CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 1, 2015
From	Linda L. Lewis, M.D. Medical Officer Team Leader, DAVP
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 207561 Original
Applicant	Gilead Sciences
Date of Submission	November 5, 2014
PDUFA Goal Date	November 5, 2015
Proprietary Name / Established (USAN) names	GENVOYA™ elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide
Dosage forms / Strength	Fixed dose combination tablets containing: Elvitegravir 150 mg Cobicistat 150 mg Emtricitabine 200 mg Tenofovir alafenamide 10 mg
Proposed Indication(s)	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Recommended:	*Approval – with modifications to labeling as described in this review*

Purpose of Cross-Discipline Team Leader (CDTL) Review

The purpose of this Cross-Discipline Team Leader (CDTL) review is to convey the CDTL's assessment of the major issues pertinent to approvability of the application, provide a summary of the clinical evidence (efficacy trials, safety database, critical clinical pharmacology data), and describe key aspects of review issues relevant to other disciplines (clinical pharmacology, microbiology, CMC, non-clinical pharmacology/toxicology).

In this review, "Genvoya" and "E/C/F/TAF" will be used interchangeably.

1. Introduction

This submission provides the non-clinical and clinical data to support a New Drug Application for Genvoya, a fixed dose combination (FDC) tablet intended to provide a complete treatment regimen for HIV-1 infection. Genvoya contains elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor (INSTI), cobicistat (COBI), a CYP3A4 inhibitor included to increase elvitegravir concentrations, and emtricitabine (FTC) and tenofovir alafenamide (TAF), two HIV-1 nucleoside/tide reverse transcriptase inhibitors (NRTIs). Of the four component drugs, only tenofovir alafenamide (TAF) has not been previously approved either alone or in combination with other antiretrovirals. The submitted clinical trials were designed to demonstrate the safety and efficacy of the combination elvitegravir, cobicistat, emtricitabine, TAF (E/C/F/TAF) compared to Stribild, another FDC containing E/C/F combined with tenofovir disoproxil fumarate (TDF), a different tenofovir prodrug, and more specifically the safety and efficacy of the TAF component of the Genvoya FDC.

The submission contains study reports characterizing the chemistry/manufacturing/control (CMC) processes, nonclinical toxicology, in vitro and clinical virology, and clinical pharmacology (including multiple drug-drug interaction studies), in addition to clinical safety and efficacy of the E/C/F/TAF complete regimen. Much of the submitted information focuses on TAF because it represents the only unapproved component drug; CMC and nonclinical information relevant to the previously approved components cross-references the NDAs for those drugs.

2. Background

TDF-containing regimens have become preferred antiretroviral treatment regimens for adult patients but have been associated with clinically significant renal and bone toxicity. TDF also has excellent antiviral activity against hepatitis B virus (HBV) and has also become a mainstay of treatment for chronic HBV infection. However, use has been restricted in patients with impaired renal function and even some patients with normal renal function at initiation of treatment have developed significant renal injury. The “signature” TDF renal toxicity is development of proximal renal tubule dysfunction, including Fanconi’s syndrome. Renal tubule dysfunction has been associated with phosphorus wasting and, in a small number of patients, manifested as osteomalacia, a finding previously associated with tenofovir in animal toxicology studies. More often, asymptomatic loss of bone mineral density (BMD), osteopenia, or osteoporosis was identified by the dual X-ray absorptiometry (DXA) monitoring performed in the clinical trials or in clinical practice. Labeling for TDF-containing products includes Warnings and Precautions describing the potential for new or worsening renal impairment and for the deleterious bone effects.

The original IND 63737 for TAF was opened in November, 2001, but inactivated in May, 2005, presumably due to the success and wide-spread use of TDF following its approval in 2001. From early in the TAF development program, the Applicant noted TAF appeared to have greater antiviral activity in some cell lines than either the parent drug tenofovir or the

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approved pro-drug TDF and appeared to provide greater intracellular distribution of tenofovir in PBMCs and lymphatic tissue while yielding lower plasma levels. As the renal and bone limitations of TDF were better characterized over ensuing years, Gilead reactivated the TAF IND in November, 2010, and began to focus development on the assumption that lower plasma levels of tenofovir would lead to less toxicity.

Phase 1, pharmacokinetic/pharmacodynamic studies demonstrated that doses as low as 8 to 25 mg of TAF had antiviral activity comparable to the approved dose of TDF 300 mg. These results provided Gilead a basis for developing TAF in (b) (4) products for treatment of both HIV and hepatitis B virus (HBV) infection, similar to products now containing TDF. The Applicant has chosen to base all antiretroviral product development programs on the efficacy and safety generated for E/C/F/TAF as a complete treatment regimen for HIV. The E/C/F/TAF FDC tablet contains the same dosages of EVG, COBI, and FTC that are currently approved as Vitekta (EVG), Tybost (COBI), Emtriva (FTC), Truvada (F/TDF), and Stribild (E/C/F/TDF) for use in adults: 150 mg of EVG, 150 mg COBI, and 200 mg of FTC. (b) (4)

The submitted clinical trials package includes multiple clinical trials in HIV-infected adults with no prior history of treatment, in adults on a stable treatment regimen with effective HIV suppression and no prior virologic failure, and in adolescents 12 to 18 years of age with no prior history of treatment. The Applicant also submitted (b) (4) which were not considered pertinent to evaluation of E/C/F/TAF and were not reviewed as part of the NDA. An outline of the reviewed clinical trials is included in Table 1.

Table 1: Pivotal and Supportive Clinical Trials Submitted and Reviewed for NDA 207561

Study	Trial Arms	Comments/Results
Active Comparator-Controlled Double Blinded		
GS-US-292-0104	▪ Phase 3, randomized, double blind, multicenter, international ▪ E/C/F/TAF FDC 1 qd x 48 weeks (N=438) ▪ Stribild FDC 1 qd x 48 weeks (N=434)	▪ Pivotal Study ▪ International study conducted US, CDN Australia, Japan, Thailand, Austria, Belgium, Italy, Spain, Switzerland, UK, PR. 120 study sites ▪ Showed non-inferiority E/C/F/TAF to Stribild
GS-US-292-0111	▪ Phase 3, randomized, double blind, multicenter, international ▪ E/C/F/TAF FDC 1 qd x 48 weeks (N=431) ▪ Stribild FDC 1 qd x 48 weeks (N=435)	▪ Pivotal Study ▪ International study conducted US, FR, Italy, NL, Portugal, Sweden, UK, DR, PR, Mexico, CDN. 121 study sites ▪ Showed non-inferiority E/C/F/TAF to Stribild
GS-US-292-0102	▪ Phase 2 randomized 2:1 , double blind, multicenter, treatment naïve subjects ▪ E/C/F/TAF FDC 1 qd x 24 weeks	▪ Supportive Study ▪ International, conducted US and PR. 37 study sites ▪ Supported progression to Phase 3 trials

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	(N=112) ▪ Stribild FDC 1 qd x 24 weeks (N=58)	
Active Controlled, Open Label		
GS-US-292-0109	▪ Phase 3, open label, switch study of subjects with no history of virologic failure successful on TDF containing regimen switched to E/C/F/TAF or remain on prior regimen ▪ E/C/F/TAF one qd (n=959) ▪ FTC/TDF + prior 3rd agent (n=477) Stribild, Atripla, Atazanavir/COBI or ATZ + RTV	▪ Supportive Study ▪ Conducted in US, Australia, Thailand, Austria, Belgium, Denmark, France, Germany, Italy, NL, Portugal, Spain, Sweden, Switzerland, UK, Brazil, DR, Mexico, CDN, PR. 168 study sites, last observation 8/14 ▪ Showed non-inferiority of E/C/F/TAF to continuing prior regimen at 48 weeks
Phase 2/3 Open Label, Uncontrolled		
GS-US-292-0112	▪ Open-label, non-randomized, non-comparative, Phase 3 study of subjects with "mild" (50-69mL/min) to "moderate" (30-49mL/min) renal impairment either switched from successful therapy to E/C/F/TAF (n=246) or treatment naïve (n=6). Renal function eGFR 30-69 mL/min at least 3 months ▪ All subjects received E/C/F/TAF in usual doses ▪ Primary objective was renal parameters at 24 weeks	▪ Supportive Study ▪ Conducted in US, Australia, Thailand, France, NL, Spain, UK, DR, Mexico. 70 study sites. ▪ No significant changes eGFR through week 24 ▪ Switch subjects: At week 24 virologic success was 95%, at week 48 success 93%
Pediatric Studies		
GS-US-292-0106	▪ Phase 2/3, open-label, single-arm, study of adolescents 12 to < 18 years of age. PK, safety, tolerability, antiviral activity (n=23) through 24 weeks, total enrollment 48 ▪ Treatment naïve ▪ E/C/F/TAF FDC adult dosage	▪ Supportive Study ▪ Conducted in US, Thailand, South Africa, Uganda. 9 study sites ▪ Interim analysis at week 24: virologic success rate of 91%

This CDTL Review will focus on issues related to the approval of E/C/F/TAF as a complete regimen for treatment of HIV infection with emphasis on aspects of the review specific to TAF, not previously approved as a single entity. Evidence supporting the approval of EVG, COBI, and FTC will not be addressed as these data have been previously reviewed.

3. CMC/Device

The NDA submission included adequate information to allow the CMC review team to evaluate the characteristics and quality of the drug substance for the new entity TAF and

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the final FDC drug product, Genvoya tablets. For a complete discussion of the CMC issues, please refer to the full Product Quality Review provided by the CMC review team: Drs. Jeff Medwid, George Lunn, Lin Qi, and Jessica Cole, and the Biopharmaceutics Reviewer Dr. Salaheldin Hamed. Their combined review includes only the aspects of the CMC issues related to EVG, COBI, or FTC which are relevant to the Genvoya tablet, as these individual active ingredients have been reviewed previously. The following descriptions of key CMC issues are summarized from the Chemistry Review.

- ***General product quality considerations***

The Drug Substance Quality review focused on review of the TAF component (tenofovir alafenamide fumarate) as all other active drug substances have been reviewed under other NDAs. TAF is considered a New Molecular Entity because it is a novel prodrug of tenofovir that differs from the currently approved prodrug TDF by features such as the phosphonamide linkage. The drug substance is produced (b) (4) Starting materials for TAF synthesis and their specifications were reviewed and agreed upon after some discussion with the Applicant. Drug substance specifications for all key tests were reviewed and agreed upon, including: identity, clarity of solution, water content, impurity content (for specified and unspecified impurities), residual solvents, melting point, and particle size.

As noted in the Product Quality Review, the applicant provided sufficient data to demonstrate the consistency of the proposed Genvoya commercial manufacturing process at the proposed commercial scale. The Genvoya drug product contains EVG 150 mg, COBI 150 mg, FTC 200 mg, and TAF 10 mg (as 11.2 mg of TAF fumarate) in a green, capsule-shaped, immediate-release, film-coated tablet. Tablets are manufactured using an (b) (4) Tablets are packaged as a 1-month supply in 30-count HDPE bottles with child-resistant closure; each bottle contains a silica gel dessicant and a polyester coil. There are no novel excipients; all are compendial except the film coating which is made from compendial components. Tablets are debossed with "GSI" on one side and "510" on the other side. All analytical methods are described in reasonable detail and have been validated.

