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APPLICATION NUMBER:

207561Orig1s000

SUMMARY REVIEW

Decisional Review for NDA 207561

Date	October 19, 2015
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supplement #	NDA 207561
Applicant Name	Gilead Sciences
Date of Submission	November 5, 2014
PDUFA Goal Date	November 5, 2015
Proprietary Name / Established (USAN) Name	Genvoya® elvitegravir (EVG), cobicistat (COBI), emtricitabine (FTC), and tenofovir alafenamide (TAF) [E/C/F/TAF]
Dosage Forms / Strength	Fixed-dose combination tablet of E/C/F/TAF 150 mg/150 mg/200 mg/10 mg
Proposed Indication(s)	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Drs. William Tauber, Peter Miele and Andres Alarcon
Statistical Review	Drs. Tom Hammerstrom and Greg Soon supervised by Dr. Dionne Price
Pharmacology Toxicology Review	Drs. Claudia Wrzesinski and Mark Powley supervised by Dr. Hanan Ghantous.
CMC Review	Drs. Jeff Medwid, George Lunn, Lin Qi and Jessica Cole with Dr. Stephen Miller, CMC- Lead; Dr. Salaheldin Hamed, Biopharmaceutics
Microbiology Review	Dr. Lisa Naeger supervised by Dr. Jules O'Rear
Clinical Pharmacology/Pharmacometrics Review	Dr. Mario Sampson supervised by Dr. Islam Younis/Dr. Jeffry Florian
DDMAC	Jessica Fox, Pharm.D.
OSI	Antoine El Hage, Ph.D.
CDTL Review	Dr. Linda Lewis
OSE/DMEPA	Mónica Calderón, PharmD, BCPS Rhiannon Leutner, PharmD., MPH, MBA
OPM/DMPP	Sharon Mills, BSN, RN

OSE/DRISK	Jasminder Kumar, Pharm.D.
DPMHM	Miriam Dinatale, DO
DCRP	Dr. Kimberly Smith
DDDP	Dr. John Kelsey
DBRUP	Dr. Stephen Voss

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader
DMPP=Division of Medical Policy Programs
DPMHM=Division of Pediatric and Maternal Health Memorandum
DCRP=Division of Cardiovascular and Renal Products
DDDP=Dental Officer, Division of Dermatology and Dental Products
DBRUP=Division of Bone, Reproductive and Urologic Products

1.Introduction

This Division Director's memorandum provides a topline summary of NDA 207561 to support a regulatory action of approval for Gilead Sciences' New Drug Application (NDA) for Genvoya (E/C/F/TAF), a fixed dose combination tablet for use as a single treatment regimen for adults and adolescents 12 years of age and older with HIV-1 infection. This summary review focuses on pertinent findings from the NDA submission, FDA's multidisciplinary reviews and consults, and product labeling.

2. Background

Genvoya contains three previously approved drugs and one new molecular entity: elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor; cobisistat (COBI), a CYP 3A inhibitor; emtricitabine (FTC), a nucleoside analog reverse transcriptase inhibitor; in addition to the new tenofovir (TFV) prodrug, tenofovir alefenamide fumarate (TAF). TAF was developed in an effort to provide similar activity to TDF with lower TFV plasma exposures with the expectation that TFV-related toxicities would be reduced. Genvoya was studied as a single treatment regimen 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 patients who are already virologically suppressed, with an HIV-1 RNA less than 50 copies per mL, on a stable regimen for at least 6 months with no history of treatment failure and no known resistance substitutions. Genvoya will join other fixed-dose antiretroviral combinations available as single treatment regimens in the HIV armamentarium as well as other single and dual fixed-dose entities for use in combination to treat HIV-1 infection. Single treatment regimens are important for adherence and ultimately successful treatment of HIV-1 infection.

The focus of the multidisciplinary review was on TAF, a new molecular entity, as Genvoya includes three previously approved drugs. This summary will also highlight the components of Genvoya where appropriate. Further, the NDA included clinical data from two randomized controlled trials in naïve patients (Study 104 and 111) as well as a switch study with an endpoint of maintenance of viral suppression after switching to Genvoya (Study 109). Additional data from a renal impairment study (Study 112) and an interim analysis from an adolescent study (Study 106) helped to inform the indicated patient population and safety profile of Genvoya. Nonclinical toxicology, nonclinical virology, clinical virology and clinical pharmacology studies were also conducted and reviewed. See reviews by respective multidisciplinary primary reviewers and the CDTL review by Dr. Linda Lewis.

