0	0	0	1 (<1%)	1(<1%)	0
Renal	2 (<1%)	1 (<1%)	1 (<1%)	0	0	1 (1%)	1 (<1%)

There were 5 treatment-emergent SAEs assessed as related by the investigator in pivotal studies 292-0104 and 292-0111.

Subject GS-US-0104-4704 is a 31 year old man who developed a generalized rash over his body which spared his face. The severity was judged as moderate. The cause for the rash was not determined but he was treated with anti-histamines. He discontinued participation in the study. His study medication was E/C/F/TAF.

Subject GS-US-0104-1553-4841 is a 52 year old man who presented to ER-ICU with hypovolemic shock with mild renal failure. He initially received supportive care before influenza A was recovered from his respiratory secretions. He was treated for influenza A and ultimately recovered. Treatment was interrupted during his resuscitation and not

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restarted. His study medication was E/C/F/TAF. The investigator felt that the hypovolemic shock was probably not related to the study drug but rather to the “intercurrent illness”. Due to his interpretation of reporting requirements he coded this SAE as related.

Subject GS-US-0104-1995-4232 is a 26 yo man with multiple carbuncles growing MRSA. He was hospitalized for vancomycin therapy. He remained in study. His study meds were E/C/F/TAF. The investigator assessed the cause as possibly related to study drug as well as provided an alternative causality of pre-existing condition.

Subject GS-US-0104-2728-4019 is a 48 year old man who developed Hepatitis B immune reconstitution syndrome and discontinued his Stribild®.

Subject GS-US-0111-0986-5542 is a 44 yo Hispanic woman who underwent elective cholecystectomy for cholelithiasis. She remained in study and was taking Stribild®.

There were 4 SAEs in the SOC of Eye Disorders. Among E/C/F/TAF recipients there were 2: one syphilitic chorioretinitis responsive to penicillin and one traumatic retinal detachment. In the Stribild® there were also 2: one bilateral anterior uveitis (iridocyclitis) and one age related retinal detachment. None of these 4 were considered to be study drug related.

7.3.3 Dropouts and/or Discontinuations

Dropouts and Discontinuations for non-AE reasons were discussed in Section 6.1.3.

Overall, the number of discontinuations due to adverse events was low in both the E/C/F/TAF and its comparator arms. There were 29 adult subjects (1.5%) in E/C/F/TAF groups, and 23 adult subjects (1.6%) in comparator groups who had at least one AE leading to discontinuation. In the treatment naïve population, discontinuations for renal function deterioration were most prominent, occurring entirely in the Stribild® group. Discontinuations for other SOC groups were balanced across the study arms. Among the virologic suppressed, psychiatric issues were numerically the most prevalent but were balanced between arms. In the renal impairment group, there were two individuals whose renal function losses were sufficient to preclude further treatment. In addition, there were two individuals who discontinued because of persistent symptoms of generalized body aching and arthralgias. Both had baseline eGFRs of < 50 mL/min. The significance of these symptoms is unknown. Most of the AEs leading to discontinuation were non-serious and considered by the investigator as related to study drug.

Table 38 Discontinuations (AE) 292-0104, 292-0111, 292-0102, 292-0109, 292-0112

	ART Naive				Viral Suppress		Renal Impaired
	292-0104/0111		292-0102		292-0109		292-0112
	TAF N=866	TDF N=867	TAF N=112	TDF N=58	TAF N=959	Control N=477	TAF N=268
Discontinuation	8 (1%)	16 (2%)	4 (4%)	0	9 (1%)	7 (1.5%)	8 (3%)
Renal worsening	0	5 (<1%)	0	0	2 (<1%)	1 (<1%)	2 (<1%)
Psychiatry	0	1 (<1%)	0	0	4 (<1%)	2 (<1%)	1 (<1%)
Infection/IRIS	0	1 (<1%)	2 (2%)	0	1 (<1%)	0	0
Swallowing	1 (<1%)	1 (<1%)	0	0	0	0	2 (<1%)
Respiratory	1 (<1%)	0	0	0	0	3 (<1%)	0
Cardiovascular	2 (<1%)	1 (<1%)	0	0	0	0	0
Derm Rash	1 (<1%)	2 (<1%)	1 (1%)	0	0	0	0
Neurologic	0	0	1 (1%)	0	3	1	0
Neoplastic	0	2 (<1%)	0	0	0	0	1
Eye disorders	1 (<1%)	1 (<1%)	0	0	0	0	0
Rheumatologic	0	0	0	0	0	0	2 (<1%)
Osteoporosis	0	1 (<1%)	0	0	0	0	0
ED	1 (<1%)	0	0	0	0	0	0
Laboratory Investigations	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0

7.3.4 Significant Adverse Events

All AEs were graded by the study sites using the modified WHO grading system for grading the severity of AEs with the exception of laboratory values. Gilead provided guidelines for assessment of laboratory SEs.

In treatment naïve subjects the percentage of AEs of Grade 2 (moderate) severity or higher was 53% in E/C/F/TAF recipients compared to 48 % in the Stribild® recipients in Studies 292-0104 and 292-0111. The percentages of AEs of this severity are noted to be higher in Phase 2 Study 292-0102. The most likely explanation for this disparity is the small size of Study 292-0102. There is a slight preponderance of Grade 2 and higher infections and musculoskeletal disorders in the E/C/F/TAF arm compared to the Stribild arm. In all three studies infections were the most prevalent disorders followed by gastrointestinal, musculoskeletal and psychiatric disorders

Table 39 Adverse Events Grade 2 or Higher 292-0104, 292-0111, 292-0102

	Treatment Naïve			
	292-0104 and 292-0111		292-0102	
	E/C/F/TAF N=866	Stribild® N=867	E/C/F/TAF N=112	Stribild® N=58
Any Grade 2,3,4	460 (53%)	416 (48%)	76 (68%)	35 (60%)
Infection/IRIS	305 (35%)	237 (27%)	72 (64%)	30 (52%)
GI disorders	129 (15%)	129 (15%)	26 (23%)	7 (12%)
Musculoskeletal	96 (11%)	63 (7%)	13 (12%)	6 (10%)
Psychiatry	72 (8%)	74 (9%)	18 (16%)	9 (16%)
Respiratory	46 (5%)	37 (5%)	11 (10%)	4 (7%)
Dermatologic	46 (5%)	33 (4%)	15 (13%)	7 (12%)
Neurologic	53 (6%)	57 (7%)	12 (11%)	4 (7%)
Dental	35 (4%)	21 (2%)	0	0
Neoplastic	10 (1%)	14 (2%)	6 (5%)	2 (3%)
Eye disorders	11 (1%)	8 (<1%)	4 (4%)	2 (3%)

The prevalence of specific disorders causing Grade 2 and higher TEAEs was examined in the two pivotal studies. Table summarizes treatment emergent adverse events of at least moderate intensity reported in at least 2% of subjects in the E/C/F/TAF group. The incidences of these specific disorders are balanced across the two treatment arms.

Table 40 Specific Disorders Grade 2 or higher 292-0104, 292-0111

Studies 292-0104/292-0111 High Prevalence Disorders Grade 2 +	E/C/F/TAF N=866	Stribild® N=867
Any Grade 2,3,4	460 (53%)	416 (48%)
Depression	43 (5%)	39 (4%)
Upper Respiratory Infection	40 (5%)	36 (4%)
Headache	30 (3%)	23 (3%)
Diarrhea	26 (3%)	21 (2%)
Bronchitis	24 (3%)	18 (2%)
Nausea	18 (2%)	20 (2%)
Herpes Virus Infection	18 (2%)	12 (1%)
Sinusitis	13 (2%)	18 (2%)
Fatigue	15 (2%)	13 (2%)

The vast majority of the events summarized in Table 40 were of moderate (grade 2)

severity in both treatment groups. Grade 3 AEs occurred in 80 (9%) members of the E/C/F/TAF treatment group and 67 (8%) of the Stribild® treatment group. There were 7 (0.9%) E/C/F/TAF recipients and 10 (1.2%) Stribild® recipients with TEAEs assessed as life threatening (Grade 4). The total number of combined Grade 3 and 4 were 87 for the E/C/F/TAF group and 77 for the Stribild® group.

Table 41 summarizes the grade 3 and grade 4 treatment-emergent adverse events grouped by System Organ Category. Overall there is balance between the two study arms. Specific disorders of 3 or more number are expanded below the SOC title. Imbalances between specific disorders are noted for certain bacterial infections and psychiatric disorders. The significance of these imbalances is currently uncertain.

Table 41 Adverse Events* Grade 3 and 4 Studies 292-0104 and 292-0111

	292-0104 and 292-0111	
	E/C/F/TAF N=866	Stribild® N=867
Number Subjects with Grade 3,4 AEs	87 (10%)	77 (9%)
Infection/IRIS	21 (24%)	19 (22%)
Staph Skin Infections	3 (3.5%)	0
GI disorders	10 (1.2%)	9 (1%)
Psychiatry	8 (1%)	13 (1.5%)
Depression	2 (0.2%)	9 (1%)
Suicidal ideation/attempt	1 (0.1%)	7 (0.8%)
Psychosis	3 (0.4%)	1 (0.1%)
Neurologic	8 (1%)	8 (1%)
Headache	4 (0.5%)	3 (0.4%)
Musculoskeletal	3 (0.4%)	5 (0.6%)
Respiratory	2 (0.2%)	2 (0.2%)
Investigations	5 (0.6%)	7 (0.8%)
Dental	3 (0.4%)	1 (0.1%)
Metabolic (Lipids)	4 (0.5%)	5 (0.6%)

* These are separate events Individual subjects could have multiple different Grade 3 or 4 AEs

7.3.5 Submission Specific Primary Safety Concerns

Bone Safety

The bone toxicity of TDF has been appreciated for many years. Animal studies identified TDF related bone toxicity early in development. In animals, TDF administration was associated with reduced BMD and increased bone turnover

markers. Non-human primates developed dose and duration related bone toxicity which included mineralization defects, bone loss, fractures, hypophosphatemia, elevated alkaline phosphatase, normoglycemic glycosuria and proteinuria.

In clinical trials of HIV-1 infected subjects, greater reductions in lumbar and spine BMD and increases in bone biomarkers were demonstrated with TDF use compared to reductions associated with other antiretrovirals. The exact mechanisms underlying these changes are not fully understood but are thought to involve the renal effects of the active antiviral tenofovir diphosphate (TFV) and to be proportional to its systemic exposure. Although fragility fractures have not been documented in clinical trials of TDF, none were adequately powered to assess fractures.

Associated with its 90% lower TFV systemic exposure TAF is anticipated to have a more favorable bone toxicity profile. The percentage changes from baseline in Bone Mineral Density (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 292-0104 and 292-0111 respectively.

Fractures

Overall in this development program the incidence of fractures was low. In Studies 292-0104 and 292-0111 the incidence of fractures was low and similar in both treatment groups; 11 (1.3%) subjects in the E/C/F/TAF arm and 15 (1.7%) in the Stribild® arm. There were 2 serious fractures resulting from significant trauma (gunshot wound and motor vehicle accident). Both of these fractures occurred in Stribild® recipients. All other fracture events were the result of trauma but were rated non-serious. In Study 292-0102, there was a single serious fracture event due to trauma occurring in an E/C/F/TAF recipient, the other 2 fractures occurred in Stribild recipients and were not considered serious. In Study 292-0109, 14 (1.5%) E/C/F/TAF recipients experienced fractures, three of which were considered serious and 3 subjects (0.5%) receiving Stribild® also experienced non-serious fractures. In Study 292-0112 a total of 5 subjects experienced 6 fractures. One of these fractures (vertebral compression fracture) was considered to be serious. This fracture occurred in a 71 year old and was due to falling from a ladder striking back against a hard surface. This was not a fragility fracture. The remaining fractures were assessed as non-serious. No fractures were reported in 292-0106. Fractures in all studies were assessed as due to trauma, none were considered to be fragility fractures.

Bone Mineral Density (BMD)

In all studies, DEXA scan measurements were performed at 24 week intervals beginning at baseline with the secondary endpoint to be measured at 48 weeks.

BMD in Treatment Naïve Subjects

Treatment naïve adults were enrolled in Studies 292-0104, 292-0111 and 292-0102. All three studies are continuing at this time. The populations of all three were similar with exclusions for systemic corticosteroids, active malignancy or serious infection. The median age was 35-36 with a strong male predominance. Concomitant medications of special interest included systemic steroids, testosterone, calcium supplements, alendronates, estrogen all of which except for systemic steroids and calcium supplements were taken by less than 3% of the population.

Mean percentage decreases in BMD from baseline to Week 48 for both hip and spine were demonstrated in the E/C/F/TAF group but were smaller compared to the Stribild® group. This differential was evident on all DEXA measurements. In the pivotal studies, 16.8% of hip and 26.5% of spine DEXA in E/C/F/TAF demonstrated a > 3% decrease from baseline. In comparison, 50.1% and 45.8% respectively of Stribild® recipients had a > 3 % decrease at 48 weeks. In Phase 2 study 292-0102, 11.4% and 24.3% of E/C/F/TAF and 44.4% and 53% of Stribild® recipients had experienced a >3% decrease from baseline in hip and spine BMD respectively. Four to 10 percent of E/C/F/TAF recipients compared to 22-23 percent of Stribild® recipients experienced a > 5% decrease in their respective DEXA measurements. In previous studies with TDF BMD measurements stabilized at about 48 weeks. It is possible that the same will occur with E/C/F/TAF. Preliminary DEXA results beyond 48 weeks appear to indicate BMD stability after 48 weeks of treatment.

Table 42 Treatment Naïve Subjects Total Hip BMD (DXA)

	Studies 0104 and 0111		Study 0102		p-value
	E/C/F/TAF N=866	STB N=867	E/C/F/TAF N=103	STB N=57	
Baseline BMD (g/cm ²) (mean)	1.041	1.028	1.03	1.04	0.098*
Baseline Z score (mean)	-0.19	-0.19	N/A	N/A	
Week 24 n	789 (91%)	815 (94%)	97 (94%)	57 (100%)	
% change from BL mean (SD)	-0.41 (2.15)	-1.73 (2.24)	-0.42 (1.68)	-2.02 (2.66)	< 0.001
Week 48 n=	780 (90%)	767 (88%)	96 (93%)	54 (95%)	
% change from BL mean (SD)	-0.66 (3.26)	-2.95 (3.41)	-0.67 (2.18)	-3.12 (3.37)	< 0.001
Week 48 Change Z score (mean)	-0.03	-0.20	N/A	N/A	
Week 48 BMD declines >5 % from BL	4%	22%	4%	22%	< 0.001

Source ISS Table 20.2/ Study report 292-0102 Tables 37.1.1.2 , Week 48 CSR Table 41.2

The spine DEXA results demonstrated greater decreases than those of the hip. Although the severity is higher with Stribild®, it remains noteworthy that 10% of E/C/F/TAF recipients had evidence of a > 5% loss of BMD in their spines at 48 weeks of treatment.

Table 43 Treatment Naïve Subjects Lumbar Spine BMD (DXA)

	Studies 0104 and 0111		Study 0102		p-value
	E/C/F/TAF N=866	STB N=867	E/C/F/TAF N=103	STB N=58	
Baseline BMD (g/cm ²) (mean)	1.135	1.114	1.12	1.14	0.011*
Baseline Z score (mean)	-0.27	-0.33	N/A	N/A	
Week 24 n	797 (92%)	816 (94%)	101 (98%)	58 (100%)	
% change from BL mean (SD)	-1.25 (2.80)	-2.83 (2.90)	-0.93 (2.97)	-2.55 (2.51)	< 0.001
Week 48 n=	784 (91%)	773 (89%)	96 (93%)	54 (93%)	
% change from BL mean (SD)	-1.30 (3.08)	-2.86 (3.25)	-1.02 (3.45)	-3.24 (3.22)	< 0.001
Week 48 Change Z score mean	-0.12	-0.26	N/A	N/A	
Week 48 BMD declines >5 % from BL	10%	22%	8%	23%	< 0.001

Source ISS Table 20.2/ Study report 292-0102 Tables 37.1.1.2 ,Week 48 CSR Table 41.2

During the initial 48 weeks of studies 292-0104 and 292-0111 more Stribild® subjects (103) compared to E/C/F/TAF (76) began osteoporosis medications. Hip and spine BMD changes in younger adults (18-25 year olds) in these studies pooled with those in 292-0102 were the subject of ad-hoc analysis by the Applicant. Hip and spine BMD changes in these individuals were noted to be similar to those seen in all adults (ISS Tables Req6799.1.1 and Req6799.1.2). The Applicant's explanation for conducting this

analysis was upon the premise that the 18-25 year old population were still in the midst of bone formation analogous to adolescents which might provide additional evidence of the differences in BMD between the products.

There were 3 E/C/F/TAF and 4 Stribild® patients whose hip BMD declined $\geq 12\%$. There were 3 subjects with $> 20\%$ decline in hip BMD; -34% in a Stribild® subject and -26.1% and -23.9% in E/C/F/TAF subjects at 48 weeks of treatment. There were 7 E/C/F/TAF and 11 Stribild® subjects whose lumbar spine BMD declined $\geq 12\%$. Two of these subjects were among the hip subjects mentioned above with the same BMD decline. All but 2 of the 18 subjects were men, 6/18 were ≥ 40 years of age. Most of these declines were at week 48. There were 5 subjects with week 72 data, in 3 of these the BMD had declined from week 48 and in the other two it increased. The largest decline in spine BMD was -20.3% in a Stribild® subject. One of the 18 had used oral prednisone for 2 weeks.

Fracture Probability Analysis: FRAX scores were calculated for all subjects. FRAX is a fracture risk assessment tool which utilizes validated clinical risk factors such as previous fracture, smoking, glucocorticoid use in combination with BMD of the hip in patients older than 40 to calculate a risk of osteoporotic fracture within 10 years. In subjects ≥ 40 years the mean 10 year probabilities of hip fracture calculated at baseline were 0.34% and 0.47% for E/C/F/TAF and Stribild® respectively. The 10 year probabilities of a major osteoporotic fracture were 2.82% for E/C/F/TAF and 3.21% for Stribild® recipients. The mean increases in these probabilities from baseline at week 48 were smaller for the E/C/F/TAF subjects.

Bone Biomarkers

The Bone Biomarkers were elevated in both study arms in all three studies, but to a greater extent in Stribild® recipients. The disparity between the CTx values in Stribild® arms between Studies 0104/0111 and 0102 may relate to the small size of study 292-0102.

Table 44 Bone Biomarker Changes Studies 292-0104, 292-0111, 292-0102

	Studies 0104 and 0111		Study 0102		p-value
	E/C/F/TAF N=866	STB N=867	E/C/F/TAF N=103	STB N=58	
Serum C-type Collagen Sequence (CTx)					
% change from BL at 24 weeks	16.3	27.7	22.1	62.2	<.001
% change from BL at 48 weeks	17.3	27.9	19.3	78.3	<.001
Serum Procollagen type 1 (P1NP)					
% change from BL at 24 weeks	26.2	71.4	3.7	45.1	<.001
% change from BL at 48 weeks	37.5	93.0	8.8	69.4	<.001
Serum Parathyroid Hormone (PTH)					
% change from BL at 24 weeks	21.2	36.5	N/A	N/A	0.003
% change from BL at 48 weeks	33.3	56.3	N/A	N/A	<.001

BMD in Switch Study Subjects

The BMD issues encountered with the baseline virologically suppressed populations were somewhat different. For those switching from other antiretroviral therapy, especially TDF, the prospect of increasing BMD was deemed likely.

In Study 292-0109, 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 study. Dr. Miele, the reviewer of this study found that overall there were increases from baseline in mean (SD) BMD at the hip or spine in the E/C/F/TAF group as compared to minimal changes in baseline in both parameters at both Weeks 24 and 48 in subjects retaining their TDF containing regimen. The Applicant calculated the p-value of the differences and found them to be significant ($p < 0.001$). Dr. Miele's tabular portrayal of the mean (SD) percent changes from baseline to Week 48 is reproduced below. For more information, please see Dr. Miele's review in Appendix 1.

Table 45 Study 292-0109 Total Hip and Spine BMD- Mean Values and Mean Percent

Changes from Baseline, Weeks 24 and 48	E/C/F/TAF			TDF		
	N	Mean (SD) BMD (g/cm ²) ^a	Mean (SD) % Change from Baseline	N	Mean (SD) BMD (g/cm ²) ^a	Mean (SD) % Change from Baseline
Total Spine						
Baseline	912	1.09 (0.17)	--	457	1.09 (0.17)	--
Week 24	862	1.11 (0.17)	1.52 (2.7)	433	1.08 (0.18)	-0.19 (3.0)
Week 48	742	1.12 (0.18)	1.86 (3.1)	356	1.09 (0.18)	-0.11 (3.7)
Total Hip						
Baseline	902	1.00 (0.14)	--	452	0.99 (0.14)	--
Week 24	851	1.01 (0.14)	1.02 (2.1)	428	0.99 (0.14)	-0.22 (1.9)
Week 48	733	1.02 (0.15)	1.95 (3)	350	1.0 (0.15)	-0.14 (3)

The other study enrolling virologically suppressed subjects was 292-0112 conducted in subjects with mild to moderate renal impairment. In this open label study, all individuals were switched to E/C/F/TAF from other regimens, some of which contained TDF. In this study there was a small group (6 individuals) who were treatment naïve. Although BMD hip and spine increases were seen in former TDF recipients and non-recipients, the magnitude of the increases were greater in those switched from TDF. Decreases in BMD are noted in the treatment naïve group.

Table 46 Changes in DEXA Scan Results HIP 292-0104, 292-0111

	Pre-Switch TDF N=154	No Pre-Switch TDF N=82	Total N=236	No prior treatment
Baseline BMD (g/cm ²) (mean)	0.918	0.919	0.918	0.973
Week 24 n=	148	77	225	6
% change from BL, mean (SD)	+1.15 (2.93)	-0.07 (2.23)	+0.733 (2.77)	-0.02 (1.69)
Week 48 n=	144	72	216	6
% change from BL, mean (SD)	+1.85 (3.31)	+0.70 (5.49)	+1.47 (4.19)	-0.07 (1.61)

Table 47 Changes in DEXA Scan Results Spine 292-0104, 292-0111

	Pre-Switch TDF N=154	No Pre-Switch TDF N=82	Total N=236	No prior treatment
Baseline BMD (g/cm ²) (mean)	1.056	1.12	1.075	1.034
Week 24 n=	147	79	226	6
% change from BL, mean (SD)	+2.37 (3.71)	+0.29 (3.04)	+ 1.64 (3.53)	-2.69 (4.58)
Week 48 n=	142	72	214	6
% change from BL, mean (SD)	+2.95 (4.19)	+0.96 (4.07)	+2.29 (4.24)	-4.14 (4.59)

Reviewer comments: Data in this NDA appears to indicate better BMD preservation with administration of E/C/F/TAF compared to TDF containing antiretroviral regimens. In the treatment naïve E/C/F/TAF caused less bone turnover as indicated by bone biomarkers and smaller declines in hip and spine BMD over 48 weeks of treatment. In subjects virologically suppressed on other regimens, switching to E/C/F/TAF appeared to have favorable effects including BMD increases in hip and bone DEXA values. This was especially true when the previous antiretroviral therapy contained TDF. Preliminary clinical trial data from beyond 48 weeks suggests that the bone loss advantage of E/C/F/TAF may continue beyond 48 weeks.

Longer duration of follow-up is needed. It is known that TDF bone loss does not appear to be progressive after the first year of therapy. This is not yet known for TAF. There have been reported cases of TDF associated symptomatic osteomalacia which were present for years before they were correctly diagnosed. In the two pivotal trials (0104 and 0111) there were 23 subjects (9 E/C/F/TAF; 14 Stribild®) who experienced a > 12% decline from baseline in spine or hip BMD. Warnings and Precautions language for E/C/F/TAF appears to be reasonable until additional data is available.

The bone loss benefits to date have focused on DEXA findings, no data currently exist that demonstrates a difference between TAF and TDF in terms of observed fractures. Other limitations on approval analysis include the individuality of DEXA results; it is not possible to use DEXA results to compare products. The exploratory biomarkers used in this submission support the overall conclusion of increased bone turnover but are not validated as comparative instruments.

Renal Issues

The companion issue to BMD decline with TDF usage is TDF associated renal toxicity. TDF is known to cause renal toxicity including Fanconi Syndrome and acute renal failure. Although the estimates vary, the incidence of nephrotoxicity severe enough to warrant discontinuation of TDF therapy is approximately 1% with < 0.2% experiencing severe renal failure. As with BMD, renal toxicity is thought to be due to TFV exposure concentrations making the lower TFV exposures with TAF attractive as potentially renal function sparing. There are two renal issues in this submission. The first is the comparison of potential renal toxicity in the two prodrugs TAF and TDF. The second issue is the safety of expansion of treatment indication for E/C/F/TAF to renally impaired individuals with eGFR creatinine clearances of ≥ 30 mL/min. The comparator in these studies, Stribild® is not recommended for individuals with creatinine clearance of less than 70 mL/min.

The target for TDF and TFV appears to be the renal proximal tubules. TFV accumulates in the renal proximal tubules in an OAT (renal organic anion transporters) dependent manner leading to toxicity. In preclinical studies unlike TFV, TAF did not interact with OAT1 and OAT 3 and exhibited no OAT-dependent cytotoxicity in human epithelial kidney cells transiently expressing these transporters. This may imply potential for an improved renal safety profile.

Renal Laboratory Assessments

Treatment Naïve Populations

Increases in serum creatinine measurements were seen in both study arms in treatment naïve populations. In general, these increases were smaller in the E/C/F/TAF groups than in the Stribild arms. In Studies 292-0104 and 292-0111 the median increase in serum creatinine in E/C/F/TAF recipients at 48 weeks was 0.08mg/dL compared to 0.11mg/dL in subjects receiving Stribild®. This change in serum creatinine occurred within the first 2 weeks of treatment and remained stable and statistically significant for the remainder of the 48 weeks. As demonstrated below, median serum creatinines

increased slightly between 4 weeks and 48 weeks. The eGFR creatinine clearances were essentially unchanged after 4 weeks.

Table 48 Serum Creatinine/Creatinine Clearance BL-48 weeks 292-0104, 292-0111

	E/C/F/TAF N=866		STB N=867	
	Median Analysis Value	Change from BL	Median Analysis Value	Change from BL
Number Tested	826	N/A	816	N/A
Baseline Serum Creatinine	0.93 mg/dL	N/A	0.93 mg/dL	N/A
Baseline Creatinine Clearance	116.9 mL/min	N/A	113.6 mL/min	N/A
Number Tested	821		814	
Serum Creatinine 4 weeks	0.99 mg/dL	+0.06	1.02 mg/dL	+0.09
Creatinine Clearance 4 weeks	109.7mL/min	-7.1	103.6 mL/min	-10.0
Number Tested	822		812	
Serum Creatinine 48 weeks	1.01 mg/dL	+0.08	1.04mg/dL	+ .11
Creatinine Clearance 48 weeks	109.4mL/min	-7.5	103.6 mL/min	-10.0

Approximately 87 E/C/F/TAF subjects and 85 Stribild® subjects had proteinuria by dipstick (any grade) at baseline. During the study fewer E/C/F/TAF subjects (269, 31%) developed treatment emergent proteinuria by urinalysis (dipstick) through Week 48 compared to subjects taking Stribild® at (318, 37%). Most of this new proteinuria was grade 1. The Applicant reports that there were decreases from baseline in median urine protein to creatinine ratio (UPCR) and urine albumin to creatinine ratio (UACR) in the E/C/F/TAF group compared to increases in these factors in the Stribild® arm.

Virologically Suppressed Populations

In Study 292-0109 the mean change in serum creatinine was negligible or negative in subjects who switched from Stribild® or boosted Atazanavir/Truvada® to E/C/F/TAF compared to those who remained on their baseline regimens where the change from baseline was minimal. In subjects who switched from Atripla® to E/C/F/TAF there was a mean increase in serum creatinine of 0.11 at 48 weeks.

This analysis was performed by Dr. Miele and for more information please see his review in the Appendix 1.

Table 49 Changes Serum Creatinine BL-Week 48 Study 292-0109

	N	Mean Value (SD)	Mean Change from Baseline (SD)	N	Mean Value (SD)	Mean Change from Baseline (SD)
	E/C/F/TAF			STB		
Baseline	306	1.07 (0.188)	--	153	1.09 (0.196)	--
Week 24	303	1.05 (0.179)	- 0.02 (0.112)	151	1.12 (0.216)	0.02 (0.111)
Week 48	266	1.07 (0.180)	- 0.02 (0.111)	132	1.13 (0.194)	0.03 (0.110)
	E/C/F/TAF			ATV/boosted + FTC/TDF		
Baseline	402	1.02 (0.196)	--	199	1.02 (0.188)	--
Week 24	384	1.03 (0.184)	0.01 (0.114)	184	1.05 (0.211)	0.02 (0.109)
Week 48	279	1.05 (0.197)	0.00 (0.121)	134	1.10 (0.231)	0.05 (0.134)
	E/C/F/TAF			ATR		
Baseline	251	0.95 (0.171)	--	125	0.95 (0.150)	
Week 24	244	1.06 (0.176)	0.10 (0.107)	121	0.96 (0.163)	0.01 (0.087)
Week 48	229	1.06 (0.189)	0.11 (0.124)	106	0.97 (0.163)	0.02 (0.088)

Similar to serum creatinine, the eGFR by Cockcroft-Gault demonstrate improvement or minimal change in those switching to E/C/F/TAF from a TDF containing baseline regimen compared to progressive decreases in the TDF group.

Table 50 Changes Creatinine Clearance BL-Week 48 Study 292-0109

		E/C/F/TAF		TDF		
Estimated Creatinine Clearance – Cockcroft-Gault						
	N	Median (Q1, Q3)		N	Median (Q1, Q3)	
		Analysis Value	Δ from Baseline		Analysis Value	Δ from Baseline
Baseline	708	103.8 (87.6, 121)	--	352	102.4 (84.3, 121.7)	--
Week 24	687	105.5 (89, 122.8)	1.2 (-6, 9)	335	101.3 (82.4, 119.4)	-2.5 (-8.5, 5.4)
Week 48	545	104 (89.5, 123.4)	1.8 (-6.6, 9.7)	265	98 (80.6, 120.9)	-3.7 (-11.2, 3.65)
Estimated Creatinine Clearance – CKD-EPI, creatinine						
	N	Median (Q1, Q3)		N	Median (Q1, Q3)	
		Analysis Value	Δ from Baseline		Analysis Value	Δ from Baseline
Baseline	708	89.8 (76.6, 103.7)	--	352	89.8 (77.1, 100.7)	--
Week 24	687	90.7 (76.7, 101.7)	0 (-6.24, 6.1)	335	88 (75.4, 101.4)	-2.49 (-7.17, 3.65)
Week 48	545	88.6 (76.5, 100.6)	-0.26 (-6.4, 6.7)	266	84.9 (71.1, 96.7)	-3.48 (-9.0, 2.41)

The majority of subjects had no proteinuria at baseline and Week 48. For those with proteinuria at the time of enrollment, a higher percentage of those in the E/C/F/TAF group (7.1%) had improvement in their baseline compared with the TDF group (5.6%). Assessment of other renal biomarkers such as quantitative proteinuria (UPCR, UACR), urine retinol binding protein (RBP) to creatinine ratio and beta-2 microglobulin to creatinine ratio demonstrated decreases from baseline in the E/C/F/TAF group compared to increases in the TDF containing arms.

The primary renal endpoints of Study 292-0112 were defined as change from baseline at week 24 in eGFR using all three methodologies (Cockcroft-Gault, CKD-EPI creatinine and CKD cystatin C). A 32 subject substudy also had a GFR iohexol creatinine clearances performed.

Similar to the results from Study 292-0109, subjects in 292-0112 all switched to E/C/F/TAF either had minimal or no subsequent changes noted in their creatinine or creatinine clearance. The median change in serum creatinine at Week 24 was an

increase of 0.03 mg/dL. The median change in eGFR at Week 24 was a decrease of 0.4 mL/min. The minimal response to switching to E/C/F/TAF may be related to the fact that the majority of enrollees (180) were taking tenofovir disoproxil fumarate at baseline. There were changes noted in both the incidence and severity of proteinuria. The two laboratory modalities Urine Protein Creatinine Ratio (UPCR) and Urine Albumin Creatinine Ratio (UACR) are generally regarded by the Division of Cardiovascular and Renal Products (DCRP) as the most useful of the laboratory assessments of proteinuria. At baseline, subjects with moderate renal impairment had higher prevalence of clinically significant proteinuria compared to the mild renal impairment group. Over the course of 24 weeks, approximately 9% of the moderately impaired and 4% of the mildly impaired developed clinically significant proteinuria compared to 33% and 66% respectively of those whose level of proteinuria improved as determined by both UPCR and UACR. It must be noted that 24 weeks of treatment may be inadequate to evaluate the development of clinically significant proteinuria or its long term improvement.

Table 51 Quantitative Proteinuria Measurements Study 292-0112

	Baseline eGFR < 50mL/min N=80	Baseline eGFR ≥ 50mL/min N=162	Totals N=242
Urine Protein to Creatinine Ratio (UPCR)			
Subjects with UPCR Values at BL and Week 24	75	151	226
No significant proteinuria (UPCR ≤200mg/g) at Base Line and Week 24	32/75 (43%)	101/151 (67%)	133/226 (59%)
Developed proteinuria UPCR > 200mg/g by 24 weeks	3/32 (9%)	5/101 (5%)	8/133 (6%)
Subjects with significant proteinuria (UPCR >200mg/g) at Base Line	43/75 (57%)	50/151 (33%)	93/226 (41%)
Subjects with proteinuria at BL not significant at Week 24 (≤200mg/g)	16/43 (37%)	37/50 (74%)	53/93 (57%)
Urine Albumin to Creatinine Ratio (UACR)			
Subjects with UACR Values at both BL and Week 24	70	153	223
No significant proteinuria (UACR < 30 mg/g) at Base Line and Week 24	25/70 (36%)	92/153 (60%)	117/223 (52%)
Developed significant proteinuria UACR ≥ 30mg/g by 24 weeks	2/25 (8%)	2/92 (2%)	4/117 (3%)
Subjects with significant proteinuria (UACR ≥ 30mg/g) at Base Line	45/70 (64%)	61/153 (40%)	106/223 (48%)
Subjects Significant proteinuria BL not significant at Week 24 (< 30 mg/g)	14/45 (31%)	36/61 (59%)	50/106 (47%)

There were no AEs suggestive of proximal renal tubulopathy including Fanconi syndrome. Of 8 subjects who discontinued study drug due to an adverse event, 6 had a baseline eGFR of < 50 mL/min and 2 had an eGFR of \geq 50 mL/min. Two of the discontinuations were for renal failure and acute renal failure superimposed on chronic renal insufficiency.

Other renal deterioration AEs include an SAE involving an individual with mild renal impairment due to polycystic kidney disease hospitalized for diuretic adjustment following the initiation of study medication. Two moderate renal impairment subjects met criteria for renal failure but were continued on study meds without event.

Reviewer comments: The renal laboratory findings may provide some support the Applicant's contention of less renal toxicity associated with E/C/F/TAF administration compared to administration of Stribild®. For the treatment naïve subjects, serum creatinine and eGFR by Cockcroft-Gault do demonstrate a difference favoring E/C/F/TAF. In Study 292-0112, the creatinine and creatinine clearances do not distinguish between TAF versus TDF. In 292-0112, the quantitative proteinuria assessments using UPCR and UACR do suggest some potential benefit but this may be difficult to assess in subjects switching from tenofovir disoproxil containing regimens. Dipstick urine protein measurements, however, are problematic since results are variable depending on urine concentration, operator experience and skill. The biomarkers retinol binding protein and beta-2 microglobulin are not validated. It must be recalled that there were subjects whose renal function and quantitative proteinuria worsened. The period of observation is approximately 24 weeks with a small population of subjects with the more severe renal compromise. It may be prudent to obtain additional data before concluding that the issue has been settled by laboratory results.

Safety of use of E/C/F/TAF in Subjects with Creatinine Clearance < 50 mL/min

Safety of emtricitabine in subjects with Creatinine Clearance < 50 mL/min

The product label for emtricitabine (FTC), the F component of E/C/F/TAF recommends increasing the dosing interval from 200mg per day to 200mg every 48 hours in subjects with creatinine clearance of \geq 30mL/min and < 50mL/min. It was understood in the design of 292-0112 that FTC serum levels would increase in the moderate renal impairment group. It was judged in the design of Study 292-0112 that this increase would not have clinical consequences.

As documented earlier in Section 4.4, emtricitabine exposures increase by 115 % when 200mg of FTC are given daily to subjects with moderate renal impairment. There are data which may represent evidence of clinical consequence. As previously discussed in all grade TEAEs, there is evidence of increased dizziness and syncope in the moderate renal impaired group compared to the mildly impaired. Dizziness is specifically mentioned as an adverse event in the FTC label. When grade 3 and 4 laboratory adverse events are considered, serum amylase, serum glucose, and liver function tests (GGT) are observed as higher in subjects with moderate renal impairment (eGFR $\geq 30 < 50$ mL/min) compared to those with milder impairment. Additionally, incidence of grade 3 elevations of total cholesterol and LDL cholesterol levels are noted to be higher in the moderate renal impairment group

Table 52 Grade 3 and 4 Laboratory AEs Study 292-0112

Grade 3 and 4 Laboratory Adverse Events 292-0112	eGFR Creatinine Clearance $\geq 30 < 50$ mL/min N=82	eGFR Creatinine Clearance $\geq 50 < 70$ mL/min N=165
Serum Amylase	8 (10%)	3 (2%)
Glucose	6 (7%)	5 (3%)
Total Cholesterol	5 (6%)	7 (4%)
LDL Cholesterol	10 (12%)	11 (7%)
Creatine Kinase	5 (6%)	3 (2%)
GGT	4 (5%)	1 (<1%)

Reviewer comments: It is understood that the symptoms of dizziness/syncope as well as the increased incidence of Grade 3 amylase, total cholesterol, LDL cholesterol, and GGT in the moderate renal impairment group may be incidental or due to the more advanced renal disease. None the less, these could also be related to the increased exposures to emtricitabine. It remains prudent to maintain close clinical monitoring of all renally impaired individuals taking this drug.

Serum Lipids

Treatment Naïve Population

Elevations in serum lipids associated with E/C/F/TAF were appreciated early in its development program. (b) (4)

Both E/C/F/TAF and Stribild® were associated with increases in all species of serum lipids but this review will concentrate on total cholesterol and LDL as being the most important

in the development of atherosclerotic disease. The median increase in fasting total cholesterol at 29mg/dL at 48 weeks was nearly double that observed with Stribild®. The mean increase in total cholesterol with Stribild® was higher and more resembled that seen with E/C/F/TAF.

Table 53 Changes in Total Cholesterol 292-0104 and 292-0111

Studies 0104/0111 Laboratory Changes in Total Cholesterol	E/C/F/TAF N=866	Stribild® N=867
Total Number Lab Data beyond Screening	827 (95%)	830 (96%)
Median Change	+29 mg/dL	+15 mg/dL
Mean Change	+ 31 mg/dL	+23 mg/dL
Mode	13, 18	11

The differences between the two products in fasting LDL cholesterol increases were more striking. Where the comparative increase in fasting total cholesterol with E/C/F/TAF was twice as high as with Stribild; with LDL the comparative increase was four times as high.

Table 54 Changes in LDL Cholesterol 292-0104 and 292-0111

Studies 0104/0111 Laboratory Changes in LDL Cholesterol in Treatment Naïve	E/C/F/TAF N=862	Stribild® N=864
Total Number Lab Data beyond Screening	830 (96%)	837 (97%)
Median Change	+14 mg/dL	+3 mg/dL
Mean Change	+ 16 mg/dL	+4 mg/dL
Mode	12	-7,-1,5,13

The grading system used by the Sponsor to assess severity of elevations of fasting total cholesterol and LDL cholesterol is reproduced below.

Table 55 Lipid Grading System Gilead

	Grade 1	Grade 2	Grade 3
Total Cholesterol	200-239mg/dL	>239-300mg/dL	> 300mg/dL
LDL Cholesterol	130-160mg/dL	>160-190mg/dL	>190mg/dL

The severities of the lipid elevations were observed to be higher with E/C/F/TAF compared to Stribild. When maximal elevation observed is considered, 37 (4.3%) E/C/F/TAF compared to 20 (2.3%) of Stribild recipients had maximal elevation in their

LDL cholesterol. The differences in Grade 3 fasting total cholesterol were not as great.

Table 56 Grade 3 Total and LDL Cholesterol Studies 292-0104 292-0111

Studies 0104/0111 Grade 3 Laboratory AEs	E/C/F/TAF N=866	Stribild® N=867
Total Cholesterol	14/866 (1.6%)	10 (1.2 %)
LDL Cholesterol	37/866 (4.3%)	20 (2.3%)

The amplitude of elevations after beginning E/C/F/TAF or Stribild® in the individual appears to be idiosyncratic. When treatment naïve subjects with normal (Grade 0) fasting total cholesterol and LDL cholesterol are given E/C/F/TAF approximately 38% developed a gradable elevation in total cholesterol and 32% developed a gradable elevation in LDL cholesterol. In contrast, with Stribild®, the corresponding numbers were 21% and 20% respectively. Approximately 8 % of the E/C/F/TAF subjects and 3% of the Stribild® subjects skipped Grade 1 and the LDL cholesterol of 9 individuals in the E/C/F/TAF group went from less than 130 mg/dL to > 190mg/dL within 48 weeks.

Table 57 Total Cholesterol, LDL Cholesterol Changes from Normal Levels

Studies 0104/0111 Total Cholesterol/LDL Cholesterol Grade 0 at Baseline	E/C/F/TAF N=701	Stribild® N=714
Treatment for 48 weeks		
Total Cholesterol Grade 1	211/701 (30%)	128/714 (18%)
Total Cholesterol Grade 2	58/701 (8%)	24/714 (3%)
Total Cholesterol Grade 3	0	0
Total number/% with change in Total Cholesterol at 48 weeks	269/701 (38%)	152/714 (21%)
LDL Cholesterol Grade 1	173/701 (25%)	125/714 (18%)
LDL Cholesterol Grade 2	51/701 (7%)	21/714 (3%)
LDL Cholesterol Grade 3	9/701 (1.3%)	0
Total number/% with change in LDL Cholesterol at 48 weeks	233/701 (33%)	146/714 (20%)

The current treatment of hyperlipidemia is evolving. The use of physician counseling and risk assessment is gaining more importance. The use of categorical triggers at certain numeric values is diminishing. None the less, it remains worthwhile to consider the categories and acknowledge that HIV infected individuals are in an increased risk for atherosclerotic disease.

The use of lipid modifying medications was scant but balanced between the study arms in Studies 0104 and 0111. A total of 38 E/C/F/TAF recipients (4%) were on lipid modifying drugs at baseline with an additional 28 (3%) begun on lipid modifying medications during the conduct of the trial. A total of 39 Stribild® recipients (4%) were taking lipid modifying drugs at baseline and an additional 25 (3%) were begun on lipid modifying medications during the trial.

A snapshot of the current status of elevations of total cholesterol and LDL cholesterol measured at the week 48 sampling is presented below. A total of 36-39% of E/C/F/TAF recipients evidenced graded elevations compared to 26-30% of Stribild® recipients. Based on an assessment of having a LDL cholesterol of > 190mg/dL 27 (3.1%) E/C/F/TAF subjects and 13 (1.5%) Stribild® subjects would be undisputed candidates for lipid modifying agents at this time.

