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RESEARCH**

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D., M.P.H.
Subject	Deputy Office Director Decisional Memo
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)
Dosage Forms / Strength	Fixed-dose combination tablet of E/C/F/TAF 150 mg/150 mg/200 mg/10 mg
Proposed Indication	Treatment of HIV-1 infection in adults and pediatric patients 12 years of age and older
Action:	Approval

1. Introduction

The Applicant, Gilead Sciences, submitted NDA 207561 for Genvoya®, a fixed dose combination (FDC) tablet intended to provide a complete treatment regimen for HIV-1 infection dosed once daily. Genvoya® contains elvitegravir (EVG), an HIV-1 integrase strand transfer inhibitor, 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. TAF is considered a new molecular entity (NME) because it is a novel prodrug of the active metabolite, tenofovir diphosphate that differs from the currently approved prodrug tenofovir disoproxil fumarate (TDF) by features such as the phosphonamide linkage. TDF was originally approved in 2001.

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®. Stribild® is an approved FDC tablet containing EVG, COBI, FTC, and TDF. Additional supportive efficacy data were submitted from Study 0109 in which subjects were either switched from a suppressive treatment containing FTC/TDF plus a third active antiretroviral drug to Genvoya® or continued on their prior regimen. Other data submitted included the results of Study 0112, a non-comparative study in subjects with renal impairment treated with Genvoya®, and Study 0106, a non-comparative study in adolescents.

The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of Genvoya® for the indication proposed. The focus of the multi-disciplinary review is TAF, a new molecular entity, as Genvoya® includes three previously approved drugs. For a detailed discussion of NDA 207561, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) Review by Dr. Linda Lewis, and the Division Director Decisional Review by Dr. Debra Birnkrant.

2. Background/Regulatory

While TDF-containing regimens are recommended in treatment guidelines for treatment naïve adult and adolescent HIV-infected patients¹, these regimens are associated with clinically significant renal toxicity, with proximal renal tubule dysfunction the best characterized toxicity. Renal tubule dysfunction has been associated with phosphorus wasting, with osteomalacia and more commonly asymptomatic loss of bone mineral density identified on dual X-ray absorptiometry (DXA) monitoring. TAF was developed under IND 63737. During development, the Applicant observed that TAF appeared to provide greater intracellular distribution of tenofovir and the active metabolite tenofovir diphosphate in PBMCs and lymphatic tissue yielding lower plasma tenofovir levels than TDF. 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. It was hypothesized that lower tenofovir plasma levels would be associated with a reduced rate of tenofovir toxicities.

3. Product Quality

The Product Quality Review was completed by a team of reviewers with Dr. Stephen Miller as the lead. The NDA was recommended for approval from the Product Quality perspective, and I concur that there are not Product Quality issues precluding approval. Drug substance controls were deemed acceptable. The drug product specifications and microbial controls were also deemed acceptable. Stability data supports a 24 month expiry. The Offices of Compliance and New Drug Quality Assessment determined that all manufacturing facilities were acceptable.

4. Non-Clinical Pharmacology Toxicology

The Pharmacology Toxicology Review was completed by Dr. Claudia Wrzesinski. The Reviewer concluded that there are no Non-Clinical Pharmacology and Toxicology issues that would preclude approval, and I concur.

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. After long term toxicity studies with TAF, 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. Based on

¹ Available at: <https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0>

studies with other drugs in the FDC product, exacerbation of TAF effects on the kidney or bone are not anticipated. Posterior uveitis was observed in dogs, and the NOAEL was 5 (TAF) and 15 (tenofovir) times the exposure seen in humans at the recommended Genvoya® dose. Monitoring for ocular symptoms was included in clinical trials, and there was one case of uveitis described in labeling. In dogs, TAF showed PR prolongation at the mid and high dose, and a reversible reduction in heart rate associated with mild QT prolongation at the high dose. At the NOAEL, the systemic TAF exposure was lower in dogs than humans, so no safety margin could be established. The Reviewer noted that the potential for cardiac toxicity in humans is low, but cannot be excluded. The Agency agreed that the Applicant not conduct carcinogenicity, perinatal, and postnatal studies as TAF is rapidly converted to tenofovir resulting in no appreciable TAF exposure in rats and mice. TAF was not found to be genotoxic, and the components of Genvoya® have not been found to be teratogenic.