The application was not presented before the Antimicrobial Drugs Advisory Committee because a preliminary review of the NDA, including labeling, did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), FDA inspected four domestic and four foreign clinical sites with high enrollment that were part of this marketing application. OSI concluded that while two sites were found to have regulatory deviations listed as VAI, these deviations were adequately addressed and considered unlikely to have a significant impact on the trials. Overall, the sites adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. Based on the inspection findings, the data generated were found to be reliable and acceptable in support of this application.

3. CMC

The CMC review team included Drs. Jeff Medwid and George Lunn, Drug Substance and Drug Product reviewers, respectively, and Drs. Lin Qi and Jessica Cole. Dr. Salaheldin Hamed was the Biopharmaceutics reviewer. Dr. Stephen Miller served as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity, and quality of Genvoya. All CMC issues were addressed during this review.

The Applicant provided sufficient stability data to support a 24-month product expiry. Because TAF is (b) (4), the Applicant committed to continue manufacturing processes (b) (4). The drug product specification contains tests for appearance, identity, (b) (4) degradants, dose uniformity, dissolution, and microbial limits that were considered acceptable to the Chemistry Review Team.

An overall recommendation of Acceptable has been made by the Offices of Compliance and New Drug Quality following GMP inspections. Therefore, from a CMC perspective, NDA 207561 is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

Please see the review of submitted nonclinical toxicology studies by Dr. Claudia Wrzesinski, supervised by Dr. Hanan Ghantous. From a nonclinical pharmacology/toxicology perspective, NDA 207561 is recommended for approval. The pharmacology/toxicology of EVG, COBI and FTC has been reviewed previously. Dr. Wrzesinski focused her review on TAF and potential overlapping toxicities with EVG, COBI and FTC. Renal and bone nonclinical toxicities seen with TAF were similar to those seen with tenofovir disoproxil fumarate (TDF), a different prodrug of TFV that was previously approved as a single entity and as part of the fixed-dose combinations of Truvada, Stribild, Atripla, and Complera.

In nonclinical studies, chronic administration of TAF led to a dose-dependent, slight-to-moderate renal cortical tubular degeneration/regeneration and karyomegaly in the dog as well as renal karyomegaly in the rat, with partial recovery in the dog after three months. TAF-related dose-dependent reductions in bone mineral density and mineral content, as well as changes in bone turnover markers and in related hormones, were observed in rats and dogs with partial recovery in the dog after three months. Further, TAF lead to a reversible PR prolongation at the mid and high dose, and a reversible reduction in heart rate associated with mild QT prolongation in the high dose animals at week 39 in the chronic dog study. Per Dr. Wrzesinski's review, posterior uveitis was seen in dogs with chronic dosing. At the NOAEL for eye toxicity, the systemic TAF/TFV exposure in dogs was 5 (TAF) and 15 (TFV) times the exposure seen in humans at the recommended daily Genvoya dosage. Wording appears in section 6 of product labeling describing uveitis in a 13 year old female subject who required steroid treatment.

Genvoya is pregnancy category B. None of the components of Genvoya has been shown to be teratogenic. There were no fertility effects; nor were there effects on mating or early embryonic development. Wording in product labeling states that animal reproduction studies are not always predictive of human response, therefore Genvoya should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Healthcare providers are further encouraged to enroll their patients who become pregnant in the Antiretroviral Pregnancy Registry. Because of the potential for HIV transmission, the potential for serious adverse reactions in nursing infants, and the risk of breastfeeding infants developing viral resistance to FTC that is present in human milk, mothers should be instructed not to breastfeed while taking Genvoya.

Specific TAF carcinogenicity studies were not conducted because TAF is rapidly converted to TFV and a lower TFV exposure is observed in rats and mice after TAF administration compared to TDF. Per Dr. Wrzesinski's review and product labeling, long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 10 times (mice) and 4 times (rats) those observed in humans at the 300 mg therapeutic dose of TDF for HIV-1 infection. The TFV exposure

in these studies was approximately 167 times (mice) and 5 times (rat) those observed in humans after administration of Genvoya. At the high dose in female mice, liver adenomas were increased at exposures 10 times (TDF) and 167 times (TAF) that in humans. In rats, the study was negative for carcinogenic findings.

