CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203100Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 16, 2012
From	Linda L. Lewis, M.D. Medical Team Leader Division of Antiviral Products, CDER, FDA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	203100/000 Original submission
Applicant	Gilead Sciences, Inc. Foster City, CA
Date of Submission	October 27, 2011
PDUFA Goal Date	August 27, 2012
Proprietary Name / **Established (USAN) names**	Stribild™ Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate fixed dose combination
Dosage forms / Strength	Tablets containing: Elvitegravir 150 mg Cobicistat 150 mg Emtricitabine 200 mg Tenofovir DF 300 mg
Proposed Indication(s)	Stribild is indicated as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve
Recommended:	*Approval – with modifications to proposed labeling as noted*

Note: This CDTL Review reflects the findings of each discipline's assessment and the inter-disciplinary discussions of the entire FDA review team. Sections 9, 12, and 13 incorporate the discussions and recommendations of the Antiviral Advisory Committee held on May 11, 2012.

1. Introduction

This NDA contains information to support the approval of Stribild™, a new fixed dose combination (FDC) product containing a complete HIV-1 treatment regimen of elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 300 mg, developed by Gilead Sciences.

Stribild represents a novel product review in several ways. Stribild contains two new molecular entities (NMEs): elvitegravir (EVG), a new HIV-1 integrase inhibitor, and cobicistat (COBI), a mechanism-based pharmacoenhancer included to boost the exposure of EVG. The NMEs are combined with emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), two approved and widely-used nucleoside reverse transcriptase inhibitors (NRTIs). Both EVG and COBI are under development as single products. To our knowledge, this will be the first approval of two NMEs simultaneously in an FDC. In addition, unlike the process used to approve earlier antiretroviral FDCs on the basis of bioequivalence to the individual component drugs, this NDA package provides two adequate and well-controlled clinical trials conducted with the FDC in the target treatment-naïve population. This allows Stribild to be reviewed on its own merits, independent of the efficacy of any individual component drug. In an era in which HIV treatment is becoming increasingly simple and effective, Stribild offers a one-pill-once-a-day alternative to non-nucleoside reverse transcriptase inhibitor (NNRTI)-anchored FDCs.

This NDA contains the results of the nonclinical and clinical development program conducted by Gilead Sciences. 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) of the single products and the FDC, in addition to clinical safety and efficacy of the FDC complete regimen.

2. Background

The development program for Stribild evolved out of the development programs for the individual products EVG and COBI and was submitted as a new IND for the FDC in July, 2008. The investigational plan for the FDC focused on treatment-naïve patients and, because substantial evaluation of EVG and COBI had been conducted, the development program progressed rapidly to discussion of clinical treatment trials with the FDC. An End-of-Phase 2 meeting held in March, 2010, combined discussion of COBI Phase 3 clinical trials and discussion of the FDC Phase 3 clinical trials. During that meeting, the Division of Antiviral Products (DAVP) and Gilead Sciences agreed on the study design of the Stribild Phase 3 clinical trials and agreed that trials conducted with the FDC could support the COBI single-drug program. We also agreed on a portfolio of clinical pharmacology studies needed to support both programs. At the time of the EOP2 meeting, DAVP requested the Applicant develop a management and monitoring plan for elevations of serum creatinine, a treatment-related effect of COBI identified earlier in the development program.

Between January and July, 2011, DAVP provided numerous responses to the Applicant's questions regarding dataset requirements and recommended analyses for a planned NDA. In July, 2011, a pre-NDA meeting was held and the final plans for NDA submission were discussed. At this meeting, it was decided that the NDA for Stribild would be submitted first, followed several months later, by the NDAs for EVG and COBI. The timing of submitting CMC and nonclinical modules as part of a rolling submission was discussed; but these modules were not submitted earlier than other modules and the complete NDA was submitted on October 27, 2011.

3. CMC/Device

The NDA submission included adequate information to allow the CMC review team to evaluate the characteristics and quality of the two NME drug substances (EVG and COBI) and the final FDC drug product (Stribild tablets). For a complete discussion of the CMC issues, please refer to the full Chemistry Review provided by the CMC review team, Drs. Celia Cruz, Milton Sloan, and Fuqiang Liu, and the Biopharmaceutics Reviewer Dr. Deepika Lakhani. Their combined review includes only the aspects of the CMC issues related to FTC or TDF which are relevant to the Stribild 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***

Stribild is an immediate release tablet containing the four active ingredients (EVG, COBI, FTC, and TDF) and commonly used excipients (microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, silicon dioxide, lactose monohydrate, magnesium stearate, and hydroxypropyl cellulose). The tablets are green, capsule shaped, film-coated, and debossed with "GSI" on one side and " 1 ", on the other side. All drug product specifications and degradation product specifications are adequately justified for drug product release and shelf life. EVG has no specified individual degradation products, as no degradation of this drug substance has been observed at any condition. However, there are six degradation products specified for COBI, three for FTC, and five for TDF.

EVG drug substance is manufactured (b) (4) at three different manufacturing sites (DMF 25187 for Elvitegravir). Drug substance is white to pale yellow powder that is very poorly soluble in water. A total of 31 compounds were identified as potential impurities; 17 have limits specified at (b) (4) or less, and any other impurities will be limited as unspecified impurities at (b) (4) The total impurities are limited to no more than (b) (4) Most of these impurities can be attributed to starting material or from the manufacturing process and not from degradation.

COBI drug substance is manufactured and adsorbed onto silicon dioxide in order to provide a stable solid form that is suitable for pharmaceutical manufacturing (DMF 25188 for Cobicistat on Silicon Dioxide). Review of the COBI drug substance information identified four impurities with mutagenic potential. Two of the impurities (b) (4) are

(b) (4) The review team concluded that the data provided were adequate to support the use of Cobicistat on Silicon Dioxide as a drug substance for use in the FDC.

As noted in the CMC Review, Stribild tablets are manufactured (b) (4) Layer 1 containing EVG + COBI and Layer 2 containing FTC + TDF. (b) (4)

Stribild drug product has been stability tested in the primary container at 25º C/60% RH and 30º C/ 75% RH for 12 to 24 months and also at high temperature (50º C ambient) and high humidity (80% RH) for 6 weeks. (b) (4) No significant changes in appearance, assay, or dissolution were observed during storage. The NDA also includes stability data on a tablet variant ("Access Tablet") that is intended for use in resource poor countries throughout the world, for example in the PEPFAR focus nations. The Access tablet is differentiated by the color of the film coat and the tablet imprint, but is otherwise identical to the US product. The CMC review team concluded that the stability data supported a shelf life of 24 months for either tablet version when stored in the approved container at 25 ºC (with excursions permitted 15 to 30 ºC) [labeling for the US tablet], or at less than 30ºC [labeling for Access tablet].

Stribild tablets will be packaged in white, high density polyethylene bottles containing 30 tablets and 3 grams silica gel desiccant. Each bottle has a child-resistant screw cap. Container labeling notes that tablets should be dispensed in the original container.

- ***Facilities review/inspection***

A total of 14 manufacturing, testing, packaging and labeling facilities were evaluated for this NDA. At the present time, the (b) (4) facility, which is one of the sites where FTC drug substance is manufactured, has pending GMP issues which could potentially preclude approval of the NDA. Additionally, at this time the final assessment of three facilities are pending in the Establishment Evaluation System: (b) (4) Gilead Alberta, ULC (Alberta, Canada), and Gilead Sciences, Inc (Foster City, CA). The Gilead Sciences facility in Foster City, CA, was issued an SF-483 citing inspection deficiencies but has not yet responded.

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

At the time of writing this CDTL Review, the CMC review team can not recommend approval of Stribild as the manufacturing site inspections have not been successfully completed and GMP issues identified at one site have not been resolved.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a portfolio of nonclinical study reports describing the results of acute and chronic toxicity studies, genotoxicity studies, carcinogenicity studies (studies of COBI are still in progress) and reproductive toxicology studies for both EVG and COBI (some studies done with EVG+COBI). Nonclinical studies were not conducted with the Stribild 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 Drs. Pritam Verma, L. Peyton Myers, and Mark Powley. Their combined review does not include evaluation of nonclinical studies conducted for approval of FTC or TDF as these studies have been reviewed previously. Key points from the Pharmcology/Toxicology review are summarized in this section.