Eighteen months of stability data obtained at 25°C/60% RH and 30°C/75% RH and 6 months of data obtained at 40°C/75% RH were provided for 3 batches and lesser amounts of data were provided for a further 5 batches. Stability testing demonstrated trends to (b) (4) . However, the results and statistical analysis support a 24 month expiration dating period. (b) (4) the Applicant committed to continue manufacturing processes to reduce the risk of TAF degradation. The drug product specification contains tests for appearance, identity, (b) (4) assay, degradants, dose uniformity, dissolution, and microbial limits that were considered acceptable to the Review Team.

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- ***Facilities review/inspection***

The facilities listed in this submission have been carefully reviewed. Initial risk assessment were conducted and GMP inspections were issued based on the 2, 3, 4 years rule for GMP inspection in November, 2014 prior to the CDER policy change with regards to surveillance inspection. In-depth review was conducted for each of the facilities according to the previous inspection history, nature of FDA 483 and firm's response, product recalls, product characteristics, as well as the FDA observations related to the current manufacturing process of the drug substance or the drug product. One site, (b) (4) , was submitted as a manufacturer of FTC, however on Feb 6, 2015 an amendment to NDA 207561 was submitted to remove this facility from the application. At the time of this CDTL Review, all facilities inspections and reviews have been completed for all drug substances and final drug product. The Offices of Compliance and New Drug Quality Assessment have determined these facilities to be acceptable.

- ***Other notable issues (resolved or outstanding)***

There are no outstanding product quality issues related to either TAF drug substance or the Genvoya tablet drug product. The Product Quality Review team recommends approval of Genvoya with an expiration dating period of 24 months.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a portfolio of nonclinical study reports describing the results of acute and chronic toxicity studies, genotoxicity studies, and reproductive toxicology studies for TAF. Nonclinical studies were not conducted with the E/C/F/TAF FDC, as considered acceptable in the ICH M3(R2) guidance. For a complete discussion of the in vitro safety assessments and animal toxicology studies, please refer to the Pharmacology/Toxicology Review performed by Dr. Claudia Wrzesinski. Her review does not include evaluation of nonclinical studies conducted for approval of EVG, COBI, or FTC as these studies have been reviewed previously. Key points from the Pharmacology/Toxicology review are summarized in this section.

- ***General nonclinical pharmacology/toxicology considerations***

TAF was evaluated in a series of nonclinical studies designed to assess the toxicologic properties of circulating TAF (prior to prodrug conversion to tenofovir) and identify potential differences between TAF and TDF. Overall, the four drugs included in the Genvoya FDC exhibit different patterns of main target organ toxicity, therefore, administration of TAF in combination with EVG, COBI, and FTC is unlikely to exacerbate known toxicities of the individual agents. The property of COBI to inhibit tubular secretion of creatinine may have implications for monitoring potential renal toxicity but is unlikely to contribute to renal pathology/toxicity.

The Pharmacology/Toxicology Reviewer focused special attention on the nonclinical toxicities previously demonstrated with TDF, particularly the renal and bone toxicity, as those were also identified in TDF clinical trials and in clinical practice. In her review, Dr.

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Wrzesinski noted that chronic administration of TAF led to dose-dependent, slight to moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog as well as renal karyomegaly in the rat. In the dog, partial recovery was observed after three months. These findings were qualitatively similar to the renal findings in the TDF nonclinical program. In addition, dose dependent reductions in bone mineral density and mineral content, as well as changes in markers of bone turnover and in related hormones, were observed in rats and dogs. Partial recovery was observed after three months in dogs. The bone findings were also qualitatively similar to those identified in the TDF nonclinical program.

The TAF exposure levels at the no-effect level for bone and kidney toxicity in the dog were lower than the human TAF exposure after Genvoya administration. However, the bone and kidney toxicities were previously observed in TDF nonclinical studies and are believed to be due to tenofovir (post-prodrug conversion) exposure. Tenofovir exposures at the no-effect level were 13- and 4-times for rats and dogs, respectively, the human tenofovir exposure after Genvoya administration. Since TAF has a very short half-life in rats, no plasma exposure for TAF could be measured. The Applicant provided nonclinical data supporting their assertion that TAF more easily permeated cells where it was efficiently converted to the active metabolite, the tenofovir diphosphate .

Dr. Wrzesinski's review of the TAF nonclinical studies noted two potential toxicities not observed in the TDF nonclinical studies, ocular and cardiac. In dogs, a minimal to slight infiltration of mononuclear cells of the posterior uvea was seen in animals receiving the high dose with similar severity after three and nine month administration of TAF. Reversibility was seen after a three months recovery period but a mechanism for this finding was not identified. At the no-effect level for eye toxicity the systemic TAF exposure in dogs was 5 times the exposure seen in humans receiving the recommended Genvoya dose and 15 times the tenofovir exposure. The TAF chronic dosing study in dogs showed a PR prolongation at the mid and high doses, and a reversible reduction in heart rate associated with mild QT prolongation in the high dose animals at week 39. These changes were associated with decreases in serum T3. Recovery was observed after 13-weeks. The systemic TAF exposure at the no-effect level, was lower in dogs than expected in humans; therefore, no safety margins for this toxicity were established.

No novel excipients are used in the manufacture of E/C/F/TAF tablets. The proposed specifications for impurities in the EVG, COBI, FTC and TAF drug substances were deemed acceptable based on results from general toxicology studies, genotoxicity data, and/or assessments of potential mutagenicity using (Q)SAR.

- ***Carcinogenicity***

None of the components of Genvoya were considered genotoxic based on a standard battery of the reverse mutation bacterial test (Ames test), the mouse lymphoma assay, or mouse/rat micronucleus assays. Early in the development program, the Applicant demonstrated that the rapid conversion of TAF to tenofovir resulted in very low TAF exposure in rats and TgRasH2 mice. Because TAF is so rapidly converted to tenofovir in these rodent species usually employed in carcinogenicity studies, the

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Pharmacology/Toxicology review team previously agreed with the Applicant that a TAF carcinogenicity study was unlikely to be informative. The carcinogenicity studies conducted for the TDF development program were considered adequate to inform the labeling for TAF because of the common tenofovir active metabolite. TDF was considered to have low carcinogenic potential in previous studies; liver adenomas were identified in mice but at exposures far above expected human exposure (167 times).

- ***Reproductive toxicology***

The reproductive toxicology of TAF was evaluated in a series of standard animal studies as noted in the Pharmacology/Toxicology Review. In a rat fertility study, no drug related changes occurred at dose equivalent to 155 times the human dose based on body surface area comparison. The reproductive developmental toxicity was evaluated in pregnant rats and rabbits and there was no evidence of embryolethality, fetal toxicity, or teratogenicity attributed to TAF in either species.

As with the assessment of carcinogenicity, a perinatal and postnatal study was not conducted for TAF registration due to the rapid conversion of TAF to tenofovir resulting in very low TAF exposure in the relevant species. The peri/postnatal study conducted with TDF adequately characterized the potential postnatal toxicity of tenofovir. The measured tenofovir exposures in the dams at the no-effect level for developmental toxicity (150 mg/kg/day) and F1 toxicity (50 mg/kg/day) were 27 and 14 times higher than the exposure in humans at the recommended daily dose of TAF.

- ***Other notable issues (resolved or outstanding)***

In summary, TAF represents a prodrug of tenofovir with somewhat different properties than TDF leading to lower plasma concentrations of the tenofovir "parent" drug. The nonclinical toxicity profile of TAF was similar to that of TDF, although there is some nonclinical evidence the lower circulating concentrations of tenofovir may mitigate these toxicities. Administration of TAF in combination with EVG, COBI, and FTC is unlikely to lead to overlapping toxicity profiles that might result in increased clinical toxicity.

At this time, there are no unresolved nonclinical review issues and the Pharmacology/Toxicology Reviewer and Team Leader recommend approval of E/C/F/TAF.

5. Clinical Pharmacology/Biopharmaceutics

TAF, either alone or as part of Genvoya, was extensively evaluated to assess its clinical pharmacologic characteristics, to determine dose- and exposure-response relationships, and to identify relevant drug-drug interactions. For a complete discussion of the clinical pharmacology issues, please refer to the integrated Clinical Pharmacology Review submitted by Drs. Mario Sampson (Pharmacokinetics) and Jeffry Florian (Pharmacometrics). The Clinical Pharmacology Review did not focus on the pharmacologic properties of EVG, COBI, or FTC as single drugs but did evaluate aspects of these drugs as related to the Genvoya FDC. Complete clinical pharmacology information for EVG, COBI, and FTC can be found in the

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reviews and labeling for those drugs. The following points summarize the analyses and conclusions of the Clinical Pharmacology review team.

- ***General clinical pharmacology/biopharmaceutics considerations***

The NDA provided information regarding the general pharmacologic properties of TAF. As noted in the Clinical Pharmacology Review, TAF is readily absorbed and can be detected in plasma. Plasma concentrations of tenofovir are substantially lower than those resulting from the approved dose of TDF. When E/C/F/TAF is administered with food to HIV-infected subjects, TAF T_{max} is 1 hour. Relative to fasting conditions, administration of E/C/F/TAF with a light meal or high fat meal results in TAF AUC increased by 15% and 18%, respectively. Both EVG and COBI are recommended to be taken with food and, consequently, the clinical trials recommended administration of E/C/F/TAF with food. In samples collected during clinical trials, ex-vivo binding of TAF to plasma proteins was about 80%. Pharmacokinetic parameters were comparable in healthy subjects and HIV-1 infected subjects receiving Genvoya.

Dose selection of TAF for the Phase 3 clinical trials was based on data from a short (X days) monotherapy trial comparing TAF 8 mg, TAF 25 mg, and TAF 40 mg to the approved dose of TDF 300 mg. Decreases in HIV RNA levels were similar to the TDF dose for TAF 8 mg and were larger for the TAF 25 mg and TAF 40 mg doses and the 25 mg dose was selected as the optimal dose for further development. However, TAF 10 mg was included in the Genvoya FDC because coadministration with COBI increases TAF exposure (i.e., COBI/TAF 10 mg results in TAF exposure similar to TAF 25 mg).

Exposure-response relationships for efficacy and safety parameters were evaluated for TAF and the combined E/C/F/TAF. Based on monotherapy studies, each of the three antiretroviral drugs included in the FDC were at near maximal antiviral activity. Exposure-response was not evaluated for COBI because it has no antiviral activity. Evaluation of data in the Genvoya (and earlier Stribild) Phase 3 trials, suggested exposure-response relationships for efficacy of EVG, TAF, and tenofovir were flat. As noted in the Clinical Pharmacology review, logistic regression analysis showed a trend between TAF exposure and nausea at the highest 4% of TAF exposure, and vomiting was associated with the highest 19% of TAF exposure. TAF and tenofovir Cmax and AUC were not associated with a significant percent change from baseline in hip or spine BMD at Week 48 or maximum increase from baseline in serum creatinine. Similarly, change from baseline in lipid levels observed among subjects receiving E/C/F/TAF in the clinical trials were not associated with either TAF or tenofovir exposure. No clinical safety parameter was found to have an exposure-response relationship to the other component drugs.