Table 58 Snapshot Lipid Values Week 48 Studies 292-0104 and 292-0111

Treatment Naive Total Cholesterol and LDL Cholesterol drawn Week 48 Without regard to BL Result	Studies 0104/0111		Study 0102	
	E/C/F/TAF N=828	Stribild® N=820	E/C/F/TAF N=108	Stribild® N=56
Total Cholesterol Grade 1	215/828 (26%)	149/820 (18%)	30/108 (28%)	13/56 (23%)
Total Cholesterol Grade 2	99/828 (12%)	61/820 (7%)	8/108 (7.4%)	4/56 (7%)
Total Cholesterol Grade 3	9/828 (1%)	4/820 (<1%)	1/108 (<1%)	0
Total	323/828 (39%)	214/820 (26%)	39/108 (36%)	17/56 (30%)
LDL Cholesterol Grade 1	204/828 (25%)	152/820 (19%)	27/108 (25%)	11/56 (20%)
LD Cholesterol Grade 2	70/828 (8.45%)	50/820 (6%)	5/108 (5%)	5/56 (9%)
LDL Cholesterol Grade 3	27/828 (3.3%)	13/820 (1.6%)	5/108 (5%)	0
Total	301/828 (36%)	215/820 (26%)	37/108 (34%)	16/56 (29%)

Virologically Suppressed Population

An imbalance in lipid elevations between E/C/F/TAF and Stribild was also noted in the virologically suppressed switch studies. In general, increases in baseline in fasting total cholesterol, LDL cholesterol and Triglycerides were noted in the E/C/F/TAF group while these parameters remained unchanged or minimally changed in the comparator group.

Table 59 Lipid Elevations Study 292-0109

Fasting Lipid Parameter	E/C/F/TAF N=959		TDF N=477	
	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Fasting Total Cholesterol (mg/dL)				
Baseline	942	182 (156, 208)	467	181 (158, 205)
Change from Baseline Week 24	911	+21 (4, 40)	444	+1 (-13, 16)
Change from Baseline Week 48	758	+20 (1, 41)	367	+6 (-9, 19)
Fasting Direct LDL Cholesterol (mg/dL)				
Baseline	942	116 (94, 142)	467	116 (96, 139)
Change from Baseline Week 24	911	+11 (-3, 27)	444	-2 (-15, 9)
Change from Baseline Week 48	757	+9 (-9, 25)	367	0 (-13, 11)
Fasting HDL Cholesterol (mg/dL)				
Baseline	942	50 (42, 59)	466	49 (42, 58)
Change from Baseline Week 24	911	+2 (-3, 8)	443	0 (-5, 5)
Change from Baseline Week 48	758	+2 (-4, 8)	366	+1 (-4, 5)
Fasting Triglycerides (mg/dL)				
Baseline	942	119.5 (82, 169)	466	113.5 (81, 164)
Change from Baseline Week 24	911	+10 (-21, 47)	443	+2 (-29, 28)
Change from Baseline Week 48	758	+10 (-18, 48)	366	0 (-28, 27)

Table 60 Lipid Shift Table Post Baseline Study 292-0109

Maximum Post-baseline Category	Number (%) of Subjects							
	E/C/F/TAF				TDF			
Fasting Cholesterol (mg/dL), n (%)	Baseline Fasting Cholesterol				Baseline Fasting Cholesterol			
	< 200	200 - 239	≥ 240	Total	< 200	200 - 239	≥ 240	Total
	N=616	N=264	N=62	N=942	N=324	N=113	N=30	N=467
< 200	327 (53)	25 (10)	1 (2)	353 (38)	225 (69)	29 (26)	3 (10)	257 (55)
200 - 239	212 (34)	89 (34)	9 (15)	310 (33)	72 (22)	56 (50)	10 (33)	138 (30)
≥ 240	55 (9)	140 (53)	49 (79)	244 (26)	8 (3)	22 (20)	16 (53)	46 (10)
Fasting LDL (mg/dL), n (%)	Baseline Fasting LDL				Baseline Fasting LDL			
	< 100	100-159	≥ 160	Total	< 100	100-159	≥ 160	Total
	N=285	N=540	N=117	N=942	N=130	N=285	N=52	N=467
< 100	119 (42)	21 (4)	1 (3)	141 (15)	71 (55)	23 (8)	0	94 (20)
100-159	155 (54)	350 (65)	25 (21)	530 (56)	48 (37)	226 (79)	27 (52)	301 (65)
≥ 160	4 (1)	153 (28)	87 (74)	244 (26)	1 (1)	26 (9)	24 (46)	51 (11)

The use of lipid modifying medications in Study 292-0109 was balanced. Approximately 11% of both study arms were on lipid modifying medications at baseline and the proportion of subjects initiating such agents was similar in the two treatment groups. This study was reviewed by Dr. Miele. For more details please consult his review in Appendix 1.

Forty-eight percent of the renal impaired population in Study 292-0112 had grade elevations of total cholesterol and 41% had graded elevations of LDL cholesterol at baseline. At the primary safety endpoint of 24 weeks, those numbers were 57% and 47%. In comparison, the percentages of graded total cholesterol and LDL cholesterol at the 48 week primary safety endpoint in Studies 0104 and 0111 were 39% and 36%.

Percentages of subjects in Grades 2/3 were 27% and 22% in Study 0112 compared to 13% and 12% in Studies 0104/0111. The use of lipid modifying agents was high in this study population at baseline with 124 (50%) receiving them. An additional 17 (7%) began treatment with such agents during the conduct of the trial. The average age of participants was 58 years as opposed to 35 in the pivotal trials and renal impairment may have an adverse impact on lipid metabolism as well. It may be advisable to caution older individuals with baseline renal impairment to monitor their lipids closely.

Table 61 Shift Table Lipids BL- Week 48 Study 292-0112

Shift Table Study 0112 Total and LDL cholesterol	Baseline N=249	Week 24 N=243	Week 48 N=171
Total Cholesterol Grade 1	72 (29%)	74 (30%)	52 (30%)
Total Cholesterol Grade 2	43 (17%)	56 (23%)	34 (20%)
Total Cholesterol Grade 3	4 (2%)	9 (4%)	5 (3%)
Totals	119 (48%)	139/243 (57%)	91/171 (53%)
LDL Cholesterol Grade 1	57 (23%)	61 (25%)	38 (22%)
LDL Cholesterol Grade 2	31 (12%)	41 (17%)	24 (14%)
LDL Cholesterol Grade 3	15 (6%)	13 (5%)	9 (5%)
Totals	103 (41%)	115 (47%)	71 (42%)

Ocular Safety

A 9 month toxicology study conducted in dogs during the development of E/C/F/TAF demonstrated evidence of posterior uveitis. The cause for these findings was not established and it occurred only at the highest doses. The finding was concerning because of the animals used, dogs were most relevant to issues regarding the human eye. As a result of these findings, the Applicant added extra vigilance regarding reporting and responding to any eye adverse events and also conducted a 47 subject ophthalmologic substudy in asymptomatic participants in Study 0109.

Treatment Naïve Populations

The incidences of eye disorder AEs were similar for both study groups in Studies 0104 and 0111. No cases of posterior uveitis were appreciated in the treatment naïve population. When related terms are combined, there were numerically more instances of visual blurring, visual acuity reduction, impairment among E/C/F/TAF recipients compared to Stribild®. Photophobia, a symptom suggestive of uveitis was encountered three times with E/C/F/TAF compared to once for Stribild®. Other symptoms suggestive of uveitis including eye pain and scotoma were balanced between the two study arms. Each arm had an instance of unrelated retinal detachment.

In Study 0102 there were few reported eye disorders. Of note, there were 3 instances of visual impairment or blurring among the 8 total eye disorders reported in association with E/C/F/TAF in this study.

Table 62 Eye Adverse Events Studies 292-0104, 292-0111, 292-0102

Eye Disorders Treatment Naïve Subjects 0104, 0111, 0102	Studies 0104/0111		Study 0102	
	E/C/F/TAF N=866	Stribild® N=867	E/C/F/TAF N=112	Stribild® N=58
Eye Disorders	61 (7%)	63 (7.3%)	8 (7%)	2 (3%)
Selected Pooled Entities				
Conjunctivitis/Eye Irritation	15 (1.7%)	9 (1%)	2(<1%)	2(<1%)
Visual Blurred/decreased	19 (2.2%)	11 (1.3%)	3(<1%)	0
Dry Eyes	3 (<1%)	10 (1.1%)	1(<1%)	0
Scotoma	0	1(<1%)	1(<1%)	0
Photophobia	3 (<1%)	1(<1%)	1(<1%)	0
Eye Pain	8 (<1%)	8 (<1%)	0	0
Retinal Detachment	1(<1%)	1(<1%)	1(<1%)	0

Virologic Suppressed Population

In Study 0109, Eye Disorder AEs were reported at similar rates between the E/C/F/TAF recipients and the comparator groups, 6% and 5% respectively. The only preferred terms reported for ≥ 1% were visual blurring and impairment occurring almost exclusively in the E/C/F/TAF group and icterus and vitreous floaters reported in the comparator groups. The one SAE was an unrelated retinal detachment in an E/C/F/TAF recipient who underwent cryotherapy for repair. There were seven related AEs. In the comparator groups these were scleral icterus related to atazanavir use. In the E/C/F/TAF group, there were three related AEs, two with vision blurred and one visual acuity reduced mentioned above. There were no cases of uveitis recognized.

In the ophthalmologic substudy no subject had fundoscopic findings consistent with uveitis.

Reviewer comments: The non-clinical signal of posterior uveitis was assessed as substantial. Adjustments were made to the pivotal studies and a substudy was undertaken to elucidate this potential safety signal. To this point there is one subject with intermediate uveitis enrolled in Study 0106 with investigator assessed relatedness that may be suggestive. Even that case is confounded by recovery while E/C/F/TAF treatment was continued. (For more details please see Appendix 2 Study 0106). The eye disorders seen in the pivotal studies and the virological suppression population in

Study 0109 do not appear to support a safety signal of uveitis. That being stated, the imbalance in reports of visual blurring/decreased visual acuity (mostly mild) favoring an association with E/C/F/TAF suggests that continuing vigilance may be advisable.

Dental Safety

In Studies 0104 and 0111 it was noted that Grade 2 or greater dental adverse events differed between the E/C/F/TAF arm and the Stribild arm. The total numbers of all grade dental adverse events were similar. Thirty-four E/C/F/TAF subjects had Grade 2 or higher AEs and three had Grade 3 toxicity. Twenty-nine Stribild® subjects had Grade 2 with one having Grade 3 toxicity.

Table 63 Dental Adverse Events Studies 292-0104 and 292-0111

Dental Disorders Treatment Naïve Subjects 0104, 0111	Studies 0104/0111			
	E/C/F/TAF N=866		Stribild® N=867	
Dental Disorders	92 (11%)		79 (9%)	
Selected Dental Entities	Total Number	Number G2 +	Total Number	Number G2 +
Gingivitis/Periodontal Dz	16 (2%)	8 (1%)	9 (1%)	2 (0.2%)
Dental Abscess	20 (2.3%)	9 (1%)	20 (2.3%)	9 (1%)
Toothache	26 (3%)	13 (1.5%)	26 (3%)	14 (1.5%)
Dry Mouth	11 (1.3%)	0	9 (1%)	0
Dental Caries	8 (9%)	2 (0.2%)	2 (0.2%)	0
Tooth Extractions	3 (0.4%)	2 (0.2%)	2 (0.2%)	0
Impacted Wisdom Tooth	1 (0.1%)	1 (0.1%)	3 (0.4%)	1 (0.1%)

A consultation from the Division of Dermatology and Dental Products was provided by Dr. John Kelsey D.D.S. The outcome of that consultation was the assessment that the numbers of instances were too small to draw any conclusions.

In Study 0109, an imbalance in the number of all grade dental AEs was noted. The frequency of Grade 2 or higher dental AEs did not demonstrate an imbalance between the study arms. Please see Appendix 1 for more information.

Reviewer comments: It does appear that approximately 10% of participants in pivotal trials 0104 and 0111 had dental disorders manifest during the conduct of the clinical trials. There was a small (2%) imbalance between the two study drugs overall. When at least Grade 2 severity events of the dental disorders were considered, the numbers were greater among E/C/F/TAF recipients. It is notable that there were three Grade 3 AEs of dental pain in E/C/F/TAF recipients. No conclusions are possible at this time but continued vigilance is appropriate.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Clinical AEs were common in the treatment naïve population occurring in over 90% of participants in the pivotal trials (0104 and 0111) and over 98% in the Phase 2 study 0102. Table X summarizes all AEs that occurred in at least 4% of subjects (by preferred term) in the E/C/F/TAF group regardless of causality. Multiple AEs were counted only once per subject for each preferred term.

The most common AEs in the E/C/F/TAF group by System Organ Class included “Gastrointestinal disorders” and “Infections and Infestations”. There were occasional differences in incidence of preferred terms between the pivotal studies and the Phase 2 study 0102. This may be the result of the smaller size of Study 0102. The incidence of each PT within the pivotal studies 0104 and 0111 were well balanced between study arms.

Table 64 Common Adverse Events Studies 292-0104, 292-0111, 292-0102

Common Adverse Events	Studies 0104/0111		Study 0102	
	E/C/F/TAF N=866	Stribild® N=867	E/C/F/TAF N=112	Stribild® N=58
Number of subjects experiencing any AE	778 (90%)	782 (90%)	107 (96%)	57 (98%)
Gastrointestinal AEs	394 (46%)	425 (49%)	59 (48%)	28 (48%)
Diarrhea	147 (17%)	164 (19%)	19 (17%)	9 (16%)
Nausea	132 (15%)	151 (17%)	25 (23%)	7 (12%)
Vomiting	62 (7%)	54 (6%)	9 (8%)	4 (7%)
Abdominal Pain	41 (5%)	37 (4%)	5 (4%)	1 (2%)
General disorders	181 (21%)	164 (19%)	31 (28%)	9 (16%)
Fatigue	71 (8%)	71 (8%)	18 (16%)	5 (9%)
Fever	45 (5%)	41 (5%)	4 (4%)	2 (4%)
Infections and Infestations	503 (58%)	506 (58%)	83 (74%)	33 (57%)
Upper respiratory tract infection	99 (11%)	109 (13%)	18 (16%)	12 (21%)
Nasopharyngitis	78 (9%)	80 (9%)	7 (6%)	2 (3%)
Bronchitis	46 (5%)	37 (4%)	13 (12%)	4 (7%)
Sinusitis	32 (4%)	40 (5%)	12 (11%)	1 (2%)
Musculoskeletal	241 (28%)	213 (25%)	30 (27%)	16 (28%)
Back Pain	60 (7%)	57 (7%)	3 (3%)	8 (14%)
Arthralgias	61 (7%)	39 (5%)	7 (6%)	4 (7%)
Nervous system disorders	218 (25%)	197 (23%)	23 (21%)	14 (24%)
Headache	124 (14%)	108 (13%)	11 (10%)	8 (14%)
Dizziness	44 (5%)	37 (4%)	6 (5%)	1 (2%)
Psychiatric disorders	163 (19%)	174 (20%)	28 (25%)	13 (22%)
Insomnia	57 (7%)	48 (6%)	6 (5%)	4 (7%)
Depression	34 (4%)	34 (4%)	12 (11%)	3 (5%)
Respiratory System	158 (18%)	165 (19%)	26 (23%)	13 (22%)
Cough	67 (8%)	60 (7%)	11 (10%)	6 (10%)
Skin and Subcutaneous tissue	208 (24%)	210 (24%)	37 (33%)	15 (26%)
Rash	55 (6%)	46 (5%)	11 (10%)	3 (5%)

In Study 292-0109, the following occurred at a risk difference of $\geq 2\%$ higher incidence in E/C/F/TAF recipients: headache, flatulence, nausea, oropharyngeal pain, cough, rash, gastrointestinal reflux and upper respiratory tract infection. This was an open label study and these differences were attributed to heightened attention to AEs in subjects receiving an experimental agent compared to continuing to take a familiar medication. None of these disparities in incidence was sufficient to warrant further investigation by the reviewer. For more details please consult Dr. Miele's review in Appendix 1.

In Study 292-0112, the prevalence of the diarrhea, nausea and upper respiratory

infections is seen. Arthralgias, dizziness and renal cysts are more prominent than in other trial populations.

Table 65 Common Adverse Events Study 292-0112

Common Adverse Events Adverse Events by SOC and Preferred Term	Study 292-0112 Renal Impairment		
	Baseline eGFR < 50 mL/min N=80	Baseline eGFR ≥ 50 mL/min N=163	Total N=242
Number of subjects experiencing any AE	67 (84%)	142 (88%)	209 (86%)
Diarrhea	8 (10%)	13 (8%)	21 (9%)
Nausea	5 (6%)	12 (7%)	17 (7%)
Fatigue	4 (5%)	10 (6%)	14 (6%)
Upper respiratory tract infection	1 (1 %)	16 (10%)	17 (7%)
Bronchitis	7 (9%)	12 (7%)	19 (8%)
Back Pain	2 (3%)	13 (8%)	15 (6%)
Arthralgias	6 (8%)	14 (9%)	20 (8%)
Headache	2(3%)	15 (9%)	17 (7%)
Dizziness	7 (9%)	7 (4.3%)	14 (6%)
Renal Cyst	5 (6%)	8 (5%)	13 (5%)
Cough	4 (5%)	8 (5%)	12 (5%)

7.4.2 Laboratory Findings

In the Phase 2 and 3 studies, clinical laboratory evaluations included assessment of hematologic, blood chemistry, thyroid function tests, and liver function parameters.

Approximately 20% of treatment naïve subjects had at least one Grade 3 or 4 laboratory abnormality. Taken individually, the incidence of Grade 3 or 4 laboratory abnormalities in each treatment group were low and balanced between study arms.

Grade 3 or 4 creatine kinase elevations were prominent in both study arms in the treatment naïve population as well as the virologic suppression group. These elevations occurred at a variety of time points and were not consistently present. There were no instances of rhabdomyolysis.

Table 66 Grade 3 and 4 Laboratory Abnormalities 292-0104, 292-0111,292-0102

Maximum Post Baseline Toxicity Grade	Studies 0104/0111		Study 0102	
	E/C/F/TAF Number Grade 3/4 over total sampled	Stribild® Number Grade 3/4 over total sampled	E/C/F/TAF Number Grade 3/4 over total sampled	Stribild® Number Grade 3/4 over total sampled
Total Population Tested	862	865	111	58
Grade 3 or 4 Total Subjects	172 (20%)	171 (20%)	31 (28%)	11 (19%)
Neutrophils	13 (1.5%)	21 (2.4%)	7 (6.3%)	2/58 (3.4%)
ALT	10 (1.2%)	12 (1.4%)	1 (0.9%)	1/58 (1.7%)
AST	13 (1.5%)	16 (1.8%)	1 (0.9%)	0
Amylase	13 (1.5%)	26 (3%)	3 (2.7%)	N/D
Creatine Kinase	59 (6.8%)	49 (5.7%)	7 (6.3%)	2 (3.4%)
GGT	3 (0.3%)	12 (1.4%)	1 (0.9%)	1/58 (1.7%)
Fasting Glucose	7 (0.8%)	4 (0.5%)	2 (1.8%)	1/58 (1.7%)
Serum Uric Acid	0	2 (0.2%)	0	0
Urinary Glucose	11(1.3%)	13 (1.5%)	2 (1.8%)	0
Hematuria	15 (1.7%)	19 (2.2%)	2 (1.8%)	0

In Study 0109, there was an imbalance in treatment groups in the proportion of subjects with any instance of graded hyperuricemia at 13% in the E/C/F/TAF group compared to 5% in the comparator TDF containing arm. There were also two instances of Grade 3 or 4 serum hyperuricemia in the E/C/F/TAF group compared to none in the comparator group. When the same analysis is performed on data from the pivotal studies (0104/0111) it was discovered that 12% of E/C/F/TAF had any instance of graded hyperuricemia compared to 9% of subjects receiving Stribild®. The 12-13% value appears to be valid. The lower value with Stribild® suggests that TAF perhaps itself or in combination with the other components have an impact on urate metabolism. The clinical implications of this finding are unknown. There were seven cases (0.4% incidence) of symptomatic gout in studies 0104/0111. Four of these cases occurred in Stribild® recipients and three occurred in E/C/F/TAF recipients. There were nine cases of gout (0.6% incidence) in Study 0109, seven occurring in E/C/F/TAF recipients. In Study 0112 the incidence of any gradable serum uric acid elevation was 19% and there were two cases (0.8%) of symptomatic gout. For more information regarding study 292-0109 please see Appendix 1.

7.4.3 Vital Signs

Vital signs (blood pressure, pulse, and temperature) were measured at all visits, and weight was measured at scheduled intervals in the key studies. Clinically significant

changes from baseline (Screening visit) were recorded as AEs. There were no clinically relevant changes from baseline or between treatment groups in median values for body weight or vital signs in either treatment groups for the submitted studies.

7.4.4 Electrocardiograms (ECGs)

In the five studies conducted in adults there were a total of ten clinically significant ECG abnormalities in E/C/F/TAF group and two abnormalities in the Stribild® group. There were a variety of different abnormalities including abnormal sinus rhythm with sinus arrhythmia, non-specific ST-T wave abnormalities, baseline conduction abnormality progressing to transient atrial fibrillation, development of bundle branch block and PR interval prolongation (first degree AV block). In addition, in the normal renal function subjects there were seven E/C/F/TAF subjects and three comparator subjects who had ECG considered to be not clinically significant. In the renal impairment subjects there were fifteen subjects with AEs related to abnormal ECGs or prior cardiac disease. One subject with four days of palpitations was considered clinically significant, the remainders were not. There were no ECG findings considered serious, none were considered related to study drugs and none resulted in discontinuation of study drugs.

7.4.5 Special Safety Studies/Clinical Trials

In response to non-clinical findings of the development of posterior uveitis in dogs, the Applicant implemented a 47 subject ophthalmologic substudy to intensively monitor recipients of E/C/F/TAF and Stribild® for the development of eye disorders. This study enrolled 47 participants of Study 292-0109. As of this submission, no subjects had fundoscopic findings consistent with uveitis. The central readings from the study are summarized below. These data were provided by Dr. Miele and are available in Appendix 1.

Table 67 Ophthalmologic Substudy

	E/C/F/TAF			TDF		
	N	Normal	Abnormal	N	Normal	Abnormal
Baseline	N=32	25	7	N=15	13	2
Week 24	N=31	26	5	N=15	13	2
Week 48	N=18	14	4	N=7	5	2
Normal → Abnormal	1			0		

Four subjects in the E/C/F/TAF group had a shift in central fundoscopic assessment from abnormal at baseline to normal during the study. One subject in the E/C/F/TAF group (subject (b) (6)) had a shift from normal at baseline (local and central reading) to abnormal at Week 24 (local and central reading) due to the detection of a new retinal hemorrhage in the left eye. This study is ongoing.

7.4.6 Immunogenicity

As all of the components of E/C/F/TAF are small molecules, immunogenicity issues were not anticipated and not specifically addressed during the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All of the trials submitted used the E/C/F/TAF fixed dose formulation. Assessing the true dose dependency for AEs using these datasets is not possible. For more information please consult the Clinical Pharmacology Review.

7.5.2 Time Dependency for Adverse Events

The Applicant provided a Kaplan-Meier (KM) plot of the time to premature discontinuation of study drug which demonstrated a lower percentage of subjects (1%) in the E/C/F/TAF discontinuing at Week 8 compared to Stribild® recipients (2%). The difference between the groups was not statistically significant.

7.5.3 Drug-Demographic Interactions

In the E/C/F/TAF group, approximately 15% of the subjects in the pivotal studies, 4% of the Phase 2 study population and 20% of the renal impairment population were women. Making conclusive statements related to drug demographic interactions for this population is very difficult. The overall incidences of treatment emergent AEs in the E/C/F/TAF group of the pivotal trials were similar in men and women (89% women and 91% men). The differences in incidence of SAEs were a bit wider with women experiencing 6.7% SAEs compared to 9.6% for the men. Only nine women experienced SAEs so small differences are amplified. There was only one woman among the 21 discontinuations for AEs observed in the pivotal trials (0104/0111).

In Studies 292-0104 and 292-0111, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 90.6%, 202 of 223 subjects; nonblack 89.6%, 576 of 643 subjects; STB: black 91.5%, 195 of 213 subjects; nonblack 89.8%, 587 of 654 subjects).

In Study 292-0109, the percentages of subjects experiencing any AE were comparable in black and nonblack subjects for both treatment groups (E/C/F/TAF: black 77.5%, 131 of 169 subjects; nonblack 80.2%, 632 of 788 subjects; FTC/TDF+3rd Agent: black 72.5%, 74 of 102 subjects; nonblack 78.3%, 293 of 374 subjects).

7.5.4 Drug-Disease Interactions

Hepatic Impairment

The PK of TAF and TFV in HIV-uninfected subjects were evaluated in subjects with mild or moderate hepatic impairment (Child-Pugh Class A or B) versus matched healthy adult subjects (control) in Study 120-0114. The plasma exposure parameters of TAF were comparable (AUC_{inf} , AUC_{last} , and C_{max} were 12.7%, 15.1%, and 18.7% higher, respectively) in the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function, which was not considered to be clinically relevant.

The plasma exposure parameters of TFV were comparable (AUC_{inf} , AUC_{last} , and C_{max} were 10.8%, 10.7%, and 3.0% lower, respectively) in the subjects with mild hepatic impairment relative to matched control subjects with normal hepatic function; the observed decreases are not considered to be clinically relevant. The plasma exposure parameters of TFV were comparable (AUC_{inf} , AUC_{last} , and C_{max} were 2.8%, 4.5%, and 12.4% lower, respectively) in the subjects with moderate hepatic impairment relative to matched control subjects with normal hepatic function which was not considered to be clinically relevant. The effect of severe hepatic impairment on the PK of TAF has not been studied.

Co-infection with Hepatitis B and C

Subjects who were hepatitis C antibody positive were excluded from all Phase 2 and 3 studies of E/C/F/TAF. The exclusion criteria for Study 292-0104 were updated in Amendment 1 of the protocol to exclude subjects with positive HBV surface antigen. All of the other Phase 2 and Phase 3 studies of E/C/F/TAF excluded subjects with positive HBV surface antigen.

In Study 292-0104, Subject 2728-4019 in the STB group tested positive for HBV surface antigen at screening and discontinued study drugs on Day 32 due an SAE of Grade 3 immune inflammatory syndrome due to HBV, which resulted in unblinding of study drug.

Subject 4142-4719 in the E/C/F/TAF group of Study GS-US-292-0104 had normal liver function tests (LFTs) at screening, and high aspartate aminotransferase (AST; Grade 2) and alanine aminotransferase (ALT; Grade 3) at baseline (AST = 117 U/L, ALT = 237 U/L). AST returned to within the normal range on Day 18, and ALT was within the normal range by Day 26. On Day 84, ALT was again elevated (55 U/L, Grade 1). On Day 113, the subject had a nonserious AE of Grade 2 hepatitis C (ALT = 788 U/L, Grade 4; AST = 383 U/L, Grade 4) considered unrelated to the study drugs by the investigator. On Day 133 the subject tested positive for HCV antigen. The study drugs were discontinued. On Day 181, the subject commenced treatment with subcutaneous pegylated interferon and oral ribavirin (treatment ongoing). By Day 253, all LFTs were within the normal range; however the event of hepatitis C was ongoing.

The PK of FTC was evaluated in a Phase 1 study in subjects with chronic HBV (Study FTCB-101). Based on the steady-state data from FTCB-101, FTC PK in HBV-infected subjects are generally similar to those determined previously in healthy subjects and in HIV-infected subjects.

Study GS-US-292-1249 is a Phase 3b, open-label study of E/C/F/TAF FDC in adult subjects who are coinfecting with HIV-1 and hepatitis B. The study is ongoing.

No dose adjustment of E/C/F/TAF is necessary for patients with mild to moderate hepatic impairment (Child Pugh Class A or B).

7.5.5 Drug-Drug Interactions

Please refer to the Clinical Pharmacology Review for a full discussion of the PK of this product. The relevant issues have been summarized earlier in Section 4.4.2.

A drug-drug interaction study with E/C/F/TAF and sertraline (study GS-US-292-1316) found exposure changes of <16% for each component of E/C/F/TAF and sertraline. Based on flat exposure-response relationships, no dose adjustment is recommended for based on a <16% exposure change.

Coadministration of EVG/COBI and carbamazepine in drug-drug interaction study GS-US-216-0137 resulted in EVG AUC decreased 69%, COBI AUC decreased 84%, carbamazepine AUC increased 43%, and carbamazepine-10,11-epoxide (CYP3A-mediated active metabolite of carbamazepine) AUC decreased 35%. Based on significant EVG exposure decreases, coadministration of E/C/F/TAF and carbamazepine is contraindicated.

Coadministration of TAF and COBI in drug-drug interaction study GS-US-311-0101 resulted in TAF AUC increased 2.7-fold and TFV AUC increased 3.3-fold. This drug interaction was addressed by a dose reduction of the TAF dose from 25 mg to 10 mg in the E/C/F/TAF tablet.

Within the E/C/F/TAF regimen, drug-drug interactions occur via COBI-mediated CYP3A and Pgp inhibition, resulting in increased exposures of EVG (CYP3A substrate) and TAF (Pgp substrate). EVG and TAF exposures may also be increased via inhibition of BCRP, OATP1B1, and OATP1B3 as EVG, TAF, and COBI are substrates of these transporters and COBI is an inhibitor of these transporters.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

None of the components of E/C/F/TAF had positive findings on genotoxicity studies. The combination is not anticipated to alter the genotoxicity of the individual agents. EVG, FTC, and TDF demonstrated low carcinogenic potential in the 2 year bioassays. The proposed specifications for impurities in the EVG, COBI, FTC and TAF drug substances were deemed acceptable based on results from general toxicology studies, experimental genotoxicity data and assessments of potential mutagenicity using (Q) SAR.

Please refer to Section 4.3 for more information related to non-clinical studies assessing carcinogenesis and mutagenesis.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy and breastfeeding were exclusion criteria for all clinical trials. In addition, pregnancy was a predefined condition triggering discontinuation of study drug. Therefore, the use of E/C/F/TAF in the setting of pregnancy has not been studied.

There were a total of seven pregnancies among the treatment naïve populations. Of these seven, six subjects were taking Stribild® and one was taking E/C/F/TAF. Of the seven pregnancies, one was an ectopic pregnancy which was surgically treated, one resulted in an early delivery at week 32 due to severe (<5%) intrauterine growth retardation, one delivered a healthy full term girl, one resulted in a live birth with no additional details available, and the remainder are listed as continuing. The single subject receiving E/C/F/TAF was the individual with the ectopic pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of E/C/F/TAF in adolescents was demonstrated in this submission (292-0106). Please consult the clinical review of Dr. Alarcon in Appendix 2.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

If an overdose with E/C/F/TAF occurs, the patient must be monitored for evidence of toxicity, and should receive general supportive measures including close clinical assessment. Limited clinical experience is available at doses higher than the therapeutic doses of EVG, COBI, FTC, or TAF. No severe adverse reactions were reported at supratherapeutic doses in studies of EVG (Study GS-US-183-0128), COBI (Studies GS-US-216-0113 and GS-US-216-0107), or FTC. As EVG and COBI are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Up to 30% of the FTC dose may be removed by

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William B. Tauber, M.D.
NDA 207561
E/C/F/TAF (Genvoya)

hemodialysis. TFV is efficiently removed by hemodialysis with an extraction coefficient of approximately 54%.

Most overdoses were characterized by isolated, inadvertent administrations of single extra daily doses of blinded study medication and not associated with clinical symptoms or sequelae. Adverse events possibly associated with overdoses were observed in 2 of the subjects: (E/C/F/TAF: mild headache [Subject 1537-4450], and event not specified [Subject 0364-4154]).

In Study GS-US-292-0104, 23 subjects reported at least one overdose during the study (E/C/F/TAF 1.6%, 7 subjects, STB 3.7%, 16 subjects). In the E/C/F/TAF group, 6 subjects were classified as overdose of study drug, while one additional subject who reported an overdose was classified as a procedural deviation. In the STB group, 12 events were classified as overdose of study drug in 11 subjects, while 3 additional subjects who reported an overdose were classified as procedural deviations and 2 were classified as non-adherence of study drug.

In study GS-US-292-0111, 19 subjects reported at least one overdose during the study (E/C/F/TAF: 1.8%, 8 subjects, STB 2.5%, 11 subjects). In the E/C/F/TAF group, seven subjects were classified as overdose of study drug, while one additional subject who reported an overdose was classified as a procedural deviation. In the STB group, 10 subjects were classified as overdose of study drug, while 1 additional subject who reported an overdose was classified as a procedural deviation.

7.7 Additional Submissions / Safety Issues

The Applicant submitted the Safety Update Report in February 2015 and the data have been integrated into the appropriate sections of this review.

8 Postmarket Experience

This product has not yet been approved for marketing in any country and therefore there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

No literature References are attached to this review.

9.2 Labeling Recommendations

The proposed Package Insert (Pi or label) is being reviewed by all disciplines. Labeling discussions are ongoing and the recommendations have not been finalized at the time of this review. Please refer to the Cross Discipline Team Leader Memo by Dr. Linda Lewis for detailed labeling recommendations.

9.3 Advisory Committee Meeting

No advisory Committee Meeting was held for this application

9.4 DAVP Medical Officer Reviews of Studies GS-US-292-0109 and GS-US-292-0106

Appendix 1: Review of GS-US-292-0109 by Dr. Peter Miele

Appendix 2: Review of GS-US-292-0106 by Dr. Andreas Alarcon

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**Appendix 1 Medical Officer Review GS-US-292-0109 Dr. Peter Miele,
M.D.**

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Secondary Clinical Review

Study GS-US-292-0109

*A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing
Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR)
in Virologically-Suppressed, HIV-1 Positive Subjects*

Peter Miele, MD
Division of Antiviral Products
OAP/CDER/FDA

June 10, 2015

Page 108**EXECUTIVE SUMMARY**

Study GS-US-242-0109 (Study 109) is an ongoing Phase 3 randomized, open-label, multicenter, active-control trial to evaluate the efficacy, safety, and tolerability of switching to a fixed-dose combination tablet of elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF) from regimens containing tenofovir disoproxil fumarate (TDF) in virologically suppressed HIV-1 infected subjects. The primary objective is to evaluate the noninferiority of switching to E/C/F/TAF relative to maintaining a TDF-containing regimen in virologically suppressed subjects as determined by the FDA-defined snapshot algorithm (HIV-1 RNA < 50 copies/mL) at Week 48. All subjects were drawn from a predefined set of Gilead Sciences clinical trials and were virologically suppressed on one of the following TDF-based regimens: EVG/COBI/FTC/TDF (Stribild®; STB); efavirenz (EFV)/FTC/TDF (Atripla®; ATR); COBI-boosted atazanavir (ATV/co) + FTC/TDF (Truvada®; TVD), and ritonavir (RTV)-boosted atazanavir (ATV/r) + TVD. The study is designed to continue through 96 weeks, but an interim analysis was conducted after all subjects randomized by October 31, 2013 had been followed through the lower limit of the Week 48 analysis window. This interim analysis, not specified in the protocol, was submitted to the NDA and serves as the primary basis for this review.

Among the 1,436 subjects who received at least 1 dose of study drug (E/C/F/TAF 959 subjects; TDF 477 subjects), demographics, baseline disease characteristics, and distributions of prior treatment regimens were comparable between the two treatment groups. Using the Week 48 Full Analysis Set (FAS), which contained all subjects randomized by October 31, 2013 and who had been followed through the lower limit of the Week 48 analysis window (N=1,186), virologic success rates at Week 48 using the FDA snapshot algorithm were 95.6 % in the E/C/F/TAF group and 92.9% in the TDF group; the difference between the two groups was 2.7% (95.01% CI: -0.3% to 5.6%). Because the lower bound of the 2-sided 95.01% CI of the difference in response rate was greater than the prespecified -12% margin, switching to E/C/F/TAF was noninferior to maintaining a TDF-based regimen at Week 48. The proportion of subjects with pure virologic failure (PVF) by Week 48 was 3% in the E/C/F/TAF group and 2% in the TDF group; time to PVF was comparable between the two treatment groups. Mean changes in CD4 cell counts were similar between groups through Week 48, with both groups having slight increases from baseline. There were no differences in efficacy by subgroup (i.e., age, sex, race, geographic regions, prior treatment regimen, and study drug adherence).

In Study 109, switching to E/C/F/TAF was well tolerated through a median of 48.0 weeks of exposure, as evidenced by the low rate of discontinuations due to adverse events (AEs) (1%) and absence of study drug-related serious adverse events (SAEs). Overall, the AE profile for E/C/F/TAF was similar across the subgroups of age, sex, race, region, and prior treatment regimen. Among subjects who switched to E/C/F/TAF, there was a higher incidence of any AEs considered related to study drug by the investigator (E/C/F/TAF 19% versus TDF 11%), as might be expected in an open-label switch study of virologically suppressed subjects who were tolerating their baseline regimen.

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Notably, there were statistically significant differences at Week 48 favoring E/C/F/TAF over TDF for four key predefined safety endpoints: mean percentage changes from baseline in hip bone mineral density (BMD) and spine BMD using dual-energy x-ray absorptiometry (DXA), mean change from baseline in serum creatinine, and change from baseline in efavirenz-related symptom assessment composite score.

Overall, there were increases from baseline in BMD at both the hip and spine in the E/C/F/TAF group as compared with minimal changes in both parameters in the TDF group. In a small cohort of subjects with pre-TDF DXA results, subjects who switched to E/C/F/TAF after an average of 3 years on a TDF-based regimen experienced some reversal of BMD loss, although their mean BMD values at Week 48 did not fully return to pre-TDF levels; however, it is possible that longer duration of treatment with TAF may result in continued improvement in BMD. In contrast, subjects who remained on TDF continued to experience BMD loss compared to their pre-TDF baseline values. The BMD results in the overall study were supported by changes in markers of bone turnover that indicate a decrease in bone remodeling following switch to E/C/F/TAF. There were no differences between the two treatment groups in the overall incidence of fracture events and no subject experienced a pathological bone fracture.

There were either small increases or no changes from baseline in serum creatinine at most time points among subjects who switched to E/C/F/TAF from ATV/boosted regimens. However, in subjects who switched to E/C/F/TAF from STB, decreases from baseline in mean values for serum creatinine were observed at Weeks 2 (the first post-baseline assessment) through 48 as compared with increases from baseline in subjects who stayed on STB. In contrast, for subjects who had not previously been exposed to COBI (i.e., subjects who switched from ATR to E/C/F/TAF), increases in serum creatinine were observed at Week 2 (consistent with the established COBI effect on serum creatinine) and through Week 48. Corresponding changes from baseline in eGFR (by various formulae) were observed in both treatment groups through 48 weeks of treatment, regardless of prior treatment regimen. Decreases from baseline in proteinuria, albuminuria, and tubular proteinuria, and other measures of proximal renal tubular function in the E/C/F/TAF group, as compared with increases from baseline in the TDF group, corroborate a potentially reduced effect of TAF on the kidney compared with TDF; however, no notable change in renal phosphate handling was observed. There was only one case consistent with Fanconi syndrome in this trial, and it occurred in the TDF group (in a subject on ATV/co + TVD).

There were no between-group differences in the incidence of Grade ≥ 2 dental disorders, musculoskeletal and connective tissue disorders, or eye disorders – safety concerns that were raised in the main NDA review or from nonclinical studies. There were no reports of uveitis during the study, nor were there any subjects with fundoscopic findings consistent with uveitis in a small ophthalmologic substudy (n=47).

Switching from a TDF-based regimen to E/C/F/TAF was not associated with greater risk of

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neuropsychiatric events, however the risks were not significantly lessened either. Using an unvalidated efavirenz-related symptom questionnaire, switching to E/C/F/TAF resulted in greater improvement from baseline in mean efavirenz-related symptom composite scores at each visit compared to remaining on ATR therapy. Other subjective quality of life measures (i.e. health utilization assessment, EQ-5D-3L, and SF-36 questionnaires) did not demonstrate any differences between treatment groups.

To counterbalance the relatively favorable renal, bone, and efavirenz-related symptom effects of switching to E/C/F/TAF, treatment with E/C/F/TAF also resulted in significantly greater median increases from baseline in fasting values of total cholesterol, LDL cholesterol, and triglycerides compared to remaining on a TDF-based regimen. Specifically, the median changes from baseline at Week 48 for E/C/F/TAF and TDF, respectively, were 20 vs. 6 mg/dL for fasting cholesterol, 9 vs. 0 mg/dL for LDL cholesterol, and 10 vs. 0 mg/dL for triglycerides. Consistent with these results, higher percentages of subjects in the E/C/F/TAF group than the TDF group had categorical shifts from baseline based on clinically relevant cholesterol treatment categories; however, the percentage of subjects initiating lipid-lowering agents during the study period was comparable between treatment groups. The Applicant considers that the differences between treatment groups in these lipid parameters may be due to the purported lipid-lowering effect of TFV and the lower circulating levels of TFV seen with E/C/F/TAF compared with TDF.

The incidence of laboratory abnormalities of any grade for most other chemistry, hematology, and urinalysis parameters was balanced in both treatment groups; however, there was a greater incidence of mostly mild hyperuricemia in the E/C/F/TAF group compared with the TDF group. The etiology and clinical significance of this imbalance is not clear; there were no between-group differences in the incidence of gout AEs. There were also no notable differences with respect to vital signs, ECG findings, and weight changes between the two groups. The 120-day Safety Update did not reveal any new safety concerns compared with the original submission.

INTRODUCTION

Study Design

Study GS-US-242-0109 (Study 109) is an ongoing Phase 3 randomized, open-label, multicenter active-control trial to evaluate the efficacy, safety, and tolerability of switching to a fixed-dose combination tablet of elvitegravir (EVG; E)/cobicistat (COBI; C)/emtricitabine (FTC; F)/tenofovir alafenamide (TAF) (E/C/F/TAF) from regimens containing tenofovir disoproxil fumarate (TDF) in virologically suppressed HIV-1 infected subjects. The trial is being conducted in 168 sites in Europe, Australia, Thailand, North and South America and is designed to follow subjects through 96 weeks.

The primary objective is to evaluate the noninferiority of switching to E/C/F/TAF relative to maintaining a TDF-containing regimen in virologically suppressed subjects as determined by the FDA-defined snapshot algorithm (HIV-1 RNA < 50 copies/mL) at Week 48.

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Secondary objectives are:

- To determine the percentage change from baseline in hip and spine bone mineral density (BMD) at Week 48
- To determine the change from baseline in serum creatinine at Week 48
- To evaluate the safety and tolerability through Week 48
- To evaluate the durability of the efficacy, safety and tolerability of the two treatment groups through Week 96.

All subjects are adults drawn from a predefined set of Gilead Sciences clinical trials who were virologically suppressed on one of the following TDF-based regimens:

- EVG/COBI/FTC/TDF (Stribild®; STB)
- Efavirenz (EFV)/FTC/TDF (Atripla®; ATR)
- COBI-boosted atazanavir (ATV/co) + FTC/TDF (Truvada®; TVD)
- Ritonavir (RTV)-boosted atazanavir (ATV/r) + TVD

Eligible subjects had to have been receiving antiretroviral therapy for at least 6 months preceding the final visit in their earlier study, and maintained plasma HIV-1 RNA at undetectable levels for at least 6 consecutive months prior to screening. They also had to have an estimated glomerular filtration rate (eGFR) as calculated by Cockcroft-Gault equation ($eGFR_{CG}$) ≥ 50 mL/min at screening.

Subjects were randomized in a 2:1 ratio to switch to E/C/F/TAF (n=1000) or stay on their preexisting TDF regimen (n=500). Randomization was stratified by prior treatment regimen at screening. Study visits were scheduled at Weeks 2, 4, 8, and 12, and then every 12 weeks through Week 96.