- ***General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise)***

Oral bioavailability of EVG was moderate in rats (30-35%) and in dogs (27-33%). EVG is extensively bound to human plasma proteins and albumin. The drug is metabolized by oxidation and glucuronidation and multiple metabolites have been identified and are similar across species including humans. Metabolism is inhibited by CYP3A4 inhibitors such as COBI and ritonavir. Animal toxicology studies have not identified target organ toxicity for EVG with single doses or chronic dosing regimens. Observations of lipid-like vacuoles in the lamina propria of the upper small intestine in rats and dog were not accompanied by GI symptoms or other histologic abnormalities, and were not considered adverse.

Oral bioavailability of COBI is low to moderate in all tested species. It is also highly bound to human serum proteins and was widely distributed, particularly to the GI tract. It is extensively metabolized and excreted primarily in the feces. COBI inhibits CYP3A4, which is the basis for its clinical utility. Toxicology studies in rats and dogs identified the liver as the target organ for pathologic changes after chronic dosing. The histologic findings in the liver appeared to be the consequence of microsomal enzyme induction with increases in liver weight and mild hepatocellular hypertrophy. Animals also demonstrated changes in urinalysis parameters, judged to be due to increased water intake with resulting urine dilution. COBI caused elevations in serum creatinine in rats and dogs, attributable to inhibition of renal transporters.

COBI resulted in noticeable effects in the *in vitro* cardiotoxicity evaluations. It inhibited hERG potassium current and caused negative inotropic effects in rabbit Purkinje fibers. The negative inotropic effects of PR interval prolongation and decreased left ventricular function were also observed in an isolated rabbit heart study. *In vivo* correlates in dogs included mild PR interval prolongation but no effect on QT interval. These findings were explored in the thorough QT study conducted in healthy volunteers (see Section 5).

A 13-week combination study of EVG + COBI in rats did not identify any new or additive toxicity.

- ***Carcinogenicity***

Neither EVG nor COBI is considered genotoxic based on negative findings in the Ames assay, *in vitro* chromosomal aberration assay, and *in vivo* rat micronucleus assay. Long-term carcinogenicity studies in mice and rats have been done with EVG and no drug-related increases in tumors were identified at exposures approximately 14-fold the human exposure at the clinical dose. Carcinogenicity studies of COBI were not included in this NDA submission and have not been fully reviewed at this time. Previous evaluation of TDF and FTC demonstrated low carcinogenic potential in 2-year studies.

The Pharmacology/Toxicology review team also reviewed the potential for the identified impurities to be genotoxic. Carcinogenicity data were available for (b) (4) an impurity found in EVG drug substance, allowing calculation of a threshold of toxicologic concern. Two of the four COBI impurities (b) (4) are thought to be potentially genotoxic and two impurities are known mutagens in the Ames test. CMC and Pharmacology/Toxicology reviewers worked together to determine that these impurities could be adequately controlled during the manufacturing processes and to set appropriate specifications.

Based on the accumulated data for all four component drugs and major metabolites, the Pharmacology/Toxicology review team considers the Stribild FDC to be of low carcinogenic potential as it is unlikely that combination of the drugs will exacerbate carcinogenicity.

- ***Reproductive toxicology***

No adverse drug effects on male or female fertility or embryofetal development were identified in rats receiving EVG and there were no perinatal/postnatal effects. COBI was evaluated in a full battery of reproductive toxicology studies and no effects were observed on male or female fertility, embryofetal development, postnatal development, or lactation. COBI was excreted in milk of lactating rats.

Based on the reproductive toxicology studies for the component drugs, Stribild is considered a Pregnancy Category B drug (no studies in pregnant women but no significant embryofetal toxicity in animal studies). Product labeling will note that it should be used during pregnancy only if the potential benefit justifies the potential risk, the standard risk language for Category B drugs.

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

Multiple impurities have been identified related to the manufacturing processes for EVG and COBI. The proposed specifications appear to be acceptable based on two rat toxicology studies evaluating EVG spiked with EVG impurities. Similar toxicologic evaluation was conducted for COBI spiked with COBI impurities. The level of the impurities qualified in these toxicologic studies exceeded the proposed specifications for manufacture of the drug substances.

After careful review of all the submitted nonclinical information, the Pharmacology/Toxicology review team recommended that Stribild tablets be approved.

5. Clinical Pharmacology

Stribild, or its component drugs, 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 Clinical Pharmacology Review submitted by Dr. Vikram Arya and the collaborating team of reviewers (Drs. Stanley Au and Leslie Chin, Clinical Pharmacology Reviewers, and Dr. Jeffry Florian, Pharmacometrics Reviewer). The Clinical Pharmacology Review did not focus on the pharmacologic properties of FTC and TDF as single drugs but did evaluate some aspects of TDF exposure as related to the Stribild FDC. The following points summarize the conclusions of the Clinical Pharmacology review team.

[Note: In this memo, the term "Stribild exposure" refers to exposure of multiple component drugs derived from administration of the FDC while comments specific to an individual component will reference the relevant component drug.]

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

EVG and COBI are both absorbed well and are not affected by changes in gastric pH. EVG exposure is affected by antacid administration but this appears to be due to complexing with divalent cations in the antacids. EVG exposure is affected by food, with a 34% to 87% increase in exposure when FDC is taken with a light or high fat meal, respectively, compared to fasting. Consequently, the drug will be labeled to be taken with food.

The composition of Stribild was determined on the basis of exposure-response analysis of EVG, initially boosted with ritonavir, and the dose of COBI required to achieve a similar EVG exposure. A phase 2 trial evaluating an investigational formulation of EVG at doses of 20 mg, 50 mg and 125 mg boosted with RTV 100 mg demonstrated best suppression of HIV-1 RNA with the 125/100 mg dose. A revised formulation of EVG 150 mg boosted with RTV 100 mg provided similar exposure to the original 125/100 mg dose and was taken forward into phase 3 trials. The current Stribild FDC containing EVG 150 mg and COBI 150 mg provides similar EVG exposure to the previously selected dose of EVG 150 mg/ritonavir 100 mg. The doses of FTC and TDF are the currently approved doses of these drugs.

The Clinical Pharmacology review team evaluated the exposure-response data for both efficacy and safety. A relatively flat exposure-response relationship was identified for efficacy across the EVG exposure range achieved in the Stribild clinical trials, confirming that the dose selected was appropriate. In addition, no relationship was observed between EVG exposures and the most common adverse events observed during the clinical trials.

- ***Pathway of elimination***

Components of Stribild are subject to both hepatic metabolism (EVG and COBI) and renal elimination (FTC and TDF). EVG is primarily metabolized by CYP3A4, with some

metabolism by CYP3A5 and glucuronidation by UGT1A1. COBI is metabolized by CYP3A4 and CYP2D6. In addition, EVG and COBI are both P-glycoprotein substrates. Both EVG and COBI are eliminated primarily in feces. FTC and TDF are eliminated unchanged in urine by a combination of active tubular secretion and glomerular filtration.

The Applicant conducted studies to evaluate the effects of renal and hepatic impairment on Stribild exposures. No clinically meaningful differences in EVG or COBI exposures were noted in a study of subjects with severe renal impairment (ie, estimated creatinine clearance < 30 mL/min) and no dose adjustments are required for those components. However, previous studies determined that the renally eliminated components FTC and TDF require dose adjustment for subjects with estimated creatinine clearance < 50 mL/min. Because Stribild is an FDC, it can not be appropriately adjusted for patients with creatinine clearance < 50 mL/min and will be labeled accordingly.

No clinically relevant differences were identified in EVG and COBI exposures in a study of subjects with moderate hepatic impairment (Child-Pugh Class B). No dose adjustment of either of these components is required in the setting of moderate hepatic impairment; Stribild has not been evaluated in subjects with severe hepatic impairment. Neither FTC nor TDF require adjustment for hepatic impairment.

- ***Drug-drug interactions***

Based on the determination that both EVG and COBI are metabolized by CYP3A4, and COBI is a potent inhibitor of CYP3A4, many clinically relevant drug interactions were anticipated by the Applicant. The effectiveness of Stribild is directly dependent on COBI's property to inhibit metabolism of EVG by CYP3A4 and thereby increase EVG exposure. In addition, TDF exposure is approximately 30% higher when administered as Stribild compared to the approved 300 mg dose of TDF given alone.