Similar to other NRTI drugs, the mechanism of action of TAF is dependent on intracellular phosphorylation of tenofovir and incorporation of tenofovir diphosphate into viral DNA. The Clinical Pharmacology Reviewers were unable to document adequate validation of the bioanalytic methods used in the Applicant's assay for intracellular tenofovir diphosphate. Therefore, although the Applicant asserts TAF provides higher intracellular concentrations of this active moiety, these assay results will not be included in the Genvoya labeling.

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- ***Drug-drug interactions***

The Genvoya FDC contains multiple components that have clinically relevant drug-drug interactions. COBI was specifically developed as a CYP3A inhibitor designed to increase exposure of CYP3A substrates such as EVG. This interaction was effectively exploited in the earlier Stribild development program. COBI is also metabolized to some extent by CYP2D6 and inhibits multiple transporters (Pgp, BCRP, OATP1B1, and OATP1B3). EVG is a modest inducer of CYP2C9. Many of the drug-drug interactions relevant to EVG/COBI and concomitant medications were evaluated in the Stribild development program and assumed to be applicable to Genvoya.

TAF is a substrate of efflux transporters Pgp and BCRP, in addition to uptake transporters OATP1B1 and OATP1B3. TAF exposure is increased by COBI because COBI is an inhibitor of these transporters. TAF is a weak inhibitor of CYP3A but does not inhibit or induce other CYP isoenzymes and does not inhibit any transporters.

FTC is not metabolized and has no clinically significant drug-drug interactions.

Overall, the drug-drug interaction potential and appropriate labeling of the Genvoya FDC is complex. As will be noted in Genvoya labeling, drugs that induce CYP3A activity are expected to increase the clearance of EVG and COBI, resulting in decreased plasma concentration of COBI, EVG, and TAF, which may lead to loss of therapeutic effect and development of resistance. Coadministration of Genvoya with other drugs that inhibit CYP3A may decrease the clearance and increase the plasma concentration of COBI.

- ***Pathway of elimination***

TAF is primarily eliminated by metabolism to tenofovir by cathepsin A in peripheral blood mononuclear cells, the site of action, and carboxylesterase 1 in hepatocytes. TFV is intracellularly phosphorylated to the active moiety tenofovir-diphosphate which is ultimately eliminated by the kidneys via glomerular filtration and active tubular secretion. In a mass balance study in healthy volunteers given radiolabeled TAF, tenofovir represented 86% and 99% of the radioactivity dose recovered in urine and feces, respectively. EVG and COBI are eliminated by the hepatobiliary route, primarily metabolized by CYP3A. FTC is also eliminated by the kidneys via glomerular filtration and active tubular secretion.

- ***Critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment***

The components of Genvoya have been evaluated in the settings of hepatic and renal impairment. TAF PK was determined in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment. Compared to subjects with normal hepatic function, TAF exposure was minimally increased (13%) in subjects with moderate impairment. No dose adjustment will be recommended for subjects with mild to moderate hepatic impairment. Genvoya will not be recommended for subject with severe hepatic impairment (Child-Pugh C) as it has not been evaluated in this population. These recommendations are similar to those for Stribild.

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Because tenofovir is eliminated renally and TDF has been associated with renal toxicity, the Applicant conducted a dedicated safety and efficacy study of Genvoya in subjects with estimated glomerular filtration rate (eGFR) as determined by the Cockcroft-Gault method between 30 mL/min to 69 mL/min. The clinical aspects of this study (Study 0112) are further discussed in Sections 7 and 8 of this CDTL Review. Key PK data from this study was described in the Clinical Pharmacology Review. As noted in that review, compared to PK data from a study in HIV-infected subjects with normal renal function, subjects with moderate renal impairment (defined as eGFR 30-49 mL/min) had about 2-fold increased FTC and tenofovir AUC values. However, FTC was only measured in a small cohort of participants (TAF and tenofovir were measured in all subjects) and FTC exposure-response relationships for safety could not be fully evaluated in subjects with renal impairment. Therefore, the clinical significance of 2-fold increased FTC exposures is unclear. The changes in some key PK parameters for the component drugs are summarized in Table 2 abstracted from Dr. Sampson's review. In a small PK study of subjects with severe renal impairment, TAF and tenofovir were markedly increased but tenofovir concentrations were still lower than those observed in subjects receiving the approved dose of TDF 300 mg. Because Genvoya dosing is fixed, it will not be recommended for use in patients with eGFR less than 30 mL/min.

Table 2: Percent Changes in PK Parameters of E/C/F/TAF in HIV-infected Subjects with Renal Impairment Compared to HIV-infected Subjects with Normal Renal Function

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	↔
Tenofovir	AUC_{tau} (ng*h/mL)	↑109	↑55

Source: Clinical Pharmacology Review, M. Sampson, page 35.
Values are percent change (parameter mean in renally impaired group/parameter mean in normal renal function group*100) relative to subjects with normal renal function (Phase 2 study GS-US-292-0102, n=19).

As noted in the Pharmacometrics Review integrated into the Clinical Pharmacology Review, the effects of age, sex, race, weight, BMI, BSA, and creatinine clearance (CrCL) on TAF and tenofovir exposure were evaluated in a population PK analysis. There were no significant covariates in the TAF model. Significant covariates in the tenofovir model were CrCL, HIV status (infected versus healthy), sex, and black race which each resulted in a 2-fold or lower tenofovir exposure change.

- ***Demographic interactions/special populations***

In general, the Pharmacometrics Reviewer confirmed the Applicant's conclusions that TAF exposure was not significantly affected by demographic factors. Because pediatric

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approval is usually based on extrapolating efficacy from the adult clinical trials by matching drug exposure, the PK of E/C/F/TAF in HIV-infected adolescents was evaluated in Study 0106. Compared to HIV-infected adults, mean TAF and COBI exposures were decreased by 23% and 14%, respectively. TAF has flat exposure-response relationships for efficacy, thus the reduced exposures were considered acceptable. COBI exposures are of secondary importance, as the purpose of COBI is to increase the exposure of EVG which was comparable in HIV-infected adolescents and adults. In addition, the Pharmacometrics Reviewer noted the lack of PK data in subjects older than 75 years and could not confirm appropriate exposure in this age group.

- ***Thorough QT study or other QT assessment***

The effect of the Genvoya FDC on the QT interval is not known, however, three of the four component drugs have been evaluated individually for the potential to cause cardiac arrhythmias, including QT and PR prolongation. A thorough QT/QTc study of TAF was conducted in 48 healthy subjects at the recommended dose or at a dose approximately 5 times the recommended dose. In this study, TAF did not affect the QT/QTc interval and did not prolong the PR interval at either the recommended therapeutic dose or at the supratherapeutic dose.

Thorough QT assessments were previously reviewed for EVG and COBI as part of the original development programs for those drugs. EVG did not affect the QT/QTc interval and did not prolong the PR interval. COBI did not affect the QT/QTc interval but modest prolongation of the PR interval was noted in subjects receiving COBI at doses 1.67 and 2.67 times the doses in Genvoya. The Review Team's conclusion related to PR prolongation with COBI was that because the 150 mg cobicistat dose used in Genvoya is lower than the lowest dose studied in the thorough QT study, it is unlikely that treatment with Genvoya will result in clinically relevant PR prolongation.

FTC has not been evaluated in a thorough QT study as it was approved for use prior to the recommendation to conduct these studies. As there has been no postmarketing signal for cardiac arrhythmias, a formal study was not required, but the effect of FTC on QT or PR intervals cannot be definitively determined.

- ***Other notable issues (resolved or outstanding)***

There are no unresolved clinical pharmacology issues identified in the review. The Clinical Pharmacology Reviewers determined that information submitted with the NDA adequately informed the dose selection of TAF as a component of Genvoya and characterized the pharmacologic properties of Genvoya. Many drug-drug interactions with Genvoya were established or predicted to inform use with a variety of frequently-administered drugs. Additionally, the Review Team noted that while exposures of TAF and COBI following administration of Genvoya in adolescents were somewhat decreased compared to adults, exposures were considered overall acceptable based on exposure-response relationships. The Clinical Pharmacology Reviewers and Team Leader recommend approval of this NDA.

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6. Clinical Microbiology

The Applicant submitted multiple studies and analyses evaluating the antiviral mechanism of action of TAF, the emergence of resistance substitutions to the Genvoya component drugs, and the patterns of cross-resistance with other antiretrovirals. Some of the evaluations were conducted as part of the development programs for either the individual component drugs or Stribild and were referenced from previous Virology Reviews as applicable. Please refer to the Virology Review submitted by Dr. Lisa Naeger for a detailed discussion of these data and analyses. As with other discipline reviews, Dr. Naeger's review focuses on assessment of TAF and its contribution to Genvoya's overall antiviral effects. The main conclusions of her review are summarized below.

- ***General virology considerations***

The Virology Review describes TAF as a prodrug that is metabolized intracellularly to the active metabolite, tenofovir diphosphate. Assessment of the intracellular metabolism of TAF in immune cells including $CD4^+$ T-cells, lymphocytes, and monocytes showed efficient conversion of the prodrug to the active metabolite tenofovir diphosphate. Tenofovir diphosphate is an inhibitor of HIV-1 reverse transcriptase that competes with the natural nucleotide deoxyadenosine triphosphate (dATP) for incorporation into viral DNA and acts as a viral DNA chain terminator during the process of retroviral reverse transcription, thus blocking HIV replication. TAF has EC_{50} values ranging from 0.14 to 12.0 nM, with a mean of 3.5 nM, against primary HIV-1 isolates. The activity of TAF against HIV-1 in cell culture is 100- to 600-fold greater than tenofovir and 4- to 6-fold greater than TDF. TAF was also shown to be a potent inhibitor of hepatitis B virus replication but has minimal activity against other viruses. In cell culture systems, TAF has the same cytotoxicity profile as TDF and tenofovir. Results of earlier non-clinical testing suggest tenofovir has low potential to inhibit human DNA polymerases or mediate mitochondrial damage.

- ***Resistance***

TAF and TDF have a similar resistance profile in cell culture and in clinical trials. Cell culture resistance selection experiments with TAF selected for the K65R substitution, previously described in association with TDF. Phenotypic analyses showed 6.5-fold reduced TAF susceptibility of K65R selected viruses. A K70E substitution, also previously described in clinical trials with TDF and associated with small decreases in susceptibility, was also identified in in TAF resistance selection experiments as a mixture with wild-type virus.

Emergence of resistance-associated substitutions was investigated in the Genvoya clinical trials. Resistance testing was performed in any subject who received at least one dose of study drug and demonstrated either suboptimal virologic response or virologic rebound as defined in the study protocols or who was HIV-1 viremic at the final study timepoint; genotyping required HIV-1 RNA > 400 copies/mL. Subjects meeting these criteria were assessed with genotyping of the protease, reverse transcriptase, and integrase genes and results were compared to baseline testing (performed on all subjects at study entry). Baseline testing was not available for subjects enrolled in Study 0109 as they were

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required to be fully suppressed at the time of enrollment; some comparisons were made to subjects' historic genotype results. Baseline genotype testing was analyzed for the presence of known resistance-associated substitutions for the component drugs. On-study genotype testing was compared to the baseline results to determine newly emergent substitutions.

