

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208341Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration Center for  
Drug Evaluation and Research Office of  
Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management  
Risk Evaluation and Mitigation Strategy (REMS) Review**

Date: April 18, 2016

Reviewer: Erin Hachey, PharmD, Division of Risk Management (DRISK)

Acting Team Leader: Jamie Wilkins Parker, PharmD, DRISK

Acting Division Director: Kellie Taylor, PharmD, MPH, DRISK

Subject: Evaluation to determine if a REMS is necessary

Drug Name(s): Sofosbuvir/Velpatasvir 400 mg / 100 mg fixed-dose combination (FDC)

Therapeutic Class: Nucleotide analog inhibitor of Hepatitis C virus (HCV) nonstructural protein 5B (NS5B) polymerase and nonstructural protein 5A (NS5A) inhibitor

Dosage and Route: One tablet orally once daily

Proposed Indication: Treatment of hepatitis C virus (HCV) infection in adult patients with HCV genotypes (GT) 1, 2, 3, 4, 5, or 6

Application Type/Number: NDA 208341

Sponsor: Gilead Sciences, Inc.

OSE RCM #: 2015-2434

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# 1 INTRODUCTION

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) fixed-dose combination (FDC) of sofosbuvir/velpatasvir (SOF/VEL) is necessary to ensure the benefits of this product outweigh its risks. A new drug application (NDA 208341) for SOF/VEL was received on October 28, 2015, from Gilead Sciences, Inc. (Gilead). The proposed indication for SOF/VEL is the treatment of adult patients with chronic Hepatitis C virus (HCV) genotypes (GT) 1, 2, 3, 4, 5, or 6. Velpatasvir is the NME component of the application and will be available only in the FDC product currently under review. Sofosbuvir is approved for use as a single entity (Sovaldi, NDA 204671) and in combination with ledipasvir in an FDC tablet (Harvoni, NDA 205834) for the treatment of chronic HCV in adults, and does not have a REMS. The Sponsor did not include a proposed REMS or risk management plan for SOF/VEL in this submission.

## 1.1 Background

### 1.1.1 Disease Background

HCV infection is a serious and potentially life-threatening disease. It affects 3-5 million people in the U.S. Infection with the single-stranded RNA virus hepatitis C can result in both acute and chronic hepatitis. Approximately 20 to 30 percent of newly infected persons develop signs and symptoms of an acute illness, which can include fever, fatigue, loss of appetite, and other non-specific symptoms. Although the acute disease is usually self-limited, the immune response is mostly insufficient to eradicate the virus such that acute infection leads to chronic infection in 60% to 80% of cases. Chronic HCV infection is associated with ongoing liver inflammation and often follows a progressive course over years to decades, increasing the risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma.

HCV lacks a proofreading mechanism during replication that leads to frequent viral mutations and viral heterogeneity. At least seven distinct HCV genotypes and more than 60 subtypes have been identified, with varying geographic distribution. Genotype 1 (GT 1) is the most common genotype in the United States (72%), with GT 2 (11%), GT 3 (9%), and GT 4 (6%) being less common, and GT 5 and 6 occur uncommonly ( $\leq 1\%$ ) in the U.S. The viral diversity and heterogeneity have prevented the development of a vaccine and also affect the completeness of response to antiviral therapy.

The standard measure of efficacy for antiviral therapy is the absence of detectable HCV RNA, termed sustained virologic response (SVR), documented 12 weeks after the end of treatment (SVR12)<sup>1</sup>, and considered a virologic cure. The type and duration of antiviral therapy selected is dependent on the viral genotype, the patient's baseline disease and host factors, the patient's prior treatment experience and response, among other factors.

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<sup>1</sup> Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.

HCV has been treated with combinations of indirect acting antivirals and direct acting antivirals (DAA). The indirect acting agents typically used include interferon alpha and ribavirin (RBV), which have broad antiviral activity, but are associated with many toxicities and modest efficacy against HCV. DAA are designed to target specific non-structural HCV proteins involved in RNA replication. Some agents inhibit the non-structural protein (NS) 3/4A serine protease, which cleaves the HCV polyprotein into several polypeptides with distinct functions. Other DAAs target the NS5A protein necessary for viral assembly and replication, or inhibit the NS5B RNA-dependent RNA polymerase responsible for replication of HCV RNA. Various DAAs of the same class may have similar targets; however, their degrees of activity across the HCV GTs may differ.<sup>2</sup>