Baseline and post-baseline assessments include adverse events (AEs), vital signs, weight, clinical laboratory tests (chemistry, hematology, urinalysis, and pregnancy testing), including bone biomarkers (type I collagen C-telopeptide [C-telopeptide] and procollagen type 1 N-terminal propeptide [P1NP]), parathyroid hormone (PTH), serum creatinine, $eGFR_{CG}$ and $eGFR$ by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine method ($eGFR_{CKD-EPI, creatinine}$), proteinuria by urinalysis and quantitative assessment (protein to creatinine ratio [UPCR], urine albumin to creatinine ratio [UACR]), and renal biomarkers (retinol binding protein [RBP] to creatinine ratio, beta-2-microglobulin to creatinine ratio, renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate [TmP/GFR], fractional excretion of phosphate [FEPO₄], and fractional excretion of uric acid [FEUA]). BMD using dual-energy x-ray absorptiometry (DXA) is assessed at baseline and Weeks 24, 48, 72, and 96. Fracture probabilities are assessed using a computer-based algorithm (FRAX®). Subjects participating in the ophthalmologic substudy are undergoing fundoscopic and slit-lamp examinations, and are having retinal photographs taken of both eyes (see below). Additionally, neuropsychiatric symptoms related to EFV are being evaluated in subjects who took ATR as their prior regimen (see below).

The primary endpoint is the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48. Noninferiority is assessed using a conventional 95% confidence interval (CI) approach, with a noninferiority margin of 12%. The 95% CI is constructed using Mantel-Haenszel proportion stratified by prior treatment regimen weighted difference in the response rate between groups. For the interim analysis performed by the independent data monitoring committee (IDMC) at Week 24, an alpha of

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0.0001 was spent. Therefore, the significance level for the 2-sided test in the primary analysis at Week 48 is 0.0499 (corresponding to 95.01% CI).

Secondary and tertiary efficacy endpoints at Week 48 include:

- The proportion of subjects with HIV-1 RNA < 20 copies/mL at Week 48 (snapshot algorithm)
- Changes from baseline in CD4 cell count at Week 48 (observed data and Missing = Last Observation Carried Forward [M = LOCF] analysis)
- Pure virologic failure (PVF) with HIV-1 RNA cutoff at 50 copies/mL by Week 48
- Percentage of subjects who have HIV-1 RNA < 50 copies/mL at Week 48 (Missing = Failure [M = F] and Missing = Excluded [M = E])
- Change from baseline in CD4% at Week 48

Four key safety endpoints are defined as follows:

- Percentage change from baseline in hip BMD at Week 48
- Percentage change from baseline in spine BMD at Week 48
- Change from baseline in serum creatinine at Week 48
- Change from baseline in EFV-related symptom assessment score at Week 48.

Ophthalmologic Substudy

A small ophthalmologic substudy is being conducted at selected sites (targeted sample size is 75 subjects; 2:1 randomization). Ophthalmologic assessments comprising of fundoscopic examinations, slit-lamp examinations, and retinal photography of both eyes are being performed by an ophthalmologist at each investigational center (local reader). The full retinal field is being examined noting changes or abnormalities. Photographs of the retina are taken at each examination and filed in the subjects' source medical records. The retinal photographs from all participating subjects are also evaluated centrally by a qualified ophthalmologist (central reader) without knowledge of treatment assignment for an independent assessment of any abnormalities, including uveitis. Assessments are performed prior to study drug administration at baseline (Day 1) and every 24 weeks thereafter until Week 96 and at the Early Study Drug Discontinuation (ESDD) visit if it occurred prior to Week 96.

Efavirenz-Related Symptoms Assessment

Change from baseline at Week 48 in an EFV-related symptom composite score for subjects on ATR as their prior treatment regimen is one of the four prespecified key safety endpoints. The analysis set includes all subjects who were on ATR as the prior treatment regimen, received at least 1 dose of study drug, and had nonmissing symptom scores at both baseline and at least 1 post-baseline visit. The five EFV-related symptoms are dizziness, trouble sleeping, impaired concentration, sleepiness, abnormal or vivid dreams, and each symptom is scored individually at each visit using a 4-point scale (0 = I don't have the symptom; 1 = It doesn't bother me; 2 = It bothers me a little; 3 = It bothers me a lot; and 4 = It bothers me terribly). A composite score is then calculated at each visit by summing the scores for each symptom. Baseline and change from baseline for the composite score are summarized by treatment group and visit using descriptive statistics.

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Study Status

The first subject in GS-US-292-0109 was screened on March 27, 2013. The protocol specified that the Week 48 analysis would be performed after the last subject completed 48 weeks on study or prematurely discontinued from the study. However, the submitted interim analysis, which was not mentioned in the protocol, was conducted after all subjects randomized by October 31, 2013 had been followed through the lower limit of the Week 48 analysis window (Week 42, or August 28, 2014). The decision to conduct this interim analysis was made during a study management team meeting on October 28, 2013. The rationale for performing the current analysis was to include the most current Week 48 data in the initial marketing application for E/C/F/TAF from a sufficient number of virologically suppressed population subjects (1,196 subjects) who had reached the primary time point of interest. The last subject observation for this interim report was August 28, 2014.

REVIEWER METHODS

This reviewer used the Applicant's Analysis Data Model (ADaM) datasets to evaluate efficacy and safety in Study GS-292-0109. The following reviewer tools were used to analyze the data and generate the tables and figures included in this review (unless otherwise noted): JReview®, Integrated Clinical Systems, Inc. (Version 9.2.5); JMP®, SAS Institute Inc. (Version 11); and the MedDRA-based Adverse Event Diagnostic Tool (MAED), developed by the FDA (Version 1.2).

For the analysis of efficacy, the Week 48 Full Analysis Set (FAS) was used, which included all subjects randomized by October 31, 2013 and who had received at least 1 dose of study drug.

For the analysis of safety, the Safety Analysis Set was used, which included all randomized subjects who received at least 1 dose of study drug. Subjects who remained on their TDF-based regimen were pooled together for the safety comparisons, unless otherwise specified.

Adverse events and any laboratory abnormalities recorded as AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 17.0). Treatment-emergent AEs (TEAEs) were defined as follows:

- Any AEs with onset date on or after the study drug start date and no later than 30 days after the study drug stop date; or
- Any AEs leading to study drug discontinuation.

Treatment-emergent laboratory abnormalities were defined as values that increased at least one toxicity grade from baseline at any post-baseline visit up to and including the date of last dose of study drug plus 30 days. If the relevant baseline laboratory data were missing, any laboratory abnormality of at least Grade 1 was considered treatment emergent.

Adverse events and laboratory abnormalities were graded by the investigator according to toxicity criteria specified in the study protocol (Gilead's Grading Scale for Severity of Adverse Events and Laboratory Abnormalities).

The Applicant also performed an analysis to detect AEs where the symptoms reported might

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potentially represent uveitis. This was done by selecting a subset of non-specific eye disorder preferred terms (PTs), and this list of terms was reviewed and edited by an external ophthalmologist for comprehensiveness. A total of 63 selected PTs were used to identify potential cases of uveitis.

EFFICACY RESULTS

Subject Disposition

One thousand five hundred and ninety-two (1,592) subjects were screened (Table 1), of whom 1,443 subjects were randomized, and 1,436 subjects received at least 1 dose of study drug (E/C/F/TAF 959; TDF 477). Seven randomized subjects did not receive study drug (E/C/F/TAF 4; TDF 3). The submitted analysis of the primary efficacy endpoint used the Week 48 FAS (E/C/F/TAF 799; TDF 397), which included all subjects randomized by October 31, 2013 and who had received at least 1 dose of study drug.

Table 1: Subject Disposition

Screened	1592		
Screen failures	135	Most common reasons: detectable HIV-1 RNA, Hepatitis C Ab positive, HBsAg positive, total bilirubin >1.5 mg/dL	
Eligible	1457		
Eligible but not randomized	48		
Eligible and randomized	1409		
Screen failures but randomized	34	31 were treated (E/C/F/TAF 17; TDF 14): reasons for failing screening: total bilirubin >1.5 mg/dL (7), Hepatitis C Ab positive (6), inadequate hematologic function (6), abnormal ECG (5)	
		E/C/F/TAF	TDF
Randomized total	1443	963	480
Randomized but never treated	7	4	3
Randomized and treated (Safety Set)	1436	959 (100)	477 (100)
Subjects in Week 48 Full Analysis Set	1196	799 (83)	397 (83)
Discontinued study drug	50	20 (2)	30 (6)
Adverse event	16	9 (1)	7 (2)
Death	2	2 (<1)	0
Withdrawal by subject	16	4 (<1)	12 (3)
Lost to follow-up	8	3 (<1)	5 (1)
Lack of efficacy	1	1 (<1)	0
Physician decision	5	1 (<1)	4 (1)
Non-compliance with study drug	2	0	2 (<1)
Subjects still on study drug	1386	939 (98)	447 (94)
Dropouts from study	39	17 (2)	22 (5)

Withdrawal by subject	15	3 (<1)	12 (3)
Adverse event	12	7 (1)	5 (1)
Lost to follow-up	8	3 (<1)	5 (1)
Death	2	2 (<1)	0
Physician decision	2	2 (<1)	0
Subjects still on study	1397	942 (98)	455 (95)

Source: Reviewer's analysis of Applicant's dataset (ADLS)

Of the 1,436 treated subjects, 50 subjects (4%) discontinued study drug (E/C/F/TAF 2%; TDF 6%), and 39 subjects (3%) prematurely discontinued from the study (E/C/F/TAF 2%; TDF 5%) 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 (0.4%, 4 subjects) compared with TDF (3%, 12 subjects) due to withdrawal of consent, possibly a reflection of the open-label study design. Two subjects (0.2%) in the E/C/F/TAF group discontinued study drug due to death; both deaths were considered by the investigators as unrelated to study drug. Adverse events led to discontinuation of study drug in 9 subjects (1%) in the E/C/F/TAF group and 7 subjects (2%) in the TDF group.

Through the data cutoff date, 1,386 subjects are continuing study drug treatment (E/C/F/TAF 98%; TDF 94%), and 1,397 subjects remain on the study (E/C/F/TAF 98%; TDF 95%).

Subject Demographics

Demographic and general baseline characteristics were similar between the two groups (Table 2) with the exception of ethnicity as a higher proportion of subjects in the E/C/F/TAF group (26%) compared with the TDF group (17%) were of Hispanic ethnicity. The majority of subjects were male (89%), with a mean age of 41 years. Two-thirds of subjects were from the U.S.; most were either white (67%) or black (19%), and non-Hispanic (77%). Median BMI at baseline was 25.9 kg/m². Most subjects had normal renal function at baseline, with similar values for eGFR (as measured by CG or CKD-EPI methods) in each group, and most (91%) had no proteinuria (Grade 0 by dipstick) on urinalysis. Treatment groups were also similar with respect to the probability of hip or major osteoporotic fracture by FRAX estimation.

Table 2: Demographic and Baseline Characteristics (Safety Analysis Set)

	E/C/F/TAF (N=959)	TDF (N=477)
Age, years		
Mean (SD)	41 (10.1)	41 (10.1)
Range	21-77	22-69
Sex, n (%)		
Male	856 (89)	427 (90)
Female	103 (11)	50 (10)
Race, n (%)		
White	651 (68)	314 (66)
Black	169 (18)	102 (21)
Asian	59 (6)	35 (7)
Other	67 (7)	22 (5)
Native Hawaiian Or Other Pacific Islander	6 (1)	1 (<1)
American Indian Or Alaska Native	5 (1)	2 (<1)

Not Permitted	2 (<1)	1 (<1)
Ethnicity, n (%)		
Hispanic	248 (26)	82 (17)
Non-Hispanic	709 (74)	392 (82)
Not Permitted	2 (<1)	3 (1)
Region, n (%)		
US	648 (68)	316 (66)
Ex-US	311 (32)	161 (34)
Baseline BMI (kg/m ²)	N=957	N=476
Mean (SD)	26.6 (5.3)	26.9 (5.3)
Median	25.8	26.1
Q1, Q3	23.1, 29.1	23.1, 29.4
eGFR (mL/min) Cockcroft-Gault	N=959	N=477
Mean (SD)	111.9 (33.4)	112 (32.7)
Median	105.7	107.7
Q1, Q3	89.4, 126	88.7, 128.8
Range	48.0 - 344.1	45.7 - 304.8
Proteinuria, dipstick	N=959	N=477
Grade 0	873 (91)	430 (90)
Grade 1	81 (8)	44 (9)
Grade 2	4 (<1)	3 (1)
Grade 3	0	0
Missing	1 (<1)	0
10 Year Probability of Hip Fracture (%) by FRAX	N=900	N=451
Mean (SD)	0.39 (0.67)	0.41 (0.67)
Median	0.16	0.16
Q1, Q3	0.04, 0.43	0.05, 0.47
10 Year Probability of Major Osteoporotic Fracture (%) by FRAX	N=900	N=451
Mean (SD)	2.53 (2.11)	2.56 (2.13)
Median	1.92	1.94
Q1, Q3	1.2, 3.07	1.17, 3.27

Source: Reviewer's analysis of Applicant's dataset (ADLS, ADLB)

Overall, the study population was reflective of a virologically-suppressed, HIV-1 infected population. Baseline HIV disease characteristics were similar between the two treatment groups (Table 3). Most subjects had baseline CD4 cell count \geq 500 cells/ μ L (median 669 cells/ μ L). Study enrollment was stratified by the prior treatment regimen present at study screening (i.e., STB, ATR, ATV/boosted+TVD). The distributions of prior treatment regimens were comparable between the two treatment groups. At enrollment, about a third of the subjects were taking STB, 42% were taking ATV/boosted + TVD, and about a quarter were taking ATR.

Table 3: Baseline Disease Characteristics (Safety Analysis Set)

	E/C/F/TAF (N=959)	TDF (N=477)
HIV-1 RNA Categories (copies/mL)		
< 50	943 (98)	466 (98)
\geq 50	16 (2)	11 (2)
CD4 count (/ μ L)		
Mean (SD)	701 (261)	688 (248)

Median	675	662
CD4 Categories (μL)		
≥ 500	749 (78)	378 (79)
≥ 350 to < 500	151 (16)	70 (15)
≥ 200 to < 350	54 (6)	25 (5)
≥ 50 to 200	5 (1)	4 (1)
Previous TDF-based Regimen		
STB	306 (32)	153 (32)
ATV/boosted + TVD	402 (42)	199 (42)
ATV/r + TVD	255 (27)	130 (27)
ATV/co + TVD	147 (15)	69 (15)
ATR	251 (26)	125 (26)

Source: Source: Reviewer's analysis of Applicant's dataset (ADLS, ADLB)

Only 3 subjects had HIV-1 RNA \geq 50 copies/mL at Screening. At randomization, however, 27 subjects detectable viral loads. Nineteen of these subjects had HIV-1 RNA < 100 copies/mL, while five had HIV-1 RNA \geq 100 to < 1000 copies/mL and three had HIV-1 RNA \geq 1000 copies/mL (max 1730 copies/mL). Of these 27 subjects, one withdrew from the study and another was not included in the Full Analysis Set (FAS). Of the remaining 25 subjects, 21 subjects were suppressed by Week 48, one subject had virologic failure (in the TDF group), and three subjects had missing data at Week 48 but remained on study drug.

Primary Endpoint Analysis

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 using the FDA-defined snapshot algorithm. Using the Week 48 FAS (Table 4), the percentage of subjects meeting the primary endpoint was similar for both groups (E/C/F/TAF 96%, TDF 93%), with a difference of 2.7% (95.01% CI: -0.3% to 5.6%). Because the lower bound of the 2-sided 95.01% CI of the difference in response rate was greater than the prespecified -12% margin, switching to E/C/F/TAF was noninferior to maintaining a TDF-based regimen at Week 48.

Table 4: Virologic Outcomes at Week 48 (Week 48 Full Analysis Set)

	Number (%) of subjects	
	E/C/F/TAF N=799	TDF N=397
Virologic Success at Week 48		
HIV-1 RNA < 50 copies/mL	764 (96)	369 (93)
Virologic Failure at Week 48	9 (1)	5 (1)
HIV-1 RNA \geq 50 copies/mL	6 (1)	5 (1)
Discontinued Study Drug due to Lack of Efficacy	1 (0.1)	0
Non-study ARV Added between the First Dose Date and the Last HIV-1 RNA Collection Date during Window	2 (0.3)	0
No Virologic Data	26 (3)	23 (6)
Discontinued Study Drug Due to AE/Death	8 (1)	3 (1)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	5 (1)	15 (4)
Missing Data during Window but on Study Drug	13 (2)	5 (1)

Source: Reviewer's analysis of Applicant's dataset (ADEFF). Abbreviations: ARV = antiretroviral

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Similar trends in virologic outcomes were noted when the primary efficacy endpoint analysis was done using the M = F method (E/C/F/TAF 96%, TDF 95%), the M = E method (E/C/F/TAF 99%, TDF 99%), or Per Protocol (PP) Analysis Set (E/C/F/TAF 748/755 [99%], TDF 363/367 [99%]; difference in percentages: 0.2% [95.01% CI: -1.3% to 1.6%]).

The percentage of subjects with virologic failure at Week 48 was balanced between both treatment groups using the Week 48 FAS (E/C/F/TAF 1.1%, TDF 1.3%), as were the reasons for the virologic failure. In the E/C/F/TAF group, 3% of subjects had no virologic data at Week 48 compared with 6% of subjects in the TDF group; the difference between treatment groups was primarily driven by a lower rate of study drug discontinuation for 'other' reasons (i.e., not AE or death) in the E/C/F/TAF group (0.6%) compared with the TDF group (4%).

Secondary Endpoint (s) Analysis

HIV-1 RNA < 20 copies/mL at Week 48 (snapshot algorithm)

A high percentage of subjects in both treatment groups had virologic success defined as HIV-1 RNA < 20 copies/mL at Week 48 using the FDA-defined snapshot algorithm (E/C/F/TAF 92%, TDF 90%; difference in percentages: 1.8%, 95% CI: -1.7% to 5.3%). The percentage of subjects with HIV-1 RNA ≥ 20 copies/mL at Week 48 was 4% in each treatment group.

Change in CD4 cell count from baseline

The mean (SD) change in CD4 cell count from baseline at Week 48 was 33 (166) cells/ μL in the E/C/F/TAF group and 26 (160) cells/ μL in the TDF group for the Week 48 FAS, based on observed data (i.e., M = E). Similar trends were noted when the analysis was based on the last observation carried forward (LOCF) imputation method. The CD4 % Week 48 mean (SD) increases from baseline were 0.3% (3.8) in the E/C/F/TAF group and 0.9% (3.7) in the TDF group.

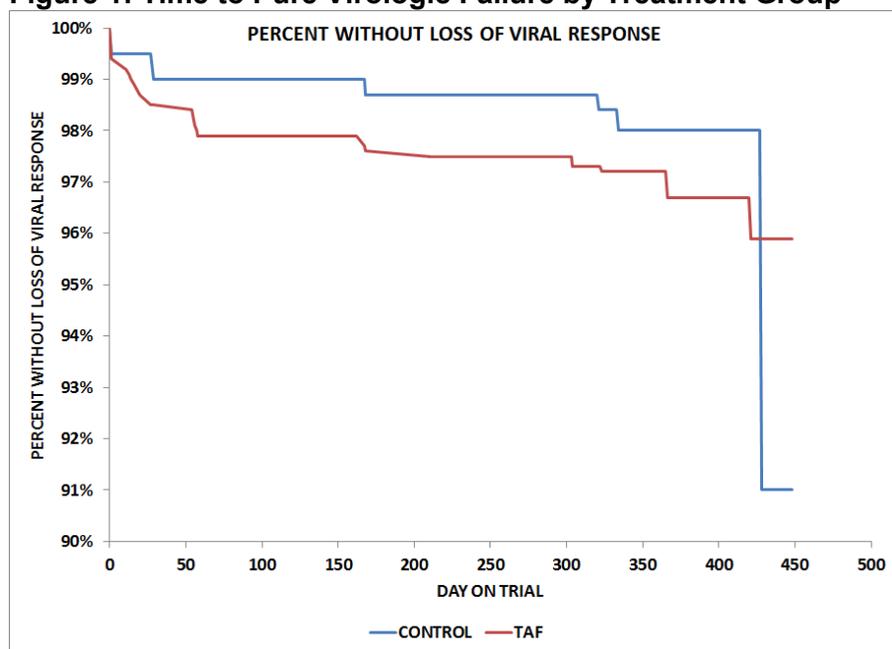
Other Endpoints

Pure Virologic Failure (PVF) Analysis

The proportions of subjects who were pure virologic responders, i.e., had not had confirmed virologic rebound (HIV-1 RNA ≥ 50 copies/mL on two consecutive visits or the last available HIV-1 RNA ≥ 50 copies/mL followed by premature discontinuation of study) by the upper limit of the Week 48 analysis window were high and similar in both treatment groups (E/C/F/TAF 776/799 [97%], TDF 389/397 [98%]).

Conversely, the proportion of subjects with pure virologic failure (PVF) by Week 48 was 3% in the E/C/F/TAF group (24/799 subjects) and 2% in the TDF group (8/397 subjects). Time to PVF was analyzed by Kaplan-Meier method by treatment group (Figure 1); subjects without observed loss of viral response were censored at their last measurement. Neither the Kaplan-Meier confidence intervals nor the log rank and Wilcoxon tests indicated a significant difference between the treatment groups.

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Figure 1: Time to Pure Virologic Failure by Treatment Group

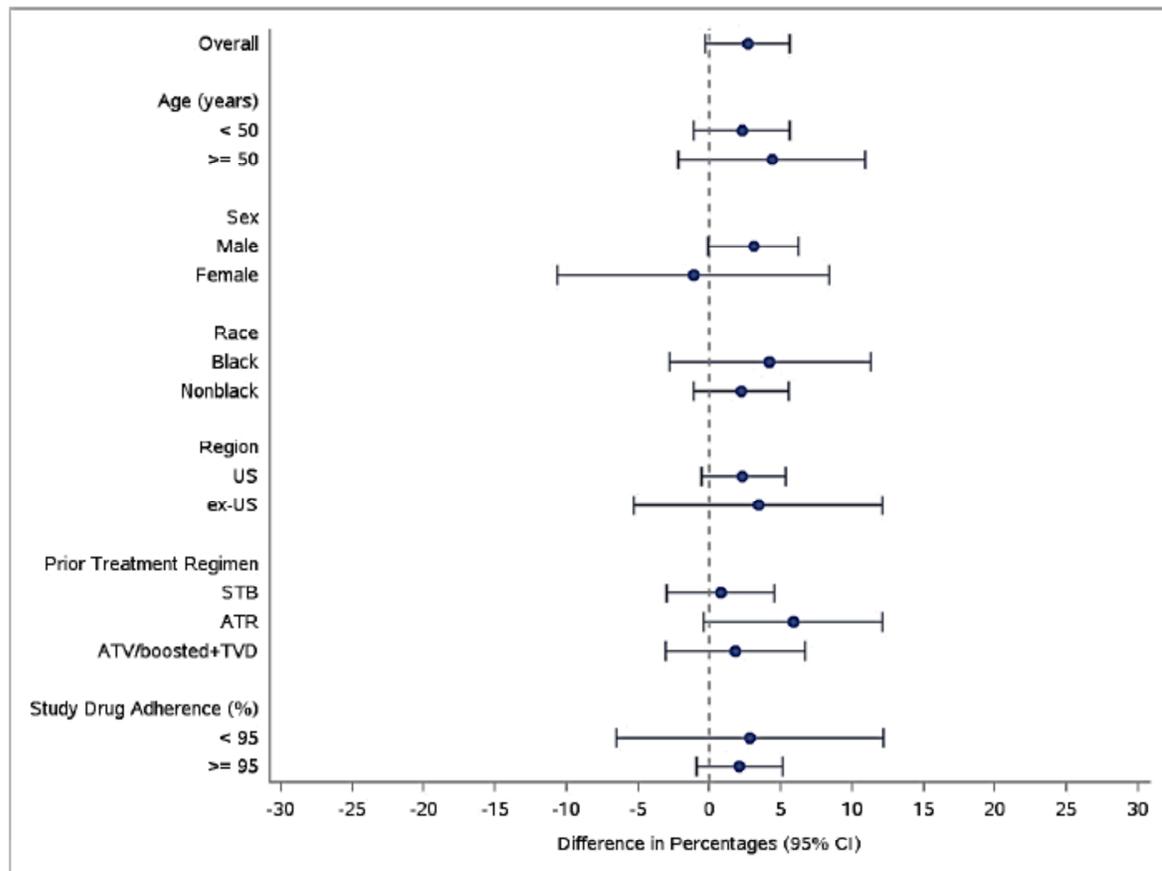
Source: FDA Statistical Review by Dr. Thomas Hammerstrom (Section 3.5)

Subpopulations

The Applicant evaluated the primary efficacy endpoint by several predefined subgroups (i.e., age, sex, race, geographic regions, prior treatment regimen, and study drug adherence). Virologic success rates at Week 48 were generally higher for the E/C/F/TAF-treated subgroups compared with TDF-treated subgroups using the Week 48 FAS; however, the 95% CIs for the differences in response rates included 0 for all subgroups (Figure 2).

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Figure 2: Forest Plot of Treatment Differences in Virologic Success at Week 48 by Subgroup (Week 48 Full Analysis Set)



NOTE: Difference in response rate and its 95% CI were calculated based on the MH proportion and normal approximation adjusted by the prior treatment regimen (except for prior treatment regimen subgroup).

NOTE: For prior treatment regimen subgroup, difference in response rate and its 95% CIs were from normal approximation.

NOTE: Relative to the vertical line at 0, differences on the right favor the E/C/F/TAF group and differences on the left favor the FTC/TDF+3rd Agent group.

Source: Study GS-US-292-0109 Week 48 Interim Clinical Study Report (Figure 9-3, page 103)

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SAFETY RESULTSOverall Exposure

The median duration of exposure to study drug was 48.0 weeks in both treatment groups (Table 5). The rate of adherence was high and similar in both groups, with a median study drug adherence rate through the Week 48 Visit of 98.8% in each.

Table 5: Duration of Exposure to Study Drug (Safety Analysis Set)

Exposure to Study Drug (weeks)	E/C/F/TAF N=959	TDF N=477
Mean (SD)	47 (10.5)	46 (11.8)
Median	48	48
Q1, Q3	42, 50	42, 50

Source: Reviewer's analysis of Applicant's dataset (ADSL)

The majority of the subjects in each treatment group received study drug for ≥ 36 weeks (E/C/F/TAF 90%; TDF 87%); however, only about half had received study drug ≥ 48 weeks (E/C/F/TAF 52%; TDF 50%).

Deaths

There were two deaths during the study, both in E/C/F/TAF group. Neither death was considered related to study drug by the investigator. Cause of death is as follows:

- Subject (b) (6): died on Day 148 of septic shock
- Subject (b) (6): died on Day 391 of stage 4 adenocarcinoma

In the 120-day Safety Update, submitted to the NDA on February 24, 2015, one additional death was reported, also in the E/C/F/TAF group. This death, in a 63-year-old black female, was also considered unrelated to study drug:

- Subject (b) (6): died on Study 391 of sudden death

Serious Adverse Events

Serious AEs (SAEs) were reported for a similar percentage of subjects in each treatment group (4%). Table 6 lists the SAEs that were reported for > 1 subject in either treatment group. Numerically, some imbalances were noted between the two groups in the incidence of certain SAEs (e.g. aseptic meningitis); however, the total number of events for any PT was too small to determine a significant risk difference. Further, the case narratives indicate that none of these SAEs was considered related to study drug. Indeed, only one SAE (not listed) was considered related to study drug: Grade 3 acute renal failure in a 48-year-old male (Subject (b) (6) in the TDF group (Atripla) that occurred on Study Day 366 and did not result in discontinuation of study drug.

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Table 6: SAEs Occurring in More Than One Subject in Any Treatment Group

MedDRA Preferred Term	E/C/F/TAF N=959	TDF N=477
Any SAE	42 (4)	21 (4)
Diarrhoea	1 (<1)	2 (<1)
Chest pain	2 (<1)	1 (<1)
Meningitis aseptic	3 (<1)	0
Pneumonia	3 (<1)	0
Anaemia	1 (<1)	1 (<1)
Abdominal pain	2 (<1)	0
Bronchitis	1 (<1)	1 (<1)
Osteomyelitis	1 (<1)	1 (<1)
Sepsis	2 (<1)	0
Sinusitis	2 (<1)	0
Hodgkin's disease	1 (<1)	1 (<1)
Headache	1 (<1)	1 (<1)

Source: Reviewer's analysis of Applicant's dataset (ADAE)

Discontinuations

The percentage of subjects who discontinued study drug due to AEs was low in each group (E/C/F/TAF 1%; TDF 2%). By PT, no AE that led to study drug discontinuation was reported for more than 1 subject in the E/C/F/TAF group (Table 7). In the TDF group, three subjects, all of whom were taking ATV/boosted+TVD regimens, had jaundice that led to study drug discontinuation. When the AEs were analyzed by SOC, no notable differences, other than jaundice, were noted between the two groups. Most of the AEs leading to discontinuation were nonserious and considered by the investigator as related to study drug.

Table 7: TEAEs Leading to Study Drug Discontinuation

MedDRA System Organ Class and Preferred Term	E/C/F/TAF N=959	TDF N=477
Any AE leading to study drug discontinuation	9 (1)	7 (2)
Psychiatric disorders	4 (<1)	2 (<1)
Depression	1 (<1)	1 (<1)
Abnormal dreams	0	2 (<1)
Apathy	1 (<1)	0
Insomnia	0	1 (<1)
Nightmare	0	1 (<1)
Panic attack	1 (<1)	0
Suicide attempt	1 (<1)	0
Hepatobiliary disorders	0	3 (1)
Jaundice	0	3 (1)
Investigations	1 (<1)	1 (<1)
Blood creatinine increased	1 (<1)	1 (<1)
Renal and urinary disorders	2 (<1)	1 (<1)
Fanconi syndrome acquired	0	1 (<1)
Renal failure acute	1 (<1)	0
Tubulointerstitial nephritis	1 (<1)	0

Gastrointestinal disorders	1 (<1)	0
Nausea	1 (<1)	0
Vomiting	1 (<1)	0
General disorders and administration site conditions	1 (<1)	0
Local swelling	1 (<1)	0
Infections and infestations	1 (<1)	0
Reiter's syndrome	1 (<1)	0
Nervous system disorders	3 (<1)	1 (<1)
Amnesia	1 (<1)	0
Disturbance in attention	1 (<1)	0
Headache	1 (<1)	0
Memory impairment	0	1 (<1)
Speech disorder	1 (<1)	0

Source: Reviewer's analysis of Applicant's dataset (ADAE)

Significant Adverse Events

The percentage of subjects reporting Grade 3 and 4 AEs was similar between the two groups (E/C/F/TAF 6%; TDF 7%). As shown in Table 8, no AE by PT was reported in more than 1% of subjects in either treatment group. No discernable differences were noted between the groups in the types of severe AEs reported.

Table 8: Grade 3-4 TEAEs Occurring in More than One Subject in Any Treatment Group

MedDRA System Organ Class and Preferred Term	E/C/F/TAF N=959	TDF N=477
Any Grade 3-4 AE	61 (6)	32 (7)
Nervous system disorders	7 (1)	5 (1)
Headache	2 (<1)	2 (<1)
Migraine	1 (<1)	1 (<1)
Gastrointestinal disorders	8 (1)	4 (1)
Abdominal pain	2 (<1)	1 (<1)
Diarrhoea	2 (<1)	1 (<1)
Vomiting	1 (<1)	1 (<1)
General disorders and administration site conditions	2 (<1)	2 (<1)
Pyrexia	2 (<1)	1 (<1)
Hepatobiliary disorders	3 (<1)	2 (<1)
Hyperbilirubinaemia	2 (<1)	1 (<1)
Infections and infestations	19 (2)	9 (2)
Meningitis aseptic	3 (<1)	0
Pneumonia	2 (<1)	1 (<1)
Gastroenteritis	2 (<1)	0
Osteomyelitis	1 (<1)	1 (<1)
Sepsis	2 (<1)	0
Investigations	5 (1)	4 (1)
Blood creatine phosphokinase increased	2 (<1)	1 (<1)
Renal and urinary disorders	2 (<1)	2 (<1)
Renal failure acute	1 (<1)	1 (<1)
Psychiatric disorders	7 (1)	2 (<1)
Depression	2 (<1)	1 (<1)

Blood and lymphatic system disorders	3 (<1)	1 (<1)
Anaemia	1 (<1)	1 (<1)
Ear and labyrinth disorders	1 (<1)	1 (<1)
Vertigo	1 (<1)	1 (<1)
Immune system disorders	2 (<1)	0
Seasonal allergy	2 (<1)	0
Musculoskeletal and connective tissue disorders	5 (1)	4 (1)
Intervertebral disc protrusion	1 (<1)	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (<1)	1 (<1)
Hodgkin's disease	1 (<1)	1 (<1)

Source: Reviewer's analysis of Applicant's dataset (ADAE)

When causality was considered in the safety evaluation, the percentage of subjects reporting adverse drug reactions (ADRs) was greater in the E/C/F/TAF group (19%) compared with the TDF group (13%), likely reflecting the trial's open-label, switch-study design. This imbalance was most prominent for gastrointestinal disorders (Table 9), but was also apparent for psychiatric and nervous system disorders. However, as noted above, the rate of discontinuations due to AEs was low in both treatment arms.

Table 9: Treatment-emergent ADRs Occurring in ≥ 1% of Subjects in Any Treatment Group

MedDRA System Organ Class and Preferred Term	Number of Subjects (%)	
	E/C/F/TAF N=959	TDF N=477
Any ADR	185 (19)	61 (13)
Gastrointestinal disorders	74 (8)	11 (2)
Diarrhoea	24 (3)	6 (1)
Nausea	21 (2)	2 (<1)
Flatulence	18 (2)	1 (<1)
Psychiatric disorders	38 (4)	9 (2)
Abnormal dreams	12 (1)	7 (2)
Insomnia	10 (1)	6 (1)
Nervous system disorders	44 (5)	8 (2)
Headache	17 (2)	0
Dizziness	11 (1)	6 (1)
Musculoskeletal and connective tissue disorders	19 (2)	9 (2)
Osteopenia	8 (1)	6 (1)
Hepatobiliary disorders	1 (<1)	11 (2)
Jaundice	0	9 (2)
Eye disorders	2 (<1)	5 (1)
Ocular icterus	0	5 (1)

Source: Reviewer's analysis of Applicant's dataset (ADAE)

Submission Specific Safety Concerns

Based on nonclinical and preliminary findings from the current NDA review, the following safety issues were examined in greater detail in the review of Study 109.

❖ *Dental*

While there was an overall imbalance between the E/C/F/TAF and TDF groups with respect to the proportion of subjects with dental and gingival TEAEs (4% vs. 2%, respectively), most of these events were mild. When Grade 3 and 4 AEs were reviewed, no differences were noted between the two groups (Table 10).

Table 10: Dental TEAEs Grade 2 or Higher

MedDRA High Level Term and Preferred Term	Number of Subjects (%)	
	E/C/F/TAF N=959	TDF N=477
Any AE	34 (4)	11 (2)
Any AE Grade 2 or higher	13 (1)	4 (0.8)
HLT: Dental and oral soft tissue infections	6 (0.6)	1 (0.2)
Tooth abscess	2 (0.2)	0
Tooth infection	1 (0.1)	1 (0.2)
Gingivitis	1 (0.1)	0
Periodontitis	1 (0.1)	0
Pulpitis dental	1 (0.1)	0
HLT: Dental pain and sensation disorders	5 (0.5)	1 (0.2)
Toothache	5 (0.5)	1 (0.2)
HLT: Dental and periodontal infections and inflammations	1 (0.1)	0
Dental caries	1 (0.1)	0
HLT: Dental and gingival therapeutic procedures	0	1 (0.2)
Tooth extraction	0	1 (0.2)
HLT: Gingival disorders NEC	0	1 (0.2)
Gingival hypertrophy	0	1 (0.2)
HLT: Site specific injuries NEC	3 (0.3)	0
Tooth fracture	3 (0.3)	0

Source: Reviewer's analysis of Applicant's dataset (ADAE). Abbreviations: HLT= High Level Term; PT = Preferred Term

❖ *Musculoskeletal*

There was a numerical imbalance between the treatment groups in the proportion of subjects reporting musculoskeletal and connective tissue disorders (E/C/F/TAF 27%, TDF 23%). Arthralgias and myalgias, of any severity, were the predominant PTs that occurred with greater frequency in the E/C/F/TAF group compared with the TDF group (5% vs. 3% for arthralgia and 2% vs. 1% for myalgia, respectively). The majority of these events were mild.

With respect to more severe events, 124 subjects experienced 158 Grade 2-4 musculoskeletal TEAEs (E/C/F/TAF 83 [7%]; TDF 41 [9%]). The vast majority of these were not considered to be related to study drug by the investigators. TEAEs that were considered related to study drug occurred predominantly in the E/C/F/TAF arm, and included musculoskeletal pain (E/C/F/TAF 1,

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TDF 0); musculoskeletal stiffness (E/C/F/TAF 1, TDF 0); osteopenia E/C/F/TAF 3, TDF 0); osteoporosis (E/C/F/TAF 1, TDF 1); and pain in extremity (E/C/F/TAF 1, TDF 0). Four subjects, all in the E/C/F/TAF group, had five Grade ≥ 2 SAEs, none of which were considered related to study drug, and most of which were related to trauma.

❖ Ocular

Adverse events in the Eye Disorders SOC were reported at similar rates in the two treatment groups (E/C/F/TAF 53 [6%], TDF 22 [5%]). The only PT reported by $\geq 1\%$ of subjects in any treatment group was 'vision blurred', which occurred almost exclusively in the E/C/F/TAF group, and 'ocular icterus' and 'vitreous floaters', which occurred predominantly in the TDF group (Table 11).

Table 11: Eye Disorder TEAEs

MedDRA Preferred Term	Number (%) of Subjects	
	E/C/F/TAF N=959	TDF N=477
Any AE	53 (6)	22 (5)
<i>Possible uveitis symptoms *</i>	18 (2)	4 (1)
Vision blurred	10 (1)	1 (0.2)
Visual impairment	3 (0.3)	0
Visual acuity reduced	2 (0.2)	0
Panophthalmitis	1 (0.1)	0
Photophobia	1 (0.1)	0
Blindness	1 (0.1)	0
Vitreous floaters	1 (0.1)	3 (1)
Eye irritation	4 (0.4)	1 (0.2)
Blepharospasm	3 (0.3)	1 (0.2)
Cataract	3 (0.3)	0
Conjunctival haemorrhage	2 (0.2)	2 (0.4)
Conjunctivitis allergic	2 (0.2)	1 (0.2)
Ocular discomfort	2 (0.2)	0
Chalazion	2 (0.2)	0
Eye discharge	2 (0.2)	0
Eye allergy	1 (0.1)	0
Diplopia	1 (0.1)	0
Dacryostenosis acquired	1 (0.1)	1 (0.2)
Eye pain	1 (0.1)	0
Eye pruritus	1 (0.1)	0
Eyelid oedema	1 (0.1)	0
Corneal scar	1 (0.1)	0
Lacrimation increased	1 (0.1)	0
Mydriasis	1 (0.1)	0
Arcus lipoides	1 (0.1)	0
Ocular hyperaemia	1 (0.1)	1 (0.2)
Ocular icterus	1 (0.1)	7 (1.5)
Pigment dispersion syndrome	1 (0.1)	0

Presbyopia	1 (0.1)	0
Pterygium	1 (0.1)	0
Retinal detachment	1 (0.1)	0
Scleral hyperaemia	1 (0.1)	0
Ulcerative keratitis	1 (0.1)	0
Blepharitis	1 (0.1)	0
Glare	1 (0.1)	0
Keratitis	0	1 (0.2)
Macular hole	0	1 (0.2)
Myopia	0	1 (0.2)
Optic disc disorder	0	1 (0.2)
Astigmatism	0	1 (0.2)

* Selected PTs that may represent symptoms of uveitis

Source: Reviewer's analysis of Applicant's dataset (ADAE)

Nearly all ocular TEAEs were nonserious, most were considered unrelated to study drug by the investigators, and none resulted in discontinuation of study drugs. Only one subject (Subject (b) (6) in the E/C/F/TAF group) reported a serious ocular AE. This was a 59-year-old man who developed Grade 3 retinal detachment on Study Day 167 that was not considered related to study drug by the investigator, but age-related by the retinologist. The subject underwent cryotherapy procedure to repair the torn retina on Study Day 168 and the event was considered recovered that same day.

Seven subjects (E/C/F/TAF 2; TDF 5) had ocular AEs that were considered related to study drug. In the TDF group, all events were related to ocular icterus in subjects taking ATV. In the E/C/F/TAF group, two subjects had three AEs considered related to study drug: 'vision blurred' (2 subjects) and 'visual acuity reduced' (1 subject). All of these events were mild and ongoing at the time of the database lock.

There were no reports of uveitis during the study. Using the selected pre-specified PTs, 22 subjects (E/C/F/TAF 18 [2%]; TDF 4 [0.8%]) were identified with nonspecific TEAEs that could represent symptoms of uveitis (the identified AEs are highlighted in Table 6). All of these AEs were Grade 1 or 2 and, aside from the aforementioned three AEs in the E/C/F/TAF group, none were considered related to study drug. Most of these events were still ongoing at the time of the database lock. The one event of 'blindness' reported in the E/C/F/TAF group was in a 30-year-old man with a history of nearsightedness since childhood, who underwent laser eye surgery two years prior to study enrollment and reported "worsening of vision loss" (verbatim) on Week 2 (Study Day 16).

In the ophthalmologic substudy (n=47), no subjects had fundoscopic findings consistent with uveitis; the central readings from the substudy are summarized in Table 12. Four subjects in the E/C/F/TAF group had a shift in central fundoscopic assessment from abnormal at baseline to normal during study. However, one subject in the E/C/F/TAF group (Subject (b) (6)) had a shift from normal at baseline (local and central reading) to abnormal at Week 24 (local and central reading) due to detection of a new retinal hemorrhage in the left eye.

Table 12: Ophthalmic Substudy - Central Readings

	E/C/F/TAF		TDF			
	N	Normal	Abnormal	N	Normal	Abnormal

Baseline	N=32	25	7	N=15	13	2
Week 24	N=31	26	5	N=15	13	2
Week 48	N=18	14	4	N=7	5	2
Normal → Abnormal	1			0		

Source: Reviewer's analysis of Applicant's dataset (ADOPTH)

❖ Neuropsychiatric

The incidence of neuropsychiatric events based on selected High Level Group Terms (HLGT) and Preferred Terms is shown in Table 13. All events in the Psychiatric Disorders and Nervous System Disorder SOCs are listed; in addition, selected PTs from other SOCs are included that may be relevant to ATR use (e.g. 'feeling drunk', 'hangover', and 'vertigo').

Overall, there were no major differences ($\geq 1\%$ risk difference) between the two treatment groups with respect to most terms, with the exception of headache (HLGT and PT) and 'Neurological disorders NEC' (HLGT only), which occurred more frequently in the E/C/F/TAF group, and the HLGTs of 'Anxiety disorders and symptoms' and 'Depressed mood disorders and disturbances', which occurred more frequently in the TDF group. In the latter, with the exception of 'depression', the differences between the two groups did not exceed 1% at the PT level. Similar findings were noted when the analysis excluded subjects receiving STB (EVG) as the lead-in regimen (except there were no notable differences in the rates of depression).