Virologic outcomes at Week 48 were good in the clinical trials included in the resistance analysis (Studies 0104, 0111, and 0109) with > 90% of subjects receiving E/C/F/TAF achieving HIV-1 RNA < 50 copies/mL. For the pooled treatment-naïve Studies 0104 and 0111, the FDA virologic failure analysis included 14 virologic failures in the E/C/F/TAF arm and 17 virologic failures in the Stribild arm of whom 7 E/C/F/TAF and 5 Stribild recipients had resistance-associated substitutions emerge. In the E/C/F/TAF arm, all 7 of the virologic failures with emergent substitutions had the M184V substitution and one subject had the K65R substitution. Three subjects had emergent Q207E/H/R in reverse transcriptase. Five of the 7 subjects had emergent INSTI resistance substitutions. In the Stribild arm, 5 of the 6 subjects with emergent substitutions had emergent M184V substitutions and one had the K65R substitution. Four the 6 subjects had emergent INSTI resistance substitutions.

Subjects in Study 0109 (N=1196) were required to have suppressed HIV RNA at the time of enrollment and historic genotype results were available as subjects had previously participated in other Gilead-sponsored clinical trials. As subjects entered Study 0109 fully suppressed and without significant resistance associated substitutions, very few subjects met the virologic failure criteria by Week 48. Four subjects receiving E/C/F/TAF and 1 subject remaining on F/TDF-containing regimen were included in the FDA resistance analysis. Among this small group, one subject had identifiable M184V-associated resistance to FTC at Week 8; discontinuation of study drug and initiation of a new regimen led to resuppression of HIV-1 RNA. No other resistance emerged and other subjects who met virologic failure criteria were noted to have resupression of HIV-1-RNA without a change in regimen, suggesting that other reasons contributed to their initial virologic failure.

Study 0106 achieved good virologic outcomes similar to those observed in the adult trials. No subjects in this small trial met the criteria for virologic failure and inclusion in the resistance analysis.

- ***Cross-resistance***

In phenotypic testing, TAF was shown to have the same resistance profile as tenofovir against a panel of patient-derived HIV-1recombinant isolates with a range of NRTI resistance substitutions and susceptibilities in two different assays (Monogram Biosciences PhenoSense assay and MT-2 assay). As noted in Dr. Naeger's review, clinical susceptibility cutoffs for TDF in the same assay have been previously established at 1.4-fold. Susceptibility to TAF for the panels of mutants in each of these assays was similar to tenofovir. High levels of resistance to tenofovir and TAF were observed in isolates with T69 double insertions (PhenoSense assay) and in isolates harboring multiple TAMs including T215Y and L210W in the absence of the M184V or with the Q151M substitution

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complex (MT-2 assay). The established tenofovir resistance-associated substitutions K65R and K70E also result in reduced susceptibility to other NRTIs including abacavir, didanosine, FTC, lamivudine.

- ***Notable issues (resolved or outstanding)***

There are no unresolved virology issues. The Virology Reviewer concluded the number and type of emergent NRTI and INSTI resistance substitutions was similar across Genvoya and comparator arms in the reviewed trials. TAF did not reduce the frequency of virologic failure or the number of resistance-associated substitutions emerging during treatment compared to TDF. The FDA assessment of resistance and cross-resistance patterns for TAF will be included in labeling along with a summary of resistance and cross-resistance related to the other component drugs of Genvoya. After careful review of the submitted virology data, both the Virology Reviewer and Team Leader recommend approval of Genvoya.

7. Clinical/Statistical- Efficacy

To support their proposed indication for Genvoya, the Applicant conducted two adequate and well-controlled, Phase 3 trials: Studies 0104 and 0111 in treatment-naïve, HIV-1-infected adult subjects. These two pivotal clinical trials were identical in study design and study population and compared Genvoya to Stribild. Results from these two trials will be presented as pooled analyses. The primary efficacy endpoint in both clinical trials was the proportion of subjects achieving HIV-1 RNA < 50 copies/mL at 48 weeks of treatment using the FDA's standardized "snapshot" analysis as described in the published *Draft Guidance for Industry, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (June, 2013)*. A non-inferiority margin of 12% was agreed upon for both trials and pre-specified in the protocols. Additional supportive efficacy data were submitted from Study 0109 in which subjects were either switched from a suppressive treatment containing F/TDF plus a third active antiretroviral drug to Genvoya or continued on their prior regimen. In addition, while not intended primarily to support efficacy, Study 0112 provided noncomparative outcome data in subjects with renal impairment treated with Genvoya. Finally, the Applicant submitted an interim analysis of Study 0106, an open-label, noncomparative study in adolescent HIV-1-infected subjects to support dosing recommendations in that age group. The primary efficacy endpoint for all supportive studies was the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48 (for Study 0109) or Week 24 (for Studies 0106 and 0112). For detailed descriptions of the registrational and supportive clinical trial designs, please refer to the Clinical Review provided by Drs. William Tauber, Peter Miele, and Andres Alarcon.

Overall, the clinical and statistical reviewers' independent analyses confirmed the Applicant's primary efficacy findings and many secondary endpoint analyses for the pivotal clinical trials. Dr. Thomas Hammerstrom, the Statistical Reviewer, conducted numerous analyses to assess the robustness of the results and homogeneity in different demographic subgroups. In general, all of these methods produced very similar results. The following points summarize the key findings of the FDA's clinical and statistical reviewers.

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A total of 1733 subjects were included in the pooled efficacy analysis population of the combined pivotal Studies 0104 and 0111: 866 received Genvoya and 867 received Stribild. Both trials enrolled predominately at study sites in North America and Europe but included sites in Thailand, Japan, Australia, Mexico, and Dominican Republic. Baseline demographic and disease characteristics were balanced across treatment arms in both trials. The pooled trial population was 85% male, 57% white, 25% black/African American, 10% Asian, 19% identified as Hispanic/Latino. The median age was 36 years (range 18 to 76 years). The trial population had a median HIV-1 RNA of 4.5 log10 copies/mL and a median CD4+ cell count of 427 cells/mm^3 at baseline, with 23% of participants having HIV-1 RNA > 100,000 copies/mL and 13% having CD4+ cell count < 200 cells/mm^3.

Genvoya met the pre-specified primary efficacy endpoint in both of the clinical trials and was found to be non-inferior to Stribild (see Table 3). Both treatment regimens resulted in high rates of viral suppression and low rates of study drug discontinuation for any reason. A relatively small number of subjects in any treatment arm failed to have virologic data available at the Week 48 evaluation. Efficacy was similar across population subgroups analyzed according to age, sex, race/ethnicity, and baseline viral load. The information in Table 3 will be displayed in the product label.

Table 3: Pooled Virologic Outcomes of Randomized Treatment at Week 48[a] in Treatment Naïve Subjects (Studies 0104 and 0111)

	Genvoya (N=866)	**STRIBILD (N=867)**
HIV-1 RNA < 50 copies/mL	92%	90%
Treatment Difference	2.0% (95% CI: -0.7% to 4.7%)	
HIV-1 RNA ≥ 50 copies/mL[b]	4%	4%
No Virologic Data at Week 48 Window	4%	6%
Discontinued Study Drug Due to AE or Death[c]	1%	2%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	2%	4%
Missing Data During Window but on Study Drug	1%	<1%

Source: Clinical Review NDA 207561, W. Tauber, page

[a] Week 48 window was between Day 294 and 377 (inclusive).

[b] Included subjects who had ≥ 50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.

[c] Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.

[d] Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

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The Applicant conducted Study 0109 to test the hypothesis that switching from a TDF-based regimen to the TAF-based Genvoya FDC might provide some measurable safety benefit in this otherwise stable and virally-suppressed, relatively well population. This study was designed to enroll 1500 subjects and treat them through 96 weeks. The trial is being conducted in 168 sites in Europe, Australia, Thailand, North and South America. The submitted data represents an interim analysis timed in order to complete the analysis of a large representative population for NDA submission. At the time of submission, Study 0109 had enrolled 1,436 subjects who received at least 1 dose of study drug (E/C/F/TAF 959; TDF 477). The Applicant's analysis of the primary efficacy endpoint included the Week 48 "analysis population" of 1196 subjects (E/C/F/TAF 799; TDF 397), defined as all subjects randomized by October 31, 2013 and who had received at least 1 dose of study drug.

Demographic and baseline disease characteristics were similar between the two treatment groups in Study 0109 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. In the randomized study population, 90% of subjects were male, 67% were white, 21% were black, 6% were Asian, and 23% identified as Hispanic/Latino. The mean age was 41 years (range 21 to 77 years). Mean eGFR was 112 mL/min (median 106 mL/min). Mean CD4+ cell count was 705 cells/mm^3. At the time of entry into the study, 42% of subjects were receiving FTC/TDF plus atazanavir (given with either cobicistat or ritonavir), 32% were receiving Stribild, and 26% were receiving Atripla (FTC/TDF/efavirenz).

Study 0109 met its prespecified primary efficacy endpoint and demonstrated that in this select patient population, switching to Genvoya was noninferior to remaining on a suppressive TDF-based regimen (see Table 4). In this study, efficacy was determined by maintaining the previously achieved virologic suppression. The switch study design of this trial is not as rigorous a test of virologic suppression as the design of Studies 0104 and 0111 and very few subjects (1% in each arm) had a true virologic failure. The difference in overall efficacy, defined as HIV-1 RNA < 50 copies/mL, is primarily due to small differences in the numbers of subjects discontinuing the study drug due to "other reasons" not related to either virologic failure or adverse events. The information in Table 4 will be displayed in the product label.

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Table 4: Virologic Outcomes of Randomized Treatment at Week 48[a] in Virologically-Suppressed Subjects who Switched to Genvoya (Study 109)

	Genvoya (N=799)	**FTC/TDF + 3rd Active Antiretroviral (N=397)**
HIV-1 RNA < 50 copies/mL	96%	93%
HIV-1 RNA ≥ 50 copies/mL[b]	1%	1%
No Virologic Data at Week 48 Window	3%	6%
Discontinued Study Drug Due to AE or Death[c]	1%	1%
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL[d]	1%	4%
Missing Data During Window but on Study Drug	2%	1%

[a] Week 48 window was between Day 294 and 377 (inclusive).
[b] Included subjects who had ≥ 50 copies/mL in the Week 48 window; subjects who discontinued early due to lack or loss of efficacy; subjects who discontinued for reasons other than an adverse event (AE), death or lack or loss of efficacy and at the time of discontinuation had a viral value of ≥ 50 copies/mL.
[c] Includes subjects who discontinued due to AE or death at any time point from Day 1 through the time window if this resulted in no virologic data on treatment during the specified window.
[d] Includes subjects who discontinued for reasons other than an AE, death or lack or loss of efficacy; e.g., withdrew consent, loss to follow-up, etc.