5. Clinical Pharmacology

Drs. Mario Sampson, Jeffry Florian, and Islam Younis completed the Clinical Pharmacology Review. They concluded that the Clinical Pharmacology information submitted supports approval, and I concur.

A 10 day monotherapy study was conducted in HIV-infected subjects administered 300 mg TDF compared with 8 mg, 25 mg, and 40 mg of TAF. The TAF 25 mg dose yielded better anti-viral activity than 300 mg TDF. The TAF 10 mg dose was included in Genvoya® because it provides similar exposure to TAF 25 mg when co-administered with COBI 150 mg.

In HIV-infected subjects, tenofovir plasma AUC was reduced approximately 90% in subjects administered Genvoya® compared with Stribild®, while the intracellular AUC in PBMCs of the active metabolite tenofovir-diphosphate was similar.

Relative to fasting conditions, administration with a light or high fat meal resulted in a TAF AUC increase of 15% and 18% respectively. EVG and COBI are recommended to be taken with food. The Genvoya® clinical trials recommended administration with food, and labeling will also recommend administration with food.

TAF is a substrate of efflux transporters Pgp and BCRP, in addition to uptake transporters OATP1B1 and OATP1B3. TAF is a weak inhibitor of CYP3A. Drug-drug interaction information, including contraindications and recommended dose adjustments that are largely related to the EVG and COBI components of Genvoya®, is included in labeling.

In separate thorough QT studies, EVG, COBI, and TAF did not affect the QT/QT_c interval. FTC was approved prior to the thorough QT study requirement, but there have been no arrhythmia safety signals of concern post-marketing.

TAF is primarily eliminated by metabolism to tenofovir in PBMCs and hepatocytes. Tenofovir is intracellularly phosphorylated to the active metabolite tenofovir diphosphate. Based on a single dose study in subjects with Child-Pugh A and B hepatic impairment, no dose adjustment is recommended for this group. Study 0112 in subjects with renal impairment treated with Genvoya®, and Study 0106 in adolescents are discussed in Sections 8 and 10 of this memo.

6. Clinical Virology

The Clinical Virology Review was completed by Dr. Lisa Naeger. She concluded that the NDA was approvable from a Clinical Virology perspective for the indication proposed, and I concur with this assessment.

The active metabolite 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. The activity of TAF against HIV-1 in cell culture is 4- to 6-fold greater than TDF. Cell culture resistance selection experiments with TAF selected for the K65R substitution, previously described in association with TDF. In the treatment-naïve studies (Studies 0104 and 0111) comparing the efficacy of Genvoya® with Stribild®, there were a similar number of failures in each arm and a similar resistance pattern. In the “switch study”, Study 0109, in virologically-suppressed subjects, there were 4 virologic failures and one of these had emergent FTC resistance (M184M/I).

7. Clinical/Statistical Efficacy

The Statistical Review was completed by Dr. Thomas Hammerstrom. The Clinical Review was completed by Drs. William Tauber, Peter Miele, and Andres Alarcon. The Statistical Reviewer, Clinical Reviewers, CDTL, and Division Director all concur that substantial evidence of efficacy has been provided. I concur with their conclusions.