Most neuropsychiatric AEs were not serious, nor were they considered related to study drug or led to study drug discontinuation. Serious AEs in the E/C/F/TAF group were reported in three subjects: convulsion (1 subject), hallucination (1 subject), and major depression (1 subject). In the TDF group, two subjects had SAEs of depression (1 subject) and substance use (1 subject). None of these SAEs was considered study drug-related by the investigators and none led to study drug discontinuation.

Six subjects (3 from each treatment group) discontinued study drug due to 10 nonserious neuropsychiatric TEAEs. None of these AEs occurred in > 1 subject in any group, except for depression which occurred in one subject in each group. In the E/C/F/TAF arm, the AEs by PT that led to study drug discontinuation were amnesia, apathy, depression, and disturbance in attention, and in the TDF arm, these were abnormal dreams, insomnia, depression, memory impairment, and nightmare. All of these AEs were considered related to study drug by the investigators, but only 4 events had resolved by the time of the database lock (the two events of depression, the 1 event of disturbance in attention in the E/C/F/TAF group, and the 1 event of abnormal dreams in the TDF [ATR] group).

In sum, other than the potential risk of headache, which is not unexpected with a new antiretroviral regimen based on previous trials, switching from a TDF-based regimen to E/C/F/TAF was not associated with a greater risk of neuropsychiatric events, however the risks were not significantly lessened either.

Table 13: Neuropsychiatric TEAEs Based on Selected HLGTs and PTs

MedDRA System Organ Class, High Level Group Term, and Preferred Term	Number (%) of Subjects	
	E/C/F/TAF N=959	TDF (n=477)

Psychiatric disorders SOC	127 (13)	67 (14)
HLGT: Sleep disorders and disturbances	68 (7)	31 (7)
Insomnia	41 (4)	23 (5)
Initial insomnia	1 (0.1)	0
Abnormal dreams	21 (2)	10 (2)
Nightmare	5 (1)	1 (0.2)
Somnambulism	1 (0.1)	0
Sleep disorder	6 (0.6)	1 (0.2)
HLGT: Depressed mood disorders and disturbances	26 (3)	23 (5)
Depression	24 (3)	19 (4)
Depressed mood	1 (0.1)	2 (0.4)
Dysthymic disorder	1 (0.1)	0
Major depression	1 (0.1)	2 (0.4)
HLGT: Sexual dysfunctions, disturbances and gender identity disorders	10 (1)	1 (0.2)
Libido decreased	8 (1)	1 (0.2)
Loss of libido	2 (0.2)	0
HGLT: Anxiety disorders and symptoms	21 (2)	13 (3)
Anxiety disorder	2 (0.2)	1 (0.2)
Generalised anxiety disorder	0	1 (0.2)
Agitation	2 (0.2)	0
Anxiety	20 (2)	11 (2)
Stress	1 (0.1)	3 (1)
Panic attack	3 (0.3)	5 (1)
Acute stress disorder	1 (0.1)	0
HLGT: Mood disorders and disturbances NEC	6 (1)	1 (0.2)
Mood swings	5 (1)	1 (0.2)
Apathy	1 (0.1)	0
HLGT: Disturbances in thinking and perception	2 (0.2)	2
Hallucination	1 (0.1)	0
Illusion	1 (0.1)	0
HLGT: Psychiatric disorders NEC	3 (0.3)	3 (1)
Alcohol abuse	2 (0.2)	0
Drug abuse	1 (0.1)	0
Substance abuse	0	3 (1)
HLGT: Adjustment disorders (incl subtypes)	2 (0.2)	0
Adjustment disorder	2 (0.2)	0
HLGT: Cognitive and attention disorders and disturbances	1 (0.1)	2 (0.4)
Attention deficit/hyperactivity disorder	1 (0.1)	2 (0.4)
HLGT: Deliria (incl confusion)	1 (0.1)	0
Confusional state	1 (0.1)	0
HLGT: Manic and bipolar mood disorders and disturbances	1 (0.1)	1 (0.2)
Bipolar disorder	0	1 (0.2)
Bipolar I disorder	1 (0.1)	0
HLGT: Personality disorders and disturbances in behaviour	1 (0.1)	0
Aggression	1 (0.1)	0
HLGT: Suicidal and self-injurious behaviours NEC	1 (0.1)	1 (0.2)
Suicidal ideation	0	1 (0.2)
Suicide attempt	1 (0.1)	0
Nervous system disorders SOC	159 (17)	50 (11)
HGLT: Headaches	71 (7)	17 (4)

HLGT: Neurological disorders NEC	67 (7)	29 (6)
Dizziness	30 (3)	14 (3)
Presyncope	1 (0.1)	0
Ataxia	1 (0.1)	0
Somnolence	13 (1)	7 (2)
Lethargy	2 (0.2)	2 (0.4)
Syncope	1 (0.1)	0
Loss of consciousness	0	1 (0.2)
Hypoaesthesia	13 (1)	5 (1)
Paraesthesia	5 (1)	6 (1)
Dysaesthesia	1 (0.1)	0
Hyperaesthesia	0	2 (0.4)
Restless legs syndrome	2 (0.2)	0
Dysgeusia	1 (0.1)	0
Speech disorder	2 (0.2)	0
HLGT: Mental impairment disorders	16 (2)	12 (3)
Disturbance in attention	14 (2)	9 (2)
Amnesia	2 (0.2)	0
Memory impairment	0	3 (1)
HLGT: Seizures (incl subtypes)	3 (0.3)	0
Convulsion	3 (0.3)	0
HLGT: Sleep disturbances (incl subtypes)	1 (0.1)	0
Circadian rhythm sleep disorder	1 (0.1)	0
General disorders and administration site conditions SOC	107 (11)	53 (11)
HLGT: General system disorders NEC	75 (8)	38 (8)
Fatigue	29 (3)	12 (3)
Malaise	2 (0.2)	1 (0.2)
Asthenia	1 (0.1)	1 (0.2)
Feeling drunk	1 (0.1)	0
Hangover	1 (0.1)	0
Gait disturbance	1 (0.1)	0
Ear and labyrinth disorders SOC	17 (2)	10 (2)
HLGT: Inner ear and VIIIth cranial nerve disorders	7 (1)	7 (2)
Vertigo	4 (0.4)	5 (1)
Vertigo positional	0	2 (0.4)
Injury, poisoning and procedural complications SOC	103 (11)	52 (11)
Fall	1 (0.1)	0

Source: Reviewer's analysis of Applicant's dataset (ADAE). Abbreviations: HLGT = High Level Group Term

In the 120-day Safety Update, three additional suicide attempts were reported in the E/C/F/TAF group. As of the data cutoff date for the safety update, the cumulative incidence of suicide attempt (all SAEs) was 0.4% (4 subjects) in the E/C/F/TAF group and 0% in the TDF group. None of these new SAEs were considered related to study drug.

Efavirenz-Related Symptoms

To evaluate whether switching from ATR to E/C/F/TAF resulted in improvement of specific EFV-related symptoms (i.e., dizziness, trouble sleeping, impaired concentration, sleepiness, and abnormal or vivid dreams), questionnaires were administered at baseline and at every post-baseline

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visit in subjects receiving ATR as their lead-in regimen. Each individual symptom was scored using a 0-4 scale and composite scores for all five symptoms were calculated at each visit. At baseline, the two treatment groups had comparable scores for individual symptoms and for the composite score.

Reviewer Comment:

The EFV-related symptom questionnaire used here is not a validated tool but appears to have been used by the Applicant in other antiretroviral switch studies involving ATR. It should be noted that the questionnaires were not administered to subjects taking other TDF-based regimens, thus it is not known if these symptoms are truly EFV-related.

Table 14 shows the change from baseline in the composite scores at selected 3-month intervals. At each visit, the mean change in the composite score from baseline was greater in the group that switched to E/C/F/TAF than in the group that remained on ATR therapy.

Table 14: Change in Composite Efavirenz-Related Score from Baseline

	Efavirenz-Related Symptom Composite Score					
	E/C/F/TAF			ATR		
	N	Median (Q1, Q3)	Mean (SD)	N	Median (Q1, Q3)	Mean (SD)
Baseline	239	1 (0, 4)	2.62 (3.2)	116	1 (0, 4)	2.23 (2.66)
Change from Baseline at Week 12	218	-1 (-3.25, 0)	-1.8 (3.23)	111	0 (-2, 0)	-0.5 (2.21)
Change from Baseline at Week 24	226	0 (-3, 0)	-1.5 (3.03)	106	0 (-1.25, 0)	-0.4 (2.26)
Change from Baseline at Week 36	224	0 (-3, 0)	-1.6 (2.95)	102	0 (-2, 0)	-0.4 (2.16)
Change from Baseline at Week 48	210	0 (-3, 0)	-1.6 (3.06)	96	0 (-1, 0.75)	-0.1 (2.43)

Source: Reviewer's analysis of Applicant's dataset ((ADQS))

Similarly, when individual symptom scores were analyzed at Weeks 24 and 48, the E/C/F/TAF group consistently had greater mean changes from baseline for each symptom score than the ATR group. Furthermore, for each parameter except for somnolence, the E/C/F/TAF group had a higher proportion of subjects reporting 0 score (no symptom) at each visit. The shift from baseline in the percentage of subjects reporting 0 score was greatest for the symptoms of 'abnormal or vivid dreams' and 'dizziness' in the E/C/F/TAF group, although improvement was observed in all parameters. In contrast, differences from baseline were minimal in the ATR group at each visit, except for somnolence where similar improvement was noted in both arms.

❖ Renal Safety

A total of 77 subjects (E/C/F/TAF 54 [6%], TDF 23 [5%]) reported 90 TEAEs in the Renal and Urinary Disorders SOC (Table 15). No TEAE by PT occurred in >1 % of subjects in either treatment

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group, with no major differences in incidence rates noted between the two groups.

Table 15: Renal SOC TEAEs

MedDRA Preferred Term	Number (%) of Subjects	
	E/C/F/TAF N=959	TDF N=477
Any AE	54 (6)	23 (5)
Proteinuria	13 (1)	6 (1)
Dysuria	11 (1)	3 (1)
Pollakiuria	8 (1)	2 (0.4)
Nephrolithiasis	4 (0.4)	3 (1)
Nocturia	4 (0.4)	0
Micturition urgency	3 (0.3)	1 (0.2)
Urinary retention	2 (0.2)	0
Chromaturia	2 (0.2)	1 (0.2)
Pyuria	2 (0.2)	1 (0.2)
Micturition frequency decreased	1 (0.1)	0
Polyuria	1 (0.1)	0
Leukocyturia	1 (0.1)	1 (0.2)
Haematuria	1 (0.1)	1 (0.2)
Renal failure acute	1 (0.1)	1 (0.2)
Renal failure chronic	1 (0.1)	1 (0.2)
Renal mass	1 (0.1)	0
Stress urinary incontinence	1 (0.1)	0
Tubulointerstitial nephritis	1 (0.1)	0
Urethral discharge	1 (0.1)	1 (0.2)
Urinary incontinence	1 (0.1)	1 (0.2)
Cystitis noninfective	1 (0.1)	0
Glycosuria	0	1 (0.2)
Renal cyst	0	1 (0.2)
Urethritis noninfective	0	1 (0.2)
Fanconi syndrome acquired	0	1 (0.2)

Source: Reviewer's analysis of Applicant's dataset (ADAE)

The majority of renal AEs were mild or moderate and all were nonserious except for the SAE of Grade 3 acute renal failure in an Atripla-treated subject (Subject (b) (6) discussed in Section 7.3.2. Other severe cases (Grade > 2) included:

- a Grade 3 nonserious event of acute renal failure in an E/C/F/TAF subject (Subject (b) (6)) that was not considered related to study drug but which did lead to study discontinuation (the subject had intercurrent Hodgkin's lymphoma and the renal failure was attributed to pre-existing cardiac disease with a low ejection fraction)
- A Grade 3 nonserious event of urinary incontinence in a subject in the E/C/F/TAF group that was not considered study drug-related and did not require any action with respect to study drug

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- A Grade 3 nonserious event of Fanconi syndrome in a 57-year-old male subject in the TDF group (Subject (b) (6)) that led to study drug discontinuation (ATV/co + TVD) on Study Day 305.

In addition, there was a Grade 1 event of tubulointerstitial nephritis in an E/C/F/TAF subject (Subject (b) (6)) that led to study drug discontinuation; this subject also had intercurrent Hodgkin's lymphoma and syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Serum Creatinine

The change from baseline in serum creatinine at Week 48 was one of the four prespecified key safety endpoints. Baseline values and the change from baseline in serum creatinine at Week 48 for the Safety Analysis Set were summarized by prior treatment regimen using descriptive statistics. Due to the COBI effect of E/C/F/TAF, subjects who took ATR as their prior treatment regimen were analyzed separately.

As shown in Table 16 and Figures 3-5, the mean changes from baseline in serum creatinine were negligible or negative at Weeks 24 and 48 in the group of subjects who switched from STB or boosted-ATV to E/C/F/TAF compared to those who remained on their previous TDF-based regimen, where changes from baseline were minimal. In subjects who switched from ATR to E/C/F/TAF, there was a mean increase in serum creatinine of 0.10 and 0.11 mg/dL at Weeks 24 and 48, respectively, owing to the introduction of COBI.

Table 16: Mean Serum Creatinine (mg/dL) by Treatment Week and Lead-in Regimen

	N	Mean Value (SD)	Mean Change from Baseline (SD)	N	Mean Value (SD)	Mean Change from Baseline (SD)
	E/C/F/TAF			STB		
Baseline	306	1.07 (0.188)	--	153	1.09 (0.196)	--
Week 24	303	1.05 (0.179)	- 0.02 (0.112)	151	1.12 (0.216)	0.02 (0.111)
Week 48	266	1.07 (0.180)	- 0.02 (0.111)	132	1.13 (0.194)	0.03 (0.110)
	E/C/F/TAF			ATV/boosted + FTC/TDF		
Baseline	402	1.02 (0.196)	--	199	1.02 (0.188)	--
Week 24	384	1.03 (0.184)	0.01 (0.114)	184	1.05 (0.211)	0.02 (0.109)
Week 48	279	1.05 (0.197)	0.00 (0.121)	134	1.10 (0.231)	0.05 (0.134)
	E/C/F/TAF			ATR		
Baseline	251	0.95 (0.171)	--	125	0.95 (0.150)	--
Week 24	244	1.06 (0.176)	0.10 (0.107)	121	0.96 (0.163)	0.01 (0.087)
Week 48	229	1.06 (0.189)	0.11 (0.124)	106	0.97 (0.163)	0.02 (0.088)

Source: Reviewer's analysis of Applicant's dataset (ADLB)

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Figure 3: Mean Change from Baseline in Serum Creatinine (mg/dL) - Lead-in: STB

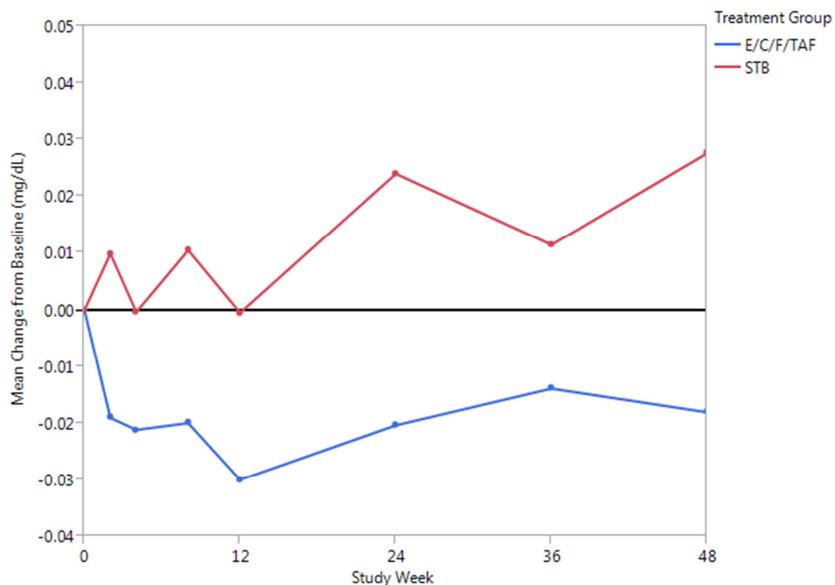
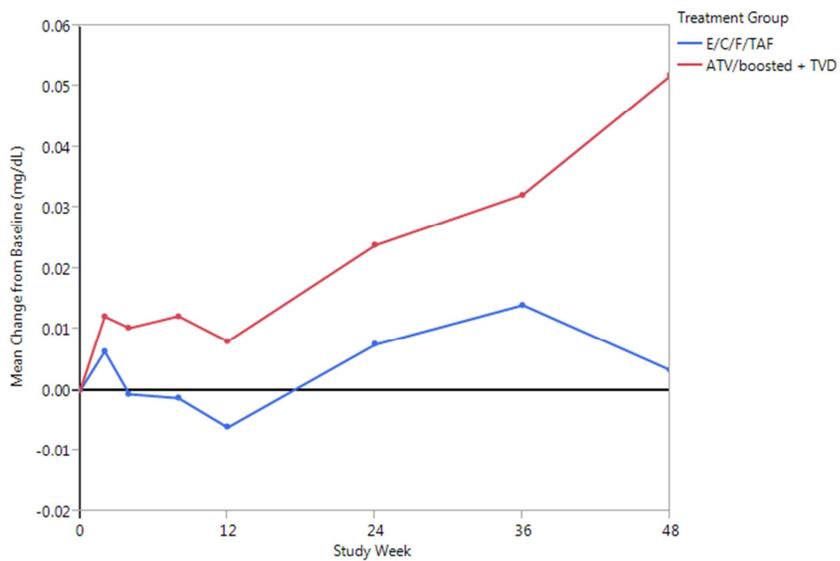
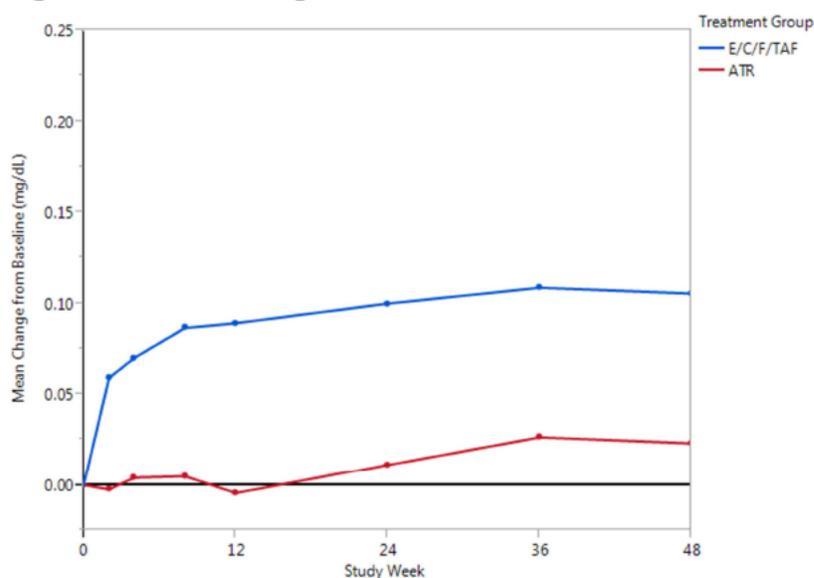


Figure 4: Mean Change from Baseline in Serum Creatinine (mg/dL) - Lead-In: ATV/boosted + FTC/TDF



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Figure 5: Mean Change from Baseline in Serum Creatinine (mg/dL) - Lead-In: ATR

Estimated Glomerular Filtration Rate

Baseline values and change from baseline in eGFR were estimated and compared between the two treatment groups, excluding subjects who took ATR as their prior treatment. Median (Q1, Q3) changes from baseline in eGFR_{CG} and eGFR_{CKD-EPI}, creatinine over time are listed in Table 17. At each 6-month visit the change from baseline in eGFR showed improvement or minimal change in the E/C/F/TAF group compared with progressive decreases in the TDF group, regardless of the eGFR formula used.

Table 17: Median Change in Estimated Creatinine Clearance (Excluding ATR subjects) by Treatment Week

	E/C/F/TAF		TDF			
Estimated Creatinine Clearance – Cockcroft-Gault						
	N	Median (Q1, Q3)		N	Median (Q1, Q3)	
		Analysis Value	Δ from Baseline		Analysis Value	Δ from Baseline
Baseline	708	103.8 (87.6, 121)	--	352	102.4 (84.3, 121.7)	--
Week 24	687	105.5 (89, 122.8)	1.2 (-6, 9)	335	101.3 (82.4, 119.4)	-2.5 (-8.5, 5.4)
Week 48	545	104 (89.5, 123.4)	1.8 (-6.6, 9.7)	265	98 (80.6, 120.9)	-3.7 (-11.2, 3.65)
Estimated Creatinine Clearance – CKD-EPI, creatinine						
	N	Median (Q1, Q3)		N	Median (Q1, Q3)	
		Analysis Value	Δ from Baseline		Analysis Value	Δ from Baseline
Baseline	708	89.8 (76.6, 103.7)	--	352	89.8 (77.1, 100.7)	--

Week 24	687	90.7 (76.7, 101.7)	0 (-6.24, 6.1)	335	88 (75.4, 101.4)	-2.49 (-7.17, 3.65)
Week 48	545	88.6 (76.5, 100.6)	-0.26 (-6.4, 6.7)	266	84.9 (71.1, 96.7)	-3.48 (-9.0, 2.41)

Source: Reviewer's analysis of Applicant's dataset (ADLB)

Proteinuria

The majority of subjects in both treatment groups had no proteinuria (Grade 0 by dipstick) at baseline and through Week 48. Furthermore, there was no difference between the two groups in the incidence of treatment-emergent proteinuria by maximum toxicity grade (E/C/F/TAF 25%; TDF 28% - see Table 24). However, a shift table by baseline toxicity grade showed a difference in the distribution of graded proteinuria at Weeks 24 and 48 (Table 18). Based on the number of subjects with baseline and Week 48 data, a slightly higher percentage of subjects in the E/C/F/TAF group (55/772 [7.1%]) had improvement in baseline proteinuria compared with the TDF group (21/372 [5.6%]). Conversely, a lower percentage of subjects in the E/C/F/TAF group than in the TDF group had worsening proteinuria at Week 48 compared to baseline (4% vs. 7%).

Proteinuria as a TEAE was reported by a similar percentage of subjects (1%) in each group (see Table 15).

Table 18: Shift Table of Proteinuria (Dipstick) by Baseline Toxicity Grade

	Toxicity Grade	Number (%) of Subjects					
		E/C/F/TAF			TDF		
		Baseline Proteinuria Grade			Baseline Proteinuria Grade		
		Grade 0 N=873	Grade 1 N=81	Grade 2 N=4	Grade 0 N=430	Grade 1 N=44	Grade 2 N=3
Week 24	Grade 0	797 (91)	58 (72)	2 (50)	373 (87)	32 (73)	1 (33)
	Grade 1	46 (5)	14 (17)	2 (50)	34 (8)	9 (21)	2 (67)
	Grade 2	2 (0.2)	3 (4)	0	4 (1)	1 (2)	0
Week 48	Grade 0	675 (77)	52 (64)	1 (25)	314 (73)	18 (41)	2 (67)
	Grade 1	30 (3)	9 (11)	2 (50)	26 (6)	12 (27)	1 (33)
	Grade 2	1 (0.1)	2 (3)	0	0	0	0

Source: Reviewer's analysis of Applicant's dataset (ADLB)

Other Renal Biomarkers

Assessments of other renal biomarkers, such as measures of quantitative proteinuria (UPCR, UACR), urine retinol binding protein (RBP) to creatinine ratio, and beta-2-microglobulin to creatinine ratio also demonstrated decreases from baseline in the E/C/F/TAF group at Week 48 compared with increases in the TDF group. On the other hand, measures of renal phosphate handling did not show significant change after subjects switched to E/C/F/TAF. The magnitude of the decrease from baseline in TmP/GFR at Week 48 was comparable in both treatment groups, excluding subjects previously on ATR (median change from baseline -0.1 mg/dL for both groups). There was minimal change from baseline in FEPO4 at Week 48 in the E/C/F/TAF compared with an increase from baseline the TDF group, also excluding subjects previously on ATR (median change from baseline at Week 48: E/C/F/TAF 0.1%, TDF 0.7%).

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Proximal Renal Tubulopathy

To identify potential subclinical cases of proximal renal tubulopathy (PRT), the Applicant employed similar thresholds for creatinine and tubular dysfunction used in the clinical trials of STB in treatment-naïve and virologically-suppressed subjects, except the sensitivity was increased, with subclinical renal tubulopathy defined as confirmed abnormalities in any two of four renal parameters (serum creatinine and 3 markers of tubular dysfunction) as follows:

- Increase in serum creatinine ≥ 0.40 mg/dL from baseline for subjects switching to E/C/F/TAF from ATR; increase in serum creatinine ≥ 0.24 mg/dL from baseline for remaining subjects. The serum creatinine cutoffs were based on the mean + 2 SD of the change in serum creatinine from baseline at Week 48 using pooled data from Studies GS-US 236-0102 and GS-US-236-0103 (STB Phase 3 trials in treatment-naïve subjects).
- ≥ 2 grade level increase from baseline in proteinuria
- ≥ 1 grade level increase from baseline in hypophosphatemia
- ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

A confirmed laboratory abnormality was defined as an abnormality observed at two consecutive post-baseline measurements or an abnormality observed at one measurement followed by study drug discontinuation.

Most subjects, regardless of treatment, had ≤ 1 confirmed renal laboratory abnormality. No subject treated with E/C/F/TAF met the criteria for PRT. One subject in the TDF group (Subject (b) (6)) had all four confirmed renal laboratory abnormalities and also had a renal AE of Fanconi syndrome. As noted previously, this subject had study drug (ATV/co + TVD) discontinued on Study Day 305 as a result of renal dysfunction.

❖ *Bone Safety*

Fractures

The percentage of subjects who reported a fracture event was comparable between the two treatment groups (E/C/F/TAF 14 [1.5%], TDF 3 [0.6%]) (Table 19). In the E/C/F/TAF group, three fractures were reported as SAEs: skull fracture (Subject 0754-6053), radius fracture (Subject 0859-6630), and hip fracture (Subject 0986-7213). All other fracture events in this study were nonserious. All reported fracture events were considered by the investigators as unrelated to the study drugs and none resulted in permanent discontinuation of study drugs. As best as can be determined from the submitted narratives, nearly all fracture events were related to trauma and none were indicative of fragility fractures.

Table 19: Fracture Events

MedDRA Preferred Term	Number (%) of Subjects	
	E/C/F/TAF N=959	TDF N=477
Any Fracture Event	14 (2)	3 (1)
Hand fracture	3 (0.3)	0
Radius fracture	2 (0.2)	1 (0.2)
Foot fracture	1 (0.1)	1 (0.2)
Upper limb fracture	1 (0.1)	1 (0.2)
Fibula fracture	1 (0.1)	0
Hip fracture	1 (0.1)	0
Jaw fracture	1 (0.1)	0
Facial bones fracture	1 (0.1)	0
Clavicle fracture	1 (0.1)	0
Rib fracture	1 (0.1)	0
Skull fracture	1 (0.1)	0
Ulna fracture	1 (0.1)	0
Wrist fracture	1 (0.1)	0

Source: Reviewer's analysis of Applicant's dataset (ADAE)

Bone Mineral Density Changes

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 this study, respectively. Overall, there were increases from baseline in mean (SD) BMD at the hip or spine in the E/C/F/TAF group as compared with minimal changes from baseline in both parameters in the TDF group at both Weeks 24 and 48; per the Applicant, the differences between groups were significant ($P < 0.001$). The mean (SD) percent changes from baseline BMD at Week 48 are shown in Table 20.

Table 20: Total Hip and Spine Bone Mineral Density - Mean Values and Mean Percent Changes from Baseline, Weeks 24 and 48

	E/C/F/TAF			TDF		
	N	Mean (SD) BMD (g/cm ²) ^a	Mean (SD) % Change from Baseline	N	Mean (SD) BMD (g/cm ²) ^a	Mean (SD) % Change from Baseline
Total Spine						
Baseline	912	1.09 (0.17)	--	457	1.09 (0.17)	--
Week 24	862	1.11 (0.17)	1.52 (2.7)	433	1.08 (0.18)	-0.19 (3.0)
Week 48	742	1.12 (0.18)	1.86 (3.1)	356	1.09 (0.18)	-0.11 (3.7)
Total Hip						
Baseline	902	1.00 (0.14)	--	452	0.99 (0.14)	--
Week 24	851	1.01 (0.14)	1.02 (2.1)	428	0.99 (0.14)	-0.22 (1.9)
Week 48	733	1.02 (0.15)	1.95 (3)	350	1.0 (0.15)	-0.14 (3)

^a Correct bone mineral density

Source: Reviewer's analysis of Applicant's dataset (ADDEXA)

A categorical analysis (Table 21) of the distribution of percent change from baseline at Week 48 in

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hip or spine BMD showed that the E/C/F/TAF group had a higher percentage of subjects with > 3% and > 6% increases from baseline and a smaller percentage of subjects with > 3% and > 6% decreases from baseline in both parameters compared to the TDF group. Nonetheless, the number of subjects in the E/C/F/TAF group with > 3% decreases from baseline in hip or spine BMD was not negligible in this predominantly middle-aged male population.

Table 21: Percentage of Subjects with > 3% and > 6% Change from Baseline in Hip and Spine BMD at Week 48

Week 48 BMD % Changes		E/C/F/TAF	TDF
		Number (%) of Subjects	
Total Spine		N=742	N=356
Decrease	> 3%	43 (6)	62 (17)
	> 6%	4 (1)	13 (4)
Increase	> 3%	249 (34)	49 (14)
	> 6%	51 (7)	11 (3)
Total Hip		N=733	N=350
Decrease	> 3%	14 (2)	39 (11)
	> 6%	3 (0.4)	8 (2)
Increase	> 3%	185 (25)	30 (6)
	> 6%	43 (6)	10 (3)

Source: Reviewer's analysis of Applicant's dataset (ADDEXA)

Clinical BMD status was assessed using BMD T-scores; normal bone status was defined as a BMD T-score ≥ -1 , osteopenia by a T-score from ≥ -2.5 to < -1 , and osteoporosis by a T-score < -2.5 . The majority of subjects in both treatment groups had normal hip and spine BMD clinical status at baseline and retained that status through Week 48. However, the distribution of clinical BMD status adjusted for baseline status differed between treatment groups at Weeks 24 and 48 at the hip and spine. Based on results for subjects with available data at Week 48, a higher percentage of subjects in the E/C/F/TAF group than the TDF group had an improvement in BMD clinical status at the hip (E/C/F/TAF 41/733 [6%], TDF 7/350 [2%]) or spine (E/C/F/TAF 56/742 [8%], TDF 13/356 [4%]). Conversely, a lower percentage of subjects in the E/C/F/TAF group than the TDF group had worsening of BMD clinical status at the hip (E/C/F/TAF 5 [0.7%], TDF 15 [4%]) or spine (E/C/F/TAF 7 [1%], TDF 18 [5%]) at Week 48.

For all subjects, regardless of age, the baseline 10-year probability of a hip fracture or of a major osteoporotic fracture by FRAX analysis was similar between treatment groups. Among subjects ≥ 40 years of age, the changes from baseline in the 10-year probability of fracture were lower in the E/C/F/TAF group than in the TDF group. The mean (SD) change from baseline in fracture risk at Week 48 was 0% (0.24) in the E/C/F/TAF group compared with 0.1% (0.44) in the TDF group; for the 10-year probability of major osteoporotic fracture, the mean (SD) changes from baseline were 0.1% (0.39) versus 0.23% (0.55), respectively.

With respect to serum biomarkers of bone turnover, there was a decrease from baseline at Week 48 in levels of the bone formation biomarker P1NP and also in parathyroid hormone (PTH) in the E/C/F/TAF group compared with an increase from baseline in both parameters in the TDF group; the differences between the groups was significant per the Applicant ($p < 0.001$). There was no change from baseline in serum levels of the bone resorption biomarker C-telopeptide in the E/C/F/TAF group

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compared with an increase from baseline in the TDF group at Week 48.

At the request of FDA, the Applicant also summarized changes in hip and spine BMD from pre-TDF baseline for a group of subjects who participated in a DXA substudy evaluating STR (Study 236-0103) and subsequently rolled over into Study 109. A total of 57 subjects (43 randomized to switch to E/C/F/TAF and 14 randomized to stay on their prior TDF treatments) were included in the hip BMD analysis and 61 subjects (E/C/F/TAF 44; TDF 17) were included for the spine BMD analysis. These subjects had been on a TDF-based regimen for an average of 3 years prior to enrollment in Study 109. As shown in Table 22, while there was notable BMD loss in hip and spine during prior treatment with a TDF-based regimen, subjects who switched to E/C/F/TAF experienced an increase in both hip and spine BMD by Week 48, consistent with the overall DXA findings of Study 109. Although the mean Week 48 values in this group did not fully return to pre-TDF baseline values, such comparisons might be confounded by the increasing age of the cohort or other undefined factors. On the other hand, it is possible that longer-term treatment with TAF might lead to continued improvements in BMD values. In contrast, subjects who stayed on their TDF-based regimen appeared to experience continued BMD loss in Study 109 compared to their pre-TDF baseline.

Table 22: Total Hip and Spine Bone Mineral Density for Subjects Rolling Over from Study GS-US-236-0103 – Mean Values and Mean Percent Change from Pre-TDF Baseline Values

	E/C/F/TAF			TDF		
	N	Mean (SD) BMD (g/cm ²)	Mean (SD) % Change from Pre-TDF Baseline	N	Mean (SD) BMD (g/cm ²)	Mean (SD) % Change from Pre-TDF Baseline
Total Spine						
236-0103 Baseline (pre-TDF)	44	1.070 (0.15)	--	17	1.087 (0.15)	--
292-0109 Baseline	44	1.032 (0.16)	-3.6 (5)	17	1.067 (0.15)	-1.8 (4.2)
292-0109 Week 48	42	1.054 (0.15)	-0.9 (4.8)	16	1.072 (0.17)	-2.4 (6.3)
Total Hip						
236-0103 Baseline (pre-TDF)	43	0.988 (0.11)	--	14	1.013 (0.12)	--
292-0109 Baseline	42	0.943 (0.12)	-4.689 (4.5)	14	0.970 (0.12)	-4.239 (3)
292-0109 Week 48	41	0.953 (0.12)	-3.419 (4.7)	13	0.962 (0.13)	-5.139 (3.6)

Source: adapted from Applicant's Response to FDA Information Request (submitted May 19, 2015), Module 1.11.3

Common Adverse Events

Table 23 lists the TEAEs that occurred in $\geq 2\%$ of subjects in any treatment group with occurrence greater in the E/C/F/TAF group than TDF group. The most common TEAES (incidence $\geq 5\%$) in the E/C/F/TAF group were upper respiratory tract infection (12%), diarrhea (8%), nasopharyngitis (7%), headache (6%) and cough (5%). Adverse events that occurred with a $\geq 2\%$ risk difference between the E/C/F/TAF and TDF groups include headache, flatulence, nausea, oropharyngeal pain, cough, rash, gastroesophageal reflux disease, hypercholesterolaemia, and upper respiratory tract infection.

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Table 23: Common TEAEs Occurring in $\geq 2\%$ of Subjects in Any Treatment Group and Occurrence Greater in Active than Control Group

MedDRA System Organ Class and Preferred Term	Number of Subjects (%)	
	E/C/F/TAF N=959	TDF N=477
Any AE	764 (80)	368 (77)
Infections and infestations	461 (48)	215 (45)
Upper respiratory tract infection	116 (12)	36 (8)
Sinusitis	36 (4)	17 (4)
Pharyngitis	29 (3)	9 (2)
Urinary tract infection	27 (3)	7 (1)
Diarrhoea	77 (8)	36 (8)
Nasopharyngitis	64 (7)	26 (5)
Influenza	23 (2)	7 (1)
Seasonal allergy	14 (2)	5 (1)
Nervous system disorders	159 (17)	50 (11)
Headache	58 (6)	17 (4)
Dizziness	30 (3)	14 (3)
Respiratory, thoracic and mediastinal disorders	149 (16)	55 (12)
Cough	49 (5)	15 (3)
Oropharyngeal pain	32 (3)	7 (1)
Nasal congestion	15 (2)	5 (1)
Musculoskeletal and connective tissue disorders	233 (24)	92 (19)
Osteopenia	45 (5)	19 (4)
Arthralgia	46 (5)	16 (3)
Pain in extremity	31 (3)	12 (3)
Myalgia	19 (2)	4 (1)
Gastrointestinal disorders	263 (27)	102 (21)
Diarrhoea	77 (8)	36 (8)
Nausea	46 (5)	13 (3)
Vomiting	29 (3)	9 (2)
Flatulence	22 (2)	1 (<1)
Abdominal pain	20 (2)	5 (1)
Abdominal pain upper	20 (2)	5 (1)
Dyspepsia	20 (2)	5 (1)
Haemorrhoids	17 (2)	6 (1)
Constipation	17 (2)	5 (1)
Gastroesophageal reflux disease	18 (2)	2 (<1)
Metabolism and nutrition disorders	76 (8)	18 (4)
Hyperlipidemia	18 (2)	4 (1)
Hypercholesterolaemia	19 (2)	0
General disorders and administration site conditions	107 (11)	53 (11)
Pyrexia	35 (4)	14 (3)
Fatigue	29 (3)	12 (3)
Chest pain	15 (2)	6 (1)
Skin and subcutaneous tissue disorders	121 (13)	53 (11)
Rash	29 (3)	6 (1)
Psychiatric disorders	127 (13)	67 (14)
Abnormal dreams	21 (2)	10 (1)

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Source: Reviewer's analysis of Applicant's dataset (ADAE)

Laboratory Findings

Table 24 lists treatment-emergent laboratory abnormalities by maximum post-baseline toxicity grade. Except for serum lipids, bilirubin, and uric acid, there were no notable differences between the two treatment groups in the incidence or severity of laboratory toxicities for the parameters measured. The greater incidence of graded hyperbilirubinemia in the TDF group is presumably due to ATV use in that group.

Table 24: Treatment-emergent Laboratory Abnormalities by Maximum Toxicity Grade

Laboratory Parameter	Toxicity Grade	Number (%) of Subjects	
		E/C/F/TAF N=959	TDF N=477
<i>Any Graded Laboratory Abnormality</i>	Grade 1	340 (36)	164 (34)
	Grade 2	335 (35)	134 (28)
	Grade 3	158 (17)	92 (19)
	Grade 4	37 (4)	30 (6)
Alanine Aminotransferase (U/L)	<i>Any Grade</i>	150 (16)	67 (14)
	Grade 1	115 (12)	50 (11)
	Grade 2	33 (3)	14 (3)
	Grade 3	4 (0.4)	1 (0.2)
	Grade 4	1 (0.1)	2 (0.4)
Aspartate Aminotransferase (U/L)	<i>Any Grade</i>	151 (16)	71 (15)
	Grade 1	113 (12)	50 (11)
	Grade 2	26 (3)	16 (3)
	Grade 3	9 (1)	4 (1)
	Grade 4	3 (0.3)	1 (0.2)
Gamma Glutamyl Transferase (U/L)	<i>Any Grade</i>	72 (8)	46 (10)
	Grade 1	58 (6)	31 (7)
	Grade 2	10 (1)	10 (2)
	Grade 3	3 (0.3)	3 (1)
	Grade 4	1 (0.1)	2 (0.4)
Bilirubin (mg/dL)	<i>Any Grade</i>	16 (2)	123 (26)
	Grade 1	13 (1)	19 (4)
	Grade 2	2 (0.2)	36 (8)
	Grade 3	1 (0.1)	54 (11)
	Grade 4	0	14 (3)
Albumin (g/dL)	<i>Any Grade</i>	11 (1)	3 (1)
	Grade 1	6 (1)	3 (1)
	Grade 2	5 (0.5)	0
Alkaline Phosphatase (U/L)	<i>Any Grade</i>	6 (1)	7 (2)
	Grade 1	4 (0.4)	6 (1)
	Grade 2	1 (0.1)	1 (0.2)

	Grade 4	1 (0.1)	0
Amylase (U/L)	<i>Any Grade</i>	134 (14)	78 (16)
	Grade 1	104 (11)	52 (11)
	Grade 2	19 (2)	17 (4)
	Grade 3	11 (1)	9 (2)
Sodium (mEq/L) - <i>Hypernatremia</i>	Grade 1	3 (0.3)	0
Sodium (mEq/L) - <i>Hyponatremia</i>	<i>Any Grade</i>	8 (1)	5 (1)
	Grade 1	5 (1)	4 (1)
	Grade 2	2 (0.2)	0
	Grade 3	1 (0.1)	1 (0.2)
Bicarbonate (mEq/L)	<i>Any Grade</i>	46 (5)	12 (3)
	Grade 1	21 (2)	9 (2)
	Grade 2	25 (3)	3 (1)
Magnesium (mg/dL) - <i>Hypomagnesemia</i>	<i>Any Grade</i>	6 (1)	1 (0.2)
	Grade 1	3 (0.3)	1 (0.2)
	Grade 2	3 (0.3)	0
Phosphate (mg/dL) - <i>Hypophosphatemia</i>	<i>Any Grade</i>	35 (4)	19 (4)
	Grade 1	34 (4)	12 (3)
	Grade 2	11 (1)	5 (1)
	Grade 3	0	2 (0.4)
Potassium mEq/L) - <i>Hyperkalemia</i>	Grade 1	5 (1)	2 (0.4)
Potassium mEq/L) - <i>Hypokalemia</i>	<i>Any Grade</i>	27 (3)	17 (4)
	Grade 1	25 (3)	16 (3)
	Grade 2	2 (0.2)	0
	Grade 3	0	1 (0.2)
Blood Urea Nitrogen (mg/dL)	Grade 1	18 (2)	7 (2)
Creatinine (mg/dL)	<i>Any Grade</i>	42 (4)	25 (5)
	Grade 1	42 (4)	23 (5)
	Grade 2	0	2 (0.4)
	Grade 3	0	0
	Grade 4	0	0
Creatine Kinase (U/L)	<i>Any Grade</i>	158 (17)	79 (17)
	Grade 1	81 (9)	44 (9)
	Grade 2	27 (3)	11 (2)
	Grade 3	26 (3)	12 (3)
	Grade 4	24 (3)	12 (3)
Fasting Glucose (mg/dL) - <i>Hyperglycemia</i>	<i>Any Grade</i>	191 (20)	93 (20)
	Grade 1	113 (12)	66 (14)
	Grade 2	71 (7)	25 (5)
	Grade 3	6 (1)	2 (0.4)
	Grade 4	1 (0.1)	0
Fasting Glucose (mg/dL) - <i>Hypoglycemia</i>	<i>Any Grade</i>	13 (1)	9 (2)
	Grade 1	10 (1)	7 (2)
	Grade 2	3 (0.3)	2 (0.4)

Uric Acid (mg/dL) - <i>Hyperuricemia</i>	<i>Any Grade</i>	127 (13)	24 (5)
	Grade 1	110 (12)	20 (4)
	Grade 2	15 (2)	4 (1)
	Grade 3	2 (0.2)	0
Uric Acid (mg/dL) - <i>Hypouricemia</i>	Grade 1	2 (0.2)	7 (2)
Fasting Cholesterol (mg/dL)	<i>Any Grade</i>	434 (45)	110 (23)
	Grade 1	217 (23)	76 (16)
	Grade 2	189 (20)	34 (7)
	Grade 3	28 (3)	0
Fasting LDL Cholesterol (mg/dL)	<i>Any Grade</i>	357 (37)	76 (16)
	Grade 1	162 (17)	45 (9)
	Grade 2	123 (13)	27 (6)
	Grade 3	67 (7)	4 (1)
Fasting Triglycerides (mg/dL)	<i>Any Grade</i>	21 (2)	4 (1)
	Grade 2	13 (1)	2 (0.4)
	Grade 3	3 (0.3)	2 (0.4)
	Grade 4	5 (0.5)	0
Hemoglobin (g/dL)	<i>Any Grade</i>	11 (1)	4 (1)
	Grade 1	11 (1)	2 (0.4)
	Grade 2	0	1 (0.2)
	Grade 3	0	1 (0.2)
Leukocytes (x10 ³ /μL)	<i>Any Grade</i>	14 (2)	7 (2)
	Grade 1	13 (1)	6 (1)
	Grade 2	1 (0.1)	1 (0.2)
Neutrophils, Segmented (x10 ³ /μL)	<i>Any Grade</i>	93 (10)	32 (7)
	Grade 1	60 (6)	20 (4)
	Grade 2	22 (2)	7 (2)
	Grade 3	8 (1)	2 (0.4)
	Grade 4	3 (0.3)	1 (0.2)
Platelets (x10 ³ /μL)	<i>Any Grade</i>	12 (1)	9 (2)
	Grade 1	8 (1)	8 (2)
	Grade 2	3 (0.3)	1 (0.2)
	Grade 3	1 (0.1)	0
Urine Glucose	<i>Any Grade</i>	32 (3)	19 (4)
	Grade 1	7 (1)	7 (2)
	Grade 2	14 (2)	7 (2)
	Grade 3	11 (1)	5 (1)
Urine Protein	<i>Any Grade</i>	242 (25)	135 (28)
	Grade 1	220 (23)	120 (25)
	Grade 2	21 (2)	15 (3)
	Grade 3	1 (0.1)	0

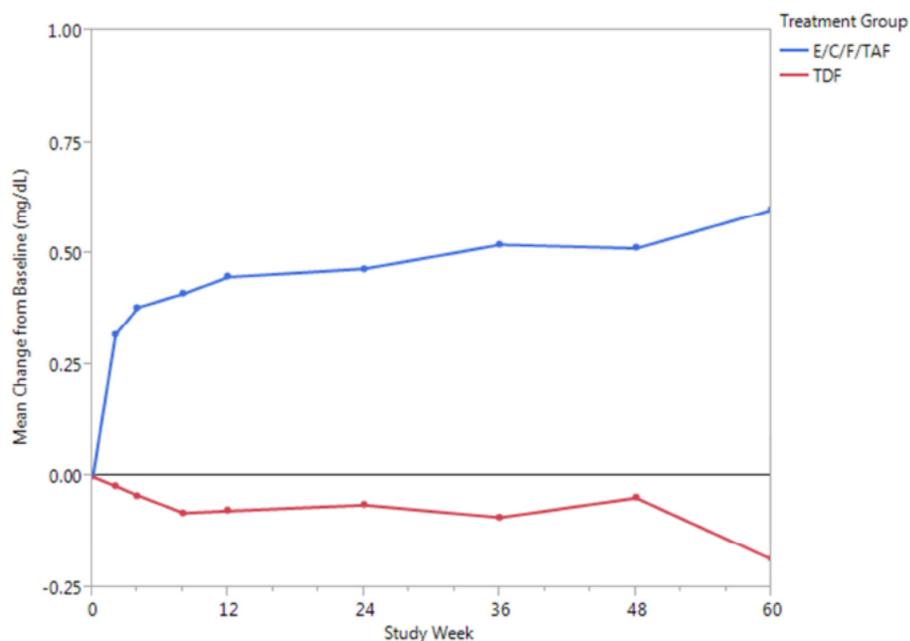
Source: Reviewer's analysis of Applicant's dataset (ADLB)

❖ Uric Acid

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There was an imbalance between treatment groups in the proportion of subjects with graded hyperuricemia: E/C/F/TAF 13%, TDF 5%. Most of these cases of hyperuricemia were Grade 1, although the imbalance was noted up through Grade 3. In the E/C/F/TAF group, the overall mean (SD) change from baseline in serum uric acid was 0.38 (0.63) mg/dL, compared with -0.06 (0.46) mg/dL in the TDF group. Increases in serum uric acid tended to occur early in the E/C/F/TAF group and appeared to plateau by Week 12 (Figure 6). There was no difference between the two groups in the incidence of clinical gout events, although the total number of events was small (E/C/F/TAF 10 events in 6 subjects [0.6%]; TDF 1 event in 1 subject [0.2%]).