TAF was not genotoxic in the Ames test, mouse lymphoma and rat micronucleus assays.

5. Clinical Pharmacology

Please see the clinical pharmacology and pharmacometrics reviews conducted by Dr. Mario Sampson, with supervisory concurrence by Dr. Islam Younis and Dr. Jeff Florian. The reviewers concluded that Genvoya is approvable with respect to clinical pharmacology/ pharmacometrics for the indicated populations.

TAF is rapidly absorbed and primarily metabolized to TFV (major metabolite) by cathepsin A in peripheral blood mononuclear cells (PBMCs) and by carboxylesterase 1 in hepatocytes. TFV is intracellularly phosphorylated to the active moiety, TFV-diphosphate (TFV-DP) which is the same active moiety of the prodrug TDF.
The anti-HIV activity of TAF was established in a monotherapy study in which HIV-infected subjects were administered TDF 300 mg, or TAF at doses of 8-40 mg for 10 days. The TAF 25 mg dose was selected for phase 2 and phase 3 studies based on antiviral activity. TAF 10 mg was included in the E/C/F/TAF tablet because it provides similar exposures to TAF 25 mg when coadministered with COBI 150 mg.

Other pertinent PK data include the following and appear in product labeling:

- Relative to fasting conditions, administration of E/C/F/TAF with a light meal or high fat meal results in TAF AUC increases of 15-18%, respectively and a TAF T_{max} of 1 hour. Genvoya should be taken with food.

- In clinical trials 104 and 111, a 10 mg oral dose of TAF in Genvoya resulted in greater than 90% lower concentrations of TFV in plasma as compared to a 300 mg oral dose of TDF in STRIBILD.

- *In vitro*, TAF is not metabolized by CYP1A2, CYP2C8, CYP2C9, CYP2C19, or CYP2D6. TAF is minimally metabolized by CYP3A4. Further, TAF is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or UGT1A1. TAF is a weak inhibitor of CYP3A *in vitro*.

- TAF and TFV have a median plasma half-life of 0.51 and 32.37 hours, respectively. TFV is eliminated from the body by the kidneys by both glomerular filtration and active tubular secretion. Renal excretion of TAF is a minor pathway with less than 1% of the dose eliminated in urine.

- Genvoya is not recommended in patients with an estimated creatinine clearance below 30 mL per minute.

- Genvoya can be dosed in patients with mild or moderate hepatic impairment, but Genvoya is not recommended in patients with severe hepatic impairment because data in this population are not available.

Section 5.4 of labeling will contain a warning and precaution related to risk of adverse reactions from greater exposures of concomitant drugs or loss of virologic response due to drug interactions. Section 7 of labeling outlines drug interactions categorized based on the potential for Genvoya to affect other drugs and the potential for other drugs to affect one or more components of Genvoya. For example, 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 of Genvoya and development of resistance. Importantly, because FTC and TFV are primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion, coadministration of Genvoya with drugs that reduce renal function or compete for active tubular secretion (such as acyclovir, valacyclovir, valganciclovir and NSAIDs) may increase concentrations of FTC, TFV, and other renally eliminated drugs which may increase the risk of adverse reactions of Genvoya, especially in patients with impaired renal function.

Regarding pediatric and geriatric populations, exposures of TAF in 23 pediatric subjects aged 12 to less than 18 years who received Genvoya in Study 106 were decreased (23% for AUC) compared to exposures achieved in treatment-naïve adults. Overall this difference was deemed acceptable based on exposure-response relationships; the other components of Genvoya had similar exposures in adolescents compared to treatment-naïve adults. Although the pharmacokinetics of EVG, COBI, FTC and TFV have not been fully evaluated in subjects 65 years of age and older, population pharmacokinetics analysis of HIV-infected subjects in Phase 2 and 3 trials of Genvoya showed that age did not have a clinically relevant effect on exposures of TAF up to 75 years of age.