The Applicant conducted two identically designed, randomized, active control, double blind, multicenter Phase 3 trials: Studies 0104 and 0111 in treatment-naïve, HIV-1-infected adult subjects. Subjects were randomized to Genvoya® or Stribild®. 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.² A non-inferiority margin of 12% was agreed upon for both trials and pre-specified in the protocols. Each trial randomized 872 subjects. Genvoya® met the pre-specified primary efficacy endpoint in both of the clinical trials and was found to be non-inferior to Stribild®. Pooling the two trials, 92% and 90% of Genvoya® and Stribild® treated subjects respectively had a HIV-1 RNA < 50 copies/mL at the week 48

² See: *Guidance for Industry, Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment* available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf>

primary endpoint. The treatment difference was 2.0% (95% CI: -0.7% to 4.7%), demonstrating non-inferiority. A similarly designed Phase 2 trial conducted in treatment-naïve subjects, Study 0102, supported this finding.

Additional supportive efficacy data were submitted from Study 0109 in which subjects were randomized to switch from a suppressive treatment containing FTC/TDF plus a third active antiretroviral drug to Genvoya® or continue on their prior regimen. This study was designed to enroll 1500 subjects and treat them through 96 weeks. The submitted data represents an interim analysis of the Week 48 outcome data for 1196 subjects randomized by October 31, 2013 who had received at least 1 dose of study drug. 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. The HIV-1 RNA was < 50 copies/mL at the week 48 primary endpoint for 96% of subjects randomized to switch to Genvoya® and 93% of subjects randomized to continue their suppressive TDF-based regimen. The rate of virologic failure was 1% in both arms. There were a higher number of subjects in the Stribild® arm who discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL (4% vs. 1%).

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 suppressive antiretroviral regimen, and 6 subjects were naïve to treatment at study entry. Among the 242 subjects switching from another regimen to Genvoya®, 95% maintained their HIV-1 RNA < 50 copies/mL through Week 24. Study 0112 is further discussed in Section 8 of this memo.

Study 0106 enrolled 48 HIV-1-infected, treatment-naïve, adolescents 12 years up to 18 years of age who 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. At the Week 24 analysis, 91% of subjects achieved HIV-1 RNA < 50 copies/mL. Study 0106 is further discussed in Section 10 of this memo.

8. Safety

The Clinical Reviewers, CDTL, and Division Director agreed that the safety and tolerability of Genvoya® is acceptable and I concur.

The safety data included comparative data in 1733 subjects in Studies 0104 and 0111 as well as data from other supportive studies. There were 10 deaths in the clinical development program that were reviewed and were not considered related to study medications. Review of SAEs failed to identify any specific pattern suggesting a serious safety signal related to TAF or Genvoya® or any substantive differences between treatment arms. Across the clinical development program, very few adult subjects prematurely discontinued study drug for any reason (3% in Genvoya® arms, 6% in

comparator arms). Adverse events were balanced across treatment arms and considered not related to study drug.

With respect to renal toxicity in Studies 0104 and 0111 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. 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.

As described in Section 7 of this memo, 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. Among those subjects who switched to Genvoya® from a stable TDF-containing regimen, renal parameters remained relatively stable through Week 24. Safety evaluations in Study 0112 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. Two subjects, both with baseline eGFR < 50 mL/min, experienced clinical AEs described as renal failure that led to study drug discontinuation. A third subject, with baseline eGFR of 55 mL/min, developed transient acute renal failure resulting in brief treatment interruption. The review team pointed out that, 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 duration of TAF exposure.

Once daily treatment options are limited for patients with eGFR < 50 mL/min and no single FDC tablet is approved for this population. As the overall safety profile was acceptable in Study 0112 for 80 subjects with eGFR 30-49 mL/min, the review team concluded that the benefit of Genvoya® treatment in patients with moderate renal impairment outweighed the potential risk and risk could be mitigated by monitoring renal function during treatment. Thus, labeling recommends no dose adjustment for patients with eGFR greater than or equal to 30 mL/min and notes that Genvoya® is not recommended for patients with eGFR less than 30 mL/min.

To assess bone toxicity, the Applicant provided serial DXA scans to evaluate bone mineral density (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®. BMD decreases are described in labeling. In Study 109, 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 with similar findings for the femoral neck.