Study 0112 was an open label, multicenter, noncomparative trial in HIV-1-infected adults whose baseline eGFR performed by Cockcroft-Gault formula was measured as being between 30 and 69 mL/min. Of the 248 subjects enrolled, 242 were switched from another antiretroviral regimen and were virally-suppressed; 6 subjects were naïve to treatment at study entry. The mean age was 58 years (range 24 to 82 years), 79% were male, 63% were white, 18% were black, 14% were Asian and 13% identified as Hispanic/Latino. The subjects' mean baseline CD4+ cell count was 664 cells per mm^3. Approximately 64% were switched from a TDF-containing regimen. Among the 242 subjects switching from another regimen to Genvoya, 95% maintained their HIV-1 RNA < 50 copies/mL through Week 24.

Efficacy in adolescents was supported by extrapolation from the adequate and well-controlled adult clinical trials with bridging PK and safety data from Study 0106 (see Section 10 for discussion of extrapolation). A total of 48 HIV-1-infected, treatment-naïve, adolescents 12 years up to 18 years of age were enrolled and received Genvoya as the standard "adult" formulation. Of these, 23 had completed at least 24 weeks of treatment at the time of the interim efficacy analysis. Among the 23 subjects in the efficacy analysis, the mean age was 14 years; 52% were male, 83% were black, and 17% were Asian. At baseline, mean plasma HIV-1 RNA was 4.8 log10 copies/mL and 35% had HIV-1 RNA >100,000 copies/mL), median

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CD4+ cell count was 456 cells per mm^3 and median CD4+ percentage was 23%. The virologic response rate in this small cohort of adolescents was similar to response rates in the trials of treatment naïve HIV-1 infected adults. At the Week 24 analysis, 91% of subjects achieved HIV-1 RNA < 50 copies/mL. In his Statistical Review, Dr. Hammerstrom graphically compared the HIV-1 RNA declines observed in adolescent subjects enrolled in Study 0106 to those of the adults enrolled in Study 0104 and found the pattern of decline to be similar. He also noted that graphs of the point estimate and 95% confidence limits for the proportion of subjects with HIV-1RNA < 50 copies/mL over time were very similar. While these analyses represent post hoc, cross-study comparisons, they do provide some assurance that the adolescents responded similarly to treatment with Genvoya compared to adults.

In summary, FDA analyses confirmed that in multiple HIV-1-infected study populations Genvoya achieved 90% or higher viral suppression. These rates were similar to those achieved in the comparator treatment arms.

8. Safety

The safety profile of TDF and tenofovir has been well-characterized in multiple previous clinical trials and is notable for renal toxicity related to proximal renal tubule dysfunction and bone toxicity related to loss of bone mineral density and evidence of increased bone turnover. The overall clinical development program for Genvoya was designed to test the hypothesis that TAF and Genvoya have less renal and bone toxicity compared to TDF-containing regimens in a variety of different patient populations. The integrated clinical safety review provided by Dr. Tauber describes pooled data from the two randomized, double-blind, trials (Studies 0104 and 0111) in 1733 treatment-naïve subjects as well as data from the other supportive trials including the Phase 2 pilot study (Study 0102). The pooled pivotal trials provide a primary safety comparison between TAF (as Genvoya) and TDF (as Stribild) in subjects initiating treatment.

- ***General safety issues: deaths, discontinuations, serious adverse events, common adverse events***

There were 10 deaths in the combined pivotal and supportive studies of adult subjects: six among subjects receiving Genvoya and four among subjects receiving the comparator regimen (all Stribild). Two subjects were noted to have died of advanced stage cancer, both after more than a year on study. Two subjects died of alcohol poisoning/drug overdose. Three deaths were related to known or presumed cardiac disease and another was due to cerebrovascular event in a patient with arrhythmia. One subject died of sepsis following soft tissue infection. In addition, there was one unwitnessed, unexplained death in a 63 year old female. These deaths were reviewed and were not considered related to study medications.

In the pooled analysis of adult subjects a total of 169/2185 (9%) subjects in the Genvoya arms and 97/1402 (7%) subjects in the comparator arms reported non-fatal serious adverse events (SAEs). The proportion of subjects reporting SAEs was lower among Study 0109 subjects who were virally-suppressed at study entry (4%) compared to the subjects in

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Studies 0104 and 0111 who were initiating treatment (8%) and was somewhat higher among subjects with baseline renal impairment in Study 0112 (11%). Of the five SAEs reported as possibly related to study drug in pooled Studies 0104 and 0111, three occurred in subjects receiving Genvoya (generalized rash, hypovolemia with mild renal failure in the setting of influenza A, and multiple carbuncles due to MRSA). The only SAE attributed to study drug in Study 0109 was a case of acute renal failure occurring in the comparator group. Review of these events failed to identify any specific pattern suggesting a serious safety signal related to TAF or Genvoya or any substantive differences between treatment arms. Of note, a single case of visual impairment and "intermediate uveitis" of unknown cause in a 13 year old female was identified in Study 0106 and attributed to study drug but did not result in treatment discontinuation.

Across the Genvoya trials, very few adult subjects prematurely discontinued study drug for any reason (3% in Genvoya arms, 6% in comparator arms). In the double-blind Studies 0104 and 0111, the differences in discontinuation rates between arms appeared to be primarily related to pregnancy and "investigator's discretion" which accounted for 12 subjects withdrawing from the Stribild arms and none from the Genvoya arms. Discontinuations related to AEs were reported in 29 (1.5%) subjects receiving Genvoya and 23 (1.6%) subjects receiving comparator treatment. However, in the pooled studies, the discontinuations due to renal adverse events occurred exclusively in the Stribild arms. There were two subjects who discontinued Genvoya dosing in Study 0112 because of worsening renal function; both had baseline eGFR < 50 mL/min. Two additional subjects with baseline eGFR < 50 mL/min discontinued study drug because of persistent, generalized fatigue and generalized arthralgias.

Assessment of the pooled pivotal studies provides the clearest comparison of the tolerability and safety profile of TAF compared to TDF as the other components of Genvoya and Stribild were the same. Over 90% of subjects (both treatment arms) enrolled in Studies 0104 and 0111 reported at least one clinical AE (see Table 5); gastrointestinal disorders and infections/infestations were most common. Overall, specific AEs were balanced across the treatment arms. AEs graded at least moderate in severity (Grade 2 or higher) were reported in 53% of subjects receiving Genvoya and 48% of those receiving Stribild but no differences in specific AEs were identified. Most of the reported AEs were considered not related to study drug. Of those events graded at least moderate in severity and assessed as related to study drug, diarrhea, nausea, fatigue, and headache were the most common and reported in approximately 1% of subjects in both treatment groups.

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Table 5: Common Adverse Events through Week 48 in Pooled Studies of Genvoya Compared to Stribild (Studies 0104 and 0111)

Adverse Events by SOC and Preferred Term	Studies 0104/0111	
	Genvoya N=866	Stribild N=867
Number of subjects experiencing any AE	778 (90%)	782 (90%)
Gastrointestinal AEs	394 (46%)	425 (49%)
Diarrhea	147 (17%)	164 (19%)
Nausea	132 (15%)	151 (17%)
Vomiting	62 (7%)	54 (6%)
Abdominal Pain	41 (5%)	37 (4%)
General disorders	181 (21%)	164 (19%)
Fatigue	71 (8%)	71 (8%)
Fever	45 (5%)	41 (5%)
Infections and Infestations	503 (58%)	506 (58%)
Upper respiratory tract infection	99 (11%)	109 (13%)
Nasopharyngitis	78 (9%)	80 (9%)
Bronchitis	46 (5%)	37 (4%)
Sinusitis	32 (4%)	40 (5%)
Musculoskeletal	241 (28%)	213 (25%)
Back Pain	60 (7%)	57 (7%)
Arthralgias	61 (7%)	39 (5%)
Nervous system disorders	218 (25%)	197 (23%)
Headache	124 (14%)	108 (13%)
Dizziness	44 (5%)	37 (4%)
Psychiatric disorders	163 (19%)	174 (20%)
Insomnia	57 (7%)	48 (6%)
Depression	34 (4%)	34 (4%)
Respiratory System	158 (18%)	165 (19%)
Cough	67 (8%)	60 (7%)
Skin and Subcutaneous tissue	208 (24%)	210 (24%)
Rash	55 (6%)	46 (5%)

Source: Abstracted from Clinical Review NDA 207561, W. Tauber, page 97.

Overall safety and tolerability were comparable in the supportive studies. Among subjects enrolled in Study 0109, the most common AEs in the Genvoya arm were upper respiratory tract infection (12%), diarrhea (8%), nasopharyngitis (7%), headache (6%), cough (5%), nausea (5%), and arthralgia (5%). AEs that occurred with a ≥ 2% risk difference between the Genvoya and TDF comparator regimens included headache, flatulence, nausea, oropharyngeal pain, cough, rash, gastroesophageal reflux disease, hypercholesterolemia, and upper respiratory tract infection. Additionally, in Study 0112, dizziness and renal cysts were among the commonly reported AEs. Not surprisingly, AEs were reported more frequently in subjects with moderate renal impairment (eGFR 30-49 mL/min) compared to those with milder renal impairment (eGFR 50-69 mL/min). Among adolescent subjects

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enrolled in Study 0106, nausea, upper respiratory tract infection, and abdominal pain were the most commonly reported AEs.

- ***Special safety concerns***

The target organ toxicity identified in nonclinical and clinical studies of TDF and tenofovir include proximal renal tubule dysfunction and bone mineral density loss. In addition, posterior uveitis was identified in nonclinical studies of TAF. The Applicant provided multiple analyses intended to address these safety concerns and demonstrate a favorable safety profile for TAF, particularly as compared to TDF. Clinical and laboratory monitoring schedules and data analyses related to bone and renal toxicity are described in detail in the Clinical Review. In addition, the Review Team sought input from FDA colleagues in the Division of Bone, Reproductive, and Urologic Products (DBRUP) and the Division of Cardiovascular and Renal Products (DCRP) who provided secondary data review and recommendations on labeling.

To assess bone toxicity, the Applicant provided serial DXA scans to evaluate BMD, measurements of biomarkers of bone turnover, and assessment of fractures in all the submitted trials. In the pooled treatment naïve Studies 0104 and 0111, decreases in both spine and hip BMD from baseline to Week 48 were observed for subjects receiving Genvoya but were smaller than those observed in subjects receiving Stribild. Mean percentage decreases in BMD from baseline to Week 48 were -1.30% with Genvoya compared to -2.86% with Stribild at the lumbar spine and -0.66% compared to -2.95% at the total hip. BMD declines greater than 5% at the lumbar spine were experienced by 10% of Genvoya subjects and 22% of Stribild subjects. BMD declines of greater than 7% at the femoral neck were experienced by 7% of Genvoya subjects and 19% of Stribild subjects. Fractures (other than fingers and toes) were reported in 7 (0.8%) subjects receiving Genvoya and 12 (1.4%) subjects receiving Stribild. In addition, the Applicant performed FRAX analyses to assess risk of either hip fracture or other major osteoporotic fracture. 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. Among subjects $\geq$ 40 years of age, the mean fracture risk increased during the treatment period but the increase was smaller in the Genvoya arm than in the Stribild arm.