Figure 6: Mean Change from Baseline in Serum Uric Acid (mg/dL) by Treatment Week



❖ Serum Lipids

As noted, there was an imbalance between the two treatment groups in the proportion of subjects with graded fasting serum lipid laboratory abnormalities. In general, increases from baseline in fasting total cholesterol, LDL cholesterol and triglycerides were noted in the E/C/F/TAF group, while these parameters remained unchanged or changed to a relatively smaller extent in the TDF group at both Weeks 24 and 48 (Table 25).

Table 25: Median Change in Fasting Lipids from Baseline

Fasting Lipid Parameter	E/C/F/TAF N=959		TDF N=477	
	N	Median (Q1, Q3)	N	Median (Q1, Q3)
Fasting Total Cholesterol (mg/dL)				
Baseline	942	182 (156, 208)	467	181 (158, 205)
Change from Baseline Week 24	911	21 (4, 40)	444	1 (-13, 16)

Change from Baseline Week 48	758	20 (1, 41)	367	6 (-9, 19)
Fasting Direct LDL Cholesterol (mg/dL)				
Baseline	942	116 (94, 142)	467	116 (96, 139)
Change from Baseline Week 24	911	11 (-3, 27)	444	-2 (-15, 9)
Change from Baseline Week 48	757	9 (-9, 25)	367	0 (-13, 11)
Fasting HDL Cholesterol (mg/dL)				
Baseline	942	50 (42, 59)	466	49 (42, 58)
Change from Baseline Week 24	911	2 (-3, 8)	443	0 (-5, 5)
Change from Baseline Week 48	758	2 (-4, 8)	366	1 (-4, 5)
Fasting Triglycerides (mg/dL)				
Baseline	942	119.5 (82, 169)	466	113.5 (81, 164)
Change from Baseline Week 24	911	10 (-21, 47)	443	2 (-29, 28)
Change from Baseline Week 48	758	10 (-18, 48)	366	0 (-28, 27)

Analysis includes only fasting samples and subjects with Baseline values.

Source: Reviewer's analysis of Applicant's dataset (ADLB)

Fasting total cholesterol and LDL cholesterol were also analyzed using the following categories, adapted from the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III categories:

- For total cholesterol (mg/dL): < 200 (desirable), 200-239 (borderline high), and ≥ 240 (high);
- For LDL (mg/dL): < 100 (optimal), 100-159 (above optimal/borderline high), and ≥ 160 (high);

Using maximum on-treatment fasting laboratory values, the number and percentage of subjects in each of the above categories was summarized by baseline category for each lipid parameter (Table 26).

Table 26: Shift Table of Fasting Total Cholesterol and LDL Cholesterol - Maximum Lipid Category during Treatment by Baseline Lipid Categories

Maximum Post-baseline Category	Number (%) of Subjects							
	E/C/F/TAF				TDF			
	Baseline Fasting Cholesterol				Baseline Fasting Cholesterol			
Fasting Cholesterol (mg/dL), n (%)	< 200	200 - 239	≥ 240	Total	< 200	200 - 239	≥ 240	Total
	N=616	N=264	N=62	N=942	N=324	N=113	N=30	N=467
< 200	327 (53)	25 (10)	1 (2)	353 (38)	225 (69)	29 (26)	3 (10)	257 (55)
200 - 239	212 (34)	89 (34)	9 (15)	310 (33)	72 (22)	56 (50)	10 (33)	138 (30)
≥ 240	55	140 (53)	49	244	8	22	16	46

	(9)		(79)	(26)	(3)	(20)	(53)	(10)
Fasting LDL (mg/dL), n (%)	Baseline Fasting LDL				Baseline Fasting LDL			
	< 100	100-159	≥ 160	Total	< 100	100-159	≥ 160	Total
	N=285	N=540	N=117	N=942	N=130	N=285	N=52	N=467
< 100	119 (42)	21 (4)	1 (3)	141 (15)	71 (55)	23 (8)	0	94 (20)
100-159	155 (54)	350 (65)	25 (21)	530 (56)	48 (37)	226 (79)	27 (52)	301 (65)
≥ 160	4 (1)	153 (28)	87 (74)	244 (26)	1 (1)	26 (9)	24 (46)	51 (11)

Source: Reviewer's analysis of Applicant's dataset (ADLB)

As shown above, the percentage of subjects who shifted from baseline to a higher lipid category during treatment was greater in the E/C/F/TAF arm than in the TDF arm. Conversely, for subjects who began treatment at higher baseline categories, the percentage of subjects who downshifted to a lower category during treatment was greater in the TDF group than in the E/C/F/TAF group. The Applicant considers that the differences between treatment groups in these lipid parameters may be due to the purported lipid-lowering effect of TFV and the lower circulating levels of TFV seen with E/C/F/TAF compared with TDF. These differences notwithstanding, the proportion of subjects who received concomitant lipid-modifying agents during the study was comparable between the two treatment groups (E/C/F/TAF 143 [15%]; TDF 64 [13%]). The proportion of subjects receiving lipid-modifying agents at baseline (E/C/F/TAF 104 [11%], TDF 51 [11%]) and the proportion of subjects who initiated treatment with lipid-modifying agents during study (E/C/F/TAF 50 [5%]; TDF 18 [4%]) were similar between the two treatment groups.

Vital Signs

There were no clinically relevant changes from baseline or between treatment groups in median values for body weight or vital signs in either treatment group.

Electrocardiograms

Clinically significant ECG findings were reported for six subjects (0.6%) in the E/C/F/TAF group and one subject (0.2%) in the TDF group. These ECG findings were reported as AEs for two subjects in the E/C/F/TAF group, but in both cases the event was considered by the investigator as unrelated to study drug and did not result in discontinuation of study drug. In addition, five subjects in the E/C/F/TAF group and three subjects in the TDF group had AEs related to ECG findings; all of these AEs were nonserious and Grade 1 or 2 and none led to discontinuation of study drugs. In one subject in the E/C/F/TAF group (Subject 5551-7418), AEs of supraventricular extrasystoles and atrial fibrillation were assessed as related to study drug by the investigator.

Drug-Demographic Interactions

Overall, the AE profile for E/C/F/TAF was similar across the subgroups of age, sex, race, region, and prior treatment regimen.

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**Appendix 2 Medical officer Review of GS-US-292-0106 Dr. Andres Alarcon, M.D.
NDA Clinical Review Page 148**

NDA Supporting Document Number NDA 207561; SDN 1

Sponsor: Gilead

**Drug: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide
(EVG/COBI/FTC/TAF [E/C/F/TAF])**

Indication: Human immunodeficiency virus type 1 (HIV-1) infection

Submission Dates: 11/05/2014

Date Received / Agency: 11/05/2014

Date Review Completed: 7/27/2015

Reviewer:

Andres Alarcon, MD

Medical Reviewer, DAVP/OAP

Materials Reviewed: Current Submission, relevant literature

1. Background and Rationale

Tenofovir alafenamide (TAF), a prodrug of tenofovir, is being developed as an alternative to tenofovir disoproxil fumarate (TDF) in the proposed once daily fixed dose combination (FDC) Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF). Protocol GS-US-292-0106 is a phase 3 study that evaluates in HIV infected ART-naïve adolescents between the ages of 12 to less than 18 years of age the steady-state pharmacokinetics, safety, and antiviral activity of E/C/F/TAF FDC. In part A of the study, subjects participated in an intensive PK evaluation which was used to confirm the dose of E/C/F/TAF. In part B, following the confirmation of EVG and TAF exposures in part A, the safety, tolerability, and antiviral activity of E/C/F/TAF will be evaluated.

Current treatment guidelines and standard of care for the treatment of HIV-1 infections encompass the implementation of combination antiretroviral therapy (ART) regimen with the goal of achieving viral suppression to undetectable levels, and increasing the CD4 cell counts, and ultimately to limit disease progression to AIDS. The ART regimen typically consists of 2 nucleoside reverse transcriptase inhibitors (NRTI) and a third drug with a different mechanism of action. The third class of ART in a regimen includes non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI), or integrase inhibitor (INTI). Current PI based ART regimens are usually administered with pharmacokinetic enhancers such as ritonavir and cobicistat to achieve higher concentrations of the active PI.

Tenofovir (TFV) belongs to the NRTI class of ART, currently manufactured as tenofovir disoproxil fumarate, and included in combination ART formulations including the following: Emtricitabine (FTC) + TDF (Truvada), efavirenz (EFV) + FTC +TDF (Atripla), FTC+ rilpivirine (RPV) + TDF (Complera). The rationale of the studied formulation of tenofovir alafenamide (TAF) is proposed to be more stable in plasma than TDF, provide higher intracellular levels of the active phosphorylated metabolite tenofovir diphosphate (TFV-DP), and have lower circulating levels of TFV relative to TDF; thus, with the proposed goal of providing an improved safety profile in comparison to TDF.

2. Study Objectives

The primary objectives are:

Part A:

- To evaluate the steady-state PK for EVG and TAF and confirm the dose of the E/C/F/TAF FDC in HIV-1 infected, ART-naive adolescents

Part B:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 24 in HIV-1 infected, ART-naive adolescents

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of the E/C/F/TAF FDC through Week 48 in HIV-1 infected, ART-naive adolescents

- To evaluate the antiviral activity of the E/C/F/TAF FDC through Week 48 in HIV-1 infected, ART-naïve adolescents

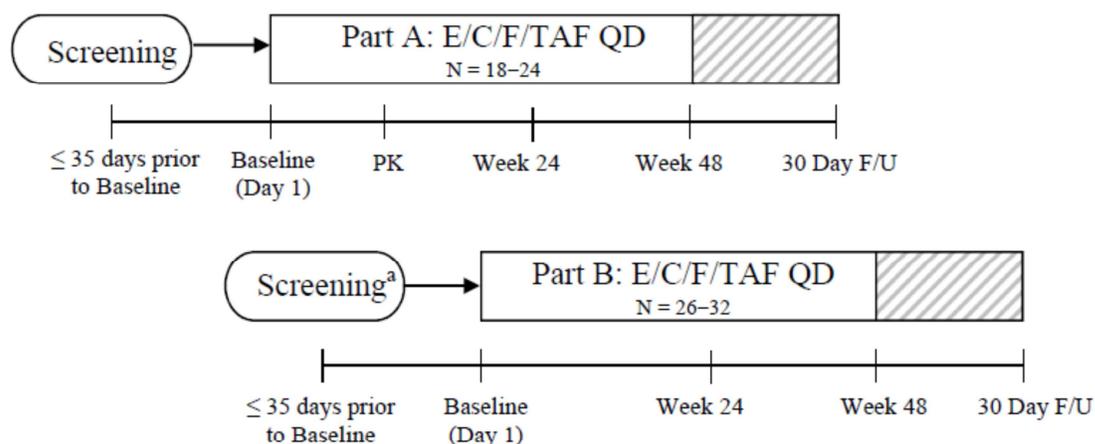
3. General Investigational Plan

3.1. Overall Study Design

This is an ongoing, open-label, non-comparative, multi-center, prospective, 2-part, single group study of the PK, safety, tolerability, and antiviral activity of the study drug E/C/F/TAF in HIV-1 infected, ART-naïve adolescents ages 12 years to less than 18 years of age. The study has two phases, the main phase and extension phase. The main phase focuses on the objectives outlined in Part A, and B of the study, described below, in up to 48 weeks of study treatment. In the extension phase, subjects in part A and Part B are given the option to participate in an extension phase of the study in which the sponsor will provide E/C/F/TAF. Key aspects of study design are as follows:

- Part A: 24 subjects were enrolled to evaluate the steady-state PK and confirm the dose of E/C/F/TAF; subjects participated in an intensive PK evaluation at week 4 and then continued dosing. Following confirmation of EVG and TAF exposures in at least 18 subjects, preliminary safety and efficacy data was reviewed by an independent data monitoring committee before enrollment into Part B of the study.
- Part B: 26 additional subjects were enrolled to evaluate the primary objective of the safety and tolerability of the E/C/F/TAF FDC through week 24.
 - Secondary objectives:
 - Evaluate safety and tolerability through week 48
 - Evaluate antiviral activity through week 48
- Both parts of the study to continue for 48 weeks followed by extension phase
 - Subjects returned for study visits at weeks 1, 2, 4, 8, 12, 16, 24, then every 8 weeks through week 48, visits every 12 weeks in extension phase
- Safety assessments included adverse events (AEs), concomitant medications, clinical laboratory tests, physical examinations (including ophthalmology evaluation), Tanner stage, renal and bone biomarkers, DXA of the spine and total body less head (TBLH), and neuropsychiatric symptoms.

Figure 1, Visual Study Schema of Study GS-US-292-0106, Clinical Study Protocol



QD = once daily; F/U = follow-up

^a Screening for Part B commenced after the PK data from Part A confirmed the adolescent dose of E/C/F/TAF.

Source: Study GS-US-292-0106, Interim Clinical Study Report, page28.

Reviewer comment: The proposed order of enrollment was agreed upon with DAVP prior to initiation and found to be reasonable. At the time of the initial submission 48 patients were enrolled with 23/48 of the subjects in the Full Analysis Set (FAS) having completed their week 24 week visit, and one patient completing 48 weeks of study and entering the extension phase (of 24 in part A and 24 in part B). After the original NDA submission, 2 more subjects were enrolled as described in the safety update on December 12, 2014.

3.2. Selection of Study Population

3.2.1. Inclusion Criteria

- ART-naïve adolescents with no prior use of any approved or experimental ART (other than for prevention of mother-to-child transmission)
 - Ages 12 years to less than 18 years of age with screening genotype showing sensitivity to EVG, FTC, and TFV
 - Life expectancy greater than 1 year; be able to give written assent and parent or guardian was able to give written informed consent prior to any screening evaluations.
 - Patients have to be able to swallow pills, weigh ≥ 35 kg, have plasma HIV-1 RNA levels of ≥ 1000 copies/ml at screening, and have a CD4 cell count > 100 cells/ μ L.
- Additional laboratory inclusion criteria include the following:
 - Adequate renal function (Estimated glomerular filtration rate (eGFR) ≥ 90 mL/min/1.73 m²)
 - Hepatic transaminase levels ≤ 5 x upper limit of normal
 - Clinically normal electrocardiogram (if abnormal, determined by the investigator to be not clinically significant)
 - Total bilirubin ≤ 1.5 mg/dl, or normal direct bilirubin
 - Absolute neutrophil count $\geq 500/\text{mm}^3$ (subjects with chronic neutropenia with no evidence of opportunistic or serious infection could enroll upon approval from the Gilead study medical monitor)
 - Platelets $\geq 50,000/\text{mm}^3$, hemoglobin ≥ 8.5 g/dL

- Documented negative screening for active pulmonary tuberculosis per local standard of care within 6 months of the screening visit.
- Additional inclusion criteria for female and male subjects of reproductive potential include the following:
 - A negative serum pregnancy test,
 - Any female of childbearing potential needs to meet the following:
 - Agree to use highly effective contraception methods (if using hormonal contraceptive method, the same method for at least 3 months prior to initiation of study drug) or practice sexual abstinence from screening throughout the duration of the study treatment, and 30 days following discontinuation of the study drug.
 - Male subjects must have agreed to utilize highly effective contraception methods during heterosexual intercourse or practice sexual abstinence from day 1 to 30 days after discontinuation of study drug.

Reviewer comment: Inclusion criteria were reasonable and comprehensive. Regardless of heterosexual or homosexual activity for males or females, safer sexual practices such as condom use were advocated in clinical encounters and counseling. This aligns with AAP guidelines recommending, “encourage abstinence, discourage multiple partners, and provide “safer sex” guidelines to all adolescents. Discuss the risks associated with anal intercourse for those who choose to engage in this behavior, and teach them ways to decrease risk”.^{1,2}

3.2.2. Exclusion Criteria

Exclusion criteria of importance are the following:

- Any subject with a new AIDS-defining condition (diagnosed within the 30 days prior to screening)
- Positive hepatitis C virus (HCV) antibody, positive hepatitis B virus (HBV) surface antigen or other evidence of active HBV infection (subjects with positive HBV surface antibody and no evidence of active HBV infection were permitted to enroll).
- Prior treatment with any approved or investigational or experimental anti HIV-1 drug for any length of time (other than that given for prevention of mother-to-child transmission)
- Evidence of active pulmonary or extra pulmonary tuberculosis disease within 3 months of the screening visit
 - Anticipated to require rifamycin treatment for mycobacterial infection while participating in the study (prophylactic isoniazid therapy for latent tuberculosis treatment was allowed)
- Subjects experiencing decompensated cirrhosis (eg, ascites, encephalopathy)
- Pregnant or lactating subjects
- Subjects with an implanted defibrillator or pacemaker
- Any serious or active medical or psychiatric illness which, in the opinion of the investigator, would have interfered with subject treatment, assessment, or compliance with the protocol
 - uncontrolled renal, cardiac, hematological, hepatic, pulmonary, endocrine, central nervous, gastrointestinal, vascular, metabolic Immunodeficiency disorders, active infection, or malignancy that were clinically significant or required treatment within 30 days prior to study dosing).

Additional exclusion criteria were related to substance abuse, drug allergies/interactions, concomitant medications and include the following:

- Any subject with current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
- History of significant drug sensitivity or drug allergy; known hypersensitivity to the study drugs, the metabolites, or formulation excipients
- Subjects who had been treated with immunosuppressant therapies or chemotherapeutic agents within 3 months of study screening or expected to receive these agents during the study (eg, immunoglobulins and other immune- or cytokine-based therapies).
- History of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi sarcoma; basal cell carcinoma; or resected, noninvasive cutaneous squamous carcinoma (subjects with cutaneous Kaposi sarcoma were eligible, but must not have received any systemic therapy for Kaposi sarcoma within 30 days of baseline and must not have been anticipated to require systemic therapy during the study)
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline
- Participation in an investigational trial involving administration of any investigational agent within 30 days prior to the study dosing
- Participation in any other clinical trial (including observational trials) without prior approval from the study sponsor was prohibited while participating in this trial. Lastly, subjects receiving ongoing therapy with any of the medications in the table below are excluded from the study (including drugs not to be used with EVG, COBI, FTC, TDF, and TAF; or subjects with any known allergies to the excipients of E/C/F/TAF tablets).

Table 1 List of Medications Leading to Subject Exclusion from the Study
(Obtained from the Sponsor's study protocol, page 33)

Drug Class	Agents Disallowed ^a
Alpha Adrenergic Receptor Antagonists	Alfuzosin
Analeptics	Modafinil
Antibacterials	Telithromycin
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antifungals	Voriconazole
Antihistamines	Astemizole, Terfenadine
Antimycobacterials	Rifampin, Rifapentine, Rifabutin
Endothelin Receptor Antagonists	Bosentan
Calcium Channel Blockers	Bepidil
Ergot Derivatives	Ergotamine, Ergonovine Dihydroergotamine Methylegonovine Ergometrine
GI Motility Agents	Cisapride
Herbal Supplements	St John's Wort, Echinacea
HMG-CoA Reductase Inhibitors	Simvastatin, Lovastatin, Cerivastatin
Neuroleptics	Pimozide
Sedatives/Hypnotics	Midazolam, Triazolam
Systemic ^b Glucocorticoids with the exception of short-term (≤ 1 week) use of prednisone as a steroid burst	All agents, including dexamethasone

^a Administration of any of the above medications must have been discontinued at least 21 days prior to the baseline/Day 1 visit and for the duration of the study.

^b Systemic use was defined as intravenously or orally administered corticosteroid.

Reviewer comment: The exclusion criteria were appropriate.

3.3. Efficacy, Safety, and Pharmacokinetic Assessments/Endpoints

3.3.1. Efficacy Assessments/Endpoints

The efficacy assessment was based on achieving virologic suppression, suboptimal virologic response or virologic rebound measuring HIV-1 RNA viral quantitative load as described below:

- Criterion for suboptimal virologic response:
 - HIV-1 RNA $< 1 \log_{10}$ reduction from baseline and ≥ 50 copies/mL at the Week 8 visit, confirmed at the Week 12 visit or an unscheduled visit post Week 8 (If suboptimal virologic response was confirmed, and HIV-1 RNA was ≥ 400 copies/mL, HIV-1 genotype and phenotype testing were performed).
- Criterion for virologic rebound:
 - At any visit after achieving HIV-1 RNA < 50 copies/mL, a rebound in HIV-1 RNA to ≥ 50 copies/mL, which was subsequently confirmed at the following scheduled or unscheduled visit (if virologic rebound was confirmed, and HIV-1 RNA was ≥ 400 copies/mL, HIV-1 genotype and phenotype testing were performed).

The efficacy endpoints were as follows: (Obtained from the Sponsor's study protocol, page 56)

- The percentage of subjects with plasma HIV-1 RNA < 50 copies/mL at Weeks 24 and 48, as defined by the FDA snapshot algorithm
- The percentage of subjects with plasma HIV-1 RNA < 400 copies/mL at Weeks 24 and 48 as defined by the FDA snapshot algorithm
- The change from baseline in plasma HIV-1 RNA (\log_{10} copies/mL) at Weeks 24 and 48
- The change from baseline in CD4 cell count (cells/ μ L) and percentage at Weeks 24 and 48
- The percentage of subjects with HIV-1 RNA < 50 and < 400 copies/mL at Weeks 24 and 48
Missing = Failure (M = F and missing = excluded [M = E] analyses).

3.3.2. Safety Assessments

AEs and laboratory abnormalities recorded as AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. All AEs and serious adverse events (SAEs) were treatment emergent, defined as events that began on or after the date of the first dose of study drug through 30 days following the completion of study drug administration (follow-up off-study drug period), and were, therefore, considered treatment emergent AEs (TEAEs). AEs, and SAEs were graded according to the Gilead Sciences Grading Scale of Severity of Adverse Events and Laboratory Abnormalities from a scale of grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life threatening).

3.3.3. Pharmacokinetic Measurements

(Obtained from the Sponsor's study protocol, page 43, 48, 52, 57)

The number, frequency, and timing of sampling for PK analysis were based on a concentration-time profile of the individual E/C/F/TAF antiviral components, and were estimated for all subject in the PK Substudy Analysis Set from the week 4 intensive PK evaluation (includes all enrolled and treated subjects in Part A who did not have any missing key PK parameters including AUC_{τ} , C_{\max} , and C_{trough}).

Per the protocol, the primary PK endpoint in Part A of the study was AUC_{τ} for EVG and AUC_{last} for TAF. The secondary endpoints included C_{max} , apparent CL/F, and apparent V_z/F for TAF; C_{trough} , C_{max} , apparent CL/F and apparent V_z/F for EVG; and AUC_{τ} , C_{max} , and C_{trough} for TFV, COBI, and FTC. CL/F and V_z/F were also estimated for TFV, COBI, and FTC.

Reviewer comment: For a complete description of the PK analysis, please refer to the clinical virology review by Mario Sampson, PhD.

3.4. Statistical Methods

(Obtained from the Sponsor's study protocol, pages 51-52)

There were multiple analysis populations that included the following: All Enrolled Analysis Set, used as the primary analysis set for by-subject listings (included all subjects who were enrolled in the study); Full Analysis Set, used as the primary analysis set for efficacy analysis and the Safety Analysis Set (included all subjects who were enrolled in the study and received at least 1 dose of study drug); Week 24 Full Analysis Set in which the FDA snapshot algorithm analysis of HIV-1 RNA data was performed (included all subjects who were enrolled in the study by February 11th, 2014 and received a minimum of one dose of study drug); DXA Analysis Set that was subdivided into the Spine DXA Analysis Set and the TBLH DXA Analysis Set (included all enrolled subjects who had received at least 1 dose of study drug and had a nonmissing baseline and at least 1 postbaseline spine or TBLH BMD value); PK Substudy Analysis Set that was defined separately for TFV, TAF, EVG, COBI, and FTC (included all enrolled and treated subjects from Part A of the study and who had nonmissing key PK parameters from the week 4 intensive PK evaluation. Descriptive summaries were provided.

Reviewer comment: The interim Clinical Study Report for Study GS-US-292-0106 was reviewed with a focus on the safety profile for the Week 24 interim data submitted to the original NDA. The Week 24 interim data, data and outcome tables submitted to the original NDA for Study GS-US-292-0106 were analyzed and verified, and subsequently generated tables in the current clinical review were compiled using J-Review[®], a statistical analysis software package. The analyses were focused on the disposition of subjects, and safety assessments (discussed in section 3.1 in the study design section of the current review). As discussed in section 5.3, the PK analysis was performed by Mario Sampson, PhD, in the clinical pharmacology review; bone safety was analyzed by Stephen Voss, MD, in the DRUP consult review (discussed in section 6.4 of the current review); efficacy was analyzed by the statistical reviewer Thomas Hammerstrom, PhD, and discussed in section 5.2 of the current review.

4. Study Participants/Disposition

A total of 50 adolescent subjects were enrolled in the study, per the safety update on December 12, 2014. Subjects were enrolled from 9 sites: 3 in Thailand, 3 in the US, 2 in South Africa, and 1 in Uganda

The numbers of participants and study safety analyses set are presented in Table 2 at the time of the first NDA data submission on October 1st, 2014:

Table 2: Disposition

Screened	63
Screened subjects not enrolled	15
Subjects Enrolled	48
Enrolled in Part A	24
Enrolled in Part B	24
Subjects in Safety Analysis Set	48
Subjects in Full Analysis Set	48
Subjects Still in Study	47
Subjects Completing Study	1
Drug discontinuation	0
Dropouts from study	0

Reviewer comment: A safety update submitted by the sponsor with an analysis date of December 10, 2014 describes the enrollment of 2 additional subjects to part B of the study. The safety update increased the subjects in the safety analysis set to 31 patients completing 24 weeks of the study and 19 subjects completing 48 weeks of the study. One patient withdrew consent and prematurely discontinued the study on October 16, 2014 “saying he left the state, wants to be taken off the study, and will not be coming back for any more visits”.

5. Efficacy Evaluation

5.1. Demographic and Baseline Characteristics

The following table outlines the demographic characteristics of the enrolled safety analysis set.

Table 3 Demographics of Original NDA submission

Characteristics	Statistics	E/C/F/TAF
Subjects		48
Sex [n (%)]	F	28 (58.3%)
	M	20 (41.7%)
Age	12-17 Median: 15	48 (100.0%)
Race [n (%)]	ASIAN	6 (12.5%)
	BLACK OR AFRICAN AMERICAN	42 (87.5%)
Ethnicity [n (%)]	NOT HISPANIC OR LATINO	48 (100.0%)
Countries [n (%)]	Thailand	6 (12.5%)

	Uganda	30 (62.5%)
	United States of America	9 (18.8%)
	South Africa	3 (6.3%)
HIV-1 RNA (log 10 copies/mL)	<= 100,000	38 (79.2%)
	>100,000	10 (20.8%)
CD4 Cell count(/uL)	<=199	4 (8.3%)
	>=200 and <= 499	9 (18.8%)
	>=350 and <= 499	18 (37.5%)
	>= 500	17 (35.4%)
HIV Disease Status	Asymptomatic	40 (83.3%)
	Symptomatic HIV Infection	8 (16.7%)

Reviewer comment: The safety update informs that subjects with HIV RNA \leq 100,000 copies/ml increased to 29 subjects; HIV RNA >100,000 copies/ml increased to 11 subjects; HIV disease status being asymptomatic increased to 42 subjects, and symptomatic HIV infection remained the same.

5.2 Efficacy Analyses

The efficacy assessment and endpoints are discussed in section 3.3.1 of the current review. In general there was no virologic resistance to E/C/F/TAF in any subject, and the HIV-1 RNA outcomes were similar for the missing = failure (M=F) (week 24 FAS) and missing = excluded (M=E) (FAS) analysis. At the interim week 24 analysis, the virologic success rate was 91.3% (21/23 subjects in the week 24 FAS) using the FDA snapshot algorithm with a cutoff of HIV-1 RNA <50 copies/ml. The two subjects who did not meet the assessment criteria had viral suppression of HIV-1 RNA <50 copies/ml at previous visits to week 24, and at the week 32 assessment. For the interim week 24 analysis using the FDA snapshot algorithm with a cutoff of HIV-1 RNA <400 copies/ml, 23/24 (95.7%) had virologic success. The one subject who did not meet the virologic success, subject (b) (6) (one of the two previously described subjects who did not meet virologic success at the interim 24 week analysis for the HIV-RNA <50 copies/ml), had viral suppression in the later study visits.

Reviewer comment: Table 9.1 (GS-US-292-0106: Virologic Outcome at Week 24 (HIV-1 RNA Cutoff at 50 copies/mL, Snapshot Algorithm, Week 24 FAS), and table 9-2 (GS-US-292-0106: Virologic Outcome at Week 24 (HIV-1 RNA Cutoff at 400 copies/mL, Snapshot Algorithm, Week 24 FAS) submitted by the sponsor in the current submission were verified for virologic outcomes at week 24 for the FAS by the clinical reviewer and results are found below.

Table 4: Virologic Outcomes at Week 24 (HIV-1 RNA Cutoff at 50 copies/ml, Snapshot Algorithm, Week 24 FAS)

Snapshot 50 copies mL at week 24 FAS	E/C/F/TAF
Subjects	23
virologic failure	2 (8.7%)
virologic success (HIV RNA < 50 copies/mL)	21 (91.3%)

Table 5: Virologic Outcomes at Week 24 (HIV-1 RNA Cutoff at 400 copies/ml, Snapshot Algorithm, Week 24 FAS)

Snapshot 400 copies mL at week 24 FAS	E/C/F/TAF
Subjects	23
virologic failure	1 (4.3%)
virologic success (HIV RNA < 400 copies/mL)	22 (95.7%)

Reviewer comment: The safety update shows that 43 subjects at week 24 of the FAS were included (per the sponsor, the 24 week window is between day 140 and 195); 40 (93 %) achieved HIV RNA <50 copies/ml, and 3 (7%) were considered virologic failure. It is unclear from the submitted data in the safety update if the additional patient with virologic failure reached virologic suppression after the 24 week analysis. Additionally, week 24 FAS data for virologic success for HIV RNA <400 copies/ml was not submitted in the safety update. For a statistical review of the efficacy analysis please refer to the review by Thomas Hammerstrom, PhD.

5.3 PK Summary

Following E/C/F/TAF exposure in adolescents, TAF AUC_{last} and C_{max}, in comparison to exposure to adults, were 29.3% and 22.3 % lower, respectively; however, the differences were not considered to be clinically relevant (TAF exposure in adolescents was consistent with the range of exposure associated with viral suppression in adults). In regards to TFV, exposure in adolescents following E/C/F/TAF was about 90% lower in comparison to TFV exposure in adults following elvitegravir/cobicistat/emtricitabine/tenofovir DF (STB) administration or TDF given with boosted PIs.

Reviewer comment: The PK targets were achieved and the initial dosing strategy did not require modification. For a complete description of the PK analysis, please refer to the clinical pharmacology review by Mario Sampson, PhD.

6. Safety Evaluation

6.1 Extent of Exposure

For the interim week 24 analysis in the original NDA, 23/48 subjects in the safety analysis set had received the study drug for ≥ 24 weeks. The mean and median weeks of dosing was calculated as the exact days that the study drug was administered. The mean (SD) duration of study drug administration was 19.2 (15.14), and median duration was 12.1 weeks. For the safety update, 31/40 subjects in the safety analysis received the study drug for ≥ 24 weeks, 19/50 subjects for ≥ 48 weeks, and 3/50 subjects ≥ 60 weeks. The mean (SD) duration of study drug exposure in weeks was 34.4 (15.6) and median of 24.3.

6.2 Adverse Events

All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) central coding

dictionary, version 13.0. Serious AEs (SAEs) were recorded from the time of informed consent until 30 days after the last dose of study drug. A treatment emergent adverse event (TEAE) was defined as any AE that occurred on or after the first dose date of study drug.

Reviewer comment: All data analysis tables for adverse events provided in the current submission were generated by the clinical reviewer using J-Review[®], a statistical analysis software package.

Table 6: Summary of TEAEs in the Safety Analysis Set

292-0106 (Adverse Events)	E/C/F/TAF (N=48)
Subjects with one or more TEAE	39 (81.3%)
TEAE related to study drug	18 (37.5%)
TEAE not related to study drug	34 (70.1%)
Subjects experiencing grade 2,3,4	13 (27.0%)
Subjects experiencing grade 3,4	4 (8.3%)
TEAE grade 2,3,4 related to study drug	2 (4.2%)
TEAE grade 3,4 related to study drug	1 (2.1%)
Serious TEAE	4 (8.3%)
Serious TEAE related to study drug	1 (2.1%)
Any TEAE leading to study drug discontinuation	0
Deaths	0

One or more AEs were reported in 39/48 (81.3%) subjects, most of which were Grade 1 or 2 in severity. Eighteen subjects (37.5%) had an AE considered related to study drug by the investigators, most of which were grade 1 in severity. As noted in the table four subjects (8.3%) had a serious TEAE of grade 3 or 4 AE, with one serious TEAE being related to study drug that consisted of grade 2 visual impairment, and grade 2 intermediate uveitis. Of importance no subject had an AE that led to drug discontinuation or treatment emergent deaths.

Reviewer comment: The safety update showed that 42/50 subjects in the safety population had one or more TEAE, and no new reports of any TEAE related to study drug or any treatment emergent serious adverse event. Additionally, in the safety update no subject experienced any TEAE that lead to premature discontinuation.

Table 7, Adverse Events Grade 1-4 Considered Related to Study Drug in the Safety Analysis Set

Dictionary-Derived Term	Standard Toxicity Grade	E/C/F/TAF
Total Subjects		18 (37.5%)
Nausea	1	10 (20.8%)
Abdominal pain	1	6 (12.5%)

Vomiting	1	5 (10.4%)
Abdominal pain upper	1	3 (6.3%)
Diarrhea	1	3 (6.3%)
Somnolence	1	3 (6.3%)
Dizziness	1	2 (4.2%)
Decreased appetite	1	1 (2.1%)
Dyspepsia	1	1 (2.1%)
Fatigue	1	1 (2.1%)
Flatulence	1	1 (2.1%)
Lethargy	1	1 (2.1%)
Increased appetite	1	1 (2.1%)
Headache	1	1 (2.1%)
Headache	2	1 (2.1%)
Intermediate uveitis	2	1 (2.1%)
Visual impairment	2	1 (2.1%)
Chorioretinitis	3	1 (2.1%)

As described in table 6, 18/48 subjects (37.5%) had an AE considered related to the study drug, and were mainly grade 1 in severity. The study drug-related AEs that occurred in >1 subject were either gastrointestinal, including nausea in 10 subjects (20.8%), abdominal pain in 6 subjects (12.5%), vomiting in 5 subjects (10.4%), upper abdominal pain in 3 subjects (6.3%), and diarrhea in 3 subjects (6.3%). The next largest group of AEs related to study drug were nervous system disorders and all were grade 1 with somnolence occurring in 3 subjects (6.3%), dizziness in 2 subjects (4.2%), and headaches in 2 subjects (4.2%). Of note, visual impairment of grade 2, Chorioretinitis of grade 3, and intermediate uveitis occurred in one subject and will be discussed in the severe adverse event (SAE in section 6.3.2).

Reviewer comment: In the safety update, adverse events were not subcategorized by standard toxicity grade.

Table 8. Adverse Events Occurring in > 5% of Subjects, Regardless of Causality

Dictionary-Derived Term	E/C/F/TAF
Nausea	11 (22.9%)
Upper respiratory tract infection	10 (20.8%)
Diarrhea	8 (16.7%)
Abdominal pain	7 (14.6%)

Headache	7 (14.6%)
Respiratory tract infection	7 (14.6%)
Vomiting	6 (12.5%)
Dizziness	5 (10.4%)
Vitamin D deficiency	5 (10.4%)
Body tinea	4 (8.3%)
Bronchopneumonia	4 (8.3%)
Abdominal pain upper	3 (6.3%)
Rash popular	3 (6.3%)
Somnolence	3 (6.3%)
Urinary tract infection	3 (6.3%)

The adverse events that occurred in at least 5% of subjects are described in Table 6, with nausea being the most common adverse event in 11/48 (22.9%) followed by upper respiratory tract infection in 10/48 (20.8%).

6.3 Deaths, and Serious Adverse Events

6.3.1 Deaths

No deaths were reported by the investigators during the study.

6.3.2 Serious Adverse Events

As described previously, four subjects (8.3%) had serious AEs. One subject had a related SAE of Grade 2 visual impairment and uveitis considered related to study drug by the investigator that resolved while study drug continued. Per the original NDA submission and SAE report narrative, Subject ^{(b) (6)}, a 13-year-old Ugandan female, had Grade 2 intermediate uveitis. This subject had been infected with HIV-1 via vertical transmission (diagnosed in 2010, at which time she was started on TMP/SMX prophylaxis with no subsequent reports of opportunistic infections) and entered the study with a baseline CD4 cell count of 1,110 cells/ μ l and HIV-1 RNA of 31,300 copies/ml. The subject reported 2 months prior to the initial study drug administration with decreased visual acuity. At Day 14 of study drug administration the subject presented with visual field changes and was diagnosed with grade 1 allergic conjunctivitis, grade 2 visual impairment (reported as an SAE considered related to study drug by the investigator), and cataracts. On day 16, she was found to have conjunctival hyperemia and HIV-1 RNA of <20 copies/ml and CD4 count of 1,156 cell/u. On day 16, a fundoscopic exam revealed vitreous cells and perivascular sheathing in the left eye. She was diagnosed with allergic conjunctivitis, low grade posterior uveitis (later observed to be grade 3 chorioretinitis) and started on gentadex ophthalmic drops and oral cetirizine without discontinuation of E/CF/TAF. Infectious evaluation included a negative CMV viral load and TPHA for syphilis. Following repeat fundoscopic examination on Day 27, the chorioretinitis was reassessed as Grade 2

intermediate uveitis, reported as an SAE related to study drug by the investigator. The subject remained on E/C/F/TAF and was followed with serial fundoscopic examinations. Subsequently, at Week 16, the subject had persistent mild conjunctival hyperemia with normal fundi bilaterally. The symptoms improved significantly with topical antibiotic/steroids, nonsteroidal anti-inflammatory eye drops, and oral steroid/antihistamine therapy.

Table 9, Summary of Severe Adverse Events in the Safety Analysis Set

Organ Class	Causality	Dictionary Derived Term	E/C/F/TAF
		Subjects	4 (8.3%)
Eye disorders	RELATED	Visual impairment	1 (2.1%)
		Intermediate uveitis	1 (2.1%)
Gastrointestinal disorders	NOT RELATED	Constipation	1 (2.1%)
Nervous system disorders		Neuralgia	1 (2.1%)
Psychiatric disorders		Bipolar I disorder	1 (2.1%)
		Conduct disorder	1 (2.1%)
		Drug abuse	1 (2.1%)
		Mania	1 (2.1%)
		Substance abuse	1 (2.1%)
		Suicide attempt	1 (2.1%)
Renal and urinary disorders		Urinary retention	1 (2.1%)

Reviewer comment:

The narrative of the SAE related to the study drug in the patient with initial visual impairment, underlying cataracts, and progression to intermediate uveitis was closely reviewed. Due to the patient's ocular findings of cataracts and symptoms of vision loss prior to and near the initiation of the study drug, a clear temporal relationship of the development of intermediate uveitis to the administration to study drug is not completely supported. Therefore, close monitoring will be needed to assess for possible uveitis in other subjects being studied. As previously mentioned, no additional serious adverse events were reported in the safety update.

6.3.3 Clinical and Laboratory Evaluations

In the current review, the clinical and laboratory evaluations that are highlighted are renal laboratory parameters, bone mineral density (BMD), and cholesterol profiles.