The Applicant conducted extensive drug-drug interaction studies with EVG (alone or administered with ritonavir), COBI (alone) and with Stribild. Drug interaction studies were conducted characterizing the effect on various CYP3A4 substrates and the potential for interactions with medications commonly used in patients with HIV infection including: omeprazole, famotidine, antacids, digoxin, desipramine, a combined oral contraceptive, rosuvastatin, and rifabutin. In addition, the effects of potent CYP3A induction (rifampin) and inhibition (ketoconazole) on Stribild PK were assessed. These studies provided adequate information to allow dosing recommendations for Stribild and potentially interacting drugs used in the target population. In addition, some drug-drug interactions are assumed based on COBI's properties as a CYP3A4 inhibitor.

Adjustments will be required in dosing of some drugs and additional clinical monitoring recommended for other drugs during co-administration with Stribild. The product label will include tables identifying demonstrated or anticipated effects on exposure of concomitant medications and the corresponding recommended monitoring or dose adjustment. For example, prescribers will be advised to use caution when coadministering antiarrhythmic drugs because of the potential for increased exposure of these drugs.

Stribild will be contraindicated in combination with certain drugs that are highly dependent on CYP3A clearance and that are associated with serious or life-threatening complications at high exposures or that significantly decrease Stribild exposure. Examples of these classes include drugs such as ergot derivatives (potential for acute ergot toxicity), lovastatin (potential for rhabdomyolosis with increased statin levels), and rifampin (potential for loss of effectiveness due to reduced EVG levels).

Coadministration of Stribild and the combination contraceptive Ortho Tri-Cyclen (ethinyl estradiol + norgestimate) resulted in about 25% decreased exposure of the estradiol and about 125% increased exposure to norgestimate. These interactions raised concerns that low-dose oral contraceptives might fail (estrogen component) or there could be increased risk of thrombotic events (progestin component) and this issue was referred to our colleagues in the Division of Reproductive and Urologic Products. The consultants from DRUP confirmed that contraceptive efficacy is more closely linked to the progestin component of combined oral contraceptives and the decreased estrogen component was unlikely to result in contraceptive failures. They noted that the full clinical impact of this drug interaction is unknown and results of this drug-drug interaction study could not be extrapolated to other hormonal contraceptives. Until more data are available, alternative non-hormonal contraceptive methods can be used or patients taking Stribild may take Ortho Tri-Cyclen in consultation with an expert in women's health.

Studies evaluating interactions with other antiretroviral drugs were not reviewed with this application as Stribild provides a complete HIV treatment regimen and is not intended for use with other antiretrovirals.

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

The Applicant evaluated the effects of age, gender, race, and weight/height on Stribild exposure across the clinical development program. Differences in exposure of the component drugs based on gender, race, or ethnicity were not identified. Body weight, body surface area and body mass index were found to influence exposure; lower cohorts of these parameters had higher EVG exposure. However, as no exposure-response relationships were noted for either safety or efficacy within the observed exposure ranges, dose adjustment based on body weight, body surface area or body mass index is not necessary.

EVG and COBI are not significantly renally excreted. The PK of EVG + COBI was evaluated in patients with severe renal impairment and no significant effect on exposure was identified. However, both FTC and TDF are excreted renally and require dose adjustment in patients with estimated creatinine clearance < 50 mL/min. Because Stribild is an FDC, it can not be adjusted appropriately in patients with renal impairment. In addition, due to concern for TDF-associated renal toxicity, it will be recommended that Stribild dosing is not initiated in patients with estimated creatinine clearance < 70 mL/min.

EVG+COBI was evaluated in subjects with moderate hepatic impairment (Child-Pugh class B). Although the C_{max} of EVG was increased by 35-40% in this population, these levels were within the range observed during the clinical trials and were not associated with adverse

events. Therefore, no dose adjustment is recommended in this patient population. Subjects with Child-Pugh class C have not been studied. The Clinical Pharmacology reviewers agree, therefore, with the Applicant's recommendation that Stribild should not be administered to patients with severe hepatic impairment.

- ***Relevant issues related to clinical pharmacology arising from investigations by gender, age, including pediatrics and geriatrics, and other demographic-based investigations.***

Stribild has not been specifically evaluated in either pediatric or geriatric patients and very few elderly subjects were enrolled in the Phase 3 trials. However, patients 65 years and older might be expected to have reduced clearance and higher exposure. As noted in the section summarizing critical intrinsic factors, neither gender nor race had an impact on Stribild clearance based on the Applicant's population PK analysis. No additional demographic interactions or special populations are expected to influence Stribild exposure.

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

The Applicant conducted thorough QT studies with both EVG and with COBI to evaluate drug effects on electrocardiogram parameters. These studies were reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT) and found to represent an adequate evaluation of the highest exposures expected in the clinical setting. The IRT concluded EVG's effect on QTc prolongation was below the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals. The COBI effect on QTc was also below the level of concern but COBI did appear to have a significant effect on prolonging PR interval. In the original review of the COBI QT study, the IRT commented that the prolonged PR interval might be of clinical relevance in elderly patients, those with underlying conduction problems, or those on medications that also prolong PR. As a result, electrocardiograms were included in the Stribild clinical trials safety monitoring. After review of the NDA dose recommendation, the IRT noted that the PR findings are not likely to be clinically relevant as the treatment dose is well below the doses tested in the QT study. The IRT noted that thorough QT studies have not been conducted with FTC and TDF or with the Stribild FDC.

.

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

Although the Applicant conducted an extensive battery of drug-drug interaction studies in support of this NDA, the potential for interactions with some drugs not previously evaluated still need to be addressed. Drug interaction information was not provided for anti-addiction drugs (methadone or buprenorphine/naloxone) or the HCV direct-acting antiviral drugs (boceprevir and telaprevir), but information regarding the potential for interactions with these medications is considered important for patient management. The review team also recommends that the Applicant further evaluate drug-drug interactions with additional hormonal contraceptives.

After careful review of all the submitted clinical pharmacology information, the Clinical Pharmacology review team recommended that Stribild tablets be approved but suggested additional post-marketing studies (see Section 13).

6. Clinical Virology

The Applicant submitted multiple studies and analyses evaluating the antiviral mechanism of action of Stribild, the emergence of resistance substitutions to the component drugs, and the patterns of cross-resistance with other antiretrovirals. Please refer to the Virology Review submitted by Drs. Sung Rhee and Takashi Komatsu for a detailed discussion of these data and analyses. The main conclusions of their review are summarized below.

- ***General considerations and mechanism of action***

EVG is an HIV-1 integrase strand transfer inhibitor (INSTI) and prevents the integration of HIV-1 DNA made by reverse transcription of the viral genomic RNA into the host cell chromosome. Integrated viral DNA (provirus) is required for productive HIV-1 infection. Using recombinant HIV-1 integrase in a biochemical reaction, EVG was shown to inhibit the DNA strand transfer reaction with an IC_{50} value of 8.8 nM. The antiviral activity of EVG was shown against multiple laboratory and clinical isolates of HIV-1 with EC_{50} values ranging from 0.02 to 1.7 nM. EVG was not found to be antagonistic with any of 22 approved antiretroviral drugs when evaluated in combination antiviral activity assays. COBI functions in the FDC as a pharmacoenhancer and has no detectable antiviral activity in cell culture assays against laboratory or clinical isolates of HIV-1. Both FTC and TDF are approved HIV-1 NRTIs that target a different essential viral enzyme. Because the three active antiretroviral drugs in Stribild target two critical steps in the HIV-1 life cycle and have different resistance pathways, Stribild was expected to provide an adequate treatment regimen.

- ***Resistance***

HIV-1 variants resistant to EVG could be selected in cell culture systems and associated amino acid substitutions included: D10E, S17N, H51Y, T66A/I, E92G/Q, F121Y, S147G, Q148R, S153F/Y, E157Q, D232N, R263K, and V281M. Variants with the substitutions T66A/I, E92G/Q, F121Y, and Q148R were associated with >10-fold reduction in susceptibility to EVG.

In a pooled resistance analysis of Studies 0102, 0103, and 0104 (a small Phase 2 trial of Stribild versus ATR) in treatment-naïve subjects, genotypic and phenotypic resistance to the individual components of EVG/COBI/FTC/TDF was monitored in HIV-1 isolates from subjects with HIV-1 RNA ≥400 copies/mL at Week 48. HIV-1 variants harboring treatment-emergent substitutions in the HIV-1 proteins were detected in failure isolates from 20 of 24 evaluable subjects (see Table 1). These failure isolates had reductions in susceptibility to EVG ranging from 1 to >198-fold that of wild-type HIV-1. Failure isolates from 4 subjects with no detectable genotypic changes in integrase had fold-change values in EVG susceptibility below the biological cutoff (ranging from 1.1- to 1.8-fold). The primary EVG resistance-associated substitutions (T66I, E92Q, Q148R, and N155H) were identified in 11 of the 24 Stribild treatment failures with evaluable genotypic data (highlighted in Table 1). No new EVG-resistance associated substitutions were identified in the pooled trials. Substitutions in the reverse transcriptase (RT) associated with resistance to FTC or TDF were documented in 14 of the evaluable subjects, 12 of whom were receiving Stribild.