In Study 0109, subjects who switched to Genvoya experienced mean BMD increases (1.86% lumbar spine, 1.95% total hip) while subjects who continued their baseline regimen experienced BMD decreases (-0.11% lumbar spine, -0.14% total hip). BMD declines greater than 5% at the lumbar spine were experienced by 1% of subjects receiving Genvoya and 6% of subjects who continued their TDF-based regimen. BMD declines greater than 7% at the femoral neck were experienced by 1% of subjects receiving Genvoya and 4% of subjects who continued their TDF-based regimen. Fractures (other than fingers and toes) were reported in 10 (1%) subjects who switched to Genvoya and 2 (0.4%) subjects who continued their TDF-based regimen.

The assessment of bone toxicity in adolescents who should be growing and rapidly accruing bone mass was of particular importance. Among the 23 pediatric subjects

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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, a calculation to normalize growth parameters, were -0.10 for lumbar spine and -0.11 for total body less head at Week 24. Two subjects had significant (greater than 4%) lumbar spine BMD loss at Week 24.

The Genvoya clinical trials included serial assessments of biomarkers of bone resorption (C-type collagen sequence, CTx), bone formation (procollagen type 1, P1NP) and serum parathyroid hormone (PTH). In the pooled Studies 0104 and 0111 and in Study 0109, subjects receiving Genvoya demonstrated mean increases in CTx and P1NP from baseline to Week 48 suggestive of bone turnover but these increases were less than those in the TDF-containing comparator arms. Similarly, median serum PTH also increased in subjects receiving Genvoya but less than in subjects receiving the TDF-containing regimens.

The Applicant designed the clinical trials of Genvoya to assess the difference between TAF and TDF as potential causes of renal toxicity. Renal monitoring included a comprehensive battery of tests and analyses in patients with normal renal function and in a dedicated open-label study in patients with renal impairment defined as eGFR 30-69 mL/min (Study 0112). The Clinical Review focused primarily on those measurements considered to have clinical relevance and available to clinicians.

In the pooled Studies 0104 and 0111, TAF was associated with small increases in serum creatinine and eGFR. Through Week 48, median serum creatinine increased by 0.08 mg/dL in subjects receiving Genvoya and by 0.11 mg/dL in those receiving Stribild. A corresponding decrease in median eGFR was noted, -7.5 mL/min in the Genvoya group and -10 mL/min in the Stribild group. The presence of proteinuria at baseline was similar in both treatment groups. Fewer subjects receiving Genvoya developed proteinuria during treatment and median urine protein-to-creatinine ratio (UPCR, a quantitative assessment of urinary protein) decreased compared to subjects receiving Stribild. Additional investigational renal biomarkers such as urine retinol binding protein (RBP) to creatinine ratio and beta-2-microglobulin to creatinine ratio also appeared to be less affected by treatment with Genvoya compared to Stribild in this study population.

In the Study 0109 population who had all received a prior TDF-containing regimen, minimal changes in serum creatinine and eGFR were noted in both arms through Week 48. Mean serum creatinine remained essentially unchanged in the subjects switching to Genvoya from either Stribild or a boosted atazanavir/FTC/TDF regimen while it increased by 0.11 mg/dL in those switching from Atripla, presumably due to the introduction of COBI. Median eGFR increased by 2 mL/min among subjects receiving Genvoya and decreased by 4 mL/min among those remaining on Stribild or a boosted atazanavir regimen. Overall, about 7% of subjects in the Genvoya group had improvement in baseline proteinuria by dipstick compared with 6% in the TDF group but median UPCR decreased in the Genvoya group while it increased in the group remaining on TDF. As noted in the Clinical Review, assessments of other investigational renal biomarkers also demonstrated decreases from baseline in the Genvoya group at Week 48 compared with increases in subjects remaining on TDF.

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The Applicant included analyses to identify subclinical cases of proximal renal tubulopathy (PRT) in the Genvoya trials. No cases of PRT were identified among subjects receiving Genvoya in any of the clinical trials through Week 48. One subject in Study 0109 who continued on an atazanavir/COBI/FTC/TDF regimen developed laboratory abnormalities (increased serum creatinine and proteinuria, decreased serum phosphate, and normoglycemic glycosuria) consistent with Fanconi syndrome.

Study 0112 was intended to explore the safety of Genvoya treatment in subjects with mild and moderate levels of renal impairment (eGFR 30-69 mL/min) but was not comparative in design. Of the 248 subjects enrolled who received Genvoya, 242 were switched from a stable, suppressive regimen administered in a previous Gilead sponsored trial and 6 were treatment naïve. The Clinical Review focuses on the cohort who switched to Genvoya. In this study population, 65% were switched from a stable TDF-containing regimen and 33% had baseline eGFR < 50 mL/min. The primary analysis for Study 0112 was performed at Week 24.

Renal parameters in the switch cohort of Study 0112 remained relatively stable through Week 24. Mean serum creatinine and eGFR were essentially unchanged during 24 weeks of treatment. Median UPCR decreased from 161 mg/g at baseline to 83 mg/g at Week 24. While a majority of subjects with baseline proteinuria (57%) had improvement in this parameter at Week 24, 6% developed new proteinuria; among subjects with baseline eGFR < 50 mL/min, 37% with baseline proteinuria improved and 9% developed new proteinuria. Two subjects, both with baseline eGFR < 50 mL/min, experienced clinical AEs described as renal failure that led to study drug discontinuation. No cases of PRT were identified in Study 0112.

In addition to evaluating the potential impact of Genvoya on renal impairment, Study 0112 was also intended to demonstrate the safety of Genvoya in a cohort of subjects with moderate renal impairment. Safety evaluations in this study included comparisons of AEs, SAEs, and study drug discontinuations between the cohort with eGFR 30-49 mL/min and the cohort with eGFR 50-69 mL/min. The proportions of subjects in both cohorts reporting any AE or SAE were similar but the proportions of subjects reporting Grade 2 or higher AEs, AEs attributed to study drug, and discontinuations due to AEs were slightly higher in the cohort with lower eGFR. Headache was reported more frequently among subjects in the higher eGFR cohort. Syncope/disturbances of mental functioning were more common in subjects with lower eGFR and dizziness was more than twice as frequently reported in this cohort.

As noted in Section 4, nonclinical studies identified ocular toxicity (posterior uveitis) in dogs chronically administered TAF and enhanced surveillance for similar toxicity was included in the clinical development program. The numbers of cases of eye disorders reported in the adult clinical trials were relatively similar in the Genvoya treatment arms and the comparator arms but the overall number of cases was small, occurring in 5% to 7% of subjects in any arm. No cases of uveitis were reported among adult subjects. A single case of "intermediate uveitis" attributed to study drug was reported in a 13 year old female.

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No other etiology was identified but the case responded slowly to topical steroids and study drug was not discontinued.

- ***Laboratory abnormalities***

Routine clinical laboratory monitoring was conducted in all the clinical trials. In the combined Studies 0104 and 0111, 20% of subjects in both treatment groups had at least one laboratory abnormality of Grade 3 or 4 severity. Elevated creatine kinase was reported most frequently, occurring in about 7% of subjects receiving Genvoya and about 6% of those receiving Stribild. These elevations were not associated with clinical symptoms of rhabdomyolosis. Elevated hepatic transaminases occurred in 1-2% of these treatment-naive subjects across treatment groups. The most common hematologic abnormality noted was neutropenia, occurring in 1-2% of subjects.

In Study 0109, comparable proportions of subjects developed a Grade 3 or 4 laboratory abnormality, 21% of subjects receiving Genvoya and 25% of those continuing their TDF-containing regimen. There were some notable differences in laboratory findings between the treatment groups. Subjects in the comparator group were more likely to experience elevated bilirubin (14%) compared to those receiving Genvoya (< 1%), due to the well-characterized effect of atazanavir. Thirteen percent of subjects receiving Genvoya had a graded elevation of uric acid compared to 5% of those continuing their TDF regimen; 2.2% were Grade 3 or 4 compared to 1%, in Genvoya and comparator arms, respectively. Clinical events of gout were uncommon, occurring in 6 subjects receiving Genvoya and 1 remaining on a TDF regimen.

The most clinically important laboratory abnormalities identified in the Genvoya development program include elevated fasting serum lipids, particularly total cholesterol and low-density lipoprotein (LDL). Subjects receiving Genvoya experienced significantly higher increases in serum lipids compared to those receiving Stribild. These lipid abnormalities observed in the pooled Studies 0104 and 0111, excluding subjects already receiving lipid-lowering drugs, are shown in Table 6 and will be displayed in the Genvoya label. Five percent of subjects receiving Genvoya had an LDL value > 190 mg/dL during treatment compared to 2% of subjects receiving Stribild. The Applicant noted that 4% of Genvoya recipients and 5% of Stribild recipients were receiving lipid-lowering drugs at baseline and an additional 4% and 3% initiated such treatment during the clinical trials. Given the notable increases in cholesterol and LDL in the Genvoya arms, the Review Team asked the Applicant to provide an analysis to determine how many subjects met the criteria for initiating lipid-lowering therapy according to the current American College of Cardiology/American Heart Association prevention guideline. This analysis suggested 16% of subjects receiving Genvoya and 17% receiving Stribild met the 2013 criteria for statin therapy.

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Table 6: Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving Genvoya or Stribild (Studies 104 and 111[a])

	Genvoya N=866		Stribild N=867	
	Baseline	Week 48	Baseline	Week 48
	mg/dL	Change[a]	mg/dL	Change[a]
Total Cholesterol (fasted)	164 [N=841]	+31 [N=789]	166 [N=848]	+14 [N=781]
HDL-cholesterol (fasted)	46 [N=841]	+7 [N=789]	45 [N=848]	+4 [N=781]
LDL-cholesterol (fasted)	105 [N=837]	+15 [N=785]	108 [N=849]	+4 [N=783]
Triglycerides (fasted)	116 [N=841]	+30 [N=789]	120 [N=848]	+10 [N=781]

[a] Excludes subjects who received lipid lowering agents during the treatment period.
[b] The change from baseline is the mean of within-subject changes from baseline for subjects with both baseline and Week 48 values.

Elevations of cholesterol and LDL were also noted in subjects receiving Genvoya in Study 0109 and Study 0112. In Study 109 subjects switching to Genvoya, mean change in total cholesterol from baseline to Week 48 was 20 mg/dL and mean change in LDL was 9 mg/dL. Among subjects remaining on a TDF-containing regimen mean change in total cholesterol was 6 mg/dL and LDL was unchanged. The proportion of subjects who shifted from baseline to a higher lipid category (based on National Cholesterol Education Program Adult Treatment Panel categories) during treatment was greater in the Genvoya arm than in the TDF arm. Conversely, for subjects who began treatment at higher baseline categories, the proportion of subjects who shifted to a lower category during treatment was greater in the TDF group than in the Genvoya group. As might be expected in a study population with renal impairment, graded total cholesterol abnormalities were observed in a high proportion of subjects in Study 0112 at baseline (48%) and an even higher proportion at Week 24 (57%); 41% had LDL elevation at baseline compared to 47% at Week 24.

- ***Discussion of notable safety issues (resolved or outstanding).***

In summary, the Clinical and Statistical Reviewers agree the clinical trials submitted by the Applicant support the efficacy of Genvoya for the treatment of HIV-1 infection in adults and adolescent patients (12 years and older) who have not received prior treatment or who have been switched from a stable, suppressive regimen. As with all antiretroviral treatment regimens, successful treatment is predicated on the patient having a susceptible HIV-1 isolate. In all the clinical trials, viral suppression was observed in 90% or more of subjects receiving Genvoya.