Thorough QT studies have been conducted for EVG, COBI, and TAF. The effect of FTC or Genvoya on the QT interval is not known. In a thorough QT/QTc study in 48 healthy subjects, TAF at the therapeutic dose or at a supratherapeutic dose approximately 5 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

6. Clinical Microbiology

Please see review by Dr. Lisa Naeger who conducted the review of virology and resistance data, with supervisory concurrence by Dr. Jules O'Rear. Our virology review staff concluded that Genvoya is approvable with respect to virology for the indicated population.

As stated above, TAF is metabolized to TFV and TFV is intracellularly phosphorylated to the active moiety, TFV-diphosphate (TFV-DP) which is the same active moiety of the prodrug TDF. Mechanistically, TFV-DP inhibits HIV replication through incorporation into viral DNA by the HIV reverse transcriptase, which results in DNA chain-termination. TFV-DP is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ, but there is no evidence of toxicity to mitochondria in cell culture.

TAF displayed antiviral activity in cell culture against all HIV-1 groups (M, N, O), including sub-types A, B, C, D, E, F, and G (EC_{50} values ranged from 0.10 to 12.0 nM) and strain specific activity against HIV-2 (EC_{50} values ranged from 0.91 to 2.63 nM) per review of submitted data.

TFV also has activity against hepatitis B virus. Section 5.2 of product labeling contains a warning and precaution about patients coinfected with HIV-1 and HBV. It is recommended that all patients be tested for the presence of HBV before initiating therapy with Genvoya because severe exacerbations of hepatitis B, including hepatic decompensation and hepatic failure have been reported in coinfected patients who have discontinued products containing FTC and TDF, and may occur with Genvoya.

Product labeling contains the following wording related to resistance and cross resistance:

TAF and TDF have a similar resistance profile in cell culture and in clinical trials. In cell culture, HIV-1 isolates with reduced susceptibility to TAF expressed a K65R substitution in HIV-1 RT, sometimes in the presence of S68N or L429I substitutions; in addition, a K70E substitution in HIV-1 RT has been observed.

In a pooled analysis of treatment naïve patients in clinical trials 104 and 111, genotypic resistance to EVG, FTC, or TAF was observed in 7 of 14 subjects with evaluable resistance data from paired baseline and Genvoya treatment-failure isolates compared with 6 of 17 treatment-failure isolates from subjects with evaluable resistance data in the STRIBILD treatment group. Of the 7 subjects with resistance-associated substitutions that emerged in the Genvoya group, there were the following substitutions: M184V/I (N = 7) and K65R (N = 1) in reverse transcriptase and T66T/A/I/V (N = 2), E92Q (N = 2), E138K (n=1), Q148Q/R (N = 1) and N155H (N = 1) in integrase. Three subjects had virus with emergent R, H, or E at the polymorphic Q207 residue in reverse transcriptase. In the STRIBILD group, the resistance-associated substitutions that emerged were M184V/I (N = 5) and K65R (N = 2) in reverse transcriptase and E92E/Q (N = 2), E138K (n=3) and Q148R (N = 2) in integrase. Overall, most subjects who developed substitutions associated with resistance to EVG also developed FTC resistance-associated substitutions.

Emergent resistance was rare in virologically suppressed subjects in the switch study 109.

Regarding cross resistance with other antiretrovirals, the presence of multiple TAMS or multinucleoside resistant HIV-1 including K65R showed reduced susceptibility to TAF in cell culture. TFV resistance substitutions, K65R and K70E, result in reduced susceptibility to abacavir, didanosine, emtricitabine, lamivudine, and tenofovir.

7. Clinical/Statistical-Efficacy

The clinical review was conducted by Drs. William Tauber and Peter Miele; Dr. Andres Alarcon reviewed interim data from Study 106 in adolescents. Secondary review was provided by Dr. Linda Lewis who also served as the CDTL. Clinical consults were obtained from the Division of Bone, Reproductive and Urologic Products (DBRUP), the Division of Cardio-Renal Products (DCRP) and the Division of Dermatology and Dental Products (DDDP). The Biometrics review was conducted by Dr. Tom Hammerstrom with secondary review provided by Dr. Greg Soon and supervisory review provided by Dr. Dionne Price.

The efficacy and safety of Genvoya were evaluated in the five studies summarized in Table 12 in product labeling.