Table 1: Genotypic and Phenotypic Resistance in Evaluable Virologic Failure Isolates in the Censored, As-Treated Subject Populations (Pooled Studies 0102, 0103, and 0104)

Stribild Treatment (24 VFs)					
EVG^R-associated substitutions in IN	# subjects	FTC^R- and TDF^R-associated substitutions in RT	Drug susceptibility (fold-change)		
			EVG	FTC	TFV
YES, n=11	3	K65R, M184V	111 - >198	84 - 109	1.1 - 1,6
	7	M184I/V	6 - 51	75 - >152	0.5 - 0.7
	1	not determined	20 - 54[1]	-	-
NO, n=13	1	K65R, M184I	2	42 - 116[1]	0.8
	1	M184V	1	>88	0.4
	10	NONE	1 - 2	1 - 2	0.6 - 1.1
	1	not determined	1	-	-
ATR Treatment (15 VFs)					
EFV^R-associated substitutions in RT	# subjects	FTC^R- and TDF^R-associated substitutions in RT	Drug susceptibility (fold-change)		
			EFV	FTC	TFV
YES, n=8	2	K65R, M184I/V	19 - >70	42 - >129	1.4 - 1.8
	6	NONE	1 - 68	1	0.5 - 1.1
NO, n=7	7	NONE	1 - 2	1	0.7 - 1.2

EVG^R = primary elvitegravir resistance; EFV^R = efavirenz resistance; FTC^R = FTC resistance; TDF^R = TDF resistance
[1]Two isolates evaluated for this subject.
Source: Abstracted from NDA 203100, Microbiology Review, S. Rhee and T. Komatsu

Because COBI is similar in structure and pharmacoenhancer function to ritonavir, an approved HIV-1 protease inhibitor (PI), the Virology review team analyzed the available clinical virology data for evidence of treatment-emergent PI resistance substitutions. For this analysis, data from Study 0102 was used as the ATR comparator arm was not expected to select for protease resistance. A disproportionate number of substitutions in HIV-1 protease developed in subjects receiving Stribild (9 substitutions/14 subjects) compared to those receiving ATR (4 substitutions/15 subjects). Three of the 9 protease substitutions identified from the Stribild arm have been associated with resistance to PIs (M36I, D60E, and V77I) compared to 1 out of 4 in the ATR arm (K20R). None of the observed protease substitutions are among those considered primary PI resistance-associated substitutions. The number of subjects in this analysis is small and the clinical relevance of these observations remains unclear.

- ***Cross-resistance***

As EVG has the same mechanism of action as the approved INSTI raltegravir (RAL) and similar genetic pathways to resistance identified in cell culture and *in vivo*, cross resistance between these two drugs is expected. All Stribild treatment failure isolates with evidence of treatment-emergent primary EVG resistance-associated substitutions were phenotypically resistant not only to EVG with >2.5-fold reduced susceptibility (above the biological cutoff for EVG) but also to RAL with >1.5-fold reduced susceptibility (above the biological cutoff for RAL). These results confirmed the cell-based cross-resistance findings with integrase substitutions generated by site-directed mutagenesis demonstrating broad cross-resistance between EVG and RAL. All 14 isolates harboring the M184I/V RT substitution exhibited cross-resistance to lamivudine with >43-fold reduced susceptibility and some to didanosine. In

addition, three of the six isolates harboring the K65R RT substitution in addition to M184V/I showed cross-resistance to multiple NRTIs including abacavir, didanosine, FTC, and TDF.

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

The observations regarding EVG, FTC and TDF resistance-associated substitutions and cross-resistance were well characterized in the NDA submission and were not unexpected. However, the finding of PI-associated substitutions in subjects receiving Stribild is concerning and will require careful follow-up as larger number of patients are treated.

After careful review of the nonclinical and clinical virology data, the Virology review team recommended approval of Stribild but the Applicant will be asked to continue to monitor for PI-associated resistance substitutions in on-going clinical trials (see Section 13).

7. Clinical/Statistical- Efficacy

To support the proposed indication, the Applicant conducted two adequate and well-controlled Phase 3 trials: Studies 0102 and 0103 in treatment-naïve adult subjects. These two clinical trials were identical in study design and study population but used different approved HIV treatment regimens as the comparator arms: Atripla (the FDC containing efavirenz/emtricitabine/ tenofovir DF, ATR) in Study 0102 and atazanavir boosted with ritonavir (ATV/r) + emtricitabine/tenofovir (TVD) in Study 0103. 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. A non-inferiority margin of 12% was agreed upon for both trials and pre-specified in the protocols. For a detailed description of the registrational clinical trial design, please refer to the Clinical Review provided by Dr. Adam Sherwat.

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. Wen Zeng, the Statistical Reviewer, conducted numerous analyses to assess the robustness of the results 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.

A total of 1408 subjects were included in the combined trials' ITT analysis population: 701 received Stribild, 352 received ATR, and 355 received ATV/TVDr+. Study 0102 enrolled entirely in the US (including Puerto Rico) and Study 0103 enrolled in the US (54%), Canada, Mexico, European Union, Australia, and Thailand. Baseline demographic and disease characteristics were balanced across treatment arms in both trials. The pooled trial population was 90% male, 66% white, 25% black/African American, 3% Asian, 21% Hispanic/Latino, and had a median age of 37 years. The trial population had a median HIV-1 RNA of 60,400 copies/mL and a median CD4+ cell count of 360 cells/mm^3, with 38% of participants having HIV-1 RNA > 100,000 copies/mL and 13% having CD4+ cell count < 200 cells/mm^3.

Stribild met the primary efficacy endpoint in both of the clinical trials and was found to be non-inferior to both ATR and ATV/r+TVD (see Table 2). A relatively small number of subjects in all arms failed to have virologic data at the Week 48 evaluation. The information in Table 2 will be displayed in the product label.

Table 2: Primary Efficacy Outcomes (ITT analysis population)

	Study 236-0102		Study 236-0103	
	Stribild (N=348)	ATR (N=352)	Stribild (N=353)	ATV/r + TVD (N=355)
Virologic Success (HIV-1 RNA < 50 copies/mL) at Week 48	305 (87.6%)	296 (84.1%)	316 (89.5%)	308 (86.8%)
Treatment Difference	3.6% (-1.6%, 8.8%)		3.0% (-1.9%, 7.8%)	
Virologic Failure at Week 48	25 (7.2%)	25 (7.1%)	19 (5.4%)	19 (5.4%)
No Virologic Data in Week 48 Window	18 (5.2%)	31 (8.8%)	18 (5.1%)	28 (7.9%)
Discontinued Study Drug Due to AE/Death*	10 (2.9%)	19 (5.4%)	11 (3.1%)	18 (5.1%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL**	8 (2.3%)	11 (3.1%)	7 (2.0%)	9 (2.5%)
Missing Data During Window but on Study Drug	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.3%)

* Includes patients who discontinued due to adverse event or death at any time point during the 48 week treatment period if this resulted in no virologic data on treatment during the specified Week 48 window.

** Includes subjects who discontinued for reasons other than an adverse event, death or lack or loss of efficacy, e.g., withdrew consent, loss to follow-up, etc.

Source: Abstracted from NDA 203100, Clinical Review, A. Sherwat.

A key secondary endpoint was the change from baseline in CD4+ cell count. There was a minor difference in change in CD4+ cells from baseline through Week 48 between Stribild and the ATR comparator group but the difference is not thought to be clinically relevant. Using the FDA-preferred last-observation-carried-forward analysis for change in CD4+ cell counts, the mean increase at Week 48 in Study 0102 was 230 cells/mm^3 in the Stribild arm and 193 cells/mm^3 in the ATR arm. In Study 0103, the mean increase at Week 48 was 202 cells/mm^3 in the Stribild arm and 201 cells/mm^3 in the ATV/r+TVD arm.