The Clinical Reviewers and consultants agree the safety and tolerability profile of Genvoya is acceptable. The TAF component of Genvoya does demonstrate some potential for bone and renal effects, but it appears to be associated with consistently less effect on measurable

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bone and renal safety parameters in comparison to TDF. In subjects with renal impairment (eGFR > 30 mL/min), switching to Genvoya was shown to have minimal impact on clinical AEs and renal parameters, although a small number of subjects experienced worsening proteinuria and renal function. However, Genvoya appears to be associated with clinically significant elevations of total cholesterol and LDL that may require lipid-lowering therapy.

9. Advisory Committee Meeting

An Advisory Committee was not considered warranted as three of the four component drugs in Genvoya are already approved and TAF is the second prodrug of a well-characterized NRTI. Safety and efficacy were established in a robust development program evaluating the complete regimen FDC and considered similar to or better than the currently approved TDF-containing FDC Stribild to which Genvoya was compared.

10. Pediatrics

The current NDA submission provides adequate data to support extension of the indication to adolescents 12 years to < 18 years of age. Pediatric Study 0106 was reviewed by Dr. Andres Alarcon and his review is incorporated into the Clinical Review in Section 9.4, Appendix 2. A summary of the pediatric administrative issues is provided below.

- ***A brief documentation of the scientific data supporting extrapolation***

The extrapolation of efficacy for antiretroviral drugs such as Genvoya is based on the presumption that the course of HIV disease and the effects of the drugs are sufficiently similar in adults and pediatric subjects. The Division of Antiviral Products (DAVP) has consistently agreed that HIV disease in pediatric patients is similar to adult HIV disease, noting that the routes of transmission and some clinical manifestations may be different. The pathophysiology of immune system destruction by HIV is similar in adult and pediatric subjects. In pediatric and adult subjects, treatment of HIV infection is monitored using the same two surrogate markers: HIV-1 RNA PCR (commonly referred to as "viral load") is a marker of virologic suppression and CD4 cell count is a marker of immunologic status. Treatment with other antiretroviral drugs have been shown to lower HIV RNA, raise CD4 counts, and improve general clinical outcome similarly in both adult and pediatric subjects. Therefore, pediatric approval has previously been based on extrapolation of efficacy from the adequate and well-controlled adult clinical trials with bridging pharmacokinetic and safety data provided in the pediatric trials.

- ***Peds exclusivity board review - BPCA***

A Written Request for pediatric studies has not been issued for Genvoya.

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- ***PeRC Review Outcome - PREA***

The Applicant submitted an Agreed Pediatric Study Plan according to current requirements prior to submission of the NDA. In the current NDA submission, the Applicant requested a partial waiver of pediatric studies for patients younger than 6 years of age including newborns to 27 days of age, infants and toddlers (28 days to 23 months) and children (2 to less than 6 years of age). The Review Team agreed with the request for partial waivers in these age groups.

The Review Team noted there are different reasons for requesting a partial waiver in different age groups. DAVP is currently waiving studies in newborns because it is often difficult to make the diagnosis and initiate therapy within the first month of life and there are now less than 200 HIV-infected newborns diagnosed each year across the US. In pediatric patients 28 days to < 6 years, the sponsor notes (b) (4) The Review Team did not completely agree (b) (4) but acknowledged the inherent difficulties of this development process. However, we consider this product will not provide a meaningful benefit and will not be used in a significant number of patients 28 days to < 6 years because there are other antiretroviral products available for patients in this age group (b) (4)

For patients 6 years up to 12 years of age, the Applicant requested a deferral because the product is ready for approval in adults and adolescents but studies in pediatric patients 6 to 12 years of age have not been completed. The Review Team agreed with this rationale and the timeline proposed to complete evaluation of this age group. The deferred study will be incorporated into a PREA Postmarketing Requirement:

> PMR: Conduct your deferred pediatric study in HIV-infected patients 6 years to less than 12 years to assess the pharmacokinetics, safety and tolerability, and antiviral activity of age-appropriate doses of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide given in combination. At least some of the safety data must be derived from dosing as the Genvoya fixed dose combination (duration and number of subjects on Genvoya to be agreed upon with the Agency).

In addition, the Review Team wants to ensure submission of long-term follow-up data from Study 0106, particularly as this NDA submission contained an interim report on the first cohort to reach the Week 24 endpoint. A postmarketing commitment will be requested to provide safety and antiviral activity data from the full study population through at least 48 weeks of treatment.

> PMC: Submit the long-term safety and antiviral activity data for Study GS-US-292-0106. Include data and analyses for the entire study population through Week 48 and all subjects enrolled in the extension phase through 96 weeks of GENVOYA dosing.

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11. Other Relevant Regulatory Issues

No substantive regulatory issues remain to be resolved at the time of writing this CDTL Review; however, some issues deserve mention in this memo.

- ***Financial disclosures***

The Applicant provided financial disclosure information regarding significant payments and equity for all investigators participating in the Phase 2 and 3 clinical trials and this information was reviewed by Dr. Tauber as part of the Clinical Review. He noted that a substantial number of site Principal Investigators participating in Studies 0102, 0104, 0111, 0109, and 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. No investigators in the adolescent Study 0106 reported such financial interests. Table 7 below provides a more detailed accounting of the number and proportion of investigators requiring financial disclosure by study and investigator status. As shown in the table, financial disclosure was much more common among Principal Investigators than Sub-Investigators.

Table 7: Numbers and Proportions of Investigators Requiring Financial Disclosure by Study

	Studies Submitted					
	0102	0104	0111	0109	0112	0106
Principal Investigators per study total	55	138	150	183	59	21
Principal Investigators No Financial Disclosure required	30 (55%)	93 (67%)	103 (69%)	136 (74%)	34 (58%)	21 (100%)
Principal Investigators Financial Disclosure required	25 (45%)	45 (33%)	47 (31%)	47 (26%)	25 (42%)	0
Sub-investigators per study total	215	581	678	680	371	86
Sub-Investigators No Financial Disclosure required	210 (98%)	574 (98%)	669 (98%)	673 (99%)	367 (99%)	86
Sub-Investigators Financial Disclosure required	5 (2%)	7 (2%)	9 (2%)	7 (1%)	4 (1%)	0

Source: Clinical Review NDA 207561, W. Tauber, page 18.

The Applicant was asked to provide an explanation for this finding and sensitivity analyses to identify potential impact on study results and these analyses were reviewed by the Review Team. According to the Applicant's response to our initial inquiry, about 27% to

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34% of sites for the Phase 3 adult clinical trials (Studies 0104, 0111, 0109, and 0112) were staffed by Principal Investigators or Sub-Investigators with financial interests, accounting for 21% to 35% of study subjects. This appeared to represent a higher proportion of sites and principal investigators potentially affected than the Review Team had encountered in other recent NDA submissions. This issue was discussed at the Late Cycle Meeting teleconference held with the Applicant on August 4, 2015.

The Applicant conducted an analysis of treatment efficacy excluding subjects enrolled at sites staffed by investigators with reportable financial interests. Except for the Phase 2 Study 0102, exclusion of these subjects did not have an appreciable impact on the efficacy results of the clinical trials. As the efficacy endpoint is based on an objective measurement (HIV-1 RNA) and the two pivotal trials (Studies 0104 and 0111) were randomized and blinded, the lack of impact on results is understandable. The Applicant also provided an analysis of AEs in subjects enrolled at sites with or without potential financial interest by comparing the proportion of AEs considered to be drug related between sites with financial disclosure and those without financial disclosure. The Applicant's analysis showed that there was no evidence of biased attribution of AE relatedness to study drug. There was a slight difference in the proportion of AEs scored as Grade 2 or higher at sites without financial interests (3% to 9% higher) compared to those with possible financial interests but there was no difference by treatment arm. Thus, no clear pattern of AE "down-grading" could be attributed to financial interests.

The Applicant attributed the apparent increase in reportable financial interests to increased reporting and transparency due to passage of the Sunshine Act and the large number of sites and investigators involved in the Genvoya clinical development program. In a follow-up communication late in the review cycle, they noted that their initial reporting method was not consistent with FDA Guidance *"Financial Disclosure by Clinical Investigators"* (February, 2013). They noted that the Guidance includes both Principal Investigators and Sub-Investigators in calculations, rather than only the Principal Investigators. In this case, as most of the investigators who reported financial interests were designated as Principal Investigators, the re-calculation results in a much lower proportion of overall investigators with financial interests. The Applicant also noted their original reporting provided a much wider window for assessment of financial interests than suggested in the Guidance. Their revised methodology led to an 80% reduction in the estimate of proportion of investigators with disclosable financial interests to 4.3%. The dramatic decrease in the rate of financial interests reported calls into question exactly what calculation provides meaningful information. The Review Team remained concerned that a substantial proportion of sites and enrolled subjects were potentially affected by having staff with significant financial ties to the Applicant but we could not identify any adverse consequences of these findings.

- ***Other GCP issues***

The Applicant stated that all clinical trials were conducted in accordance with the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines. All protocols were submitted to the investigational review boards (IRBs) or ethics committees as appropriate for participating investigators.

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- ***DSI audits***

Clinical site inspections were carried out by the Office of Scientific Investigations. Eight sites, four international and four in the U.S, were inspected and all were found to be acceptable. OSI concluded that while two sites were found to have regulatory deviations, these deviations were considered unlikely to have a significant impact on the trials. Overall, the sites adequately adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

- ***Other discipline consults***

As noted elsewhere in this CDTL Review, the Review Team sought input from clinical colleagues in DBRUP and DCRP. Dr. Stephen Voss (Medical Officer) and Dr. Theresa Kehoe (Medical Team Leader) provided assistance in reviewing and interpreting data related to potential bone toxicity (BMD/DXA data and bone biomarkers) and revising labeling related to potential bone toxicity. Dr. Kimberly Smith (Medical Officer) and Dr. Aliza Thompson (Medical Team Leader) provided assistance reviewing Study 112, interpreting the results of renal biomarker analyses, and revising labeling related to potential renal toxicity. Their advice has been incorporated throughout this CDTL Review.

In addition, Dr. John Kelsey (Dental Officer) was consulted to review a potential signal related to dental infections and other dental pathology. After review of the clinical adverse event data, he concluded that the observed differences across treatment arms might be due to chance and did not warrant precautionary language or specific monitoring.

12. Labeling

Although many aspects of labeling are complete, some issues remain to be negotiated at the time of writing this CDTL Review. Key aspects of labeling are summarized below.

- ***Proprietary name***

The proprietary name Genvoya was submitted for the FDC tablets containing EVG, COBI, FTC, and TAF and was reviewed by staff from the Division of Medication Error Prevention and Risk Management (DMEPA). The proposed name was submitted to the IND on August 14, 2014, and resubmitted following filing of the NDA on November 10, 2014. The proposed name was found to be acceptable and the Applicant was informed of the decision on December 10, 2014.