Reviewer comment: Renal laboratory parameters were closely evaluated due to the renal toxicity

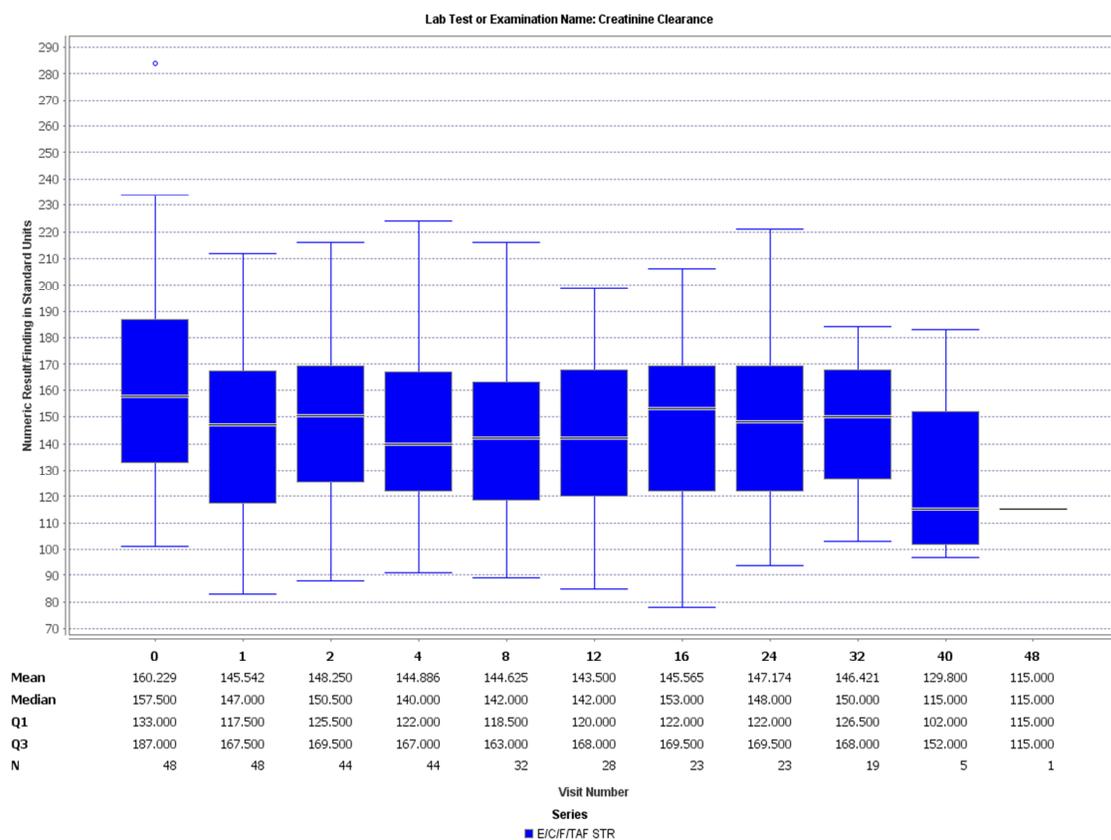
that has been associated with TFV, and the effects of COBI in inhibiting the tubular secretion of creatinine^{3,4}. Other parameters that were closely evaluated were BMD via DXA due to the known decrease in BMD associated with TDF. BMD in HIV-infected adolescents was monitored since they may have baseline low BMD due to multiple factors⁵, and additionally present with rapid growth and accruing bone mass. Lastly, cholesterol parameters were evaluated due to the observed increase from baseline in mean lipid parameters (see section 6.5).

In general, 39/48 subjects in the Safety Analysis set had at least one treatment-emergent (TE) mainly being grade 1 and 2 in severity. Four subjects had grade 3 TE laboratory abnormalities (grade 3 hematuria detected by nonquantitative dipstick analyses occurred in 3 instances but were excluded). Grade 3 TE laboratory abnormalities included neutropenia in three subjects, and one subject with transient grade 3 hematuria by quantitative analysis. No grade 4 laboratory abnormalities were reported.

6.3.3.1 Renal Safety

No adverse events of decreased eGFR or renal failure were reported, and no subjects had laboratory findings consistent with proximal renal tubulopathy. As observed in previous trials with cobicistat, patients had an increase in serum creatinine and decrease in eGFR as early as week 1, and then stabilized. This observed phenomenon is depicted in the graph below (eGFR is calculated using the Schawartz formula: mL/min/1.73²).

Figure 2: Estimated GFR by Week of Study Drug



Reviewer comment: The safety update exhibited the same characteristics of the original NDA of an initial increase in serum creatinine and decrease in eGFR as early as week 1, and then stabilized. Of note one subject had SAE of urinary retention for duration of six days, and was considered to be unrelated to study drug administration.

6.4 Bone Safety (Information incorporated from Stephen Voss MD, DRUP Consult Review NDA 207561)

In study 106, HIV-infected adolescents exhibited mean increases from baseline at 48 weeks of 3.9% in lumbar spine BMD and 1.5% in TBLH BMD. A $\geq 4\%$ decrease in spine BMD was seen in 3 of 41 subjects at week 24 and 1 of 20 subjects at week 48. No subject had a $\geq 4\%$ decrease in TBLH BMD at Weeks 24 or 48. (safety update). The sponsor implemented a cross-study comparison with STB, GS-US-236-0112 (similar endpoints, design, and enrollment criteria as with GS-US-292-0106) to attempt to demonstrate a benefit of E/C/F/TAF.

Reference is also made to study GS-US-104-0321 which enrolled 90 adolescents (age 12-17 years old), and who were randomized to receive TDF 300 mg daily or placebo (each in combination with a background regimen). Analyses from the study exhibited that mean lumbar spine BMD increased by 1.2% at week 24 and 3.2% at week 48; respective increases in the comparison (non-TDF) group were 1.9% and 3.8%. There were 6/33 TDF patients, compared to 1/33 placebo patient, who experienced $> 4\%$ decline in lumbar spine BMD at 48 weeks.

Reviewer comment: As reviewed by Stephen Voss MD (refer to DRUP consultation for full details), There are lumbar spine BMD trends in favor of E/C/F/TAF vs. STB, however results were not markedly different from the TDF regimen in study 321, and mean Z-scores for E/C/F/TAF treatment declined slightly even with appropriate height adjustment. The sponsor claims a significant difference between E/C/F/TAF vs. STB for L-spine BMD and Z-score, but these post hoc comparisons of different studies with different adolescent populations cannot provide definitive conclusions. Additionally, there were no observed fractures in the current adolescent study.

6.5 Cholesterol Safety

The clinical review analysis showed that median fasting lipid parameters increased from baseline to week 24. The median total cholesterol increased from baseline to week 24 by 31 mg/dl; LDL by 11 mg/dl, and triglycerides by 9 mg/dl. The median results described were consistent but not identical to the applicant's.

Reviewer comment: Observed changes of increase values are noted by the sponsor's submission and analysis by the reviewer. However, the sponsor does not discuss the change in fasting lipid profiles from baseline and does not discuss a possible biological plausibility for the observed phenomenon. In the safety update, the median change from baseline to weeks 24 and 36 were the following: fasting total cholesterol increased 26 mg/dl and 36 mg/dl, respectively; fasting direct LDL increased 10 mg/dl and 17 mg/dl, respectively; and fasting triglycerides increased 14 mg/dl and 19 mg/dl, respectively. An explanation for the rising fasting lipids in association with increasing duration of drug exposure is not provided by the sponsor.

7 Summary and Conclusions

In this study, 50 treatment-naïve HIV infected adolescents from 12-17 years of age received study drug E/C/F/TAF in an open label, single arm study. In general, E/C/F/TAF was well tolerated in the studied population without any observance of any risks (SAE, AE) related to study drug. The studied drug has the benefit of reaching virologic suppression and concomitantly meeting the efficacy endpoints with an acceptable safety profile. In general the PK profile was well matched to the adult PK profile, and the current dosing regimen seems acceptable for adolescents. The efficacy endpoints were reached, as seen by having greater than 90% of viral suppression at the interim 24 weeks analyses. The safety analyses did not identify any serious signals of concern in this age group, and showed that the study drug was well tolerated. Safety concerns from previous studies such as renal safety, and bone safety were evaluated and the overall benefits appear to outweigh the risks. Based on the efficacy and safety results of the current study, I recommend the approval of E/C/F/TAF in HIV infected adolescents age 12 years to 17 years of age.

8 Proposed Label Changes

The adverse events, serious adverse event, and laboratory/radiologic findings are comparable to

those observed in the adult studies. Section 6.1 of the label (Adverse Reactions from Clinical Trial Experience under Clinical Trials in Pediatric Subjects) should mention the following:

In the interim week 24 analysis, among the 23 pediatric subjects receiving GENVOYA, median fasting lipid parameters increased from baseline to week 24. The median total cholesterol increased from baseline to week 24 by 31 mg/dl, LDL by 11 mg/dl, and triglycerides by 9 mg/dl.

Among the 23 pediatric subjects receiving GENVOYA for 24 weeks, mean BMD increased from baseline to week 24, + 1.7% at the lumbar spine and + 0.8% for the total body less head. However, mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at week 24. Two GENVOYA subjects had significant (greater than 4%) lumbar spine BMD loss at week 24.

Additionally, in section 6.1 of the label, consideration should be made in integrating tables 7, 8, 9 of the current review for the adverse events related to study drug, adverse events occurring in >5% of the studied population (regardless of causality), and summary of SAE related/unrelated to study drug.

For section 12.3, Pharmacokinetics, as mentioned by Mario Sampson, PhD the following should be integrated to the label under pediatric patients:

Exposures of tenofovir alafenamide achieved in 24 pediatric subjects aged 12 to < 18 years who received GENVOYA in Study 106 were decreased (23% for AUC) compared to exposures achieved in treatment-naïve adults following administration of GENVOYA, but were overall deemed acceptable based on exposure-response relationships; the other components of GENVOYA had similar exposures in adolescents compared to treatment-naïve adults.

Andres Alarcon, MD
Medical Officer, DAVP

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1. American Academy of Pediatrics, Committee on Adolescence. Condom use by adolescents. *Pediatrics*.2001;107:1463–1469
 2. American Academy of Pediatrics, Barbara L. Frankowski and Committee on Adolescence. Sexual Orientation and Adolescents *Pediatrics* 2004; 113 6 1827-1832\
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Puthanakit T, Siberry GK. Bone health in children and adolescents with perinatal HIV infectio

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/s/

William B. Tauber, MD
07/10/15

Linda L. Lewis, MD
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WILLIAM B TAUBER
07/28/2015

LINDA L LEWIS
07/29/2015



MEMORANDUM

Date: May 22, 2015

From: John V. Kelsey, D.D.S., M.B.A., Dental Officer, Division of Dermatology and Dental Products (DDDP)

Through: David Kettl, M.D., Acting Deputy Director, DDDP
Kendall Marcus, M.D., Director, DDDP

To: Myung-Joo Patricia Hong, RPM, Division of Antiviral Products (DAVP)

Cc: Julie Beitz, M.D., Director, Office of Drug Evaluation III (ODEIII), Office of New Drugs (OND)
Maria Walsh, Associate Director for Regulatory Affairs (ADRA), ODEIII, OND
BJ Gould, Chief, Project Management Staff (CPMS), DDDP

Re: DDDP Consult #1643 – DAVP NDA 207561 GENVOYA
Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) Fixed Dose Combination Tablet

Material Reviewed :

1. DAVP Request for Consultation
2. Various published articles

Assignment:

Per the consult request from DAVP,

“The current NDA is for a new 4 drug Fixed Dose Combination (Genvoya) which is intended as a complete regimen for the treatment of HIV-1 infection. Genvoya closely resembles Stribild, an approved 4 drug FDC complete regimen. Genvoya differs from Stribild in the substitution of unapproved tenofovir alafenamide fumarate (TAF) for the approved tenofovir disoproxil fumarate (TDF-Viread) component. TAF and TDF are both prodrugs of the antiretroviral

tenofovir (TFV). In all of its single and combination uses, TDF has been associated with instances of proximal tubular injury, renal function decline and decreased bone mineral density as measured by DXA scan. Circulating TFV exposure is thought to be the cause. TAF differs from TDF in demonstrating better entry and concentration in target cells where the conversion to the active moiety tenofovir diphosphate takes place. The improvements of entry and concentration permits reduced dosage of the TAF prodrug with lowered circulating TFV exposure. The potential safety advantage of lowered TFV exposure has been an important factor in the development of TAF.

The current NDA review is a head to head safety and efficacy comparison of Genvoya and Stribild. During the conduct of the NDA review apparent increases in the number of dental infections including AELLT termed dental abscess, dental necrosis, dental caries, gingival infection and inflammations were noted in the two pivotal studies 0104 and 0111. The total numbers of all grade dental adverse events were similar between study arms; 92 (11%) for Genvoya and 79 (9%) for Stribild. When Grade 2 or greater dental adverse events were considered, however, there were greater differences. Thirty-nine (45% of dental events) Genvoya subjects had Grade 2 or higher AEs including 4 with Grade 3 toxicity. Twenty-four (30% of dental events) Stribild subjects had Grade 2 or higher with 1 having Grade 3 toxicity. There was one serious dental adverse event Grade 2 palatal dysplasia in a Stribild patient enrolled in 0111. There were no discontinuations or treatment interruptions for dental events. The incidence of oral dryness, dyspepsia, stomatitis, GERD was low and balanced between the two study arms of 0104 and 0111.

In the other large study 0109, which is a switch study with 2:1 randomization, the incidence of any dental AE was higher in subjects randomized to Genvoya (30 subjects or 3% of population) compared to a number of agents all sharing TDF as a component (10 patients or 2% of the population). The Grade 2 or higher incidence populations were more closely matched with infections noted in 6 (0.6%) compared to 1 (0.2%). The causes and significance of these findings are unknown. There are other safety data from the NDA review that might be considered in assessing these findings. Theoretically there could be a consequence of higher tenofovir diphosphate concentrations in the target white blood cells. Other infections with increased incidence among Genvoya recipients include infections of the skin, upper respiratory tract, herpes virus and gastrointestinal tract. Grade 2 or higher infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* were numerically higher with Genvoya. The cause of the improved BMD documented by DXA scans of the hip and spine might be different than thought and a paradoxical effect on tooth enamel might occur. This incidence of notable dental disease may be common in HIV infected participants of clinical trials and the differences between the treatment arms may be due to chance alone.

We ask for your help in our interpretation of these data. Please provide answers to the following questions:

1. Does the imbalance in the incidences of dental infections in these studies seem noteworthy to you?

2. Are there published data reporting on the incidence of dental disease similar to this in the untreated HIV infected population?
3. If there are such data, would the incidence observed in studies 0104, 0111 and 0109 be considered to be increased compared to untreated HIV infected adults?
4. Are there instances of approved drugs associated with increased incidence of dental infections for reasons other than decreased saliva production or direct damage to tooth enamel?
5. Is there information regarding these dental cases which would assist in the elucidation of their cause which we could ask Gilead to provide?
6. In your opinion, are there enough data provided to warrant precautionary language and/or specific monitoring recommendations being placed in the product label?"

Background:

The two principal categories of oral disease are dental caries, which affects the teeth and periodontal disease (including gingivitis), which affects the soft tissue around the teeth. Of the LLTs mentioned in your consult request, *Dental abscess*, *Dental necrosis*, and *Dental caries* would presumably affect the teeth, while *Gingival infection* and *Inflammations* would presumably affect the soft tissue around the teeth.

A brief review of the literature on HIV and oral disease shows that patients with HIV infection are often in poor dental health.^{i,ii} They may have various manifestations of dental caries (including dental abscesses and dental necrosis), though these conditions develop relatively slowly and may reflect chronic neglect. HIV patients may also have gingival infections and inflammation. These conditions may reflect poor oral hygiene, lack of dental care, or impaired immune function.

Concerns about the rating scales:

Investigators in clinical trials for drugs (other than dental drugs) are rarely dentists, so the terms chosen to describe an oral AE may not be accurate.

You used MedDRA lowest level terms (AELLT) to identify specific adverse events. I looked at v. 17.1 of MedDRA. You mention, in particular the terms,

- *Dental abscess* (an LLT under the PT tooth abscess)
- *Dental necrosis* (an LLT under a PT of the same name, under an HLT Dental disorders NEC) [*not elsewhere classified*]
- *Dental caries* (an LLT under a PT of the same name)

- *Gingival infection* (LLT under PT Gingivitis, HLT Dental and oral soft tissue infections, HLT Infections- pathogen unspecified and SOC Infections and infestations)
- *Inflammations* (an HLT under General system disorders NEC, under SOC General disorders and administrative site conditions).

The other scoring system employed in the studies supporting severity in your submission is the CTC AE. I looked at CTC AE v. 3.0. The CTC AE was developed to assess the toxicities associated with therapies for cancer. There are three categories of dental AEs under the Gastrointestinal section;

- *Dental: periodontal disease*
- *Dental: teeth*
- *Dental: teeth development.*

The *Dental: teeth* series turns on the need for extractions;

- 1 requires no extractions
- 2 is one or more but less than the full mouth
- 3 is full mouth extractions.

The *Dental: Periodontal Disease* section of the CTC AE is also difficult to interpret

- 1 is Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss
- 2 is Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss
- 3 is Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of the maxilla or mandible

In your consult you note an apparent disparity in severity scores between groups. In the case of dental disease, which tends to be chronic, the value of these severity scores is questionable, especially when the grading is done by a non-dentist. This, in turn, raises questions about the reliability of the scores computed.

Conclusions:

The numbers of AEs are small and may not be statistically significant, so it would be difficult to argue that the differences between the treatment arms are not due to chance alone, or differences in the dental health characteristics of these HIV subjects at baseline. The argument that, “a paradoxical effect on tooth enamel might occur,” is speculative.

The placement of the dental terms within the MedDRA nomenclature varies, which may impact on the specificity and selection of the term. In addition, the options for reporting oral toxicity using the CTC AE are limited, which raises concern about the reliability of the scores reported. These concerns are exacerbated by the fact that it is unlikely that a dentist formally assessed the dental AEs.

In addition, you note that, “There were no discontinuations or treatment interruptions for dental events. The incidence of oral dryness, dyspepsia, stomatitis [*an infection in the mouth*], and GERD was low and balanced between the two study arms of 0104 and 0111.”

In summary, the data is not sufficient to require precautionary language and/or specific monitoring recommendations being placed in the product label.

Response to Questions:

1. Does the imbalance in the incidences of dental infections in these studies seem noteworthy to you?

The significance of the data you provided on dental infections in the studies you reviewed is unclear.

The numbers of dental adverse events were small and may not be statistically significant or clinically meaningful.

2. Are there published data reporting on the incidence of dental disease similar to this in the untreated HIV infected population?

I was unable to find published data on the incidence of dental disease in untreated HIV patients. There were a number of articles that addressed dental disease in patients receiving highly active antiretroviral therapy (HARRTS). Most of these patients were children and most studies were conducted in third world countries, especially in Africa.

3. If there are such data, would the incidence observed in studies 0104, 0111 and 0109 be considered to be increased compared to untreated HIV infected adults?

See response to 2.

4. Are there instances of approved drugs associated with increased incidence of dental infections for reasons other than decreased saliva production or direct damage to tooth enamel?

Candidiasis is an oral soft tissue infection that is often associated with use of corticosteroids, antibiotics and/or chemotherapy.

Oral mucositis is a common complication of some types of chemotherapy and the oral mucositis lesions may become secondarily infected.

The drug class bisphosphonates are also associated with dental adverse reactions. These products, which are used to treat osteoporosis, have caused osteonecrosis in a number of patients; though bisphosphonate induced osteonecrosis doesn't occur through an infectious mechanism.ⁱⁱⁱ

5. Is there information regarding these dental cases which would assist in the elucidation of their cause which we could ask Gilead to provide?

You might inquire regarding the training of the investigators who evaluated the dental adverse events.

6. In your opinion, are there enough data provided to warrant precautionary language and/or specific monitoring recommendations being placed in the product label?

Based on the data presented, labeling changes or warnings do not appear to be warranted. Specific monitoring recommendations in the product label, based on these data, are not recommended.

ⁱ Subramaniam P, Kumar K, Oral mucosal lesions and immune status in HIV-infected Indian Children, [J Oral Pathol Med](#). 2015 Apr;44(4):296-9. doi: 10.1111/jop.12243. Epub 2014 Sep 12.

ⁱⁱ [Herrera D](#), [Alonso B](#), [de Arriba L](#), [Santa Cruz I](#), [Serrano C](#), [Sanz M](#)., Acute periodontal lesions, [Periodontol 2000](#). 2014 Jun;65(1):149-77. doi: 10.1111/prd.12022

ⁱⁱⁱ Allen MR, Burr DB, The Pathogenesis of bisphosphonate-related osteonecrosis of the jaw: so many hypotheses: so few data, [J Oral Maxillofac Surg](#). 2009 May;67(5 Suppl):61-70. doi: 10.1016/j.joms.2009.01.007

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06/04/2015

DAVID L KETTL
06/04/2015

KENDALL A MARCUS
06/04/2015



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products**

Date: May 29, 2015
Drug Name: Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fixed dose combination tablet; E/C/F/TAF)
NDA: 207561
Applicant: Gilead Sciences, Inc.
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Myung-Joo Hong, Regulatory Project Manager, Division of Antiviral Products
Subject: Consult to review the renal safety of a single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

Background

Genvoya is a new four drug fixed-dose combination product with a proposed indication of treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older. This product combines the approved drugs elvitegravir (integrase inhibitor; EVG; Vitekta), cobicistat (pharmacokinetic enhancer for EVG; COBI; Tybost), and emtricitabine (nucleoside reverse transcriptase inhibitor; FTC; Emtriva) along with a novel nucleotide reverse transcriptase inhibitor tenofovir alafenamide fumarate (TAF). Genvoya is similar to the fixed-dose combination product Stribild approved in 2012 under NDA 203100 for patients with an estimated creatinine clearance ≥ 70 mL/min, except Stribild includes tenofovir disoproxil fumarate (TDF; Viread) instead of TAF. Both TAF and TDF are prodrugs of tenofovir and are converted to the active moiety tenofovir diphosphate upon entry into target cells.

TDF is known to cause renal toxicity including Fanconi Syndrome and acute renal failure. Although estimates vary, the incidence of nephrotoxicity severe enough to warrant discontinuation of TDF therapy is approximately 1% with <0.2% of patients experiencing severe renal failure. Nephrotoxicity often develops over a period of months but can also develop after years of therapy.

According to the applicant, TAF has better entry and concentration in HIV-target cells than TDF, thereby allowing the administration of smaller doses and reducing systemic tenofovir exposure and renal toxicity. In preclinical studies, TAF, unlike TFV, did not interact with the renal organic anion transporters 1 or 3 (OAT1 or OAT3), and TAF exhibited no OAT-dependent cytotoxicity in human epithelial kidney cells transiently expressing these transporters. In addition, the selectivity index (considering CC50 in renal HEK293 cells expressing OAT1 or OAT3 relative to EC50 in primary CD4+ T lymphocytes) for TAF (29,000 and 4270, respectively) was much higher than for TFV (14 and 82, respectively). Therefore, TAF is less likely to accumulate in renal proximal tubules in an OAT-dependent manner, supporting the potential for an improved renal safety profile.

With the current NDA, Gilead submitted a renal safety study GS-US-292-0112 intended to support use of Genvoya in patients with an estimated creatinine clearance of ≥ 30 mL/min. The Division of Cardiovascular and Renal Products was consulted to help with interpretation the study's findings, specifically whether the population adequately represents patients with mild to moderate renal impairment, whether the data adequately support use in patients with renal impairment, whether renal

function monitoring should be recommended, and how to describe the study in labeling. This review focuses on the renal findings. We defer to the expertise of the primary review division regarding efficacy and the non-renal safety findings.

Materials Reviewed

1. Interim Week 24 Clinical Study Report for Study GS-US-292-0112.
2. Response to FDA Information Request of 01 April 2015 submitted April 6, 2015.
3. Draft labeling submitted March 13, 2015.
4. Consult by Shona Pendse regarding NDA 203100 dated March 26, 2012.
5. Prescribing information for Stribild, Viread, and Emtriva.

Overview of Study GS-US-292-0112

Study GS-US-292-0112 is an ongoing phase 3, open-label, safety study of Genvoya in 252 subjects with stable mild to moderate renal impairment (Cockcroft-Gault eGFR [eGFR_{CG}] 30 to 69 mL/min) with at least 30 subjects with an eGFR_{CG} of 30 to 49 mL/min. Enrollment started in March 2013 at 70 sites (51 in the United States). Subjects were enrolled in one of two cohorts:

Cohort 1: HIV-infected adults on antiretroviral therapy (ART) with undetectable HIV-1 RNA levels for at least 6 months and <50 copies/mL at screening, CD4+ count \geq 50 cells/ μ L, no history of known resistance to EVG, FTC, or TDF, and stable eGFR of 30 to 69 mL/min for 3 months before screening.

Cohort 2: Similar to Cohort 1 but ART-naïve with plasma HIV-1 RNA levels \geq 1000 copies/mL and a screening genotype showing sensitivity to EVG, FTC, and TDF.

Subjects could transfer from other Gilead studies but were not eligible for transfer from study GS-US-236-0118 if they had discontinued Stribild or TDF because of worsening renal function (eGFR_{CG} < 50 mL/min with > 20% reduction in cystatin C-based eGFR from baseline or evidence of acute renal failure).

The renal eligibility criteria included:

- eGFR_{CG} of 30 to 69 mL/min using actual weight.
- Stable renal function with at least one serum creatinine value available within three months of screening. The difference between this value and the screening value must be <25% of the screening value.
- Stable cause of chronic kidney disease with no changes to medical management for three months before baseline and no specific treatment required (e.g., corticosteroids).
- No requirement for renal replacement therapy.

Subjects in Cohort 1 stopped their baseline ART and all subjects are treated with open-label Genvoya once daily for up to 96 weeks. After Week 96, subjects will be eligible for an extension study until the drug becomes commercially available or the applicant terminates development.

Overview of Renal Monitoring

Subjects return for study visits at Weeks 1, 2, 4, 8, 12, 16, and 24 and then every 12 weeks through Week 96. Serum chemistry parameters are assessed at each visit including sodium, potassium, magnesium, bicarbonate, BUN, creatinine, cystatin C, glucose, calcium, phosphorus, albumin, uric acid, and parathyroid hormone. Urinalysis and urine chemistries are also performed at each visit including measures of proteinuria (urine dipstick, protein-to-creatinine ratio, and albumin-to-creatinine ratio), phosphate, uric acid, and creatinine. At visits 1, 2, 4, 12, 24, 48, urine retinol binding protein and beta-2-microglobulin are measured as markers of tubular proteinuria. In a PK/PD substudy, GFR was measured

using iohexol at baseline, Week 2, 4, or 8, and Week 24. No renal events were specified as adverse events of interest or were adjudicated.

Endpoints

The primary efficacy endpoint is the percentage of subjects who achieve HIV-1 RNA < 50 copies/mL at Week 24 as defined by the FDA snapshot algorithm. The secondary efficacy endpoints evaluate different HIV-1 RNA cutoff values, time points, and handling of missing data.

The primary renal safety endpoints are a change from baseline at Week 24 in eGFR calculated using one of three equations: (1) Cockcroft-Gault (eGFR_{CG}); (2) CKD-EPI creatinine adjusted for age, sex, and race (eGFR_{CKD-EPI, creat}); and (3) CKD-EPI cystatin C adjusted for age and sex (eGFR_{CKD-EPI, cysC}).

The secondary renal endpoints include descriptive statistics of the following:

- GFR measured using iohexol for subjects enrolled in the PK/PD substudy
- Serum creatinine
- Serum cystatin C
- Serum phosphorus
- Proteinuria by urinalysis and quantitative assessment
- Urine retinol binding protein to creatinine ratio and beta-2-microglobulin to creatinine ratio
- Other urine biomarkers including the renal tubular maximum reabsorption rate of phosphate to GFR ratio (TmP/GFR), urine fractional excretion of phosphate (FEPO₄), urine fractional excretion of uric acid (FEUA), and urine creatinine

Sample Size Determination

The sample size of 260 subjects was based on “practical considerations and was considered to be sufficient to evaluate the primary objective of the study.”

For the PK/PD substudy, a sample of 30 subjects with evaluable iohexol GFR was intended to provide at least 90% power at an alpha of 0.1 to detect a change in GFR from baseline of <20% assuming a clinically meaningful boundary in GFR change is 80 to 125%.

Results at Week 24 Interim Assessment

In support of their marketing application, the applicant conducted an interim analysis¹ after all subjects who initiated study drug on or before November 15, 2013 had completed their Week 48 study visit or prematurely discontinued study drug before their Week 48 visit (“Interim Week 24 Clinical Study Report”). All subjects who received at least one dose of study drug were included in the analysis.

Disposition

Overall, 246 subjects were enrolled in Cohort 1 and six in Cohort 2. From Cohort 1, 32 subjects also enrolled in the PK/PD substudy. The efficacy and safety analysis sets include 248 subjects who received at least one dose of study drug. Overall, 16 (6.5%) subjects have prematurely discontinued treatment: eight subjects because of an adverse event, three withdrew consent, two were lost to follow-up, and one each because of a lack of efficacy, a protocol violation, and investigator’s discretion.

¹ The statistical analysis plan dated September 16, 2014 specified analyses at four time points in addition to analyses performed for the independent data monitoring committee. The analyses were to be conducted after all enrolled subjects completed their Week 24, Week 48, and Week 96 visits or prematurely discontinued study drug, and after all subjects completed the study.

The median duration of exposure was 43 (36, 48) weeks (Table 1). Overall, 189 (78.1%) subjects received study drug for ≥ 36 weeks. Only 50 (62.5%) of subjects with a baseline $eGFR_{CG} < 50$ mL/min reached ≥ 36 weeks exposure compared with 139 (85.8%) subjects with a baseline ≥ 50 mL/min. A total of 67 (27.7%) subjects reached ≥ 48 weeks exposure, only 16 with an $eGFR < 50$ mL/min.

Table 1: Duration of study drug exposure

	Overall	Baseline $eGFR_{CG}$ < 50 mL/min (n=80)	Baseline $eGFR_{CG}$ ≥ 50 mL/min (n=162)
Median weeks (Q1, Q3)	43 (36, 48)	42 (25, 44)	43(42, 48)
≥ 24 weeks	222 (91.7%)	65 (81.3%)	157 (96.9%)
≥ 36 weeks	189 (78.1%)	50 (62.5%)	139 (85.8%)
≥ 48 weeks	67 (27.7%)	16 (20.0%)	51 (31.5%)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 11-1.

Baseline Subject Characteristics

The study population is predominantly male (80%) with a mean age of 57.5 years (Table 2). Most were taking TDF (64%) and nearly half were taking cobicistat or ritonavir (46%) in the 48 hours before the baseline visit. The mean baseline creatinine was 1.46 mg/dL.

Table 2: Baseline characteristics

	Cohort 1/2 (n=248)
Male	198 (80%)
Mean age (range)	57.5 (24-82)
Race	
White	154 (62%)
Black	47 (19%)
Asian	35 (14%)
Baseline HIV medications	
TDF	158 (64%)
Cobicistat/Ritonavir	115 (46%)
Cobicistat	26 (11%)
Ritonavir	90 (36%)
Creatinine mg/dL (mean [SD])	1.46 (0.4)

Source: Reviewer's analysis of applicant's dataset (*adrenout, adsl, adlb, adcm*).

The mean baseline $eGFR$ was approximately 55 mL/min using the creatinine-based equations $eGFR_{GC}$ and $eGFR_{CKD-EPI, creat}$ (Table 3). The estimates were higher using the cystatin-C based $eGFR_{CKD-EPI, cysC}$ at approximately 70.5 mL/min/1.73m². The $eGFR$ obtained using each equation did not differ by whether or not the subject had taken cobicistat or ritonavir in the 24 to 48 hours before the baseline assessment.

Table 3: Baseline estimated GFR (n=248)

	Cockcroft-Gault	CKD-Epi, Creatinine	CKD-Epi, Cystatin C
Mean $eGFR$ (SD)	54.8 (11.6)	54.7 (14.4)	70.5 (21.1)
Baseline COBI/RTV ¹	54.9 (11.3)	55.3 (14.0)	70.4 (19.8)
No baseline COBI/RTV	54.6 (11.9)	54.1 (14.8)	70.6 (22.3)

Source: Reviewer's analysis of applicant's dataset (*adcm, adlb*).

¹Baseline Cobicistat/Ritonavir (COBI/RTV) n=115; No baseline COBI/RTV n=133.

Reviewer's comment: The difference in eGFR using creatinine-based and cystatin-C based equations does not appear to result from inhibition of the tubular secretion of creatinine in patients taking cobicistat or ritonavir.

The number of subjects in each category of eGFR varies depending on the estimating equation used (Table 4). Using the applicant's eGFR categories, approximately one-third of subjects had an eGFR of 30 to <50 and over half had an eGFR of 50 to <70 using the creatinine-based equations. Using the cystatin C based equation, only 48% of subjects had an eGFR in the target range of 30 to <70 with half having an eGFR \geq 70. By CKD stage, one third of subjects were stage 2, nearly half were stage 3a, and 20% were stage 3b using the creatinine-based equations. Using the cystatin C based equation, 70% of subjects were stage 2 or 3a. Only 10% were stage 3b and 18% were stage 1.

Table 4: Baseline estimated GFR by category

	Cockcroft-Gault	CKD-Epi, Creatinine	CKD-Epi, Cystatin C
Applicant's categories			
eGFR <30	5 (2%)	10 (4%)	5 (2%)
eGFR 30 to <50	77 (31%)	81 (33%)	35 (14%)
eGFR 50 to <70	145 (59%)	131 (53%)	84 (34%)
eGFR \geq 70	21 (9%)	26 (11%)	124 (50%)
CKD Stage¹			
3b (eGFR 30 to <45)	51 (21%)	48 (19%)	25 (10%)
3a (eGFR 45 to <60)	106 (43%)	111 (45%)	49 (20%)
2 (eGFR 60 to <90)	86 (35%)	72 (29%)	123 (50%)
1 (eGFR \geq 90)	0	7 (3%)	45 (18%)

Source: Reviewer's analysis of applicant's dataset (*adlb*).

¹CKD Stage 4 includes subjects with an eGFR <30 mL/min/1.73m².

In the PK/PD substudy, the measured GFR value was between the creatinine-based and cystatin-C based estimates (Table 5); however, the measured values were generally closer to the creatinine-based estimates.

Table 5: Baseline iohexol GFR in PK substudy and estimated GFR (n=32)

	Mean (SD)	Median (Q1, Q3)
Iohexol GFR	60.1 (19.1)	59.6 (46.2, 71.4)
eGFR		
Cockcroft-Gault	56.7 (11.8)	57.6 (48.3, 64.4)
CKD-Epi, Creatinine	57.8 (17.0)	54.7 (48.3, 65.0)
CKD-Epi, CysC	69.7 (21.0)	72.6 (56.6, 79.9)

Source: Applicant, response to FDA Information Request of 01 April 2015 submitted April 6, 2015.

Reviewer's comment: Non-GFR factors that affect the serum concentration of cystatin C are not well characterized and it is not clear why the cystatin C-based estimate is providing, on average, a higher value than the measured GFR. Comparison of mean values may not be the optimal way to assess concordance. It may be more helpful to look at the concordance of values within individual subjects.

Renal Safety Findings

The applicant has reported the safety results separately for Cohorts 1 and 2. Since Cohort 1 included 242 of 248 total subjects in the safety set (97.6%), the results below are limited to Cohort 1 for simplicity.

Primary Renal Safety Endpoints:

There was no obvious change in eGFR calculated by any of the three equations (Table 6).

Table 6: Median (Q1, Q3) change from baseline in eGFR at Week 24

	Total	eGFR <50 mL/min (n=80)	eGFR ≥ 50 mL/min (n=162)
Cockcroft-Gault	-0.4 (-4.7, 4.5)	1.2 (-3.9, 5.6)	-0.9 (-4.8, 3.6)
CKD-EPI, Creatinine	-1.8 (-6.1, 4.9)	0.3 (-4.1, 7.2)	-2.2 (-8.1, 3.7)
CKD-EPI, Cystatin C	3.8 (-4.8, 11.2)	3.8 (-4.8, 12.2)	3.8 (-3.8, 10.7)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 11-2.

Secondary Renal Safety Endpoints:

Measured GFR

There was no obvious change in GFR measured using iohexol from baseline to Week 24 (Table 7).

Table 7: Iohexol GFR

	n	Mean (SD)
Baseline	32	60.1 (19.1)
Week 2/4/8	32	59.5 (18.1)
Week 24	30	61.5 (15.3)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 13.1.

The geometric least squares mean ratio for Week 24 vs. baseline was within the predefined lack of alteration boundary of 80% to 125% for both the overall population and by baseline eGFR (Table 8).

Table 8: Change in iohexol GFR from baseline to Week 24

	n	GLSM (90% CI) ¹
Overall	30	102.7 (97.1, 108.5)
Baseline eGFR < 50 mL/min	9	95.2 (85.8, 105.5)
Baseline eGFR ≥ 50 mL/min	21	106.1 (99.2, 113.4)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 13.2.

¹GLSM=Geometric Least Squares Mean ratio for Week 24 vs. baseline.

Laboratory Assessments

There were no obvious differences from baseline through Week 48 in serum creatinine, cystatin C, phosphorus, urine protein-to-creatinine (UPCR), urine albumin-to-creatinine (UACR), urine retinol binding protein, urine beta-2-microglobulin, renal tubular maximum reabsorption rate of phosphate to GFR ratio (TmP/GFR), urine fractional excretion of phosphate, or urine fractional excretion of uric acid (see Appendix).

Graded serum creatinine laboratory abnormalities were reported for 29 (36.3%) subjects with a baseline eGFR < 50 mL/min and 66 (40.7%) with a baseline eGFR ≥ 50 mL/min (grading according to the Gilead Scale for Severity of Adverse Events and Laboratory Abnormalities ranging from Grade 1=creatinine >1.5 to 2.0 mg/dL to Grade 4=creatinine >6.0 mg/dL).

Clinically significant proteinuria was defined as UPCR > 200 mg/g and clinically significant albuminuria was defined as UACR > 30 mg/g. Of subjects with non-missing values, 53/93 (57%) with clinically significant proteinuria at baseline had none by Week 24 while 8/133 (6.0%) without clinically significant proteinuria at baseline developed proteinuria by Week 24. Similarly, 50/106 (47%) subjects with clinically significant albuminuria at baseline had no significant albuminuria by Week 24 while 4/117 (3.4%) subjects developed clinically significant albuminuria by Week 24 (Source: Applicant, Interim Week 24 Clinical Study Report, Table 11-7).

Subclinical Tubulopathy

No subject met the applicant's criteria for "subclinical renal tubulopathy" defined as confirmed abnormalities in any two out of the following four renal parameters:

- Increase in serum creatinine ≥ 0.40 mg/dL from baseline.
- Confirmed ≥ 2 grade level increase from baseline in proteinuria
- Confirmed ≥ 1 grade level increase from baseline in hypophosphatemia
- Confirmed ≥ 1 grade level increase from baseline in glycosuria concurrent with serum glucose ≤ 100 mg/dL (normoglycemic glycosuria)

The serum creatinine cutoff was based on the mean + 2 standard deviations of the change in serum creatinine from baseline at Week 48 for pooled data from the Stribild arms of the two Stribild phase 3 trials (GS-US-236-0102 and GS-US-236-0103). A confirmed laboratory abnormality was defined as an abnormality observed at two consecutive post baseline measurements or an abnormality observed at one measurement followed by study drug discontinuation.

Adverse Events

Overall, 209 (86%) subjects experienced at least one AE, 26 (10.7%) experienced an SAE, eight (3.3%) discontinued study drug prematurely because of an AE, and no subjects died (Table 9). The most common AEs were diarrhea in 21 (8.7%) subjects, arthralgia in 20 (8.3%), bronchitis in 19 (7.9%), and osteopenia in 19 (7.9%). All 19 of the osteopenia events were reported within 12 days of starting study drug following baseline DXA scanning.

Table 9: Adverse Events

	Total (n=242)	eGFR_{CG} <50 mL/min (n=80)	eGFR_{CG} \geq 50 mL/min (n=162)
Adverse events	209 (86%)	67 (83.8%)	142 (87.7%)
Serious adverse events	26 (10.7%)	9 (11.3%)	17 (10.5%)
Adverse events leading to study drug discontinuation	8 (3.3%)	6 (7.5%)	2 (1.2%)
Deaths	0	0	0

Source: Applicant, Interim Week 24 Clinical Study Report, Tables 32, 40, and 42.

Of eight subjects who prematurely discontinued study drug because of an AE, six had a baseline eGFR of <50 mL/min (7.5%) and two had an eGFR ≥ 50 mL/min (1.2%). Two AEs leading to study drug discontinuation were in the renal and urinary disorders SOC (renal failure and renal failure chronic). One subject had an SAE in the renal and urinary disorders SOC (acute renal failure). An AE of "blood creatinine increased" was reported for two subjects. The narratives for these five events follow:

Case 1: Subject (b) (6) was a 52 year-old white female with hypertension and CKD with a history of a remote right nephrectomy. Her baseline creatinine was 1.4 mg/dL (eGFR_{CG} 48.6 mL/min; iohexol GFR 34.5 mL/min). She was taking concomitant ramipril and valsartan. The applicant noted that her blood pressure was elevated (~150/90 mmHg) from baseline through Week 2 and then decreased (~120s/70s mmHg) from Weeks 4 through 8. No changes were reported to her management that may have influenced renal function. On Day 28, her creatinine rose to 2.1 mg/dL (eGFR_{CG} 30 mL/min; iohexol GFR 19.9 mL/min). Study drug was discontinued on Day 83 for an AE of worsening renal insufficiency/renal failure with a serum creatinine of 1.7 mg/dL. By Week 24, her creatinine was back to her baseline of 1.4 mg/dL. She never developed glycosuria or hypophosphatemia. Her urine protein-to-creatinine ratio was 1609 mg/g at baseline and 176 mg/g at the time of study drug discontinuation. There was no change in markers of tubular proteinuria.

Case 2: Subject (b) (6) was a 51 year-old white male with hypertension and CKD with a history of remote acute renal failure from rhabdomyolysis. His baseline creatinine was 3.2 mg/dL (eGFR_{CG} 35.5 mL/min). He was taking concomitant lisinopril. By Week 36, his creatinine had gradually risen to 4.3 mg/dL (eGFR_{CG} 26.1 mL/min). The applicant noted fluctuations in his systolic blood pressure (range 128-172 mmHg). No changes were reported to his management that may have influenced renal function. Study drug was discontinued on Day 347 because of an AE of chronic renal failure at a creatinine of 5.6 mg/dL. The last available creatinine was 6.8 mg/dL on Day 438. He never developed glycosuria or hypophosphatemia. His urine protein-to-creatinine ratio was 2257 mg/g at baseline and 3321 mg/g at the time of study drug discontinuation.

Case 3: Subject (b) (6) was a 60 year old white male with a history of hypertension and polycystic kidney disease with a baseline serum creatinine of 1.85 mg/dL (eGFR_{CKD-EPI, creat} 38.7 mL/min/1.73m²). He was taking concomitant furosemide, hydrochlorothiazide, and lisinopril. Following initiation of study drug, the subject's diuretics were adjusted because of edema and hyperkalemia. On Day 17, he developed an SAE of acute renal failure with a peak serum creatinine of 3.2 mg/dL thought to be related to lisinopril and volume depletion. He was admitted to the hospital, study drug was temporarily interrupted, his lisinopril and diuretics were stopped, and he was treated with kayexalate, bicarbonate, and intravenous fluids. The event resolved on Day 19 with a serum creatinine of 1.5 mg/dL. Study drug was restarted and continued through Day 337. His creatinine remained at or below baseline through Week 48. He never developed glycosuria or hypophosphatemia. His urine protein-to-creatinine ratio was 33 mg/g at baseline and 92 mg/g at Week 48. There was no change in markers of tubular proteinuria.