The FDA Statistical Reviewer performed analyses to evaluate the applicability of the efficacy results across demographic subgroups. In general, no significant differences in virologic suppression were observed for gender, age, race, or location (US vs. non-US) between the Stribild arms and comparator arms (ATR or ATV/r+TVD). However, a few subgroups deserve specific comment. Women comprised only 10% of the study population in both clinical trials so there may be less confidence in the results in this subgroup. Response rates in

subjects who had HIV RNA ≤ 100,000 copies/mL at baseline were slightly higher than in subjects who had HIV RNA >100,000 copies/mL at baseline and response rates in subjects who had CD4 counts > 200 cells/mm^3 at baseline were slightly higher than that in subject who had CD4 counts ≤200 cells/mm^3 at baseline. These differences were not large and were observed in all treatment groups. None of the subgroup analyses alter the overall conclusion of efficacy of Stribild.

- ***Other notable efficacy issues (resolved and outstanding)***

There are no unresolved issues related to the efficacy analyses and conclusions for the two clinical trials. However, because the enrollment of women in the clinical trials was low, the Applicant will be encouraged to obtain additional data in women as part of their post-marketing program.

After careful review of the efficacy data submitted by the Applicant, the Clinical and Statistical review teams recommended approval of Stribild.

8. Safety

The Applicant provided an adequate safety database compiled during the Phase 2 and Phase 3 clinical trials. The FDA clinical safety review provided by Dr. Sherwat was conducted using pooled data from the two randomized, double-blind, Phase 3 trials (701 subjects receiving Stribild, 352 subjects receiving ATR, and 355 subjects receiving ATV/r+TVD). Because all treatment arms contained FTC/TDF, the primary safety comparison was between EVG/COBI and either efavirenz or ATV/r. The safety profile of FTC/TDF 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. In order to get a more complete assessment of potentially enhanced renal toxicity with Stribild compared to other FTC/TDF regimens, the Applicant was asked to provide additional summary safety information from the on-going development program for COBI.

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

During the 48 week treatment period six subjects died: one in the combined Stribild group, two in the ATR group and three in the ATV/r+TVD group. The Applicant notes one of these deaths (a suicide in ATR group) was considered possibly related to blinded study drug. The death (also suicide) in the Stribild group was attributed to the subject's past medical history of major depression and bipolar disorder and not considered related to blinded study drug.

Serious adverse events (SAEs) were reported in relatively small proportions of subjects in all treatment groups: 9.6% of Stribild group, 6.8% of ATR group and 8.7% of ATV/r+TVD group. Although the SAEs in aggregate occurred numerically more frequently in the Stribild group, these events were dispersed over a variety of clinical events occurring at low frequency. Only SAEs in the System/Organ Classes "Infections and Infestations" and "Gastrointestinal Disorders" occurred in more than 1% of subjects receiving Stribild (4.7% and 1.3%,

respectively) but very few of these events were attributable to study drug. Among subjects receiving Stribild, only one SAE of Burkitt's lymphoma was judged related to study drug by the investigator.

Discontinuations due to adverse events (AEs) were infrequent in all treatment arms occurring in 3.7% of Stribild recipients, 5.1% of ATR recipients, and 5.1% of ATV/r+TVD recipients. Among subjects receiving Stribild, AEs leading to premature discontinuation of study drug included blood creatinine increased (3 subjects) and diarrhea, nausea, fatigue, pyrexia, hepatitis C, and renal failure (2 subjects each).

Non-serious AEs occurred in the vast majority of subjects enrolled in the clinical trials: 93% of Stribild arm, 95% of ATR arm, and 94% of ATV/r+TVD arm. The most common clinical adverse events reported among Stribild recipients regardless of severity or causality include: diarrhea, nausea, vomiting, upper respiratory tract infection (multiple terms), insomnia, fatigue, headache, abnormal dreams, dizziness, depression, back pain, and rash. Table 3 displays the adverse drug reactions of all severity grades attributed to blinded study drug and reported in at least 5% of subjects in any of the treatment arms. This information will be displayed in the product label.

Table 3: Adverse Drug Reactions of All Severity Grades Occurring in ≥5% of Subjects Receiving any Blinded Study Drug

	Combined Stribild N=701	**ATR N=352**	**ATV/r+TVD N=355**
Nausea	16%	9%	13%
Diarrhea	12%	11%	16%
Abnormal dreams	9%	26%	3%
Headache	7%	4%	6%
Fatigue	5%	7%	6%
Dizziness	3%	20%	4%
Insomnia	3%	8%	1%
Rash*	3%	15%	6%
Flatulence	2%	< 1%	7%
Ocular icterus	< 1%	0%	13%
Jaundice	0%	< 1%	8%

*Includes combined preferred terms: dermatitis, drug eruption, eczema, pruritus, pruritus generalized, rash, rash erythematus, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, and urticaria.
Source: Abstracted from NDA 203100, amendment dated July 12, 2012, confirmed by FDA Clinical Review Team.

Some System/Organ Classes or clinically-related groups of AEs were evaluated in more detail when preliminary assessment suggested a possible imbalance across treatment arms (refer to Dr. Sherwat's Clinical Review for more detail). Musculoskeletal AEs were reviewed and several preferred terms (e.g., "back pain," "muscle spasm") were reported in slightly higher numbers of Stribild recipients. No definitive conclusions could be made based on relatively

small numbers of events. Because COBI showed potential to prolong PR interval in the thorough QT study, cardiac AEs were evaluated and electrocardiograms were obtained during the Phase 3 clinical trials. The number of cardiac AEs was too small to identify any differences between treatment arms but no treatment-emergent electrocardiogram abnormalities were documented. Psychiatric AEs, particularly sleep disorders and mood disorders, were also reviewed in more detail, as these events have been attributed to ATR in previous clinical trials. Subjects receiving Stribild had numerically slightly more mood disorder events (e.g., "depression," "anger," "bipolar disorder," etc.) than subjects receiving ATV/r+TVD but fewer of these events than subjects receiving ATR. A similar pattern was noted for sleep disorders (e.g., "abnormal dreams," "insomnia," etc.) but the differences between treatment groups were more noticeable. As the clinical trials were not powered to show differences in rates of AEs, formal statistical analysis was not performed.

As part of the general safety review, the clinical trials database was searched for cases that might represent drug-induced liver injury (i.e., Hy's Law cases). Suspect cases were identified as those subjects who demonstrated ALT or AST > 3 x ULN and total bilirubin > 2 x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes. Only two subjects receiving Stribild met the laboratory criteria for Hy's Law but both cases were confounded by other clinical conditions, acute hepatitis C in one and alcoholic hepatitis in the other.

- ***Safety issues of special interest***

The most important safety risks of Stribild use are associated with two key toxicities: renal adverse events (particularly proximal renal tubular dysfunction) and bone toxicity. Both of these events have previously been associated with use of TDF and will be highlighted in product labeling. As part of the safety review process, DAVP requested consultation from our colleagues in the Division of Cardiovascular and Renal Products (DCRP) to confirm the renal findings. Dr. Shona Pendse provided DCRP expertise and focused her review on the renal safety data and confirmed the findings of the DAVP review.

The Applicant provided sufficient data to support their assertion that modest increases in serum creatinine observed among subjects receiving Stribild are primarily due to COBI-related inhibition of tubular secretion of creatinine and do not represent true decreases in glomerular filtration rate (GFR). The Clinical review team agrees with their conclusions based on results of a dedicated trial evaluating actual GFR measured by iohexol (no difference noted after administration of either COBI or ritonavir) and based on data collected during the Stribild clinical trials. In Studies 0102 and 0103, renal function was monitored by estimating creatinine clearance using the Cockroft-Gault calculation ($eGFR_{CG}$) and by measuring the freely filtered protein cystatin C (cysGFR). In both studies, mean serum creatinine increased and mean $eGFR_{CG}$ decreased early during the 48 week then stabilized among subjects receiving Stribild. A similar but smaller magnitude change was observed in the ATV/r+TVD group. In contrast, cysGFR remained stable or increased during the study period in all treatment groups. This modest increase in serum creatinine (mean decrease 0.14 mg/dL) in subjects receiving Stribild is predictable but generally does not represent renal damage.