As described in Section 4 of this memo, posterior uveitis was observed in dogs and

enhanced monitoring was included in trials. While no cases of uveitis were reported among adult subjects, a case of “intermediate uveitis” attributed to study drug was reported in a 13 year old female in Study 0106. This is described in labeling.

The most clinically important laboratory abnormalities identified in the Genvoya® development program include elevated fasting serum lipids, particularly total cholesterol and low-density lipoprotein. Subjects receiving Genvoya® experienced significantly higher increases in serum lipids compared to those receiving Stribild®. A table summarizing lipid abnormalities in Studies 0104 and 0111 is included in labeling.

9. Advisory Committee Meeting

The NDA was not referred to an FDA advisory committee because during the review process, no substantive issues were encountered that would benefit from Advisory Committee discussion; three of the component drugs were previously approved and TAF (the only NME) represents a second prodrug of a well-characterized antiretroviral.

10. Pediatrics

Efficacy in adolescents 12-18 years of age was supported by extrapolation from the adequate and well-controlled adult clinical trials with bridging PK and safety data from Study 0106. BMD was also evaluated in the adolescents in Study 0106. Using Z-scores to normalize growth parameters, 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 subjects had significant (greater than 4%) lumbar spine BMD loss at Week 24. This will be described in labeling. With the exception of the case of uveitis described in Section 8 of this memo and the BMD monitoring results described above, the safety findings for the adolescents enrolled in Study 0106 were similar to adult studies.

For patients 6 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 and PeRC agreed. The deferred study will be incorporated into a PREA Postmarketing Requirement.

In addition, as the NDA included an interim report from Study 0106, 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

A regulatory issue of note for this review was that the proportion of sites staffed by investigators with disclosable financial interests ranged from about 27% to 34% for the Phase 3 adult clinical trials. This appeared to represent a higher proportion of sites and principal investigators potentially affected than encountered in other NDA submissions reviewed by the Division of Antiviral Products and was discussed with the Applicant.

Sensitivity analyses for efficacy and safety excluding these sites generally did not find an impact. The review team did not find any adverse consequences of these findings.

12. Labeling

Labeling agreement has been reached with the Applicant. Notable labeling decisions are highlighted throughout this memo.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: Approval

Risk Benefit Assessment:

This NDA provides substantial evidence of efficacy for this FDC drug product containing a new prodrug of tenofovir dosed once daily for the treatment of HIV-1 infection in adults and adolescents greater than 12 years of age. Efficacy and safety were demonstrated in treatment naïve adults and virologically suppressed adults changing their treatment regimen to Genvoya®. Like a number of FDC combination products for the treatment of HIV-1 infection, drug interactions will be an important consideration in patient care. While post-marketing experience with more prolonged use will provide more definitive data and close monitoring of renal function in patients is still appropriate, the risk of renal toxicity appears to be lower than that of the previously approved TDF pro-drug. The benefit risk at this time is acceptable with no dose adjustment in patients with moderate renal impairment down to an eGFR of 30 mL/min, providing a once a day FDC treatment option for this patient population. While BMD loss in adult clinical trials was less than that of the previously approved TDF pro-drug, the data in a small number of adolescents with BMD normalized for growth parameters was less favorable. In comparative clinical trials, Genvoya® was associated with greater increases in fasted total cholesterol, LDL cholesterol, and triglycerides than Stribild®. It is not known at this time whether patients treated with Genvoya® will be more likely to require lipid lowering medications or be at increased risk for adverse cardiovascular outcomes.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies: None

Recommendation for Postmarketing Requirements and Commitments as recommended in the Division Director Decisional Review:

There is a required pediatric assessment under PREA to conduct the deferred pediatric study in HIV-infected children 6 years to less than 12 years.

The Applicant has agreed to a Post-Marketing Commitment to submit the long-term safety and antiviral activity data for Study 0106.

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/s/

JOHN J FARLEY
11/04/2015