Case 4: Subject (b) (6) had a baseline creatinine of 3.0 mg/dL. On Day 56, an AE of blood creatinine increased was reported for a serum creatinine of 3.5. No action was taken with the study drug. No additional detail is available regarding this case.

Case 5: Subject (b) (6) had a baseline creatinine of 1.95 mg/dL ranging from 1.47 to 2.21 mg/dL through Week 24. On Day 264, an AE of blood creatinine increased was reported for a serum creatinine of 2.37 mg/dL. No additional detail is available regarding this case.

The applicant reports that there were no AEs of proximal renal tubulopathy including Fanconi syndrome.

Reviewer's comment: There were no clear cut cases of proximal tubular injury and it is hard to determine whether the drug (vs. other factors) played a causative role in these renal events; however, Case 3 is the only case with sufficient information to suggest an alternative explanation for the renal findings.

Consult Questions

1. In light of the discrepancy between eGFRs and the limited use of the Iohexol aGFR in a selected few, does the enrolled population adequately represent mild to moderate renal impairment?

DCRP Response: Yes, we believe the enrolled population adequately represents patients with mild to moderate renal impairment. Using the creatinine-based equations and the applicant's eGFR categories, one third of subjects had mild renal impairment (eGFR 30 to <50 mL/min) and over half had moderate renal impairment (eGFR 50 to <70 mL/min). Using the cystatin C-based equation, only 14% of subjects had mild renal impairment and 34% had moderate renal impairment. Half of subjects had a cystatin C-based eGFR ≥ 70 mL/min, which is above the target range for the study. It is not clear why the cystatin C-based GFR estimates are higher but it is not obvious that they provide a more accurate assessment of renal function. One possibility is that the 115 (46%) subjects taking cobicistat and/or ritonavir before

enrollment had artificially lower creatinine-based eGFRs because of inhibition of the tubular secretion of creatinine, a known effect of these drugs; however, this hypothesis was not supported by our analyses of eGFR in patients taking or not taking these drugs. Although there are limitations to the applicant's analyses comparing measured to estimated GFR, the results suggest that the creatinine-based estimates more closely approximate the measured GFR in this population. In addition, creatinine-based equations are most often used clinically and their limitations are relatively well-characterized and understood by clinicians.

2. Gilead desires to expand the indicated population to include patients with eGFRs ≥ 30 mL/min. Does the data from this study provide adequate support for expanding the indication to this population?

DCRP Response: We defer the assessment of efficacy and non-renal safety to the expertise of the primary review division. Since a decision on whether to expand the indication for this population depends on the overall balance of benefits and risks, we are not in a position to comment on this issue. Regarding renal safety, no obvious signal was seen; however, the study size, duration of follow-up, lack of a control arm, and selective nature of the population limits our ability to draw firm conclusions.

- *In the Stribild trials (N=701), four (1.1%) subjects who discontinued study drug because of an adverse reaction had laboratory findings consistent with proximal renal tubular dysfunction. Although estimates vary, in published studies the incidence of nephrotoxicity severe enough to warrant discontinuation of TDF therapy is approximately 1% with <0.2% of patients experiencing severe renal failure. With this relatively low incidence, it is possible that no renal events would be detected in the current study (N=248).*
 - *Although nephrotoxicity often develops over months, it can also develop after years of therapy. The phase 3 Stribild studies extended up to 144 weeks and five of 13 subjects who discontinued study drug because of a renal adverse reaction did so after 48 weeks of exposure. In the current study, only 67 subjects had exposures ≥ 48 weeks, which may have limited the ability to detect renal events.*
 - *The size of the safety database and duration of exposure is limited for subjects with lower eGFRs. Only 50 subjects with an $eGFR_{CG} < 50$ mL/min had exposures ≥ 36 weeks and only 16 had exposures ≥ 48 weeks. One of the Genvoya components, emtricitabine is primarily excreted by the kidneys and the label for the single agent recommends dose interval adjustment for patients with a creatinine clearance < 50 mL/min. Since the emtricitabine dose interval cannot be adjusted for the fixed-dose combination Stribild, the label recommends discontinuation when the creatinine clearance falls below 50 mL/min. Despite higher emtricitabine exposures in the $eGFR_{CG} < 50$ mL/min group, the applicant does not believe it is necessary to adjust the dose interval for Genvoya based on similar safety findings in subjects with lower and higher eGFRs. We do not believe the data from the current study are adequate to support this conclusion; however, the approach may be reasonable if other data suggest that such increases in emtricitabine exposure do not pose a safety concern.*
 - *Nearly all patients were on antiretroviral therapy before enrollment and 64% were taking TDF. The population may have been selected for subjects who were tolerant to TDF-based regimens.*
3. (b) (4). Would you recommend renal function monitoring and if so, what would you recommend? We also appreciate your input regarding the best way to describe this study in labeling.

DCRP Response: Given the limitations of the data noted above, if approved, we believe it would be prudent to recommend monitoring of renal function and for signs of Fanconi syndrome during treatment with Genvoya (e.g., renal function, urine glucose, urine protein).

In response to your question about how to describe the study in labeling, we recommend adding the number of subjects in different eGFR categories and the duration of follow-up.

*In addition, we recommend removal of statements from Section 14 [redacted] (b) (4)
[redacted] . Examples
from the proposed label include:*



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this page

Appendix: Laboratory measures through Week 48**Table 10: Serum creatinine (mg/dL)**

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	242	1.5 (0.4)	80	1.7 (0.5)	162	1.3 (0.3)
Week 1	230	1.5 (0.4)	74	1.6 (0.5)	156	1.4 (0.3)
Week 12	237	1.5 (0.4)	76	1.7 (0.5)	161	1.4 (0.3)
Week 24	233	1.5 (0.4)	76	1.7 (0.5)	157	1.4 (0.3)
Week 36	209	1.5 (0.4)	55	1.7 (0.6)	154	1.4 (0.3)
Week 48	165	1.5 (0.5)	42	1.8 (0.8)	123	1.4 (0.3)

Source: Applicant, Interim Week 24 Clinical Study Report, Table14.

Table 11: Serum cystatin C (mg/L)

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	241	1.2 (0.3)	80	1.3 (0.4)	161	1.1 (0.2)
Week 1	229	1.1 (0.3)	73	1.3 (0.4)	156	1.0 (0.2)
Week 12	237	1.1 (0.3)	76	1.3 (0.4)	161	1.0 (0.3)
Week 24	232	1.1 (0.3)	75	1.3 (0.4)	157	1.0 (0.3)
Week 36	209	1.1 (0.3)	55	1.3 (0.4)	154	1.0 (0.3)
Week 48	164	1.1 (0.3)	42	1.3 (0.4)	122	1.0 (0.3)

Source: Applicant, Interim Week 24 Clinical Study Report, Table15.

Table 12: Serum phosphorus (mg/dL)

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	242	3.2 (0.6)	80	3.3 (0.6)	162	3.2 (0.6)
Week 1	230	3.4 (0.6)	74	3.4 (0.7)	156	3.4 (0.6)
Week 12	237	3.3 (0.6)	76	3.5 (0.6)	161	3.3 (0.5)
Week 24	233	3.4 (0.6)	76	3.4 (0.6)	157	3.3 (0.6)
Week 36	209	3.3 (0.6)	55	3.4 (0.7)	154	3.3 (0.5)
Week 48	165	3.3 (0.6)	42	3.3 (0.6)	123	3.2 (0.6)

Source: Applicant, Interim Week 24 Clinical Study Report, Table16.

Table 13: Urine protein-to-creatinine ratio

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)
Baseline	239	160.6 (73.1, 337.1)	80	270.0 (105.5, 499.5)	159	138.5 (68.4, 269.3)
Week 1	224	110.3 (57.6, 276.2)	72	209.0 (70.1, 463.9)	152	88.9 (56.0, 172.4)
Week 12	234	87.9 (54.6, 163.5)	76	135.4 (69.1, 306.5)	158	77.4 (50.6, 128.1)
Week 24	229	92.9 (52.5, 175.5)	74	147.5 (92.0, 277.4)	154	71.9 (45.7, 143.1)
Week 36	209	90.7 (55.0, 155.4)	55	130.0 (67.4, 277.4)	154	78.0 (50.5, 128.8)
Week 48	160	80.1 (44.7, 140.1)	42	135.8 (67.2, 267.9)	118	68.9 (40.8, 109.8)

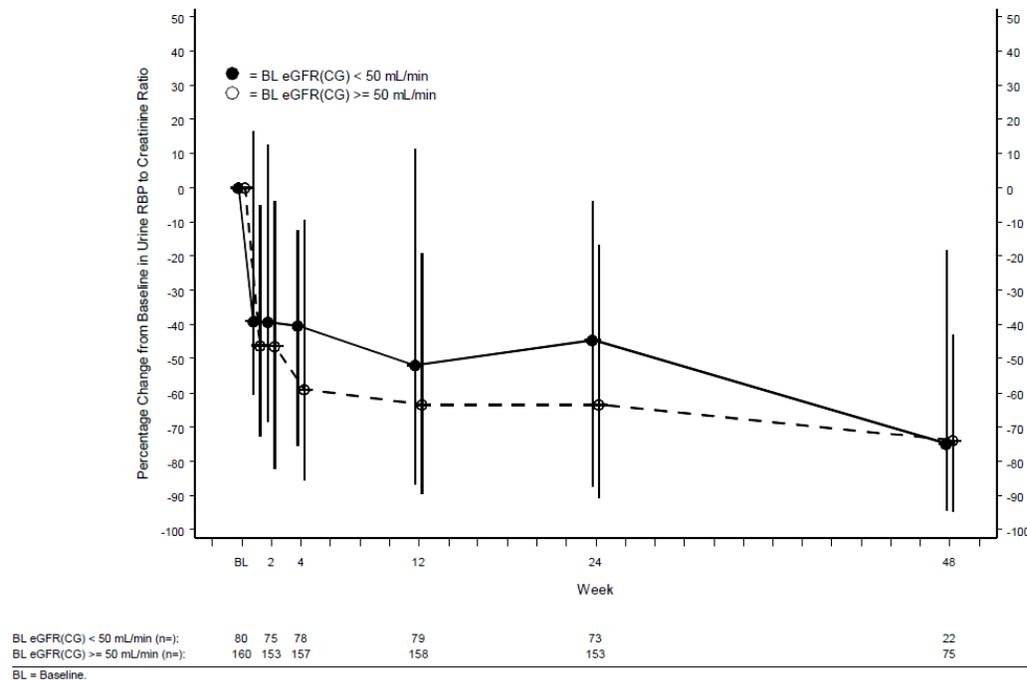
Source: Applicant, Interim Week 24 Clinical Study Report, Table11-6.

Table 14: Urine albumin-to-creatinine ratio

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Median (Q1, Q3)	n	Median (Q1, Q3)	n	Median (Q1, Q3)
Baseline	235	28.8 (7.9, 83.9)	80	53.2 (14.6, 240.8)	160	22.7 (6.0, 60.6)
Week 1	214	16.6 (5.6, 47.6)	72	30.7 (11.2, 170.0)	149	11.3 (4.9, 32.4)
Week 12	227	11.8 (5.0, 35.2)	76	32.2 (7.5, 77.1)	152	9.2 (4.6, 22.9)
Week 24	230	11.5 (4.8, 35.2)	74	26.6 (9.1, 117.9)	155	8.7 (4.4, 21.7)
Week 36	209	9.4 (4.4, 33.3)	55	25.3 (7.4, 86.0)	154	8.1 (3.9, 20.4)
Week 48	161	8.3 (4.3, 25.0)	42	29.3 (7.8, 63.6)	119	6.5 (4.0, 17.5)

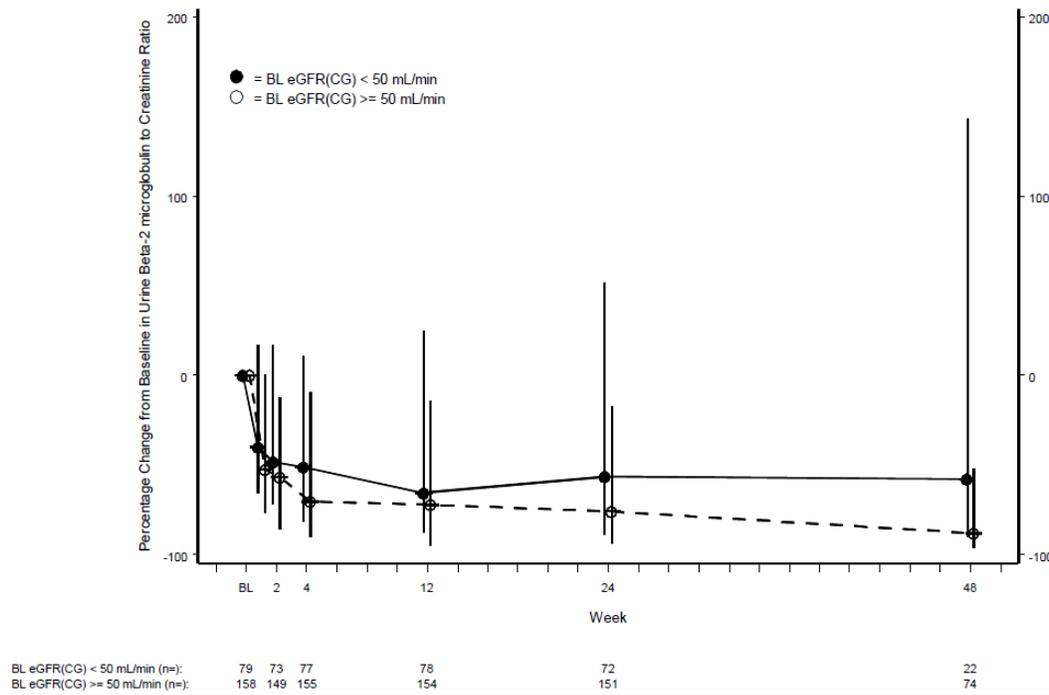
Source: Applicant, Interim Week 24 Clinical Study Report, Table11-6.

Figure 1: Median (Q1, Q3) of percentage change from baseline in urine retinol binding protein to creatinine ratio by visit



Source: Applicant, Interim Week 24 Clinical Study Report, Figure 11-1.

Figure 2: Median (Q1, Q3) of percentage change from baseline in urine beta-2-microglobulin to creatinine ratio by visit



Source: Applicant, Interim Week 24 Clinical Study Report, Figure 11-2.

Table 15: Renal tubular maximum reabsorption rate of phosphate to GFR ratio (TmP/GFR)

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	242	2.6 (0.7)	80	2.5 (0.6)	162	2.7 (0.7)
Week 1	228	2.8 (0.7)	73	2.7 (0.7)	155	2.9 (0.7)
Week 12	235	2.7 (0.6)	76	2.7 (0.7)	160	2.7 (0.6)
Week 24	230	2.7 (0.6)	75	2.6 (0.6)	155	2.7 (0.6)
Week 36	208	2.6 (0.6)	55	2.5 (0.6)	153	2.6 (0.6)
Week 48	162	2.6 (0.7)	42	2.5 (0.6)	120	2.7 (0.7)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 22.

Table 16: Urine fractional excretion of phosphate

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	242	20.4 (9.5)	80	23.7 (10.8)	162	18.8 (8.3)
Week 1	228	18.7 (8.5)	73	21.7 (10.3)	155	17.3 (7.2)
Week 12	236	20.2 (8.4)	76	22.6 (8.9)	160	19.0 (7.9)
Week 24	230	20.7 (9.0)	75	22.6 (9.9)	155	19.8 (8.4)
Week 36	208	21.7 (9.1)	55	24.7 (10.4)	153	20.7 (8.3)
Week 48	162	20.6 (9.0)	42	24.6 (11.3)	120	19.2 (7.6)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 23.

Table 17: Fractional excretion of uric acid

	Overall		eGFR <50 mL/min		eGFR ≥ 50 mL/min	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	242	10.5 (6.5)	80	11.1 (8.6)	162	10.2 (5.0)
Week 1	228	9.7 (5.5)	73	10.7 (6.9)	155	9.2 (4.6)
Week 12	236	9.0 (4.8)	76	9.4 (6.2)	160	8.8 (4.0)
Week 24	230	8.7 (4.8)	75	9.8 (6.1)	155	8.1 (4.0)
Week 36	208	8.5 (4.3)	55	8.7 (4.7)	153	8.5 (4.2)
Week 48	162	7.8 (3.6)	42	8.6 (4.5)	120	7.5 (3.3)

Source: Applicant, Interim Week 24 Clinical Study Report, Table 24.

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/s/

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Clinical Consultation

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Subject: **NDA 207561**, fixed-dose combination tablet (E/C/F/TAF) for treatment of HIV,
potential bone toxicity related to **tenofovir alafenamide fumarate (TAF)**
DBRUP Tracking #: 85

Overview

Tenofovir (TFV) is a nucleotide analog reverse transcriptase inhibitor (NRTI). As the prodrug tenofovir disoproxil fumarate (TDF), it is approved as a single agent (Viread) for treatment of HIV-1 and HBV infection, and as a component of combination products (Truvada, Atripla, Complera, Stribild) for treatment of HIV-1, and is the most widely prescribed antiretroviral drug. The main safety concerns with TDF are bone and renal toxicities, which are believed to be linked via the mechanism of proximal tubule dysfunction with phosphate wasting.

The sponsor (Gilead Sciences Inc.) has developed a second TFV prodrug, tenofovir alafenamide fumarate (TAF). Compared to TDF, TAF appears to generate higher levels of the active moiety (TFV) within lymphocytes and other HIV-target cells, and is therefore given in smaller doses, with ~90% lower circulating levels of TFV. It is believed that these lower serum levels will result in improved renal and bone safety with TAF relative to TDF.

Stribild® (STB, “E/C/F/TDF”) is a 4-drug fixed-dose combination tablet, indicated as a once-daily complete regimen for treatment of HIV-1-infected adults (NDA 203100). The NDA under review, 207561, is for a new fixed-dose tablet (“E/C/F/TAF”), identical to STB except for the substitution of TDF 300 mg by TAF 10 mg:

	E/C/F/TDF (Stribild, STB)	E/C/F/TAF (NDA 207561)
NRTI	TDF 300 mg	TAF 10 mg
NRTI	Emtricitabine (FTC, F) 200 mg	Emtricitabine (FTC, F) 200 mg
Integrase strand transfer inhibitor	Elvitegravir (EVG, E) 150 mg	Elvitegravir (EVG, E) 150 mg
CYP3A inhibitor	Cobicistat (C) 150 mg	Cobicistat (C) 150 mg

The sponsor has conducted 5 phase 2/3 studies of E/C/F/TAF in HIV-infected adults, mostly with Stribild as active control, and a small uncontrolled study in HIV-infected adolescents. Based on virologic efficacy similar to Stribild, and potential superiority in renal and bone safety data, NDA 207561 seeks approval for E/C/F/TAF as a complete regimen in HIV-1 infected adults and adolescents (age ≥ 12). The NDA was submitted on 11/5/14; the PDUFA goal date is 11/5/15 (standard review).

DBRUP has previously consulted on TDF-related bone data (NDAs 021356, 022577) and on the design of the TAF phase 3 protocols (IND 111007), and is now requested to assist in the review and interpretation of the TAF data, and provide advice on labeling particularly regarding decreases in BMD.

Background

Animal studies identified TDF-related renal and bone toxicity early in development. In rats and dogs, TDF was associated with reduced BMC and BMD and increased levels of bone turnover markers. Rhesus monkeys developed TDF dose- and duration-related bone toxicity which included mineralization defects (osteomalacia); bone loss; fractures; hypophosphatemia; elevated ALP; normoglycemic glucosuria and proteinuria. Safety margins for these effects in animals were ~6-12x the anticipated exposure in humans.

Bone safety in adults was explored in study GS-99-903, a phase 3 comparison of TDF with another NRTI (stavudine, d4T), each in combination with two other antiretroviral drugs (3TC, EFV), in 600 HIV-infected, treatment naïve adults (mean age 35 y/o, 74% men, 64% white). With TDF relative to active control, there were greater reductions in lumbar spine BMD (-2.2%, vs. -1.0% control, $p < 0.001$) and total hip BMD (-2.8% vs. -2.4% control, $p = 0.064$) at 144 weeks. The bone loss occurred in the first 24-48 weeks of treatment and then did not progress, with minimal change over the subsequent 6 years (including a 4-year open label extension). With TDF there were also significant increases, compared to control, in markers of bone turnover (BSAP, osteocalcin, serum CTX, urine NTX), and higher levels of PTH and 1,25-OH-vitamin D. Mean serum Pi showed minimal change (-1.7% TDF vs. -0.5% control, $p = 0.48$). Unlike a phase 2 study of TDF in adults which had suggested a higher-than-expected rate of fractures (all fractures, not just fragility fractures), study 903 showed no trend of increased fractures with TDF. However, no TDF study has been adequately powered to assess fractures.

Pediatric studies of TDF were consistent with the adult data: relative to control, TDF was associated with higher levels of bone turnover markers and PTH, and slower increases in BMD. Study GS-US-104-0321 enrolled 90 adolescents (age 12-17 y/o), who were randomized to receive TDF 300 mg daily (the adult dose) or placebo, each in combination with a background regimen. The TDF patients exhibited gains in lumbar spine and total body BMD that trended lower than those in control group at 1 year, and there were 6/33 TDF patients, compared to 1/33 placebo patient, who experienced > 4% decline in lumbar spine BMD at 48 weeks. BMD Z-scores showed moderate declines in both double blind groups (at 48 weeks) and in the open label extension (at 96 weeks) (b) (4)

These BMD and bone marker data are included in labeling of Viread and other TDF products, with statements that their significance with respect to long-term bone health and future fracture risk are unknown. Also, it should be noted that HIV-infected adults tend to have lower bone mass than their age/gender peers, and that small BMD reductions have been observed during the first 6-12 months of antiretroviral treatment with each of several different regimens, though to a lesser extent than TDF based regimens.

In addition to the BMD data from TDF clinical trials, there have been since approval (2001) sporadic reports of renal and/or bone toxicity. Most cases have involved proximal renal tubule (PRT) dysfunction, including Fanconi syndrome with severe hypophosphatemia. Glomerular function is generally less severely affected, if at all (however, creatinine is secreted by the PRT so may increase somewhat with only tubule damage). The mechanism of PRT toxicity is unclear, possibly related to accumulation of TFV in renal tubule epithelial cells, resulting in mitochondrial toxicity and impairment of multiple transport systems in addition to phosphate.¹ Consistent with this mechanism, serum FGF23 levels measured in several patients were not elevated^{2,3}. Serum calcitriol levels in 2 patients were inappropriately low given the hypophosphatemia, also consistent with Fanconi's syndrome - the 1α -hydroxylase enzyme is located in mitochondria of PRT cells². The risk factors for PRT toxicity of TDF include older age, lower body weight, preexisting renal impairment, concomitant use of ritonavir-boosted protease inhibitors, NSAIDs or other nephrotoxic drugs, and possibly gene polymorphisms in PRT transporters. The time from TDF initiation to detection of renal abnormalities has ranged from 1 month to >5 years, with a mean of ~2.5 years.

Many of the patients with TDF renal toxicity have presented with severe musculoskeletal symptoms suggestive of osteomalacia: bone pain, arthralgias, muscle pain or weakness, difficulty walking and/or fragility fractures. Nearly all such patients have low serum Pi and TmP/GFR at presentation. Radionuclide bone scans in some cases have shown multiple areas of increased uptake, which further imaging showed to represent insufficiency fractures. Bone biopsies in several cases have documented osteomalacia, with increased osteoid thickness, surface and volume^{2,4}. Although BMD is variable in osteomalacia, lumbar spine T-scores in 3 reported patients with TDF-related osteomalacia and bone pain were -3.8, -3.9 and -6.3²⁻⁴. Discontinuation of TDF in affected patients generally relieves bone pain and other symptoms, with at least partial improvement in Pi and other biochemical parameters.

The incidence of these TDF toxicities is unclear, as renal tubule damage, bone loss and/or osteomalacia may go undetected without active monitoring. As reports of TDF-associated osteomalacia are rare, and symptoms such as bone pain were rare in clinical trials, this is probably a late complication of TDF toxicity. Hypophosphatemia is also considered a late complication; measurement of TRP or TmP/GFR is more sensitive than serum Pi. The adult and pediatric trials discussed above did not collect urine chemistry data and reported no evidence of renal injury in adults or adolescents, (b) (4)

In clinical trials of STB (adults), some urine chemistries were monitored; 0.6% of patients discontinued the drug within 48 weeks due to lab findings consistent with PRT dysfunction. In published studies, one HIV referral center reported that ~1.6% of all TDF-treated adult patients (who presented with bone pain, hypophosphatemia, proteinuria and/or increases in creatinine) exhibited significant PRT toxicity⁵. However, studies using more sensitive urine markers (e.g. β 2-microglobulin, retinol binding protein) have reported much higher rates of TDF-related tubule dysfunction. A cross-sectional study of 284 consecutive asymptomatic HIV patients reported evidence of PRT dysfunction in 22% of patients receiving TDF (median exposure 36 months),

compared to 6% receiving other antiretrovirals and 12% of drug-naïve patients (p<0.001 in multivariate analysis)⁶. A 96-week prospective study of HIV patients on various regimens reported that 18/40 TDF-treated patients developed elevated urine β-2 microglobulin, compared to 0/17 patients receiving other drugs; %TRP declined to <90% in 21/40 TDF-treated patients and in 0/17 patients on other drugs; these abnormalities resolved with TDF discontinuation⁷.

The significance of subclinical renal tubule dysfunction with regard to bone health during long term TDF treatment is unknown. There are currently no data correlating renal tubule function parameters with BMD changes; evaluation of this is one of the objectives of a Viread PMR trial which is currently ongoing. Current labeling and guidelines advise monitoring of TDF patients with eGFR or CrCl, serum Pi and urine for proteinuria and glycosuria (dipstick). Additional monitoring, at least for patients with renal impairment or other risk factors, has been recommended by some authors: TRP or TmP/GFR, excretion of protein and/or tubule-specific proteins (not just albumin). BMD monitoring and/or Ca/Vit D supplements may be advisable for patients at risk for bone loss, and patients with new musculoskeletal symptoms require renal evaluation (see labeled Warnings and Precautions in Appendix below). For patients with extremity or bone pain, bone scintigraphy may be more sensitive than plain x-ray for initial evaluation⁴.

Clinical trials of E/C/F/TAF

Bone and renal safety measurements are included in the 6 efficacy/safety studies of E/C/F/TAF conducted in HIV-infected subjects (table below). The pivotal phase 3 trials (104 and 111) of treatment-naïve adults compare E/C/F/TAF with Stribild (STB), following the same protocol, and data are pooled for analysis. Study 109 randomized adults on a stable drug regimen including TDF, to continue same or to switch to E/C/F/TAF. These are 96-week studies; week 48 data (including the major endpoints) are reported in the NDA. Adolescents (age 12-17 y/o) and adults with mild to moderate renal impairment are evaluated in open label, single arm studies (106 and 112 respectively), which are ongoing, with interim data available.

Study	Phase	Population	Treatment groups	# subjects treated	Data available
102	2	Treatment-naïve adults	E/C/F/TAF	112	48 wk
			STB	58	
104	3	Treatment-naïve adults	E/C/F/TAF	866*	48 wk
111			STB	867*	
109	3	Treated adults (virologically suppressed)	E/C/F/TAF	959	48 wk
			Continue baseline TDF regimen	477	
106	2/3	Treatment-naïve adolescents	E/C/F/TAF	50	24-48 wk
112	3	Adults with mild to moderate renal impairment	E/C/F/TAF	248	48-72 wk

* Number of subjects in studies 104 and 111 pooled

Treatment naïve HIV-1-infected adults: Phase 2, Study 102

Design: This phase 2 study had a 48-week double blind phase in which patients were randomized (2:1) to receive E/C/F/TAF or STB (i.e., a direct comparison of TAF with TDF as the only variable), followed by an extension with open label E/C/F/TAF which is ongoing. The NDA includes data through week 96.

Study population was recruited at 37 sites in the U.S. and Puerto Rico. Entry criteria included age \geq 18 years, HIV-treatment-naïve status, eGFR \geq 70 mL/min, normal TSH; exclusions for systemic corticosteroids, active malignancy or serious infection.

Study methods: DXA of lumbar spine and hip were conducted at baseline and every 24 weeks. Standard markers of bone formation (serum ALP, osteocalcin, P1NP) and resorption (serum CTX) were collected at baseline and weeks 12, 24 and 48 in all patients. Renal parameters included TmP/GFR. Fractures were captured as adverse events.

Disposition, demographics

There were 170 patients (112 E/C/F/TAF, 58 STB) randomized and treated in the double blind phase, with mean age 36 y/o (range 18-71), 97% male, 67% white/30% black, 21% Hispanic. There were 7 E/C/F/TAF patients and 5 STB patients who discontinued during the double blind phase.

Concomitant medications used in the double blind phase included systemic corticosteroids (10% of E/C/F/TAF patients and 5% of STB patients); testosterone (13%, 7%); calcium/mineral supplements (13%, 13%); alendronate (1%, 2%); and salmon calcitonin (1%, 0%). No patients used estrogen.

BMD: At weeks 24 and 48, declines in hip and spine BMD were significantly smaller in patients receiving E/C/F/TAF relative to STB (tables below). During the open label extension, patients receiving a second year of E/C/F/TAF showed little change in BMD.

Study 102: Total hip BMD (DXA)

	E/C/F/TAF (N=103)	STB (N=57)	p-value
Baseline hip BMD (g/cm ²)	1.03	1.04	
Week 24 , n	97	57	
% change from BL, mean (SD)	-0.42 (1.68)	-2.02 (2.66)	<.001
Week 48 , n	96	54	
% change from BL, mean (SD)	-0.67 (2.18)	-3.12 (3.37)	<.001
Week 96 , n	88		
% change from BL, mean (SD)	-0.78 (2.45)		

P-values are from the ANOVA model including treatment as fixed effect
Week 24 and 48 data are from double blind treatment phase; week 96 from open label extension
Values represent observed data in all patients with nonmissing baseline hip DXA
Source: week 96 interim study report, Table 37.1.1.2 and 37.1.1.3, pp. 825-7

Study 102: Lumbar spine BMD (DXA)

	E/C/F/TAF (N=106)	STB (N=58)	p-value
Baseline hip BMD (g/cm ²)	1.12	1.14	
Week 24 , n	101	58	
% change from BL, mean (SD)	-0.93 (2.97)	-2.55 (2.51)	<.001
Week 48 , n	96	54	
% change from BL, mean (SD)	-1.02 (3.45)	-3.24 (3.22)	<.001
Week 96 , n	88		
% change from BL, mean (SD)	-0.71 (3.70)		
P-values are from the ANOVA model including treatment as fixed effect Week 24 and 48 data are from double blind treatment phase; week 96 from open label extension Values represent observed data in all patients with nonmissing baseline spine DXA Source: week 96 interim study report, Table 37.1.2.2 and 37.1.2.3, pp. 829-832			

Reviewer comment: A phase 3 study of STB showed bone loss similar to the STB arm of this study (see below).

BMD declines of >5% from baseline at week 48 were less frequent with E/C/F/TAF compared to STB: for hip BMD, 4% vs. 22%; for spine BMD, 8% vs. 23%.

Bone markers: Increases from baseline in CTx and P1NP were smaller in the E/C/F/TAF group compared with the STB group:

Study 102: Bone biomarkers: % increases from baseline in median values

	E/C/F/TAF (N=112)	STB (N=58)	p-value
Serum CTX			
% change at week 24	22.1	62.2	<.001
% change at week 48	19.3	78.3	<.001
Serum P1NP			
% change at week 24	3.7	45.1	<.001
% change at week 48	8.8	69.4	<.001
P-values are from the ANOVA model including treatment as fixed effect Source: week 96 study report Tables 38.1.1 and 38.2.1			

Renal: Median eGFR decreased by 5.5 mL/min (E/C/F/TAF group) and 10.1 mL/min (STB group); sponsor notes that cobicistat (a component of both drugs) blocks creatinine secretion by the PRT so that some (artefactual) decline in eGFR is expected. There were trends in favor of E/C/F/TAF in various measures of proteinuria. There were trends of slight decline in TmP/GFR, with no apparent difference between treatment groups. There were no cases of PRT toxicity or discontinuations due to a renal AE.

Fractures: In the randomized phase, 1 E/C/F/TAF patient sustained pelvic and upper arm fractures, and 2 STB patients had fractures (1 thoracic vertebral, 1 ankle). All resulted from trauma. There were no fractures in E/C/F/TAF patients during the OLE.

Treatment naïve HIV-1-infected adults: Studies 104 and 111

Design: These two phase 3 pivotal trials followed the same protocol. Treatment-naïve adults were randomized 1:1 to receive E/C/F/TAF or STB (double-blinded, with matching placebos) for 96 weeks. The primary efficacy objective is comparison of HIV suppression (<50 viral RNA copies/mL in serum) between treatments at week 48. Secondary objectives include comparisons of % changes from baseline in hip and spine BMD at week 48, change from baseline in serum creatinine at week 48, and safety and tolerability. The NDA includes week 48 data from both trials, which were pooled for all analyses.

Study population: Entry criteria included age ≥ 18 years, HIV-treatment-naïve status, eGFR ≥ 50 mL/min; exclusions for systemic corticosteroids, active malignancy or serious infection.

Comment: *There were no exclusions for vitamin D deficiency or a history of bone disorders e.g. osteoporosis or osteomalacia.*

Study methods: DXA of lumbar spine and hip were conducted at baseline and every 24 weeks. Scans were analyzed at a central facility ([REDACTED] ^{(b) (4)} BMD T-scores were calculated (reference to database of young adult white women), and assigned to WHO diagnostic categories: normal (T-score ≥ -1.0), osteopenia (< -1.0 to ≥ -2.5), or osteoporosis (< -2.5). The sponsor also used the WHO algorithms for fracture prediction based on femoral neck BMD and other risk factors (FRAX) to calculate the 10-year probabilities of a hip fracture or major osteoporotic fracture (i.e. clinical spine, forearm, hip or shoulder); this was not specified in the protocol.

Reviewer comment: *Z-scores, adjusted for age, gender, ethnicity and race, are currently recommended over T-scores for premenopausal women or men <50 y/o (88% of the patients in these studies), or for children. In these groups, osteoporosis should not be diagnosed solely on the basis of BMD. FRAX is only validated for age ≥ 40 y/o.*

Serum markers of bone resorption (CTX) and formation (P1NP), PTH and renal parameters including Tmp/GFR were collected at various intervals. Proximal renal tubulopathy was defined by threshold abnormalities in ≥ 2 of 4 parameters (serum Cr, serum Pi, urine protein and glucose) (there is no commonly accepted definition of this disorder). Fractures were captured as adverse events based on HGLT of fractures from MedDRA 17.0 and SMQ of osteoporosis/osteopenia.

Statistical analyses: If the primary efficacy objective of noninferiority (E/C/F/TAF vs. STB) in HIV reduction at week 48 was achieved, secondary/ safety endpoints (also at week 48) were to be evaluated in order: hip BMD (% change from BL), then spine BMD (% change from BL), followed by serum creatinine and treatment-emergent proteinuria (dipstick).

Disposition: In studies 104/111 combined, 1733 patients were randomized and treated (866 with E/C/F/TAF, 867 with STB). As of the week 48 cutoff there were 45 E/C/F/TAF patients (5%) and 71 STB patients (8%) who discontinued treatment.

Demographics and baseline characteristics: Patients enrolled in studies 104/111 were of median age 34 y/o (range 18-76), 85% male, 57% white/25% black/11% Asian, 19% Hispanic, with median BMI 24.5 kg/m². About 1/3 of patients were enrolled at U.S. sites. Median eGFR at baseline was 115.8 mL/min. About 10% had baseline proteinuria by dipstick. Baseline BMD was slightly below age/gender matched means, with total hip mean Z-score of -0.19 SD for both treatment groups, and lumbar spine mean Z-scores of -0.27 SD and -0.33 SD (E/C/F/TAF and STB groups).

Concomitant medications included as of week 48, systemic corticosteroids (7% of E/C/F/TAF patients, 6% of STB patients); testosterone (3.1%, 3.3%); estrogen replacement (0.5%, 0.3%); oral bisphosphonates (0.8%, 0.6%); calcium/mineral supplements (9%, 11%); thyroid replacement (1.3%, 1.5%); anabolic steroids (0.5%, 0.3%); and anastrozole (0.1%, 0.2%).

Exposure median was 60 weeks in each treatment group at the time of the 48-week study report.

BMD: For treatment-naive adults, baseline BMD was slightly higher in the E/C/F/TAF group relative to STB (tables below). At weeks 24 and 48, for both hip and spine, mean declines from baseline BMD were significantly smaller with E/C/F/TAF compared with STB. LOCF analyses of week 48 data gave very similar results (not shown). Week 72 data were available from ~10% of patients as of the ISS cutoff date, showing similar treatment-group differences.

Studies 104 and 111: Total hip BMD (DXA)

	E/C/F/TAF (N=866)	STB (N=867)	E/C/F/TAF vs. STB*	
			p-value	LSM difference (95% CI)
Baseline BMD (g/cm²) (mean)	1.041	1.028	0.098	
Baseline BMD Z-score (mean)	-0.19	-0.19		
Week 24, n	789	815		
% change from BL, mean (SD)	-0.41 (2.15)	-1.73 (2.24)	<0.001	1.32 (1.11, 1.54)
Week 48, n	780	767		
% change from BL, mean (SD)	-0.66 (3.26)	-2.95 (3.41)	<0.001	2.29 (1.96, 2.62)
Week 72, n	101	88		
% change from BL, mean (SD)	0.74 (4.40)	-2.09 (4.14)	<0.001	2.83 (1.60, 4.06)

* P-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
 Values represent observed data in all patients with nonmissing baseline hip DXA
 Sources: ISS Table 20.1.2 and ADDEXA dataset

Studies 104 and 111: Lumbar spine BMD (DXA)

	E/C/F/TAF (N=866)	STB (N=867)	E/C/F/TAF vs. STB*	
			p-value	LSM difference (95% CI)
Baseline BMD (g/cm²) (mean)	1.135	1.114	0.011	
Baseline BMD Z-score (mean)	-0.27	-0.33		
Week 24, n	797	816		
% change from BL, mean (SD)	-1.25 (2.80)	-2.83 (2.90)	<0.001	1.58 (1.30, 1.86)
Week 48, n	784	773		
% change from BL, mean (SD)	-1.30 (3.08)	-2.86 (3.25)	<0.001	1.56 (1.25, 1.88)
Week 72, n	106	89		
% change from BL, mean (SD)	-1.31 (4.26)	-2.32 (4.09)	0.098	1.00 (-0.19, 2.19)

* P-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment as fixed effect
Values represent observed data in all patients with nonmissing baseline spine DXA
Sources: ISS Table 20.2.2 and ADDEXA dataset

Mean Z-scores declined slightly from baseline to week 48: for total hip BMD, -0.03 and -0.20 (E/C/F/TAF and STB respectively); and for lumbar spine BMD, -0.12 and -0.26.

Reviewer comment:

In a previous phase 3 study of STB (GS-US-236-0103), with a similar population of HIV-treatment-naïve adults, mean % changes in BMD in the STB arm were similar to those in the STB arm of studies 104/111: for total hip, -1.7% at week 24 and -3.1% at week 48; for lumbar spine, -3.0% at week 24 and -2.6% at week 48. Subsequently BMD stabilized, with little further change at weeks 96 and 144.

Study GS-99-903 also enrolled HIV-treatment-naïve adults, with similar age/gender and bone status (72% not osteopenic or osteoporotic at baseline). In that study, both treatment groups had bone loss in the first year; mean BMD declines from baseline at week 48 were -3.2% hip, -3.3% spine in patients receiving the TDF based regimen, and -1.8% hip, -2.0% spine in patients receiving the non-TDF regimen. In studies 104/111, bone loss in the (TDF-containing) STB arm at week 48 was similar to the TDF arm of study 903, while bone loss in the E/C/F/TAF arm was perhaps somewhat less than in the non-TDF arm of study 903.

In both arms of study 903, BMD was stable after week 48, so patients receiving TDF did not experience progressive bone loss but their BMD remained below that of the control (non-TDF) group at week 144. Limited week 72 results of studies 104/111, and week 96 results of study 102, suggest that E/C/F/TAF and STB treatment may follow the same pattern, i.e. TAF-based treatment may retain an advantage over TDF-based treatment in longer-term BMD. Complete week 96 results of studies 104/111 will be needed to help clarify this.

During the initial 48 weeks of these studies, there were more STB patients (103), compared to E/C/F/TAF patients (76), who initiated osteoporosis medications (bisphosphonates, calcitonin, calcium or vitamin D). Sensitivity analyses excluding these patients showed BMD results similar to the overall study populations.

Young adults experience some continued increases in bone mass following epiphyseal closure, so the sponsor conducted a post hoc analysis of 18-25 year olds in studies 104 and 111, pooled with those from study 102 (total n=355). Hip and spine BMD changes in these younger adults were similar to those for all adults, with about the same treatment group differences (ISS Tables Req6799.1.1 and Req6799.1.2).

There were fewer E/C/F/TAF than STB patients with >3% bone loss from baseline at week 48: 17% vs. 50% (hip) and 27% vs. 46% (spine).

There were 3 E/C/F/TAF and 4 STB patients who exhibited a total hip BMD decline from baseline of $\geq 12\%$ at any point. Of these 7 patients, 2 were women, and all were <30 y/o except for a 50 y/o woman. BMD increased from week 48 to 72 in the two patients where week 72 data were available. There were 3 patients with >20% decline at any point in total hip BMD: -34.0% in a STB patient; and -26.1% and -23.9% both in E/C/F/TAF patients; all of these were at week 48. None of these patients used systemic steroids during the study.

There were 7 E/C/F/TAF and 11 STB patients who exhibited a lumbar spine BMD decline from baseline of $\geq 12\%$ at any point. Two of these patients (1 E/C/F/TAF and 1 STB) were among the patients with $\geq 12\%$ hip BMD decline discussed above. All but 2 were males; 6/18 were \geq age 40. Most of these declines were at week 48. There were 5 of these patients with week 72 data available; in 3 of these BMD declined from week 48, and in the other 2 it increased from week 48. The largest decline in lumbar spine BMD was -20.3% in a STB patient. One of these patients used systemic steroids during the study: a 48 y/o woman who took oral prednisone for 2 weeks at week 18, and whose lumbar spine BMD declined by 12% from baseline at week 48.

FRAX: In patients ≥ 40 y/o, the mean 10-year probabilities of a hip fracture, calculated at baseline, were 0.34% and 0.47% for E/C/F/TAF and STB patients respectively; the 10-year probabilities of a major osteoporotic fracture were 2.82% and 3.21% for E/C/F/TAF and STB patients. The mean increases in these probabilities from baseline at week 48 were smaller for E/C/F/TAF patients: 0.09% vs. 0.17% for hip fracture risk, and 0.26% vs. 0.38% for major osteoporotic fracture risk.