Of primary concern to the Clinical review team was an apparent increased rate of serious renal AEs resulting in study drug discontinuation among subjects receiving Stribild compared to ATR and ATV/r+TVD. Eight subjects receiving Stribild discontinued study drug due to a renal AE (3 with "renal failure", 3 with "blood creatinine increased", 1 with "Fanconi syndrome acquired", and 1 with "increased serum creatinine"). One subject receiving ATV/r+TVD discontinued study drug due to a renal AE ("nephropathy toxic"). Four subjects in the Stribild group developed signs and symptoms suggestive of proximal renal tubule dysfunction. These cases and the review methodology are described in detail in Dr. Sherwat's Clinical Review. Using the same methodology, no cases suggestive of proximal tubulopathy were identified in either of the comparator groups. In addition, review of multiple published trials evaluating TDF-containing regimens in treatment naïve patients failed to identify similar cases. However, published literature suggests that the renal toxicity associated with TDF may be more frequent in patients receiving TDF in combination with PIs, including ritonavir. Additional high level safety information was provided from the COBI single-drug development program (Study GS-US-216-0114 comparing ATV/COBI+TVD to ATV/r+TVD) and evidence of proximal tubulopathy was found in five subjects receiving ATV/COBI+TVD compared to two receiving ATV/r+TVD. Thus, the review team remains concerned that COBI may exacerbate the known renal toxicity associated with TDF.

Bone toxicity was difficult to assess in the Stribild clinical trials because all subjects received TDF and bone mineral density (BMD) measured by DEXA was only assessed in a subset of subjects in Study 0103. As with renal toxicity, the bone toxicity associated with TDF has been reported to be exacerbated in patients receiving PIs. In the DEXA substudy, lumbar spine BMD declined by a mean of 2.63% from baseline to Week 48 among 54 subjects receiving Stribild compared to -3.33% among 66 subjects receiving ATV/r+TVD. Hip/femur BMD declined by a mean of 3.06% compared to 3.88% in subjects receiving Stribild and ATV/r+TVD, respectively. Fractures were reported in very small numbers of subjects in any treatment arm. As in previous trials of TDF-containing regimens, the clinical implications of these changes in BMD are unknown.

- ***Laboratory abnormalities***

Clinical laboratory parameters were monitored throughout the Stribild trials. No significant hematologic laboratory abnormalities were observed during the clinical trials in any treatment arm. Elevations in ALT, AST, GGT and amylase, usually Grade 1, were observed among subjects receiving Stribild at rates ranging from 7% to 15% but none of the abnormalities were observed significantly more often than in the comparator groups.

The Applicant provided an extensive analysis of changes in serum lipids in the clinical trials and proposed detailed information regarding these changes in product labeling. The FDA analysis documented a mean change from baseline in fasting total cholesterol of +11 mg/dL in the Stribild group, +19 mg/dL in the ATR group, and +10 mg/dL in the ATV/r+TVD group. Mean change from baseline in fasting triglycerides was +13 mg/dL in the Stribild group, +14 mg/dL in the ATR group, and +32 mg/dL in the ATV/r+TVD group. Mean values for all lipids remained within the normal range in all treatment groups. Among subjects receiving Stribild, 23% had a graded cholesterol abnormality (fasting cholesterol $\geq$ 200 mg/dL) during the trial compared to 25% of those receiving ATR and 25% of those receiving ATV/r+TVD.

Twelve percent of subjects receiving Stribild had a graded triglyceride abnormality (fasting triglyceride ≥ 500 mg/dL) compared to 6% of those receiving ATR and 12% of those receiving ATV/r+TVD. The clinical relevance of these small differences is unclear.

Changes in serum creatinine and other renal laboratory parameters are discussed above in the section *Safety issues of special interest.* Overall, rates of graded serum creatinine abnormalities were more common among subjects receiving Stribild (all grades 7.1%) compared to ATR (1.2%) and ATV/r+TVD (4.3%). Although hypophosphatemia is part of the clinical syndrome of proximal renal tubulopathy, rates of graded serum phosphate abnormalities among Stribild recipients (6.5%) were similar to those observed among subjects receiving ATV/r+TVD (6.3%) and modestly higher than in subjects receiving ATR (4.5%). Similarly, rates of all grades of proteinuria were higher among Stribild recipients (38.7%) compared to ATR recipients (28.7%) and ATV/r+TVD recipients (24.2%) but most of these events were grade 1 (1+ proteinuria). Glycosuria of any grade was observed in 2.4% of Stribild recipients, 1.5% of ATR recipients, and 5.7% of ATV/r+TVD recipients. As discussed in Dr. Sherwat's review, it appeared that the occurrence of new or increased proteinuria in addition to normoglycemic glycosuria identified a subset of subjects at risk for proximal tubulopathy and preceded significant elevations in serum creatinine.

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

The data collected in the two clinical trials provided adequate information for a substantive review of Stribild's toxicity profile. Additional summary data was used to further characterize the renal toxicity profile of the FDC but the extent of COBI's potential to enhance the known renal toxicity of TDF has not been fully determined. Renal events, particularly proximal renal tubulopathy, will be described in the Warnings and Precautions section of the product label. The Applicant suggests that the rates of proximal tubulopathy and Fanconi's syndrome observed in the Stribild clinical trials are similar to those documented in patients receiving TDF in combination with a PI. The Clinical review team is concerned that the data reviewed for this NDA represents an increased hazard signal and will require ongoing and future clinical trials to collect additional renal safety data (see Section 13).

9. Advisory Committee Meeting

An Advisory Committee meeting was convened on May 11, 2012 to discuss the merits of this NDA and the risk/benefit assessment for Stribild in HIV-1-infected, treatment-naïve patients. After hearing presentations by both the Applicant and the FDA review team, the Advisory Committee was asked to discuss the following questions. A summary of the Committee's key discussion points and recommendations are included below.

1. Please comment on the safety profile of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, focusing on proximal tubulopathy and other renal adverse events leading to subject discontinuation.

Committee members uniformly expressed concern regarding the apparent increased incidence of renal events but also felt strongly that the product met its efficacy endpoint

and provided good treatment efficacy compared to two preferred treatment regimens. The Committee did not believe there was adequate data to describe the long-term risk of renal toxicity or the risk in under-represented demographic groups (i.e., women).

2. Considering the overall risks and benefits, do the available data support approval of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as a complete regimen for treatment of HIV-1 infection in treatment-naïve adults?

VOTE: Yes/No/Abstain

- If no, what additional studies are recommended?
- If yes, proceed with the remaining questions.

The Committee members voted to recommend approval; 13 yes votes, 1 no vote, 0 abstain. The consensus was that the benefit of Stribild as a complete treatment regimen outweighed the risk associated with adverse events and the risks appear to be manageable with enhanced monitoring. However, some Committee members noted that there are other treatment regimens available for treatment-naïve patients with potentially better safety profiles.

3. Are additional measures needed to improve renal safety in patients receiving elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate? As part of your discussion, please comment on the following:

a. Would additional laboratory monitoring (e.g. urine dipstick testing for protein and glucose) potentially improve renal safety? Does use in patients with baseline glycosuria and proteinuria warrant separate recommendations?

b. Would renal safety be enhanced by monitoring renal function in all patients as opposed to only patients with renal impairment or at risk of renal impairment?

c. Should laboratory cutoffs be provided to help distinguish the effect of cobicistat on serum creatinine and creatinine clearance from genuine renal dysfunction? If yes, please comment on specific parameters, including, but not limited to the Applicant's current proposal (i.e. increase in creatinine $\geq$ 0.4 mg/dL).

The Advisory Committee recommended providing clear guidelines for patient management and safety monitoring in the label. They favored testing urine glucose and protein in all patients receiving Stribild, noting that urine dipstick testing is ubiquitous and inexpensive. They also agreed that the conservative cut-off value of 0.4 mg/dL provided a reasonable balance for monitoring safety without unnecessary drug discontinuation.

4. Please discuss any post marketing studies needed to further define risks or optimal use of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.

Several Committee members expressed dissatisfaction at the low numbers of women enrolled in the Phase 3 clinical trials and suggested additional clinical trials in women. The Committee members agreed that additional clinical pharmacology assessment of drug-drug interactions might be needed (e.g., methadone, hepatitis C antivirals). The Committee also recommended that long-term follow-up data be obtained to better assess both safety and the emergence of resistance to Stribild component drugs and to PIs. In addition, the Committee was in favor of further studies to better characterize the role of COBI in TDF-associated renal toxicity but did not agree on what studies should be done.

10. Pediatrics

Studies in pediatric patients of all ages are required under the Pediatric Research Equity Act (PREA) unless they are deferred or waived. The Applicant has discussed their pediatric development plan with the DAVP review team in conjunction with the pediatric development plans for EVG and COBI as individual drugs. With submission of the NDA package, the Applicant requested a waiver from studying pediatric patients < 6 years of age and a deferral for submitting studies in pediatric patients 6 to < 18 years of age.