Great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction. However, at this time, no DAA regimens are approved for patients with decompensated cirrhosis and GT 2, 4, 5, or 6 HCV infection. Therefore, a need exists for well-tolerated and cost-effective DAA combinations that provide the highest rates of viral eradication in all patients (including those with advanced liver disease), the broadest spectrum of action on viral genotypes showing minimal or no clinical resistance, and the shortest treatment duration.<sup>3</sup>

### 1.1.2 Product Background

Sofosbuvir/velpatasvir (SOF/VEL) is a fixed dose combination (FDC) tablet containing two direct acting antiviral (DAA) agents which interfere with the replication of HCV. Velpatasvir is a novel HCV NS5A inhibitor that has demonstrated potent antiviral activity against GT 1, 2, 3, 4, 5, and 6 HCV infection. Sofosbuvir is an HCV nucleotide analog NS5B polymerase inhibitor that has been approved for use in combination with other agents for the treatment of chronic HCV infection in adults, in the United States, the European Union, and more than 20 other countries worldwide.

The Sponsor's proposed indication is treatment of patients with chronic HCV infection; intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients, and patients with compensated and decompensated cirrhosis. The Sponsor's recommended dosage and treatment duration for non-cirrhotic patients and patients with compensated cirrhosis (Child-Pugh Class A) is one (400 mg/ 100 mg) tablet by mouth once daily for 12 weeks. The recommended treatment regimen for patients with decompensated cirrhosis (Child-Pugh Class B or C) is one tablet by mouth once daily, in combination with ribavirin (RBV), for 12 weeks. When administered with SOF/VEL, the recommended dosage of RBV is based on weight: 1000 mg per day for patients < 75 kg, and 1200 mg per day for patients weighing at least 75 kg, divided and administered twice daily with food. The Sponsor has not proposed a different dose or duration of SOF/VEL based on HCV GT or prior treatment experience. At this time, dosing recommendations are still under review. A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease. The combination regimen of SOF/VEL and RBV is contraindicated in patients for whom RBV is contraindicated.

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<sup>2</sup> Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.

<sup>3</sup> Aghemo, A., & De Francesco, R. (2013). New horizons in hepatitis C antiviral therapy with direct-acting antivirals. *Hepatology*, 58(1), 428-438.

## 1.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 208341 relevant to this review:

September 30, 2013: The Sponsor was granted Fast Track designation for SOF/VEL for the treatment of chronic HCV GT 1, 2, 3, 4, 5, and 6.

May 15, 2015: The Sponsor was granted Breakthrough Therapy designation for SOF/VEL for the treatment of chronic HCV GT 3, 4, 5, and 6 infection in treatment naïve patients.

May 26, 2015: A Pre-NDA meeting was held between the Agency and the Sponsor via teleconference. One agreement resulting from this meeting was the involvement of an Independent Adjudication Committee (IAC) to screen for potential cases of drug-induced liver injury (DILI) in the pivotal Phase 2 and 3 trials for SOF/VEL.

October 28, 2015: An original NDA submission was received by the Agency from Gilead for SOF/VEL (NDA 208341) for the treatment of adult patients with chronic (HCV) genotypes 1, 2, 3, 4, 5, or 6. The Sponsor did not submit a proposed REMS.

February 11, 2016: The Mid-Cycle communication was held between the Agency and the Sponsor via teleconference. The Agency informed the Sponsor that, based on the currently available data, the review team had not identified any major safety concerns for SOF/VEL.

There is no Advisory Committee planned for this application.

## 2 MATERIALS REVIEWED

The following is a list of materials that informed our review:

- Gilead. Proposed Prescribing Information for SOF/VEL, dated October 28, 2015.
- Gilead. Clinical Overview for SOF/VEL, dated October 28, 2015.
- Gilead. Summary of Clinical Efficacy for SOF/VEL, dated October 28, 2015.
- Gilead. Summary of Clinical Safety for SOF/VEL, dated October 28, 2015.
- Gilead. Proposed Prescribing Information for SOF/VEL, dated October 28, 2015.
  - Updated March 31, 2016.
- Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.
- Pratt, B. DRISK, REMS Review for Ledipasvir/Sofosbuvir, dated July 18, 2014.

## 3 RESULTS OF REVIEW

### 3.1 Overview of Clinical Program

The safety and efficacy of SOF/VEL for the treatment of patients with chronic HCV were evaluated in a Phase 2 dose-ranging study, and four randomized pivotal Phase 3 trials which evaluated a total of 1302 subjects in the SOF/VEL treatment arms. SVR12 was the primary efficacy endpoint in all SOF/VEL Phase 2 and 3 studies. The pivotal trial populations varied based on the subjects' HCV GT and cirrhosis status, and pre-specified historical control rates were used to determine comparative statistical significance. All major HCV genotypes and many different HCV subtypes were treated with SOF/VEL.