- ***Address important issues raised by brief discussion of OPDP and OSE Division comments***

No specific issues were raised by either OPDP or OSE other than those already discussed in this CDTL Review.

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- ***Physician labeling***

The language for the Genvoya Package Insert is being discussed with the Applicant with input from the multi-disciplinary Review Team, our DBRUP and DCRP consultants, and the DAVP Associate Director for Labeling, Dr. Stacey Min. Significant revisions to the original proposed labeling have already been sent to the Applicant in an initial set of recommendations but agreement has not been reached on several key sections of the label as noted below.

The Review Team and the Applicant agreed on the following language for Section 1 Indications and Usage section of the label:

> Genvoya is indicated as a complete regimen for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Genvoya.

The Review Team also agreed that with careful monitoring, Genvoya can be recommended for use in patients with renal impairment and eGFR > 30 mL/min and this lower limit of renal function is described in Section 2 Dosage and Administration and several other sections of labeling.

The Review Team and consultants recommend including information about the potential for bone and renal toxicity with TAF in the Genvoya label in Section 5 Warnings and Precautions. While we agree that the data provided suggest TAF may have less measurable effects on bone and renal function than TDF, the data suggest TAF has some negative impact on these target organs and relatively little long-term follow-up safety information is available. The proposed Warnings and Precautions language remains a topic of disagreement with the Applicant. At the time of writing this CDTL, the following language has been proposed by the Review Team:

> <u>New Onset or Worsening Renal Impairment</u>
>
> Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular injury with severe hypophosphatemia), has been reported with the use of tenofovir-containing products in both animal toxicology studies and human trials *[see Adverse Reactions (6.2)]*. In clinical trials of Genvoya in treatment naïve subjects and in virally suppressed subjects switched to Genvoya with eGFRs greater than 50mL per minute, renal serious adverse events or discontinuations due to renal adverse reactions were encountered in less than 1% of participants treated with Genvoya. In a study of virally suppressed subjects with baseline eGFRs between 30 and 69 mL per minute treated with Genvoya for a median duration of 43 weeks, Genvoya was permanently discontinued due to worsening renal function in two of 80 (3%) subjects with a baseline eGFR of 30 to less than 50 mL per minute.
>
> Patients with impaired renal function and those taking nephrotoxic agents including nonsteroidal anti-inflammatory drugs are at increased risk of developing renal-related

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adverse reactions to tenofovir-containing products. Genvoya is not recommended in patients with estimated creatinine clearance below 30 mL per minute.

Estimated creatinine clearance, urine glucose and urine protein should be assessed before initiating Genvoya therapy and should be monitored during therapy in all patients. Serum phosphorus should be measured in patients with chronic kidney disease because these patients are at greater risk of developing Fanconi syndrome on tenofovir. Discontinue Genvoya in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Cobicistat, (a component of Genvoya), produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration *[see Adverse Reactions (6.1)]*. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.

Bone Effects of Tenofovir
Bone Mineral Density (BMD):
In both animal toxicology studies and human clinical trials, tenofovir-containing products have been associated with decreases in bone mineral density and increases in biochemical markers of bone metabolism suggestive of increased bone turnover. In clinical trials in HIV-1 infected adults, a significant decline in bone mineral density was observed in 15% of subjects treated with Genvoya *[see Adverse Reactions (6.1)]*. The long-term clinical significance of these changes has not been established.

Assessment of BMD should be considered for adults and pediatric patients treated with Genvoya 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 tenofovir-containing products. The risk of these effects with Genvoya is not known. 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 (5.7)]*.

The Applicant agreed to move data related to bone and renal assessments (b) (4) to Section 6 Adverse Reactions and removed data related to (b) (4). The Review Team considered it relevant to include language in Section 7 related to use of Genvoya with other drugs affecting renal function. This proposed text is similar to language in the Stribild labeling.

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The Review Team also considered it informative to include a description of the ocular toxicity identified in nonclinical studies of TAF in Section 13:

> Animal Toxicology and/or Pharmacology
> Minimal to slight infiltration of mononuclear cells in the posterior uvea was observed in dogs with similar severity after three and nine month administration of tenofovir alafenamide, reversibility was seen after a three months recovery period. At the NOAEL for eye toxicity, the systemic tenofovir alafenamide/tenofovir exposure in dogs was 5 (tenofovir alafenamide) and 15 (tenofovir) times the exposure seen in humans at the recommended daily Genvoya dosage.

Please refer to the CSO Labeling Review completed by Patricia Hong, Regulatory Project Manager, for the final agreed upon labeling.

- ***Carton and immediate container labels***

Carton and container labels have been reviewed by the CMC review team and the DMEPA Reviewer and found to be acceptable.

- ***Patient labeling/Medication guide***

The draft Patient Package Insert is being reviewed by the Patient Labeling Team but this review is not yet complete.

13. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action***

I concur with the conclusions of the multi-disciplinary Review Team and recommend Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) tablets be approved for the treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older who have no antiretroviral treatment history or who are virologically-suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure and no known substitutions associated with resistance to the individual components. The package of clinical trials submitted with this NDA met the regulatory standard required for approval and all trials achieved their efficacy objectives. These trials demonstrated that use of Genvoya was both safe and effective in the populations studied. In addition, the data presented in this NDA demonstrated the contribution of the TAF component of the Genvoya regimen to both safety and efficacy of the FDC.

- ***Risk Benefit Assessment***

The efficacy of Genvoya (and its TAF component) was clearly demonstrated in two adequate and well-controlled clinical trials in HIV-1 treatment-naïve adults initiating therapy (Studies 0104 and 0111). Results of these two identically-designed trials showed high rates of virologic suppression in subjects receiving Genvoya (92%), similar to the approved FDC Stribild (90%). Subgroup analyses documented similar response rates in subjects based on a variety of demographic and baseline disease characteristics (e.g., race,

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age, sex, baseline HIV-1RNA level, and baseline CD4+ cell count). Similar results were confirmed in a small cohort of adolescents 12 years up to 18 years of age in Study 0106. This magnitude and breadth of virologic success provides strong evidence of the benefits of Genvoya treatment in treatment naïve patients.

The treatment benefit is supported by the results of a large "switch" study in which subjects already on a stable, successful regimen either continued their previous treatment or switched to Genvoya. Because subjects enrolling in this trial had already achieved virologic suppression and had proven they could tolerate an antiretroviral regimen, this type of study is not, by itself, considered adequate to support a full treatment indication. However, clinicians are frequently faced with patients who are not satisfied with their treatment because of pill burden, schedule, or suboptimal tolerability (i.e., annoying but not dangerous adverse reactions) and wish to try a different regimen. Data from Study 0109 demonstrates that such patients can change their therapy to Genvoya without risking a drop-off in efficacy. The primary study endpoint of HIV-1 RNA < 50 copies/mL was achieved by 96% of those receiving Genvoya and 93% of those continuing their previous regimen. However, assertions that Genvoya may be superior to Stribild in this setting are not warranted in light of similar and extremely low virologic failure rates in both arms (1%) and discontinuations due to adverse events (1%).

The safety and tolerability profile of Genvoya (and its TAF component) was established in the clinical trials primarily by comparison to TDF-containing regimens. The toxicity associated with TDF use has been well-characterized and includes renal effects such as proximal renal tubulopathy and Fanconi syndrome and bone effects such as loss of bone mineral density and osteomalacia. TAF was developed based on the hypothesis that the lower systemic tenofovir concentrations associated with the therapeutic dose of TAF would be associated with less toxicity than TDF. The nonclinical and clinical data submitted in the NDA appear to support this hypothesis. Renal monitoring with both standard and investigational biomarkers consistently demonstrated less impact on renal parameters with Genvoya than with the TDF-containing comparator regimens. No cases of Fanconi syndrome or laboratory-defined proximal tubulopathy were identified among subjects receiving Genvoya, even in subjects with pre-existing renal impairment. Similarly, changes in BMD and biomarkers of bone turnover were less among subjects receiving Genvoya than among those receiving TDF-containing regimens. However, while changes in renal and bone parameters were less than with TDF, TAF still appeared to have some negative impact on many of the measured parameters. The Review Team recognizes that it took several years of clinical use to characterize the renal and bone toxicity of TDF and long-term follow-up for patients receiving TAF is limited. Thus, the Review Team concluded renal function should be monitored in all patients receiving Genvoya and such a recommendation will not impose an unnecessary burden on either the patient or clinician. Bone monitoring is recommended for patients with other risks for BMD loss.

As noted in Dr. Tauber's Clinical Review, the Applicant raised two issues related to renal toxicity with this NDA. The first issue is the relative potential for renal toxicity of TAF compared to TDF in HIV-1 infected patients with normal renal function as discussed above. The second issue is the applicability of the submitted data to allow dosing of

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Genvoya in patients with pre-existing renal impairment. Currently, once daily treatment options are limited for patients with eGFR < 50 mL/min and no single tablet FDC is approved for this population. FTC, either alone or as a component of other FDCs, is not approved for use in patients with eGFR < 50 mL/min. Overall, Genvoya had an acceptable safety profile in the Study 0112 cohort of 80 subjects with eGFR 30-49 mL/min, although two subjects in this subgroup had worsening renal function leading to study drug discontinuation and another had transient acute renal failure. Subjects with lower eGFR experienced more drug-related AEs, more Grade 2 or higher AEs, and more premature discontinuations due to AEs than the cohort with higher eGFR (50-69 mL/min) but perhaps this is to be expected based on their underlying renal impairment. After careful consideration and discussion with consulting staff in DCRP, the Review Team concluded that the benefit of Genvoya treatment in patients with moderate renal impairment (eGFR 30-49 mL/min) outweighed the potential risk and risk could be mitigated by monitoring renal function during treatment.

Although it may have less impact on renal and bone parameters, Genvoya (and its TAF component) was noted to have a greater impact on serum lipids than the TDF-containing comparator regimens. Both fasting total cholesterol and fasting LDL increased in subjects receiving Genvoya. In the clinical trials, this did not result in more Genvoya recipients initiating lipid-lowering therapy. However, HIV clinicians are increasingly aware that as antiretroviral therapy improves, more HIV-infected patients are living longer and more are developing cardiovascular disease. Clinicians are increasingly attentive to modifying cardiovascular risk factors. It remains to be seen whether use of Genvoya post-approval in a broader patient population will result in higher rates of cardiovascular events or increased use of concomitant lipid-lowering therapy (with the attendant drug-drug interactions).

Overall, the risk benefit assessment favors approval of Genvoya for treatment of HIV-1 in the patient populations studied in the clinical trials. The noted safety signals will be monitored in the post-marketing period and in long-term follow-up in the ongoing clinical trials.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***

At this time, neither the Review Team nor the consultants recommend a REMS.

- ***Recommendation for other Postmarketing Requirements and Commitments***

As of the writing of this CDTL Review, no PMRs are expected to be needed to address any significant safety issue. The Applicant will be issued a PMR under PREA to complete their deferred pediatric study in patients 6 years up to 12 years of age as noted in Section 10 and a PMC to request the long-term follow-up data generated in Study 0106.

- ***Recommended Comments to Applicant***

No additional comments need to be conveyed to the Applicant.

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/s/

LINDA L LEWIS
10/01/2015