The Applicant proposed to begin pediatric trials of Stribild in adolescent subjects (12 to < 18 years of age) using the tablet formulation evaluated in the adult clinical trials. The review team agreed that information regarding the PK profile of EVG and the appropriate dose of COBI to provide boosting in pediatric patients will be needed before the Applicant can determine whether a Stribild FDC can be scaled for use across the 6 to 12 year age range.

Since the component drugs in the Stribild FDC each have, or will have, age-appropriate formulations available for use across most subsets of the pediatric population, any treatment simplification benefit of the FDC is off-set by the inability to dose-adjust the individual components appropriately within the FDC to maximize safety and efficacy in a population of children whose weights increase rapidly over time. In contrast, the oral formulations of each component drug available for use in pediatric patients will allow flexible dosing on a body weight basis within the dose ranges of the individual components of Stribild currently available or to be established. The review team considered it highly unlikely that all four component drugs can be simultaneously adjusted to provide appropriate exposure in an FDC for patients in the youngest age group. For this reason, the review team agreed with the Applicant's request for a waiver in pediatric patients < 6 years of age.

The requests for waiver and deferral were discussed at a meeting between the DAVP review team and the FDA Pediatric Review Committee (PeRC) on June 27, 2012. The PeRC agreed with the review team's recommendation to defer studies in pediatric patients 6 years of age and older and waive studies in patients < 6 years. Studies in pediatric patients 6 years and older will be required under PREA but will be deferred since the adult studies have been completed and the FDC is ready for approval. The deferred PREA studies will be described in the approval letter.

11. Other Relevant Regulatory Issues

- ***Application Integrity Policy (AIP)***
  This Applicant is not on the FDA Application Integrity Policy list.

- ***Exclusivity or patent issues of concern***
  (b) (5)

- ***Financial disclosures***
  The Applicant reported a small number of investigators in the covered trials (b) (6) with significant financial interests. Collectively these investigators enrolled (b) (6) subjects. Because treatment in the clinical trials was randomized and blinded, the number of affected subjects was relatively small, and the trials were each overseen by an independent data monitoring committee, these investigators' financial interests were unlikely to introduce bias or have any impact on results of the trials.

- ***Other GCP issues***
  No other issues related to GCP were identified.

- ***DSI audits***
  Four clinical trials sites were audited by DSI, 2 domestic and 2 international, selected on the basis of enrolling a relatively large number of subjects and site-specific protocol violations. Although minor protocol and regulatory violations were identified at 1 of the sites audited, the findings were not considered serious enough to affect data integrity.

- ***Other discipline consults***
  The proposed proprietary name (Stribild) was reviewed by Morgan Walker, Pharm.D. Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA). The name was determined to be acceptable; it did not resemble other known drug names, and was not unduly promotional. Previous proposed names (b) (4) were not allowed.

  It was agreed that Stribild labeling will include a Patient Package Insert and neither a Medication Guide nor a REMS is warranted.

- ***Any other outstanding regulatory issues.***
  There are no outstanding regulatory issues.

12. Labeling

Detailed discussion of labeling can not be provided in this CDTL Review because the review team is in the process of completing labeling negotiations with the Applicant. Some key issues are addressed briefly below.

- ***Proprietary name***

As noted above, the proprietary name (Stribild) was reviewed by DMEPA and was considered acceptable.

- ***Important issues raised by DDMAC and OSE***

At this time, no specific issues have been raised by DDMAC and OSE. A pre-approval safety meeting was conducted and safety evaluators were notified that areas of special interest included AEs in women and any SAEs consistent with Fanconi's syndrome.

- ***Physician labeling***

The language for the Package Insert is being developed by the multi-disciplinary review team in collaboration with Gilead Sciences staff but is not yet complete. The FDA review team is likely to propose substantial changes in many sections of the label.

Section 1, Indication and Usage:

In general, the review team agrees with the proposed indication for Stribild, although the language regarding appropriate patient selection will include only those who are HIV-1 treatment naïve. Only treatment naïve subjects were evaluated in the Stribild clinical trials and resistance testing was available for all subjects at baseline.

Section 2, Dosage and Administration

This section will be amended by addition of a paragraph describing dosing in patients with hepatic impairment.

Section 4, Contraindications

The Applicant proposed a listing of contraindicated drugs. The Clinical Pharmacology review team recommended this section be re-formatted to be consistent with newer DAVP labels. They propose a table of "Drugs That are Contraindicated with Stribild" displaying drug classes, specific drug names, and clinical comments describing the reason for contraindication.

Section 5, Warnings and Precautions

The Package Insert will contain Warnings and Precautions that are considered "class" effects of antiretroviral drugs including: lactic acidosis/severe hepatomegaly with steatosis, patients coinfected with HIV-1 and HBV (post-treatment exacerbation of HBV), fat redistribution, and immune reconstitution syndrome. The warning language regarding lactic acidosis/severe hepatomegaly and post treatment acute exacerbation of hepatitis B is included in a Boxed Warning as previously established for all anti-HIV products containing NRTIs and those with activity against HBV.

The warning language for Section 5.3, New or Worsening Renal Impairment which was modeled after a similar subsection in the Viread (TDF) label, has been updated with

information specific to Stribild. The revised section will describe the cases of proximal tubulopathy in subjects receiving Stribild and propose appropriate monitoring. In addition to the Applicant's proposal to calculate creatinine clearance for all patients being evaluated for Stribild and not use the FDC in patients with eGFR < 70 mL/min, the FDA clinical review team recommends routine monitoring of creatinine clearance, urine glucose and urine protein (+/- serum phosphate). The FDA review team also proposes notifying prescribers that COBI may cause a modest increase in serum creatinine but that confirmed elevations > 0.4 mg/dL should prompt more intensive monitoring for renal toxicity.

The subsection Decreases in Bone Mineral Density (5.5) is also modeled on a similar section in the Viread label. The section contains a summary of bone effects related to TDF and a description of the DEXA substudy in Study 0103.

Section 6, Adverse Reactions

A summary of the safety data collected in the Stribild Phase 3 clinical trials will be included in the Adverse Reactions from Clinical Trials subsection. A table will include a display of treatment emergent adverse drug reactions of all severity grades from the pooled clinical trials. This table will include AEs considered to be possibly drug related by the study investigators. Summary descriptions of the AEs associated with FTC and TDF will be included.

Summary of the Grade 3 and 4 laboratory abnormalities reported during the clinical trials will be displayed in a table. In addition, a more detailed description of the COBI-related increases in serum creatinine not considered indicative of renal toxicity will be provided.

At the time of writing this CDTL Review, one of the labeling issues under discussion is the Applicant's proposal to include a detailed table displaying mean changes in serum lipids observed during the Phase 3 trials. There were statistically significant differences in mean change in total cholesterol between Stribild and ATR, in LDL-cholesterol between Stribild and ATR, and in fasting triglycerides between Stribild and ATV/r+TVD. However, the clinical review team notes that all treatment arms resulted in mean increases and the proportions of subjects with graded abnormalities in lipid parameters were similar. We do not think these data warrant such extensive description in labeling and believe such a display is more promotional than informative. This labeling issue is not yet resolved.

Section 7, Drug Interactions

This section was extensively edited by the Clinical Pharmacology review team in order to make it more consistent with other recent DAVP labels. A table "Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies" has been revised (b) (4) This table includes drug classes, specific drug names and clinical comments regarding the drug interactions and what actions should be taken when prescribing the drugs concomitantly with Stribild. This table includes revised language on the use of Stribild with the combination oral hormonal contraceptive Ortho Tri-Cyclen which was developed in consultation with DRUP reviewers.

Section 8, Use in Specific Populations

The subsection 8.1, Pregnancy was revised to align with current recommendations for pregnancy labeling: information available from human studies is provided first, followed by animal data. Other subsections were revised by the Clinical Pharmacology team.

Section 12, Clinical Pharmacology

This section was also extensively revised by the Clinical Pharmacology review team to provide consistency with recent DAVP labels. We have consulted the FDA IRT for advice regarding appropriate labeling of the thorough QT study reports and will provide that to the sponsor in the near future. Tables "Drug Interactions: Changes in Pharmacokinetic Parameters for Elvitegravir in the Presence of the Coadministered Drug" and "Drug Interactions: Changes in Pharmacokinetic Parameters for Coadministered Drug in the Presence of Elvitegravir, Elvitegravir plus Cobicistat, or Stribild" display specific information regarding the drug-drug interaction studies conducted with EVG, COBI, and Stribild and the magnitude of these drug-drug interactions.