Table 12 Trials Conducted with Genvoya in Subjects with HIV-1 Infection

Trial	Population	Study Arms (N)	Timepoint (Week)
Study 104[a] Study 111[a]	Treatment-naïve adults	Genvoya (866) STRIBILD (867)	48
Study 109[b]	Virologically-suppressed[d] adults	Genvoya (799) ATRIPLA or TRUVADA+atazanavir+cobicistat or ritonavir or STRIBILD (397)	48
Study 112[c]	Virologically-suppressed[d] adults with renal impairment[e]	Genvoya (242)	24
Study 106[c]	Treatment-naïve adolescents between the ages of 12 to less than 18 years	Genvoya (23)	24

a. Randomized, double blind, active controlled trial.
b. Randomized, open label, active controlled trial.
c. Open label trial.
d. HIV-1 RNA less than 50 copies per mL.
e. eGFR of 30 to 69 mL per minute by Cockcroft-Gault method.

The efficacy and safety of Genvoya in treatment naïve adults is based on results from clinical trials 104 and 111 (n=1733), two identically designed randomized trials that compared Genvoya to Stribild. In the pooled trials, the mean baseline plasma HIV-1 RNA was 4.5 log10 copies per mL (range 1.3–7.0) and 23% of subjects had baseline

viral loads greater than 100,000 copies per mL. The mean baseline CD4+ cell count was 427 cells per mm^3 (range 0-1360) and 13% had CD4+ cell counts less than 200 cells per mm^3. Overall, both the Clinical and Statistical reviewers' independent analyses confirmed the Applicant's conclusions of effectiveness based on the pooled data that appears in Table 13 in product labeling.

Table 13 Pooled Virologic Outcomes of Randomized Treatment in 104 and 111 at Week 48[a] in Treatment-Naïve Subjects

	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%

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.

Treatment outcomes were similar across subgroups by age, sex, race, baseline viral load, and baseline CD4+ cell count. The mean increase from baseline in CD4+ cell count at Week 48 was 230 cells per mm^3 in Genvoya-treated patients and 211 cells per mm^3 in Stribild-treated patients.

In the switch study 109, in virologically suppressed patients, 96% of patients who switched to Genvoya after 6 months on a stable regimen had HIV-1 RNA < 50 copies per mL compared to 93% of patients who remained on their baseline antiretroviral regimen. For the snapshot analysis, the main reason that no virologic data appeared in the week 48 window was due to treatment discontinuation due to reasons other than an adverse event, death or loss of efficacy.

Clinical trial results from Study 112 in renally impaired (eGFR of 30-69 mL per minute by Cockcroft-Gault method) HIV-1 infected patients (n=248), supported the aforementioned results. At Week 24, 95% (230/242 virologically suppressed subjects)

maintained HIV-1 RNA less than 50 copies per mL after switching to Genvoya and three patients had virologic failure at Week 24.

Lastly, the virologic response rate in treatment naïve HIV-1 infected adolescents (n=23) at week 24 was similar to response rates in trials of treatment naïve HIV-1 infected adults at week 48; 91% achieved HIV-1 RNA less than 50 copies per mL. The mean increase from baseline in CD4+ cell count at Week 24 was 212 cells per mm^3. Two subjects had virologic failure at Week 24, neither of whom had evidence of resistance to the components of Genvoya.

8. Safety

The safety of TDF and TFV has been previously described. As both TAF and TDF are prodrugs of tenofovir, the expectations were that bone and renal toxicities would emerge in the Genvoya data base. However, in clinical trials 104 and 111, a 10 mg oral dose of TAF in Genvoya resulted in greater than 90% lower concentrations of TFV in plasma as compared to a 300 mg oral dose of TDF in Stribild. It was therefore expected that the primary toxicities of TFV would occur, but at a lower rate than that seen with TDF.

The integrated clinical safety review provided by Dr.Tauber describes pooled data from the two randomized, double-blind trials (Studies 104 and 111) in 1733 treatment-naïve subjects as well as data from the other supportive trials including a Phase 2 pilot study. Based on the design of the pivotal clinical trials, safety can be directly compared between TAF (as Genvoya) and TDF (as Stribild) in subjects initiating treatment.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug in the same class and may not reflect the rates observed in practice.

Table 2 in product labeling displays the frequency of adverse reactions (all Grades) greater than or equal to 5% in the Genvoya group; the majority of events presented in Table 2 occurred at Grade 1 severity.