**Trial 342-0109** was a Phase 2 dose-ranging study that evaluated 323 patients to determine the efficacy and safety of 2 doses of VEL (25 mg and 100 mg) combined with 400 mg SOF, with or without RBV, administered for 12 weeks in treatment-experienced (TE) subjects with or without cirrhosis and GT 1 or 3 HCV infection. This trial provided the only data in the SOF/VEL clinical program for the use of RBV in GT 3 cirrhotics. The overall SVR12 rates were 89% and 96% in the SOF/VEL and SOF/VEL + RBV groups, respectively, with a treatment difference of -8% [95% CI -28%, 10%]. The Clinical reviewers concluded that the difference in SVR12 rates between the two groups was not statistically significant because the sample size was small and the 95% CI included 0. The Clinical reviewers also noted that, among GT3 subjects, SVR rates were higher for the 100 mg VEL dose than the 25 mg dose; however, the role of RBV was less clear.

**ASTRAL-1 (Trial 342-1138)** is an ongoing Phase 3, double-blind, placebo-controlled trial assessing the antiviral efficacy, safety, and tolerability of SOF/VEL in treatment-naïve (TN) and TE subjects with compensated liver disease and HCV GT 1, 2, 4, 5, or 6. A total of 740 subjects were randomized in a 5:1 ratio to receive SOF/VEL for 12 weeks (n=624) or placebo for 12 weeks (n=116). However, due to the small size of the affected population, all subjects with GT5 HCV infection were enrolled into the SOF/VEL 12-week group. The trial met its primary efficacy endpoint with an overall SVR12 rate of 99% in the SOF/VEL group and 0% in the placebo group. Four subjects in the SOF/VEL group did not achieve SVR12 due to missing data; the Clinical reviewer noted that, though they were coded as failures, they were not true virologic failures.

**ASTRAL-2 (Trial 342-1139)** is an ongoing Phase 3, open-label, active-control trial assessing TN and TE subjects with compensated liver disease and HCV GT2. A total of 266 subjects were randomized to receive SOF/VEL for 12 weeks (n=134) or SOF + RBV (n=136) for 12 weeks. The percentage of subjects achieving SVR12 was 99.3% in the SOF/VEL group, compared with 93.9% in the SOF + RBV group, a treatment difference of 5.4% with 95% CI (0.2%, 10.3%).

**ASTRAL-3 (Trial 342-1140)** is an ongoing Phase 3, open-label, active-control trial assessing TN and TE subjects with compensated liver disease and HCV GT3. A total of 552 subjects were randomized to receive SOF/VEL for 12 weeks (n=277) or SOF + RBV for 24 weeks (n=275). The percentage of subjects achieving SVR12 was 95% in the SOF/VEL group,

compared with 80% in the SOF + RBV group, a treatment difference of 15% and 95% CI (10%, 20%).

**ASTRAL-4 (Trial 342-1137)** is a Phase 3, open-label trial assessing TN and TE subjects with Child-Pugh Class B cirrhosis at screening (with no prior history of a liver transplant) with HCV GT 1-6. The Clinical reviewer noted that approximately 10% of the subjects who were Child-Pugh Class B at screening, were subsequently reclassified as Class A or C at baseline, which demonstrates the dynamic changes in Child-Pugh parameters over time. A total of 267 subjects were randomized to receive SOF/VEL for 12 weeks (n=90), SOF/VEL + RBV for 12 weeks (n=88), or SOF/VEL for 24 weeks (n=90).

The percentage of subjects achieving SVR12 was 83.3%, 94.3%, and 85.6% in the SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, and SOF/VEL for 24 weeks groups, respectively. The percentage of subjects experiencing relapse was 12.2%, 2.4%, and 8% in the SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, and SOF/VEL for 24 weeks groups, respectively. Across the four pivotal trials, SOF/VEL demonstrated SVR12 rates ranging from 83-100% depending on the regimen, HCV GT, and cirrhosis stage. In addition, SOF/VEL is the first direct acting antiviral regimen with potent activity across HCV GT 1-6. According to the Clinical reviewers, SOF/VEL is a highly effective, RBV-free, single tablet, once-daily treatment option for TN and TE patients with compensated liver disease, regardless of HCV GT. Further, treatment with SOF/VEL + RBV confers the highest SVR12 rates observed to date across HCV GT 1-6 in subjects with decompensated cirrhosis.<sup>4</sup>