The emergence of resistance substitutions associated with any of the components of Stribild are described in the Microbiology subsection, as are the potential for cross-resistance among other antiretroviral drugs. The Virology review team edited this section to include information consistent with that displayed in other antiretroviral drug labels.

Section 14, Clinical Studies

The results of the two Phase 3 clinical trials are described in the Clinical Studies section. The trial design and study populations are described, including baseline study demographic and disease characteristics. The efficacy results (as "snapshot" analysis) for Studies 0102 and 0103 are displayed in a table, "Virologic Outcome of Randomized Treatment of Study 102 and Study 103 at Week 48." The key secondary endpoint of mean change in CD4 cell count from baseline to Week 48 (using last-observation-carried-forward analysis) is described in text.

- ***Carton and immediate container labels (if problems are noted)***

The Safety Evaluator, DMEPA has also reviewed the carton and immediate container labels. The proposed packaging includes bottles containing 30 Stribild tablets, a one-month supply.

DMEPA concluded that the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information on the label to mitigate any confusion. Recommendations were forwarded to the Applicant.

- ***Patient labeling/Medication guide (if considered or required)***

Stribild labeling will include a Patient Package Insert written in consumer-friendly language. Among the key patient labeling issues will be patient-appropriate descriptions of major drug-associated adverse events such as serious skin reactions, anemia, and anorectal disorders. Patients will be reminded that Stribild contains a complete treatment regimen and must not be used in combination with other HIV drugs. In addition, patients will be warned about the potential for drug interactions between Stribild and many other drugs. Exact language for the

Patient Package Insert is being developed in collaboration with staff in DRISK and OPDP but has not been completed at this time.

13. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action***

I concur with the conclusions of the FDA review team and recommend this NDA for Stribild be approved for the treatment of HIV-1 infection in adults who are treatment-naïve and have no known resistance substitutions. The two submitted Phase 3 clinical trials met the regulatory standard of adequate and well-controlled clinical trials and achieved their stated efficacy objectives. These trials compared Stribild to the two most commonly prescribed "preferred" regimens for HIV-1-infected treatment-naïve patients, thus, providing an appropriate comparison of effectiveness in this patient population. This recommendation for approval is contingent on successful completion of all pending facility inspections and resolution of any GMP issues.

- ***Risk Benefit Assessment***

After review of this NDA for Stribild as a complete treatment regimen for HIV-1 infection, the multi-disciplinary team and I agree that the potential benefits of Stribild treatment outweigh the potential risks. Excellent rates of viral suppression were observed in all demographic and disease characteristic subgroups, although some subgroups (most notably, women) were under-represented in the clinical trials. In the context of life-long treatment, the importance of treatment simplification and improved adherence can not be overstated. Strict adherence to an effective regimen minimizes the emergence of resistant HIV-1 variants, a significant threat to both the patient and the community at large. Although two NNRTI-containing single-tablet regimens are already approved (Atripla and Complera), Stribild provides a single-tablet regimen anchored with a different drug class (integrase inhibitor). For patients who do not tolerate all drugs equally and for women of child-bearing potential, this provides a one-pill treatment option of equivalent efficacy to Atripla.

The safety profile of Stribild was acceptable over the 48 week study period. In the two clinical trials, about 10-12% of study subjects receiving Stribild either had treatment failure or dropped out of the study. Only about 3% did so because of adverse events or death. The proportions of subjects experiencing adverse events resulting in treatment discontinuation were low in all treatment groups but there were some notable differences in the types of events observed. As noted in previous clinical trials, Atripla use resulted in discontinuations due to neuropsychiatric events and rash events. The atazanavir/ritonavir regimen resulted in discontinuations due to gastrointestinal disorders (e.g., nausea and diarrhea). Subjects receiving Stribild discontinued their study drug for a variety of reasons (e.g., nausea, diarrhea, fatigue) but the signature toxicity in this group was proximal renal tubular dysfunction. Eight subjects in the Stribild treatment groups discontinued because of renal adverse events compared to one in the combined comparator groups. Four of these subjects appeared to have acquired Fanconi's syndrome compared to none in the comparator groups.

Although the Applicant suggests that this rate of severe proximal tubulopathy is consistent with that observed when TDF is used in combination with protease inhibitors, the review team believes that the known renal effects of TDF may be exacerbated by concomitant administration of COBI. We agree with Gilead's recommendation to assess creatinine clearance in all patients considering treatment with Stribild and withholding use in those with creatinine clearance < 70 mL/min. Exploratory analysis of the safety data further leads us to conclude that routine assessment of urine glucose, urine protein, and serum creatinine (possibly with serum phosphate) may allow earlier detection of patients at risk for renal toxicity and, thus, allow closer monitoring. The combination of FTC and TDF (Truvada) has become the most widely used and very effective background NRTI combination in HIV-1 treatment regimens and the review team recognizes the disadvantages of prematurely recommending patients stop an effective drug. To assess changes in serum creatinine, we concluded that advising a relatively conservative cut-off of 0.4 mg/dL increase should prompt health care providers to institute more intensive monitoring of renal function. Monitoring urine glucose and protein, in addition to serum creatinine, may allow health care providers to further distinguish COBI-associated changes in creatinine from impending tubular dysfunction. These tests are widely available, inexpensive, and already recommended as part of patient monitoring by consensus treatment guidelines groups.

Because it contains two products metabolized by CYP3A4 (EVG and COBI) and a specific CYP3A4 inhibitor (COBI), multiple drug-drug interactions were anticipated with Stribild. The Applicant has conducted a battery of clinical pharmacology studies and has committed to continuing evaluation of some drugs not yet studied. The anti-addiction medications and newer hepatitis C antiviral drugs are among the ones to be addressed in the post-marketing phase. More and better information regarding concomitant use of hormonal contraceptives will also be an important issue for women hoping to realize the potential advantages of Stribild single tablet regimen.

This risk-benefit assessment incorporates the advice received from the Advisory Committee. The Advisory Committee concluded that the benefits of Stribild treatment outweigh the risks of adverse events and I agree with their conclusion. With good health care provider training, patient education materials, and appropriate drug labeling the risks of renal toxicity with Stribild appear to be monitorable and manageable. The Advisory Committee further concluded that additional study of Stribild in HIV-1-infected women was warranted because of the small number of women enrolled in the clinical trials.

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

At this time, no formal REMS is recommended. A Patient Package Insert will be required to ensure that patients have access to important safety information and instructions for use of Stribild in consumer-friendly language.

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

The following PMC/PMRs have been requested by the review team to more fully characterize the safety profile, resistance patterns, and drug-drug interactions of Stribild. Exact protocol design, protocol submission, study completion and study report submission dates remain under discussion with the Applicant.

Clinical PMRs:

1. Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed study to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103, which included an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, GFR by cystatin C, serum phosphate, fractional excretion of phosphate, urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.

2. Perform *in vitro* and/or *in vivo* animal study(ies) to determine what impact cobicistat has on intracellular tenofovir concentration. The study(ies) should also be designed to identify the mechanism of any observed interaction.

Clinical Pharmacology PMCs:

3. Please conduct an *in vivo* drug-drug interaction trial between Stribild and telaprevir.

4. (b) (4)

5. Please conduct an *in vivo* drug-drug interaction trial of Stribild and buprenorphine/naloxone.

6. Please conduct an *in vivo* drug-drug interaction trial of Stribild and methadone.

Clinical Virology PMC:

7. Assess possible cobicistat protease inhibitory activity *in vivo* by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.

Pediatric PMRs (PREA)

8. Conduct a pediatric pharmacokinetic, safety, and antiviral activity study of Stribild with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from 12 to <18 years of age. Include in the study safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, GFR by cystatin C, urine glucose, urine protein, calculated creatinine clearance and calculated fractional excretion of phosphate) and bone toxicity (to include serial DEXA assessment).

9. Conduct a pediatric pharmacokinetic, safety, and antiviral activity study of Stribild with activity based on the results of virologic response over at least 24 weeks of dosing and safety monitored over 48 weeks in pediatric subjects from 6 to <12 years of age. Dose selection must be based on pharmacokinetic data for individual component drugs and discussed with

FDA prior to initiation of study. Include in the study safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, GFR by cystatin C, urine glucose, urine protein, calculated creatinine clearance and calculated fractional excretion of phosphate) and bone toxicity (to include serial DEXA assessment).

- ***Recommended Comments to Applicant***
  No additional comments need to be communicated to the Applicant.

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

/s/

LINDA L LEWIS
07/16/2012