Reviewer comment: *The FRAX data indicate overall low risk for osteoporotic (fragility) fractures, even in the more susceptible age group (>40 y/o), as expected with mean BMD Z-scores which were close to reference group means. The slight increases in estimated risk during the study are probably due mostly to patients being 1 year older.*

Bone markers: As in study 102, percent increases from baseline in CTx and P1NP were smaller in the E/C/F/TAF group compared with the STB group:

Studies 104/111: Bone biomarkers: % increases from baseline in mean values

	E/C/F/TAF (N=866)	STB (N=867)	p-value
Serum CTX			
% change at week 24	16.3	27.7	<.001
% change at week 48	17.3	27.9	<.001
Serum P1NP			
% change at week 24	26.2	71.4	<.001
% change at week 48	37.5	93.0	<.001
P-values are from the 2-sided Wilcoxon rank sum test to compare treatment groups Source: week 48 study reports, Table 11-7			

Median serum PTH also increased less in E/C/F/TAF patients (23%) compared to STB patients (42%) at week 48.

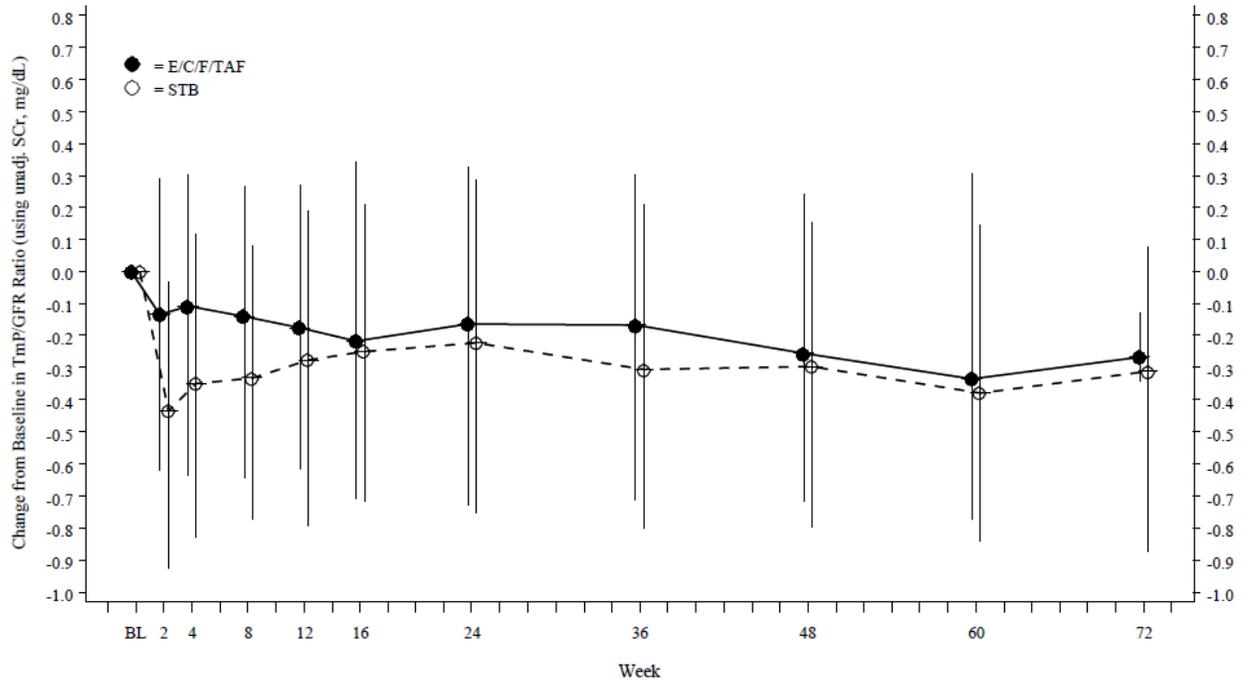
Reviewer comment: *Significant increase in serum PTH, though generally not beyond normal range, has been consistently associated with TDF in previous adult and pediatric studies. The mechanism of this is unclear. Renal tubule dysfunction would not generally be expected to cause increase in PTH, and normal PTH levels were reported in 7 cases of TDF-associated osteomalacia.^{2,4} Increased PTH may result in increased bone turnover and reduced BMD, however in study 903, analyses showed no significant correlation between changes in PTH and change in BMD.*

Renal: Similar to study 102, median eGFR decreased by 6.8 mL/min (E/C/F/TAF group) and 10.4 mL/min (STB group) (p<0.001). Various measures of proteinuria (dipstick, UACR, UPCR, urine RBP and β 2-microglobulin) and urine FE of uric acid (another PRT function indicator) all significantly favored E/C/F/TAF over STB. However, there were no cases that met the prespecified definition of PRT dysfunction.

TmP/GFR: Baseline median values were 3.6 mg/dL (E/C/F/TAF) and 3.5 mg/dL (STB). At weeks 2 and 4, there were declines in median TmP/GFR that were smaller in E/C/F/TAF patients (-0.1 mg/dL) than in STB patients (-0.3 to -0.4 mg/dL) (nominal p<.001 in each study, 104 and 111). After weeks 2-4, differences between treatment groups narrowed. In study 104 there were no significant differences between E/C/F/TAF and STB at any point beyond week 4. In study 111 (figure below) there was more separation of E/C/F/TAF and STB curves, with statistical significance (nominal p<.05) at weeks 2, 4, 8, 12 and 36.

Protocol GS-US-292-0111 (Week 48 Analysis)

Figure 15.1: Median (Q1, Q3) of Change from Baseline in TmP/GFR Ratio (Using Unadjusted SCr, mg/dL) by Visit
Safety Analysis Set



Source: Week 48 CSR study 111, report body p. 734

There were 5 E/C/F/TAF and 11 STB patients with very low TmP/GFR (<1.5 mg/dL) at least once post baseline. The lowest value in an E/C/F/TAF patient was 1.2 mg/dL, and the lowest in an STB patient was 0.64 mg/dL at 54 weeks. The latter patient (#0104-0121-4052), a 50 y/o male, also had at the time marked elevations of retinol binding protein, moderate elevation of ALP, and moderate declines in eGFR, in serum Pi (min. 2.3 mg/dL) and in BMD (-4.1% hip, -1.5% spine from baseline). He discontinued study treatment due to this AE, which was coded as decreased eGFR.

Reviewer comment: *Although it was not coded as such, this patient appears to have had significant PRT dysfunction related to STB treatment, but not of sufficient severity and duration to result in major bone loss or osteomalacia.*

Baseline median serum Pi was 3.6 and 3.5 mg/dL (E/C/F/TAF, STB arms) and did not change during treatment in either group. Hypophosphatemia grade 1 was reported in 2.7% of E/C/F/TAF and 3.0% of STB patients; grade 2 in 0.9% and 1.0% respectively; grades 3 and 4 in no patients. The lowest serum Pi individual values were 1.7 mg/dL (E/C/F/TAF) and 1.6 mg/dL (STB).

Reviewer comment: *The differences in TmP/GFR between E/C/F/TAF and STB (not a prespecified endpoint, and not discussed in the study report) are consistent with other markers of PRT dysfunction, but small (except for the one STB patient discussed above) and somewhat transient therefore of uncertain significance with respect to the risk of bone loss or osteomalacia. There was no overlap between the 16 patients with TmP/GFR <1.5 mg/dL and the 7 patients with the total hip BMD decline >12%. One of the 16 patients with lowest TmP/GFR (a 37 y/o male) was also among the 18 patients with lumbar spine decline >12%. Analysis of the*

possible correlation of TmP/GFR and BMD changes was not done by the sponsor and might be informative. The lack of severe hypophosphatemia is consistent with this being a late manifestation of PRT toxicity, at least in adults (as noted above, a previous trial suggested that hypophosphatemia may be more common in children receiving TDF).

Fractures were reported in 1.3% of E/C/F/TAF patients and 1.7% of STB patients (p=0.55). It appears that all were associated with significant trauma.

Studies 104 and 111: Fracture events

HGLT PT	E/C/F/TAF (N=866)	STB (N=867)
Fracture Events	11 (1.3%)	15 (1.7%)
Ankle fracture	1	1
Clavicle fracture	0	1
Facial bones fracture	1	0
Fibula fracture	0	2
Foot fracture	7	3
Hand fracture	0	1
Humerus fracture	1	1
Jaw fracture	0	1
Radius fracture	0	1
Rib fracture	0	3
Thoracic vertebral fracture	0	1
Wrist fracture	1	2

Source: ISS Table 24, p. 1076

Reviewer comment: One of these patients sustained osteoporotic fragility fractures: a 66 y/o male (STB group) with low baseline T-scores (hip -1.9, spine -4.3) who fractured a humerus on day 292 and a rib on 498, both from falls. Most of the other fractures were the result of moderate trauma such as falls, in patients with normal or “osteopenia” range Z-scores. Evidence suggests that BMD may be a factor in such events, though to a lesser extent than with osteoporotic fragility fractures (the exceptions to this are fractures of skull, face/jaw, metacarpals, fingers and toes, which are considered unrelated to bone fragility and are generally disregarded in fracture studies). With these low fracture rates, and small differences in BMD between the treatment groups, much larger studies would be needed to detect a difference in fractures.

Other musculoskeletal symptoms: Back pain was reported by 6.9% and 6.6% of E/C/F/TAF and STB patients respectively; arthralgia by 7.0% and 4.5%; pain in extremity by 4.0% and 2.9%; myalgia by 2.3% and 2.3%; musculoskeletal pain by 1.7% and 1.5%; muscle spasms by 0.9% and 1.0%; bone pain by 0.5% and 0.1%.

HIV-infected adults on a TDF-containing regimen (“switch” study): Study 109.

Design: This is a phase 3 study which, rather than treatment naïve patients, enrolled HIV-infected patients who were successfully treated (i.e. “virologically suppressed”) on one of the following regimens, all of which contain TDF and FTC as the NRTI “backbone”:

- STB (TDF, FTC, EVG, COBI)
- Atripla (TDF, FTC, EFV)
- Truvada + COBI-boosted atazanavir (TDF, FTC, ATV, COBI)
- Truvada + ritonavir-boosted atazanavir (TDF, FTC, ATV, RTV)

The patients are randomized (2:1) to either switch to E/C/F/TAF or remain on their TDF based regimen, for 96 weeks. Randomization was stratified by prior regimen. Treatments are open label.

As in studies 104/111, the primary efficacy endpoint is HIV suppression at week 48, and secondary endpoints are % changes from baseline in hip and spine BMD at week 48, change from baseline in serum creatinine at week 48, and safety and tolerability. The NDA includes interim week 48 data.

Study population: Entry criteria are HIV suppression (RNA < 50 copies/mL) for at least 6 months on one of the above regimens, age \geq 18 years, eGFR \geq 50 mL/min; exclusions for systemic corticosteroids, active malignancy or serious infection.

Study assessments are similar to studies 104/111 with BMD of lumbar spine and total hip every 24 weeks (DXA with central interpretation), and the same renal and bone safety markers, including the same prespecified criteria for PRT dysfunction.

Patient disposition: There were 1436 patients randomized and treated with E/C/F/TAF (n=959) or continued on their TDF based regimen (n=477). The TDF regimens were STB (32%), Atripla (26%), ATV/co + Truvada (15%) and ATV/RTV + Truvada (27%). At the week 48 cutoff date, study drug had been discontinued by 2.1% of E/C/F/TAF patients and 6.3% of TDF-regimen patients.

Demographics and baseline characteristics: About 65% of patients are enrolled at U.S. sites. Patients are 89% male, median age 41 y/o (range 21-77), 67% white/ 19% black/ 7% Asian, 23% Hispanic. Median BMI was 25.9 kg/m². About 10% had baseline proteinuria by dipstick. Consistent with these patients being (relative to patients in studies 104/111) ~7 years older and TDF-experienced, baseline BMD Z-scores were somewhat lower: for total hip, -0.36 and -0.39 (E/C/F/TAF and TDF regimen groups respectively), and for L-spine, -0.57 and -0.61 (E/C/F/TAF, TDF).

BMD: Patients continuing their TDF-based regimen, as expected, showed minimal change in BMD at 24-48 weeks (tables below). In contrast, those who switched to E/C/F/TAF had mean BMD increases of almost 2% at week 48 for both hip and spine, which were fairly consistent among the prior treatment regimen groups. Use of the LOCF method at week 48 yielded similar results.

Study 109: Total hip BMD (DXA)

	E/C/F/TAF (N=902)	TDF Regimen (N=452)	E/C/F/TAF vs. STB*	
			p-value	LSM difference (95% CI)
Baseline BMD (g/cm²) (mean)	1.000	0.994	0.42	
Baseline BMD Z-score (mean)	-0.57	-0.61		
Week 24, n	851	428		
% change from BL, mean (SD)	+1.02 (2.12)	-0.22 (1.90)	<0.001	+1.24 (1.00, 1.48)
Week 48, n	733	350		
% change from BL, mean (SD)	+1.95 (3.00)	-0.14 (2.99)	<0.001	+2.08 (1.70, 2.46)

* P-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment and prior treatment as fixed effects
Values represent observed data in all patients with nonmissing baseline hip DXA
Sources: Week 48 CSR Table 40.2 and ADDEXA dataset

Study 109: Lumbar spine BMD (DXA)

	E/C/F/TAF (N=912)	TDF Regimen (N=457)	E/C/F/TAF vs. STB*	
			p-value	LSM difference (95% CI)
Baseline BMD (g/cm²) (mean)	1.093	1.087	0.56	
Baseline BMD Z-score (mean)	-0.36	-0.39		
Week 24, n	862	433		
% change from BL, mean (SD)	+1.53 (2.71)	-0.19 (3.00)	<0.001	+1.71 (1.39, 2.04)
Week 48, n	742	356		
% change from BL, mean (SD)	+1.86 (3.09)	-0.11 (3.74)	<0.001	+1.97 (1.55, 2.39)

* P-values, difference in least squares means and its 95% CI were from the ANOVA model including treatment and prior treatment as fixed effects
Values represent observed data in all patients with nonmissing baseline hip DXA
Sources: Week 48 CSR Table 41.2 and ADDEXA dataset

Mean BMD Z-scores in patients who switched to E/C/F/TAF increased from baseline to week 48 by 0.15 (hip) and 0.19 (spine). Mean BMD Z-scores for patients who continued their TDF regimen were unchanged at week 48: +0.01 (hip) and +0.00 (spine).

During the initial 48 weeks of the study, there were more E/C/F/TAF patients (7.4%), compared to TDF-regimen patients (4.0%), who initiated osteoporosis medications (bisphosphonates, calcitonin, calcium or vitamin D). Sensitivity analyses excluding these patients showed BMD results similar to the overall study populations.

There were fewer E/C/F/TAF than TDF-regimen patients with >3% bone loss from baseline at week 48: 2% vs. 11% (hip) and 6% vs. 17% (spine).

There were 7 E/C/F/TAF patients (0.8%) and 13 TDF-regimen patients (2.9%) who exhibited a total hip BMD decline from baseline of >5% at week 24 and/or 48. There were 5 E/C/F/TAF patients (0.5%) and 10 TDF-regimen patients (2.2%) who exhibited a lumbar spine BMD decline

of >7% from baseline at week 24 and/or 48. Mean age (41 y/o) and gender mix of these patients were similar to the overall study. The largest individual declines, 16.4% for total hip and 19.4%, occurred at week 48 in a patient (██████████^{(b)(6)}) who developed Fanconi syndrome (see below). None of these patients used systemic steroids during the study.

Markers of bone turnover

Patients who switched to E/C/F/TAF from a TDF-based regimen experienced a decrease from baseline in serum P1NP, and little change in serum CTX or PTH.

Study 109: Bone markers: % change from baseline in mean values

	E/C/F/TAF (N=959)	STB (N=477)	p-value
Serum CTX			
% change at week 24	5.0	7.2	0.001
% change at week 48	6.6	11.2	0.007
Serum P1NP			
% change at week 24	-22.2	5.99	<.001
% change at week 48	-21.9	10.46	<.001
Serum PTH			
% change at week 24	-0.5	7.6	<.001
% change at week 48	2.2	16.2	<.001
P-values are from the Van Elteren test stratified by prior treatment regimen Source: week 48 study report, Tables 44.1, 44.2, 44.3			

Renal/ Phosphate: Parameters of proximal renal tubule function generally improved in patients switching from a TDF regimen to E/C/F/TAF. There was one patient who met the prespecified PRT tubulopathy criteria. This was a 57 y/o male (# ██████████^{(b)(6)}) who was randomized to continue his pre-baseline regimen of ATV/co + Truvada. On day 302 he was diagnosed with Grade 3 acquired Fanconi syndrome which included serum Cr 2.6 mg/dL, normoglycemic glycosuria 3+, proteinuria 3+, hypokalemia (2.3 mEq/L), hypophosphatemia (1.2 mg/dL), elevated FEPO4 (64%) and low TmP/GFR (0.89 with nadir 0.51 mg/dL). PTH at this point had increased from 38.7 to 64.0 i.e. high-normal; ALP remained normal. His baseline BMD was low (Z-scores: hip -2.11, spine -2.54); as noted above his BMD at day 302 had declined from baseline by 16.4% for total hip and 19.4% for lumbar spine. His treatment was discontinued.

Baseline mean TmP/GFR was 3.2 mg/dL in both treatment groups. At weeks 2 and 4 there was a slight mean increase (0.1 mg/dL) in the E/C/F/TAF group with no change in the continue-TDF group (0.0 mg/dL) (nominal p <.001 at week 2, p=0.09 at week 4). Thereafter, mean TmP/GFR was near baseline with no difference between groups. In addition to the patient with Fanconi syndrome discussed above, 2 other patients had TmP/GFR <1.0 mg/dL during the study, both on TDF regimens (RTV-boosted ATV and STB), and another had TmP/GFR of 0.86 mg/dL at screening, and after randomization to E/C/F/TAF maintained TmP/GFR ≥2.3 mg/dL.

Fractures were reported in 1.5% of E/C/F/TAF patients and 0.6% of TDF-regimen patients. All were reported to have resulted from trauma, and none classified as fragility fractures.

Study 109: Fracture events

HGLT PT	E/C/F/TAF (N=959)	TDF regimen (N=477)
Fracture Events	14 (1.5%)	3 (0.6%)
Clavicle fracture	1	0
Facial bones fracture	1	0
Fibula fracture	1	0
Foot fracture	1	1
Hand fracture	3	0
Hip fracture	1	0
Jaw fracture	1	0
Radius fracture	2	1
Rib fracture	1	0
Skull fracture	1	0
Ulna fracture	1	0
Upper limb fracture	1	1
Wrist fracture	1	0
Source: Wk 48 CSR Table 45		

HIV-1 infected adolescents (age 12-17 y/o): Study 106

Design: This is a single arm, open label phase 2/3 protocol to evaluate PK, safety and tolerability, and antiviral activity of E/C/F/TAF in an adolescent HIV treatment-naïve population. All patients receive E/C/F/TAF tab once daily (same doses as adults). The main phase of 48 weeks is currently ongoing. Interim data are included in the NDA and the Safety Update (submitted 2/24/15).

Concurrent with this E/C/F/TAF study, the sponsor is conducting a similar study in adolescents with STB (which is currently approved only in adults). The latter study, GS-US-236-0112, is of similar design to study 106 (open-label, single arm), with the same enrollment criteria and endpoints. The NDA ISS presents interim week 24 data from the two studies side-by-side.

Study population: Enrollment criteria include treatment-naïve status, age 12-17 y/o, weight ≥ 35 kg and eGFR ≥ 90 mL/min/1.73 m²; and no systemic steroids >1 week. Patients are enrolled at 9 study sites: 3 in the U.S., 3 in Africa, 3 in Thailand.

Study methods: BMD of lumbar spine and total body less head (TBLH) are evaluated at weeks 24 and 48 in study 106 (E/C/F/TAF), and also in the adolescent STB study using the same procedures. In an effort to facilitate comparison of BMD data across these studies and treatments, the sponsor uses a spine phantom to cross-calibrate Hologic and Lunar scanners in both studies. This is not done for TBLH BMD because the whole body phantom had not been validated by the DXA contractor ((b) (4)).

BMD Z-scores are calculated by comparison to a reference pediatric population matched by age, sex and race/ethnicity. In keeping with ISCD recommendations for children with short stature or

growth delay, Z-scores are further adjusted for height. Specifically, the sponsor has used two methods: adjustment for “height age” using CDC growth charts, and adjustment for height-for-age Z-score using data from an NIH sponsored study of BMD in healthy children⁸ (the method currently recommended by the ISCD).

Disposition: The NDA Safety Update indicates that enrollment (50 patients dosed with E/C/F/TAF) is complete. At the time of the initial NDA, week-24 data were available on 23 patients. Per the Safety Update, week-24 data are available on 43 patients, and week-48 data on 21 patients. One patients had discontinued (withdrew consent).

Demographics and baseline characteristics: Per the Safety Update, enrolled patients are 56% female; median age is 15 years (range 12-17); all patients are either black (88%) or Asian (12%); none are Hispanic. Half the males and 32% of the females were Tanner stage 5. As expected for HIV infected adolescents, growth is slightly below average with mean height and weight Z-scores of -0.75 and -0.31 and mean BMI of 20.0. Baseline BMD was also below average with mean Z-scores of -1.53 (lumbar spine) and -1.13 (TBLH); with adjustment for height-age these Z-scores were somewhat higher: -0.85 (lumbar spine) and -0.32 (TBLH).

TAF exposure in adolescents was ~22-29% lower than adult PK data. TFV exposure in adolescents was similar to adults i.e. ~90% lower than in adults receiving STB. Median exposure to E/C/F/TAF in study 106 is 24.3 weeks as of the Safety Update.

BMD: In healthy adolescents, areal BMD (DXA) rapidly increases, in large part due to increases in bone size. In study 106, HIV-infected adolescents exhibited mean increases from baseline at 48 weeks of 3.9% in lumbar spine BMD and 1.5% in TBLH BMD (table below, Safety Update).

Table 12. GS-US-292-0106: Baseline Value and Percentage Change from Baseline in Spine and Total-Body-Less-Head BMD (Spine and TBLH DXA Analysis Sets)

Time Point	Spine (N = 41)			TBLH (N = 40)		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline (g/cm ²)	41	0.797 (0.1947)	0.768 (0.677, 0.924)	40	0.889 (0.1209)	0.875 (0.816, 0.969)
Change from Baseline at:						
Week 24	41	1.661 (3.9624)	1.982 (-0.669, 3.952)	40	0.582 (2.5191)	0.298 (-1.184, 1.770)
Week 48	20	3.877 (3.7042)	3.255 (2.456, 6.322)	20	1.532 (2.5394)	1.301 (-0.304, 3.229)

Source: Safety Update

A ≥ 4% decrease in spine BMD was seen in 3 of 41 subjects at week 24 and 1 of 20 subjects at week 48. No subject had a ≥ 4% decrease in TBLH BMD at Weeks 24 or 48. (Safety Update)

Reviewer comment: In the previous study 321 of HIV-infected adolescents receiving a TDF regimen, mean lumbar spine BMD increased by 1.2% at week 24 and 3.2% at week 48;

respective increases in the comparison (non-TDF) group were 1.9% and 3.8%. There were 6/33 TDF patients, compared to 1/33 placebo patient, who experienced > 4% decline in lumbar spine BMD at 48 weeks.

BMD Z-scores: Mean Z-scores in adolescents, unadjusted for height, were low at baseline as noted above, and declined slightly during 24-48 weeks of E/C/F/TAF treatment:

Study 106: BMD Z-scores (not height-adjusted, mean)

	Lumbar spine	TBLH
Baseline, n	41	40
mean	-1.53	-1.13
Week 24, n	41	40
mean change from BL	-0.08	-0.11
Week 48, n	20	20
mean change from BL	-0.15	-0.21

Source: Safety Update

Reviewer comment: In previous study 321, adolescents treated with a TDF regimen had baseline mean (not height-adjusted) Z-scores of -1.00 (spine) and -0.87 (total body); at week-48 mean Z-scores declined by -0.22 (lumbar spine) and -0.25 (total body).

With adjustment for “height-age” (based on CDC charts), because patients were shorter than average, Z-scores were somewhat higher at baseline, and mean declines on E/C/F/TAF treatment were slightly less:

Table 13. GS-US-292-0106: Spine and Total-Body-Less-Head Height-Age Adjusted BMD Z-Scores at Baseline and Change from Baseline (Spine and TBLH DXA Analysis Set)

	Spine BMD Z-Score (Height-Age Adjusted)			TBLH BMD Z-Score (Height-Age Adjusted)		
	N	Mean (SD)	Median (Q1, Q3)	N	Mean (SD)	Median (Q1, Q3)
Baseline	35	-0.85 (1.283)	-0.64 (-1.90, 0.09)	33	-0.32 (1.012)	-0.19 (-1.12, 0.60)
Change from Baseline at:						
Week 24	33	-0.02 (0.363)	0.01 (-0.10, 0.21)	32	-0.09 (0.291)	-0.13 (-0.31, 0.12)
Week 48	13	-0.05 (0.373)	0.04 (-0.05, 0.12)	12	-0.19 (0.210)	-0.14 (-0.33, -0.08)

Source: Safety Update

Comparison of Week-24 BMD in different adolescent studies: In the ISS (without the added Safety Update data), the sponsor presents a comparison of interim 24-week data from two studies in HIV-infected adolescents: study 109 (E/C/F/TAF) and a similar open-label study (GS-US-236-0112) which uses STB. The table below presents some comparisons of these studies and, for further perspective, data from prior adolescent study 132, specifically the treatment arm which received TDF plus an individualized background regimen. The study populations differ in multiple aspects particularly racial/ethnic composition and baseline bone status as shown. Regarding lumbar spine BMD, patients in the STB study (b) (4)

With E/C/F/TAF, lumbar spine BMD declined by >4% at week 24 in two patients (-6.8% and -8.0%). With total body BMD there were smaller treatment group differences.

Adolescent TAF and TDF studies: comparison of week-24 data

(b) (4)

	E/C/F/TAF Study 106 N=23
HIV treatment status (pre-baseline)	Tx-naïve
Age, mean (range)	15 (12-17)
Gender (% male)	42
Race (white/black/Asian/other)	0/88%/12%/0
Ethnicity (% Hispanic)	0
Height Z-score (mean)	-0.91
Lumbar spine BMD	
Baseline (g/cm ² , mean)	0.779
Week 24, % change from BL (mean)	+1.73
Week 24, # with >4% decline	2/23
Lumbar spine BMD Z-score (unadjusted)	
Baseline (mean)	-1.60
Week 24, change from BL (mean)	-0.10
Lumbar spine BMD Z-score (height-age adjusted)	
Baseline (mean)	-0.84
Week 24, change from BL (mean)	-0.08
Lumbar spine BMD Z-score (height-Z-score adjusted**)	
Baseline (mean)	-1.04
Week 24, change from BL (mean)	-0.04
TBLH BMD	
Baseline (g/cm ² , mean)	0.872
Week 24, % change from BL (mean)	+0.77
Week 24, # with >4% decline	0/23
TBLH BMD Z-score (unadjusted)	
Baseline (mean)	-1.25
Week 24, change from BL (mean)	-0.11
TBLH BMD Z-score (height-age adjusted)	
Baseline (mean)	-0.44
Week 24, change from BL (mean)	-0.10

*data from TDF arm of study only

**adjusted by method of Zemel⁸ and with post hoc cross calibration between centers in both studies

Source: ISS adolescent summary, Tables 17.1, 17.2, 18.1, 18.2, 18.3, 18.4, ISS pediatric addendum Table 3-3, DRUP Consult Review of NDA 021356/S33

Reviewer comment:

(b) (4)

Biochemical:

(b) (4)

Adverse events:

(b) (4)

HIV-infected, renally impaired adult: Study 112

Design: This is an ongoing phase 3, single arm open-label study of HIV infected adults with renal insufficiency. Patients may be “virologically suppressed” on TDF regimens (Cohort 1) or treatment naïve (Cohort 2). All patients receive E/C/F/TAF and are monitored for 96 weeks.

Study population: adults (age ≥ 18 y/o) with either mild or moderate renal insufficiency (eGFR 30-70 mL/min).

Disposition: As of the Safety Update, enrollment was complete with 242 patients in Cohort 1 (switch) and 6 patients in Cohort 2 (treatment naïve); 17 patients (all Cohort 1) had discontinued the study drug. Median duration of exposure was 48 weeks.

Demographics and baseline characteristics: Because of the inclusion criterion of renal insufficiency, Cohort 1 patients were older (median age 58 y/o) than the other adult studies; they were 79% male, 63% white/ 18% black/ 14% Asian, 14% Hispanic. All 6 Cohort 2 patients were male with median age 54 y/o, 3 black/ 2 white/ 1 Asian.

BMD increased for the Cohort 1 patients after the switch to E/C/F/TAF, especially the patients whose pre-switch regimen included TDF. The 6 treatment naïve patients exhibited declines in spine BMD with little change in hip BMD.

Study 112: Total Hip BMD (DXA)

	Cohort 1 (switch)			Cohort 2 (treatment naïve)
	Pre-Switch TDF (N=154)	No Pre-Switch TDF (N=82)	Total (N=236)	Total (N=6)
Baseline BMD (g/cm ²) (mean)	0.918	0.919	0.918	0.973
Week 24, n	148	77	225	6
% change from BL, mean (SD)	+1.15 (2.93)	-0.07 (2.23)	+0.733 (2.77)	-0.02 (1.69)
Week 48, n	144	72	216	6
% change from BL, mean (SD)	+1.85 (3.31)	+0.70 (5.49)	+1.47 (4.19)	-0.07 (1.61)
Week 72, n	11	5	16	0
% change from BL, mean (SD)	+1.58 (4.47)	+1.40 (6.77)	+1.52 (5.06)	

Source: Safety Update Table 6.1

Study 112: Lumbar spine BMD (DXA)

	Cohort 1 (switch)			Cohort 2 (treatment naïve)
	Pre-Switch TDF (N=154)	No Pre-Switch TDF (N=82)	Total (N=236)	Total (N=6)
Baseline BMD (g/cm ²) (mean)	1.056	1.112	1.075	1.034
Week 24, n	147	79	226	6
% change from BL, mean (SD)	+2.37 (3.71)	+0.29 (3.04)	+1.64 (3.63)	-2.69 (4.58)
Week 48, n	142	72	214	6
% change from BL, mean (SD)	+2.95 (4.19)	+0.96 (4.07)	+2.29 (4.24)	-4.14 (4.59)
Week 72, n	10	5	15	0
% change from BL, mean (SD)	+2.51 (2.69)	+0.59 (3.05)	+1.87 (2.86)	

Source: Safety Update Table 6.2

Reviewer comment: *In patients who switched from a TDF-based regimen to E/C/F/TAF there were increases in BMD comparable to patients (with more normal renal function) making a similar switch in study 109. Patients switching from non-TDF regimens had much smaller increases. Labeling statements about BMD increases should probably specify that this occurs only with switching from a TDF regimen to E/C/F/TAF.*

Markers of bone turnover: Serum CTX, P1NP and PTH decreased from baseline at weeks 24 and 48 in patients switching from a TDF containing regimen, and increased from baseline in patients switching from a non-TDF regimen.

Phosphate: Among switch patients (Cohort 1), mean TmP/GFR increased from baseline by 0.1-0.3 mg/dL at weeks 1, 2, 4 and 8, and subsequently returned to near baseline. In the 6 treatment-naïve subjects, there were moderate declines in mean TmP/GFR.

Adverse events: There are no cases of proximal renal tubulopathy. There are 5 subjects (2.1%), all in Cohort 1, with a total of 6 fractures, none of which were reported as fragility fractures.

Discussion: TDF appears to have subclinical effects on renal function (mainly proximal tubule) and/or bone metabolism (decreased BMD) in substantial numbers of adult and pediatric patients. There is at least a partial connection between the renal and bone toxicities with the reports of Fanconi syndrome and osteomalacia due to phosphate wasting associated with TDF. However these reports are rare in relation to the widespread use of TDF, and the clinical importance of renal and BMD effects for most patients is unclear.

Data presented in this NDA are consistent in favoring E/C/F/TAF over STB and other TDF-based regimens in a variety of bone and renal safety endpoints in HIV-infected adults. In treatment-naïve patients, E/C/F/TAF caused substantially less stimulation of bone turnover markers and PTH, and smaller declines in hip and spine BMD over 48 weeks of treatment. In HIV patients already on treatment with a TDF regimen, switching to E/C/F/TAF appeared to have favorable effects including increases in hip and spine BMD of nearly 2% at 48 weeks. Longer term data will be important, as previous studies have shown that TDF bone loss is not progressive after the first year of treatment. Some data beyond 48 weeks from studies 102, 104 and 111 suggest that E/C/F/TAF may retain an advantage over TDF regimens with respect to BMD; additional data from week 96 will be needed to confirm this. No differences have been shown in bone fractures, which would require studies of much larger size and longer duration for adequate assessment. As shown by the sponsor's FRAX analyses, the target population for these drugs has a generally low risk for fractures, which is minimally affected by the BMD changes at least in a 1-year timeframe.

Data in HIV-infected adolescents are limited and uncontrolled, and do not show convincingly that lumbar spine and total body BMD are accrued at the expected rates while on E/C/F/TAF treatment (i.e. maintenance of height-adjusted BMD Z-scores). It has also not been established that E/C/F/TAF is superior to STB or other TDF regimens with respect to BMD in adolescents though it is very unlikely to be inferior.

The data provide limited insight into the phosphate metabolism effects that are believed to underlie the bone toxicity of TDF. Most of the patients with large declines in BMD did not have evidence of phosphate wasting. However, the largest BMD declines (16.4% hip, 19.4% spine) in study 109 occurred in a patient who developed Fanconi syndrome and hypophosphatemia during TDF-based treatment. There were also statistically significant differences in TmP/GFR between TAF and TDF based regimens in studies 104/111, but which were small and transient. It would be helpful to have a better understanding of the relationship of the various renal and bone parameters. We would recommend consideration of asking the sponsor to conduct correlational analysis, e.g. between TmP/GFR and BMD.

Although the data suggest overall-improved long term bone safety with TAF over TDF, it is uncertain whether individual patients, perhaps with the known risk factors, may still be at risk for osteomalacia, bone loss and/or fractures. TDF-related renal and bone safety issues were generally not apparent in clinical trials, and emerged postmarketing. Many of the reported cases of TDF-associated osteomalacia presented after several years of treatment, and correct diagnosis was for some patients delayed up to 1-2 years despite substantial pain and disability.^{4,5} In the E/C/F/TAF trials only one patient (out of a total of 1402 patients treated with a TDF active-control regimen) developed renal tubulopathy, which became evident through frequent lab monitoring, and no patients on any treatment had symptoms suggestive of osteomalacia. In the pivotal studies (104, 111) there were many E/C/F/TAF patients (n=9) as well as STB patients (n=14) with >12% decline from baseline in lumbar spine or hip BMD at any time. (b) (4)

Proposed E/C/F/TAF labeling: (b) (4)

We (DBRUP) advise retaining a bone safety related W&P for E/C/F/TAF, with appropriate revisions from the language for TDF products, (b) (4) we propose moving BMD data (b) (4) to section 6.1, as per the following suggested changes:

5 WARNINGS AND PRECAUTIONS (b) (4)

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF. (b) (4)

Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir [See Warnings and Precautions (5.3)].

6 ADVERSE REACTIONS

6.1 Adverse Reactions from Clinical Trials Experience

Clinical Trials in Treatment Naïve Adults

In the pooled analysis of Studies 104 and 111, bone mineral density (BMD) from baseline to Week 48 was assessed by dual-energy X-ray absorptiometry (DXA) to compare the bone safety of tenofovir alafenamide (TAF) to that of tenofovir disoproxil fumarate (TDF) when administered as [TRADENAME] or STRIBILD, respectively. Mean percentage decreases in BMD from baseline to week 48 (b) (4) at the lumbar spine (-1.30% versus -2.86%) and the hip (-0.66% versus -2.95%) (b) (4) BMD declines greater than (b) (4)% were experienced by (b) (4)% of [TRADENAME] subjects and (b) (4)% of STRIBILD subjects for lumbar spine. (b) (4)

Clinical Trials in Virologically Suppressed Adults

In Study 109, TDF-treated patients were randomized to continue their TDF regimen or switch to [TRADENAME] then changes in BMD from baseline to Week 48 were assessed by DXA. Subjects who switched to [TRADENAME] experienced mean BMD increases (1.86% lumbar spine, 1.95% hip) and subjects who continued the baseline regimen experienced small BMD decreases (-0.11% lumbar spine, -0.14% hip) (b) (4) BMD declines greater than (b) (4) at the lumbar spine were experienced by (b) (4)% of [TRADENAME] subjects and (b) (4)% of subjects who continued their TDF regimen. (b) (4)

Clinical Trials in Pediatric Subjects

Among the 23 pediatric subjects receiving [TRADENAME] for 24 weeks, mean BMD increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for total body less head.

However, mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at week 24. Two [TRADENAME] subjects had significant (greater than 4%) lumbar spine BMD loss at week 24.

(b) (4)

References

1. Hall AM et al, Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence, *Am J Kidney Dis* (2011), 57: 773-780
2. Haverkort ME et al, Tenofovir-induced Fanconi syndrome and osteomalacia in two HIV-infected patients: role of intracellular tenofovir diphosphate levels and review of the literature, *Scand. J. Infect. Dis.* (2011), 43: 821-826

3. Saldenber-Kermanac'h N et al, Normal plasma FGF23 levels kinetic in tenofovir-related hypophosphatemic osteomalacia in an HIV-infected patient with von Recklinghausen disease, *Joint Bone Spine* (2011), 78:306-308
4. Mateo L et al, Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients, *Clin Rheumatol* (2014), doi 10.1007/s10067-014-2627-x
5. Woodward CLN et al, Tenofovir-associated renal and bone toxicity, *HIV Medicine* (2009), 10: 482-487
6. Labarga P et al, Kidney tubular abnormalities in the absence of impaired glomerular function in HIV patients treated with tenofovir, *AIDS* (2009), 23: 689-696
7. Kinai E and Hanabusa H, Progressive renal tubular dysfunction associated with long-term use of tenofovir DF, *AIDS Res Human Retrovir.* (2009), 25: 387-394
8. Zemel BS et al, Height adjustment in assessing dual energy X-ray absorptiometry measurements of bone mass and density in children, *J Clin Endocrinol Metab* (2010), 95: 1265-73

APPENDIX: Current TDF labeling related to bone safety

Below is the current bone related safety labeling for Viread. The Stribild label contains the same W&P except for the second paragraph (Stribild is only approved in adults); contains BMD and fracture data from Stribild clinical trials in place of the Viread bone data in section 6.1; and lists the same postmarketing musculoskeletal symptoms in section 6.2.

VIREAD

5 Warnings and Precautions

5.6 Bone Effects

Bone Mineral Density:

In clinical trials in HIV-1 infected adults, VIREAD was associated with slightly greater decreases in bone mineral density (BMD) and increases in biochemical markers of bone metabolism, suggesting increased bone turnover relative to comparators. Serum parathyroid hormone levels and 1,25 Vitamin D levels were also higher in subjects receiving VIREAD [*See Adverse Reactions (6.1)*].

Clinical trials evaluating VIREAD in pediatric and adolescent subjects were conducted. Under normal circumstances, BMD increases rapidly in pediatric patients. In HIV-1 infected subjects aged 2 years to less than 18 years, bone effects were similar to those observed in adult subjects and suggest increased bone turnover. Total body BMD gain was less in the VIREAD-treated HIV-1 infected pediatric subjects as compared to the control groups. Similar trends were observed in chronic hepatitis B infected adolescent subjects aged 12 years to less than 18 years. In all pediatric trials, skeletal growth (height) appeared to be unaffected. [*See Adverse Reactions (6.1)*].

The effects of VIREAD-associated changes in BMD and biochemical markers on long-term bone health and future fracture risk are unknown. Assessment of BMD should be considered for adults and pediatric patients who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Although the effect of supplementation with calcium and vitamin D

was not studied, such supplementation may be beneficial for all patients. If bone abnormalities are suspected then appropriate consultation should be obtained.

Mineralization Defects:

Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of VIREAD [See *Adverse Reactions (6.2)*]. Arthralgias and muscle pain or weakness have also been reported in cases of proximal renal tubulopathy. Hypophosphatemia and osteomalacia secondary to proximal renal tubulopathy should be considered in patients at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing tenofovir DF [See *Warnings and Precautions (5.3)*].

6 Adverse Reactions

6.1 Adverse Reactions from Clinical Trials Experience

Clinical Trials in Adult Patients with HIV-1 Infection

Changes in Bone Mineral Density:

In HIV-1 infected adult subjects in Study 903, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in subjects receiving VIREAD + lamivudine + efavirenz ($-2.2\% \pm 3.9$) compared with subjects receiving stavudine + lamivudine + efavirenz ($-1.0\% \pm 4.6$) through 144 weeks. Changes in BMD at the hip were similar between the two treatment groups ($-2.8\% \pm 3.5$ in the VIREAD group vs. $-2.4\% \pm 4.5$ in the stavudine group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the trial and this reduction was sustained through Week 144. Twenty-eight percent of VIREAD-treated subjects vs. 21% of the stavudine-treated subjects lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in 4 subjects in the VIREAD group and 6 subjects in the stavudine group. In addition, there were significant increases in biochemical markers of bone metabolism (serum bone-specific alkaline phosphatase, serum osteocalcin, serum C telopeptide, and urinary N telopeptide) and higher serum parathyroid hormone levels and 1,25 Vitamin D levels in the VIREAD group relative to the stavudine group; however, except for bone-specific alkaline phosphatase, these changes resulted in values that remained within the normal range [See *Warnings and Precautions (5.6)*].

Clinical Trials in Pediatric Subjects 2 Years of Age and Older with HIV-1 Infection

Changes in Bone Mineral Density:

Clinical trials in HIV-1 infected children and adolescents evaluated BMD changes. In Study 321 (12 to less than 18 years), the mean rate of BMD gain at Week 48 was less in the VIREAD compared to the placebo treatment group. Six VIREAD treated subjects and one placebo treated subject had significant (greater than 4%) lumbar spine BMD loss at Week 48. Changes from baseline BMD Z-scores were -0.341 for lumbar spine and -0.458 for total body in the 28 subjects who were treated with VIREAD for 96 weeks. (b) (4)

(b) (4) skeletal growth
(height) appeared to be unaffected [*See Warnings and Precautions (5.6)*].

6.2 Postmarketing Experience

Musculoskeletal and Connective Tissue Disorders

rhabdomyolysis, osteomalacia (manifested as bone pain and which may contribute to fractures), muscular weakness, myopathy

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STEPHEN R VOSS
03/25/2015

THERESA E KEHOE
03/25/2015

HYLTON V JOFFE
03/25/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207561

Applicant: Gilead

Stamp Date: 11/ 5/ 2014

Drug Name: Genvoya

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	(b)(1)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: There are 14 Phase 1 and 2 Phase 2 studies that were used to determine appropriate dose and duration of the FDC	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 GS-US-292-0104 P3 indication treatment in treatment naïve HIV infected adult patients. DB active control, multicenter, randomized 872, Endpoint P 48 weeks < 50cps/mL of HIV snapshot. Pivotal Study #2 GS-US-292-0111 P3 indication treatment in treatment naïve HIV infected adult patients. DB active control, multicenter, randomized 872, End point 48 weeks < 50cps/mL of FDA snapshot. Study #3 GS-US-292-0109 P 3 indication switch study of adult HIV infected on successful ARV, no hx of ARV failure /resistance to components, randomized, open label, active control, multicenter, randomized 1443, Endpoint 48 weeks < 50cps/mL of HIV snapshot.	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
26.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? Narrative for SAEs, Deaths, Pregnancies, Discontinuations and Fracture events were provided.	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? X

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

It is fileable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

William B. Tauber	15 December 2014
Reviewing Medical Officer	Date

Linda L. Lewis	
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM B TAUBER
02/03/2015

LINDA L LEWIS
02/04/2015