### 3.2 SAFETY CONCERNS

The safety of SOF/VEL for the treatment of adult patients with chronic HCV was evaluated based primarily on the four aforementioned Phase 3 trials. The data from Trials ASTRAL-1, ASTRAL-2, and ASTRAL-3 were pooled to form the integrated summary of safety (ISS) population, while data from ASTRAL-4 were analyzed separately. Additional data was obtained from the following three Phase 2 trials:

- Trial 342-0102: A randomized, open-label, multi-center dose-ranging Phase 2 trial to evaluate safety and efficacy (using SVR12 as the primary endpoint) of SOF/VEL with or without RBV in 377 subjects with HCV GT 1-6 for 8 or 12 weeks
- Trial 342-0109: Similar in design to Trial 342-0102, this trial evaluated 323 subjects with GT 1 or 3, for 8 weeks
- Trial 337-0122: Similar in design to Trial 342-0109, this single-center trial evaluated 103 subjects with GT 3

For the purpose of this review, serious adverse events (SAEs) associated with SOF/VEL are defined by the regulatory definition of a serious outcome, such as death, a life-threatening reaction, or hospitalization (among other outcomes). Severe adverse events (AEs) associated with SOF/VEL are defined as Grade 3 or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities. The Sponsor utilized an independent adjudication

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<sup>4</sup> Viswanathan P and Connelly S. Division of Antiviral Products, Clinical Review of SOF/VEL, NDA 208341, dated March 29, 2016.

committee (IAC) to review potential cases of drug-induced liver injury (DILI) because of the difficulty in identifying it in patients with HCV. In addition, a thorough hepatic safety review was conducted by the Agency's Clinical reviewers, and the conclusions reached by the Agency's reviewers were compared to those of the IAC.

### **3.2.1 Deaths**

A total of 6 deaths occurred in the ISS population through the time of NDA submission, 3 of which occurred more than three months after completing treatment. Three of the events occurred in SOF/VEL subjects, and 3 in SOF+RBV subjects. Five of these deaths were determined by both the Sponsor and the Clinical reviewer to be unrelated or not likely to be related to SOF/VEL treatment. The remaining death was in a subject that had been taking SOF+RBV in ASTRAL-3. The subject was found dead in her bed on Day 141 of treatment, and the death was attributed to "natural causes." The Clinical reviewer noted that an autopsy was not performed and the Sponsor could not provide any additional information to help adjudicate the event. Therefore, the reviewer concluded that the cause of death was unclear, as was the contribution of SOF or RBV, or her comorbid conditions.

A total of 10 deaths were reported in ASTRAL-4, 2 of which were treatment-emergent: sepsis following duodenal ulcer perforation (SOF/VEL+RBV 12-week), and myocardial infarction in a subject with ongoing tobacco use (SOF/VEL 24-week). None of the ten deaths were considered treatment-related by the investigator, and the Clinical reviewer concurred.

### **3.2.2 Serious Adverse Events (SAEs)**

Serious adverse events (SAEs) were infrequent in the ISS population, occurring in 2% of subjects in both the SOF/VEL and SOF+RBV 12-week treatment groups, and 5% of subjects in the SOF+RBV 24-week treatment group. There were no SAEs reported in the placebo group. In ASTRAL-4, 16-19% of SOF/VEL-treated subjects experienced an SAE, with the most frequently-reported in the system organ classes (SOCs) of Infections and Infestations and Gastrointestinal disorders. However, SAEs in these SOCs were reported in  $\leq 8\%$  in any SOF/VEL-containing treatment group and no SAEs were considered by the investigator to be related to SOF/VEL. SAEs considered by the investigator to be related to study treatment occurred in 2 subjects (0.7%): dyspnea related to RBV and hepatorenal syndrome/hypertension/ peritonitis/ sepsis, which was assessed by the IAC as unlikely related to SOF/VEL treatment.

No major safety issues concerning SOF/VEL were identified by the Clinical reviewers. Sofosbuvir has been associated with serious bradycardia when co-administered with amiodarone and another DAA. Therefore, amiodarone treatment was prohibited in the four pivotal trials and no cases of serious bradycardia were observed. RBV is associated with common adverse reactions and some serious risks, but these safety issues are well known and are not exacerbated by concomitant administration with SOF/VEL.<sup>5</sup> Section 5 of the SOF/VEL

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<sup>5</sup> Viswanathan P and Connelly S. Division of Antiviral Products, Draft Clinical Review of SOF/VEL, NDA 208341.

