CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Date	June 1, 2016
From	Prabha Viswanathan, MD Sarah Connelly, MD
Subject	Clinical Review Addendum
NDA/BLA #	208341
Applicant	Gilead Sciences
Date of Submission	October 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Non-Proprietary Name	Epclusa sofosbuvir and velpatasvir (SOF/VEL)
Dosage form(s) / Strength(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic hepatitis C virus infection
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	**SOF/VEL:** Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis **SOF/VEL with ribavirin:** Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection with decompensated cirrhosis

The purpose of this addendum is to address two major review issues that were under consideration at the time the clinical review was finalized: treatment optimization for HCV genotype 3 (GT3) subjects and labeling of HIV antiretroviral drugs. This document will summarize the ultimate conclusions of the clinical review team.

1. Treatment Optimization for GT3 Subjects Without Cirrhosis or with Compensated Cirrhosis

As discussed in the clinical review, GT3 subjects treated with 12 weeks of sofosbuvir/velpatasvir (SOF/VEL) in ASTRAL-3 experienced higher rates of relapse compared to subjects infected with GT 1, 2, 4, 5, or 6 in ASTRAL-1 or ASTRAL-2. A key review issue was whether or not the addition of ribavirin (RBV) would prevent relapse and/or emergence of NS5A RAPs, particularly among subjects with cirrhosis. At the time the clinical review was finalized, the primary clinical team concluded that there are insufficient data to support the addition of RBV for GT3 cirrhotic subjects.

At the Late Cycle Meeting on April 19, 2016, the Division queried the Applicant about their perspective on the addition of RBV for GT3 cirrhotics, (b) (4) The results of this study will be submitted in response to a post-marketing requirement. (b) (4)

Reviewer Comment: Based on the currently available data, the clinical review team and the Applicant agree that SOF/VEL for 12 weeks, without ribavirin, is the most appropriate regimen for all GT3 infected subjects without cirrhosis or with compensated cirrhosis. Once data from the SOF/VEL versus SOF/VEL + RBV trial are available, the optimal regimen for GT3 cirrhotics can be reevaluated.

2. Co-administration of SOF/VEL with HIV Antiretroviral Agents (ARVs)

Phase 1 drug-drug interaction trials form the basis of the information presented in Sections 7 and 12 of the proposed label, supported by preliminary safety results from Trial GS-US-342-1202 (ASTRAL-5), a Phase 3, open-label study evaluating the safety and efficacy of SOF/VEL for 12 weeks in subjects with HIV/HCV co-infection. Interim safety results from ASTRAL-5 were included in the 90 day Safety Update Report, and follow-up summaries through the SVR4 datacut were provided for subjects receiving tenofovir disoproxil fumarate (TDF)-containing ARV regimens as well as subjects on atazanavir-based regimens who developed hepatic laboratory abnormalities.

Summary of ASTRAL-5

A total of 106 subjects with HIV/HCV coinfection and suppressed HIV viral load at study entry were enrolled and treated in ASTRAL-5. At the SVR4 datacut, 102 subjects had completed 12 weeks of SOF/VEL and 4 subjects had prematurely discontinued treatment: two discontinued due to adverse events (AEs) and two were lost to follow-up. Ninety-one subjects (86%) received TDF-containing regimens, of which 56 (53%) received ritonavir or cobicistat ("boosted TDF" regimens). Fifty subjects (47%) were on protease inhibitor (PI) - based regimens, 36 (34%) were on integrase inhibitor (INSTI)-based regimens, and the remaining 20 subjects were on non-nucleoside reverse transcriptase inhibitor (NNRTI) or INSTI+PI-based regimens.

No deaths have occurred in this study. Two subjects (2%) had SAEs that were considered unrelated to study medication: 1 subject had Grade 2 radial nerve palsy, and 1 subject had localized infection, sepsis, and urinary tract infection (all Grade 3). Two subjects (2%) prematurely discontinued SOF/VEL due to AEs: 1 subject who received lamivudine, abacavir, and ritonavir-boosted atazanavir (ATV/r) discontinued on study Day 4 due to Grade 1 vomiting; 1 subject who was receiving emtricitabine (FTC), TDF, and ATV/r discontinued on study Day 41 due to Grade 3 increased hepatic enzymes (see clinical review for additional details). A total of 75 subjects (71%) experienced at least 1 AE; 9 subjects (9%) had Grade 3 AEs and no Grade 4 AEs have been reported. The most commonly reported AEs were fatigue (25%), headache (13%), and arthralgia (9%).