Table 2 Adverse Reactions[a] (All Grades) Reported in ≥ 5% of HIV-1 Infected Treatment Naïve Adults Receiving Genvoya in Clinical Trials 104 and 111 (Week 48 analysis)

	Genvoya N=866	**Stribild** N=867
GASTROINTESTINAL DISORDERS		
Diarrhea	7%	9%
Nausea	10%	13%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	5%	4%
NERVOUS SYSTEM DISORDERS		
Headache	6%	5%

a Frequencies of adverse reactions are based on all adverse events attributed to study drugs by the investigator.

In virologically-suppressed adults who were switched from a TDF-containing combination to Genvoya in clinical trial 109, the week 48 safety profile of Genvoya was similar to treatment naïve subjects described above.

Renal Safety

Renal impairment including Fanconi Syndrome has occurred with TFV-containing products. In clinical trials of Genvoya in treatment naïve and in virally suppressed patients switched to Genvoya with eGFRs greater than 50mL per minute, serious renal adverse events or discontinuations due to renal adverse events occurred in < 1% of participants receiving Genvoya. In the renal impairment clinical trial among 80 adult patients with baseline eGFR less than 50 mL per minute receiving Genvoya, two subjects developed worsening renal impairment and discontinued treatment. A third subject with baseline eGFR of 55 mL per minute developed transient acute renal failure resulting in brief treatment interruption. For participants enrolled in the renal impairment study, mean serum creatinine was 1.5 mg per dL at both baseline and Week 24 and median UPCR was161 mg per g at baseline and 83 mg per g at Week 24. Although the safety profile of Genvoya in subjects with renal impairment was similar to that of subjects with normal renal function, these findings may differ when patients have longer exposures to TAF. It is also important to note that there were no cases of proximal renal tubulopathy in subjects who received Genvoya. One subject in Study 109 who continued to receive atazanivir/COBI/FTC/TDF developed findings consistent with Fanconi Syndrome.

It is important to also note that Genvoya is not recommended in patients with a creatinine clearance below 30 mL. Product labeling recommends assessing estimated creatinine clearance, urine glucose and urine protein before initiating and during Genvoya therapy use 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 TFV. Genvoya should be

discontinued in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

Bone and Dental Effects

Bone mineral density (BMD) effects of TAF and TDF were assessed in adults and adolescents by DXA. In Studies 104 and 111, mean BMD decreased from baseline to Week 48 -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 patients and 22% of Stribild patients. BMD declines of greater than 7% at the femoral neck were experienced by 7% of Genvoya patients and 19% of Stribild patients. The long-term clinical significance of these BMD changes is not known per our DBRUP consultants.

In switch study 109, TDF-treated subjects were randomized to continue their TDF-based regimen or switch to Genvoya; changes in BMD from baseline to Week 48 were also assessed by DXA. Switching to a TAF-based regimen while virologically suppressed appeared to have favorable bone mineralization effects including increases in hip and spine BMD of approximately 2% at 48 weeks: mean BMD increased in subjects who switched to Genvoya (1.86% lumbar spine, 1.95% total hip) while subjects who continued their baseline regimen decreased slightly (-0.11% lumbar spine, -0.14% total hip).

There was a potential signal for dental infections. Dr. John Kelsey of DDDP was consulted. After review of adverse event data, he concluded that product labeling did not warrant precautionary language or specific monitoring.

Pediatrics

Overall, the safety profile in 23 adolescents who received Genvoya for 24 weeks was similar to that in adults, however one 13 year old female subject developed unexplained uveitis while receiving Genvoya that was treated with steroids.

In adolescents, limited and uncontrolled data do not convincingly show that lumbar spine and total body BMD are accrued at the expected rates on a TAF-containing regimen even after short term exposure. Among adolescents, mean BMD increased from baseline to Week 24, + 1.7% at the lumbar spine and + 0.8% for the total body less head. Mean changes from baseline BMD Z-scores were -0.10 for lumbar spine and -0.11 for total body less head at Week 24. Two patients who were treated with Genvoya had significant (greater than 4%) lumbar spine BMD loss at Week 24.

Laboratory Abnormalities

Patients receiving Genvoya experienced greater increases in serum lipids compared to those receiving Stribild. Changes from baseline in total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides and total cholesterol to HDL ratio are presented in Table 4 in product labeling.