Prescribing Information will include a Warning and Precaution regarding risks associated with serious symptomatic bradycardia related to co-administration of sofosbuvir with amiodarone and another DAA, as well as a warning regarding risks associated with RBV therapy.

### **3.2.3 Severe Adverse Events**

Grade 3 and 4 adverse events (AEs) occurred infrequently in the ISS population. Subjects in the SOF + RBV 24-week arm of ASTRAL-3 had the highest rate of serious AEs, presumably due to the longer duration of RBV. No pattern of similar events was observed and most events occurred in a single subject. Events occurring in more than 2 subjects in the SOF/VEL group included headache (n=5), anxiety (n=3), and acute myocardial infarction determined not to be related to the study drug (n=2).

In ASTRAL-4, severe AEs considered by the investigator to be related to the study drug occurred in 1.5% of all subjects, and ranged from 0-2% across SOF/VEL-containing groups. The Clinical reviewers concluded that there was no clear safety signal emerging from the ISS and ASTRAL-4 results. The severe AEs in ASTRAL-4 were mainly attributed to infectious etiology, RBV use and/or associated with decompensated cirrhosis (hematemesis, hepatic encephalopathy, spontaneous bacterial peritonitis).

### **3.2.4 Adverse Events of Special Interest (AESI)**

#### **3.2.4.1 Safety of SOF/VEL in Subjects with Child-Pugh Class C Cirrhosis**

Safety analyses were performed to determine if any unique safety signals were identified in subjects with baseline cirrhosis (ASTRAL-4). Subjects with Child-Pugh Class C cirrhosis (n=11) had higher percentages of SAEs in the SOF/VEL+RBV 12-week (50%, n=2) and SOF/VEL 24-week (50%, n=3) groups, compared to subjects with baseline Child-Pugh Class A or B (approximately 15%) cirrhosis, reflecting more advanced underlying liver disease. These SAEs included infectious colitis and cellulitis/skin ulcer in the 12-week group, and incarcerated umbilical hernia (fatal), pulmonary hypertension, hepatorenal syndrome/ hypotension/ peritonitis/ sepsis/ adrenal insufficiency associated with orthotopic liver transplantation in the 24-week group. Additional safety data of SOF/VEL-containing therapy in the Child-Pugh Class C population is likely to be recommended as a postmarketing requirement (PMR) to further evaluate unique safety signals that may impact future labeling. The use of SOF/VEL in this population will be monitored further in the postmarketing setting for any potential serious safety signals associated with the treatment.

## **4 DISCUSSION**

DRISK does not recommend a REMS as necessary to ensure the benefits of SOF/VEL outweigh the risks. HCV is a serious and life-threatening disease that infects an estimated 3-5 million people in the U.S. If left untreated, chronic HCV can lead to life-threatening liver complications, liver failure, and possibly, death. The Warnings and Precautions section of the SOF/VEL Prescribing Information will include a warning about the risks associated with RBV therapy. These are known

risks associated with drug therapies that are currently approved without a REMS. The label will also include a warning about the serious risks associated with sofosbuvir when administered with amiodarone and another DAA. This risk can be communicated through labeling. Based on the currently available data, there is an absence of concerning safety signals unique to the SOF/VEL combination. Additional safety data of SOF/VEL-containing therapy in the Child-Pugh Class C population may be included in a PMR, which is currently under discussion. The most frequently reported severe AEs associated with SOF/VEL are also associated with the approved treatments interferon and ribavirin, and none of the currently approved antiviral drugs for HCV infection require a REMS to ensure the benefits of treatment outweigh the risks.

The most likely prescribers of SOF/VEL are specialists who are familiar with the management of chronic HCV and who understand the risks of treatment using antiviral therapies that have more serious safety profiles than this product appears to have. Like the HCV antiviral agents already approved, the risks related to SOF/VEL therapy will be communicated through the Prescribing Information, and additional measures do not appear to be necessary.

Therefore, based on the currently available data, DRISK and DAVP concurred that a REMS is not necessary to ensure the benefits of SOF/VEL outweigh the risks.

## **5 CONCLUSION**

At this time, risk mitigation measures beyond professional labeling are not warranted for SOF/VEL. Based on the currently available data, DRISK and DAVP concurred that the benefit-risk profile for SOF/VEL is acceptable for the treatment of adults with chronic HCV infection, and the risks will be communicated to the prescribing community through the labeling. Therefore, a REMS is not necessary to ensure the benefits outweigh the risks for SOF/VEL.

Should DAVP have any concerns or questions, or if new safety information becomes available, please contact DRISK.

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