Subjects Receiving Tenofovir-containing ARV Regimens

Phase 1 drug-drug interaction studies demonstrated higher TDF exposures when TDF is coadministered with SOF and VEL. Notable adverse drug reactions associated with TDF exposure include decreased bone mineral density and nephrotoxicity. Given the short duration of therapy for SOF/VEL, bone toxicity is not a great concern; in contrast, renal insufficiency can occur acutely and, if significant, may require modifications to ARV and/or SOF/VEL dosing. Hence, the Division requested the Applicant to assess renal AEs and renal laboratory abnormalities among TDF-treated subjects in ASTRAL-5 to help inform dosing recommendations for TDF with SOF/VEL.

Four subjects (4%) had an AE under the Renal and Urinary Disorders system organ class, including pollakiuria, glycosuria, and proteinuria. Of these, 2 subjects were receiving boosted TDF regimens and 2 subjects were receiving non-boosted TDF-containing regimens. All events were Grade 1 or 2 in severity. A total of 5 subjects experienced a change in serum Cr $\geq$ 0.4 mg/dL, creatinine clearance (CrCl) < 50 ml/min or normoglycemic glycosuria. Of these, 4 were receiving boosted TDF regimens and 1 subject was receiving a non-boosted TDF-containing regimen. These abnormalities were transient and asymptomatic in 4 of the 5 subjects; one subject on a boosted TDF regimen (FTC/TDF/ATV/r) with a history of chronic kidney disease developed 3+ proteinuria, normoglycemic glycosuria, elevated creatinine (3.3 mg/dL at Week 4, up from 1.4 mg/dL at baseline), and decreased CrCl following an episode of acute gastroenteritis with dehydration at Week 4, and his creatinine remained elevated at subsequent visits (2-2.7 mg/dL). No changes were made in ART in any of the five subjects and all completed 12 weeks of SOF/VEL.

Reviewer Comment: Preliminary safety data from ASTRAL-5 are adequate to support labeling for co-administration of SOF/VEL with TDF-containing ARV regimens.

Subjects Receiving ATV/r-Based ARV Regimens

Phase 1 drug-drug interaction studies demonstrated no significant changes in ATV, SOF, or VEL exposure when ATV is coadministered with SOF and VEL, and therefore no unique safety considerations are anticipated. However, review of the Safety Update Report revealed that a significant proportion of subjects on ATV/r-based regimens had elevated bilirubin (in excess of baseline elevations due to ATV/r), and additional information was requested from the Applicant.

A total of 20 subjects received ATV/r-based regimens. By the SVR4 datacut, 13/20 subjects (65%) had symptomatic elevations of total bilirubin > 2 x ULN. Twelve of the 13 subjects had increases of ≥ 0.5 mg/dL and 9/13 had increases of ≥ 1 mg/dL from baseline total bilirubin; the maximum increase was 3.2 mg/dL from baseline. The elevations peaked by Week 6 of SOF/VEL in 12/13 subjects, and the majority of subjects (9/13) had total bilirubin values that were less than or equal to their baseline value at Week 12 of SOF/VEL. All elevations in total bilirubin were attributed to increases in indirect bilirubin only; there were no significant concomitant increases in ALT, AST, alkaline phosphatase, or total bilirubin in any of the 13 subjects. The increased bilirubin values were not associated with clinical AEs and did not lead to treatment interruption or dosage adjustment of SOF/VEL or ARVs for any of the 13 subjects.

Reviewer Comment: Co-administration of SOF/VEL with ATV/r may result in increases in indirect bilirubin that are not associated with clinical adverse events or other hepatic laboratory abnormalities. The mechanism for this observation is unclear. Based on currently available information, no specific laboratory monitoring is required. The clinical review team has proposed inclusion of the following language to Section 6.1 of product labeling to inform prescribers of this observation:

> *Indirect Bilirubin: Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-HCV co-infected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPLCUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.*

In conclusion, the preliminary safety data from ASTRAL-5 are adequate to support labeling for SOF/VEL co-administration with ARVs. Labeling negotiations are ongoing at this time. A PMR will be issued to request formal submission of the final data once with trial has been completed. These data will be used to further characterize the safety and efficacy of SOF/VEL in HIV/HCV co-infected subjects, and to support the clinical pharmacology information contained product labeling.

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