Table 4 Lipid Values, Mean Change from Baseline, Reported in Subjects Receiving Genvoya or Stribild in Clinical Trials 104 and 111 [a]

	Genvoya N=866		Stribild N=867	
	Baseline	**Week 48**	**Baseline**	**Week 48**
	mg/dL	Change[b]	mg/dL	Change[b]
Total Cholesterol (fasted)	162 [N=757]	+30 [N=757]	166 [N=742]	+13 [N=742]
HDL-cholesterol (fasted)	46 [N=757]	+7 [N=757]	45 [N=742]	+4 [N=742]
LDL-cholesterol (fasted)	104 [N=753]	+15 [N=753]	107 [N=744]	+3 [N=744]
Triglycerides (fasted)	113 [N=757]	+29 [N=757]	119 [N=742]	+10 [N=742]
Total Cholesterol to HDL ratio	3.7 [N=757]	0.2 [N=757]	3.9 [N=742]	0 [N=742]

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.

Deaths

Ten deaths were reported and reviewed in the NDA data base. Per Dr. Lewis' CDTL memorandum there were six deaths among subjects receiving Genvoya and four among subjects receiving the comparator regimen, 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. In sum, these deaths were not considered related to study medications.

9. Advisory Committee Meeting

As previously stated, the application was not presented before the Antimicrobial Drugs Advisory Committee because a preliminary review of the NDA, including labeling, did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion. Additionally, Genvoya contains three already marketed drugs and TAF is the second prodrug of TFV.

10. Pediatrics

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 Applicant also requested a deferral for patients 6 years to less than 12 years of age because the product is ready for approval in adults and adolescents but studies in pediatric patients 6 years to less than 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).

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

11. Other Relevant Regulatory Issues

Recommended Postmarketing Requirement and commitment include the following to which the Applicant agreed:

a. Required Pediatric Assessments under PREA (PREA 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).

Protocol Submission:	Submitted
Trial Completion:	September, 2017
Final Report Submission:	March, 2018

b. Pediatric Post Marketing Commitment (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 for all subjects enrolled in the extension phase through 96 weeks of GENVOYA® dosing.

Protocol Submission:	Submitted
Trial Completion:	September, 2018
Final Report Submission:	March, 2019

12. Labeling

Final negotiations related to labeling have not been completed.

13. Decision/Action/Risk Benefit Assessment

This NDA examined the use of Genvoya, a four-drug, fixed dose combination of EVG/COBI/FTC/TAF for the treatment of HIV-1 infection in adults and adolescents greater than 12 years of age. Genvoya was found to be safe and effective in treatment naïve populations and in patients who were virologically suppressed and opted to switch to a single treatment regimen.The toxicity profile was qualitively similar to the other TFV prodrug, TDF, however the rates of signature TFV toxicities related to bone mineral density and renal laboratory parameters were lower, likely due to the fact that the TAF prodrug yields lower plasma concentrations of TFV. However, patients need to be followed for longer periods to ascertain whether toxicity rates approach those associated with TDF. Long-term data in the adolescent patient population is also needed to be able to assess bone and kidney effects with chronic use. Genvoya appears to be associated with elevations of total cholesterol and LDL that may require treatment with lipid-lowering drugs.

Drug interactions with Genvoya are complex. Both loss of antiviral activity and increased plasma concentrations of other drugs present challenges to healthcare providers managing the patient populations for whom Genvoya is indicated. Coadministration of Genvoya with other renally eliminated drugs also poses risks for adverse events. Close laboratory monitoring of renal function is recommended in all patients.

In sum, I am in agreement with the conclusions of the multidisciplinary review team and consultants that the benefit-risk assessment favors approval of Genvoya for the indicated populations. This single treatment regimen containing an integrase strand transfer inhibitor, EVG, along with two nucleoside/nucleotide inhibitors, FTC and TAF (additionally with a pharmacokinetic enhancer, COBI to improve the pharmacokinetics of EVG) was shown to suppress HIV-1 RNA and increase CD4+ T lymphocyte counts in a robust data base. It was well tolerated and adherence should be greater with a one pill, once-a-day regimen. I anticipate that Genvoya like other combination antiretroviral therapy regimens will have a favorable impact on HIV-related morbidity and mortality.

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/s/

DEBRA B BIRNKRANT
10/19/2015