# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 208341Orig1s000

# SUMMARY REVIEW

# Decisional Review for NDA 208341

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|---|---|
| **Date** | June 16, 2016 |
| **From** | Debra Birnkrant, M.D. |
| **Subject** | Division Director's Summary Review |
| **NDA#** | NDA 208341 |
| **Applicant Name** | Gilead Sciences, Inc. |
| **Date of Submission** | October 28, 2015 |
| **PDUFA Goal Date** | June 28, 2016 |
| **Proprietary Name / Established (USAN) Name** | Epclusa® Sofusbuvir (SOF) and velpatasvir(VEL) |
| **Dosage Forms / Strength** | Fixed dose combination tablet containing 400 mg SOF and 100 mg VEL |
| **Proposed Indication(s)** | Treatment of adult patients with chronic hepatitis C virus infection |
| **Recommended Action** | Approval |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Drs. Prabha Viswanathan and Sarah Connelly supervised by Dr. Kim Struble |
| Statistical Review | Drs. Karen Qi and Thamban Valappil supervised by Dr. Dionne Price |
| Pharmacology Toxicology Review | Dr. John Dubinion supervised by Dr. Hanan Ghantous. |
| CMC Review | Drs. Larry Bai, George Lunn, Sithamalli Chandramouli, and Ying Wang with Dr. Stephen Miller, CMC- Lead |
| Microbiology Review | Drs. Lisa Naeger and Eric Donaldson supervised by Dr. Jules O'Rear |
| Clinical Pharmacology/Pharmacometrics Review | Drs. Jenny Zheng and Abhay Joshi supervised by Dr. Shirley Seo;<br>Dr. Fang Li supervised by Dr. Jeffry Florian |
| DDMAC | Kemi Asante, Pharm.D. |
| OSI | Dr. Antoine El Hage |
| CDTL Review | Dr. Kim Struble |
| OSE/DMEPA | Mónica Calderón, PharmD, BCPS |
| OPM/DMPP | Morgan Walker, PharmD, MBA |
| OSE/DRISK | Erin Hachey, Pharm.D. |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

APPEARS THIS WAY ON ORIGINAL

1. **Benefit-Risk Assessment**

I am in agreement with the benefit-risk assessment summarized in the multidisciplinary reviews of this NDA. I am also in agreement with the summary contained in the benefit-risk framework that contains an analysis of chronic hepatitis C viral infection, current treatment options, and the benefit, risk and risk management for the pangenotypic indication for SOF/VEL. My recommendation is for approval of NDA 208341 for the fixed-dose combination of SOF/VEL for the treatment of adult patients with chronic hepatitis C viral infection for genotypes 1-6 without cirrhosis or with compensated cirrhosis and for SOF/VEL/ribavirin (RBV) for the treatment of adult patients with chronic hepatitis C viral infection for genotypes 1-6 with decompensated cirrhosis.

**Benefit-Risk Summary and Assessment**

Sofosbuvir (SOF) is a hepatitis C virus (HCV) NS5B nucleotide analog polymerase inhibitor and velpatasvir (VEL) is an HCV NS5A inhibitor. SOF/VEL is a fixed-dose combination tablet with a proposed indication for 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.

HCV infection is a serious disease, affecting an estimated 3-5 million people in the US and 170 million people worldwide (http://www.epidemic.org/theFacts/theEpidemic/worldPrevalence/). Although often asymptomatic in early stages, if untreated, chronic HCV can lead to debilitating and life-threatening liver problems, including hepatocellular carcinoma, liver failure, and death. Treatment options for chronic hepatitis C (CHC) have changed dramatically over the past 5 years as oral direct-acting antiviral (DAAs) agents have replaced interferon-based regimens, resulting in markedly improved efficacy rates. The standard measure of efficacy is the absence of detectable HCV RNA, termed sustained virologic response (SVR), documented 12 weeks after the end of treatment (SVR12); SVR12 is considered a virologic cure. Several DAA regimens were approved during this NDA review cycle that confer SVR12 rates greater than 93% for HCV genotype (GT) 1, 3, 4, 5, or 6-infected patients with compensated liver disease, defined as the absence of cirrhosis or compensated cirrhosis (Child Pugh Turcotte [CPT] A). The first approvals of DAA regimens in HCV GT 1 or 3-infected subjects with decompensated cirrhosis or liver transplant were also granted during this review cycle, with SVR12 rates ranging from 50-92% among HCV GT1 subjects and 83% for HCV GT3 subjects.

While great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction, better treatment options for patients with non-GT1 HCV are needed, especially for HCV GT3. The need for better treatment options is even greater among subjects with decompensated cirrhosis regardless of HCV GT. SOF/VEL demonstrated SVR12 rates ranging from 83-100% depending on the Phase 3 trial regimen, HCV GT, cirrhosis stage, and prior treatment history. In addition, SOF/VEL is the first DAA regimen with potent activity across HCV GT 1, 2, 3, 4, 5 and 6. 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. Similarly, treatment with SOF/VEL + RBV confers the highest SVR12 rates observed to date across HCV GT 1-6 in subjects with decompensated cirrhosis.

Consistent with results from other development programs, HCV GT3- infected subjects with cirrhosis and/or prior treatment experience had only slightly lower SVR rates than subjects with any other HCV GT studied. SVR12 rates are 89% for HCV GT3 TE cirrhotic subjects, 91% for HCV GT3 cirrhotics and 90% for HCV GT3 TE subjects. The optimal strategy for improving the SVR12 rate in these GT3 subpopulations remains unclear. The Applicant has agreed to a PMR to obtain the results from Trial GS-US-342-2097 to assess the role of RBV in HCV GT3 infected subjects with cirrhosis.

No major safety issues unique to SOF/VEL were identified in this review. The most frequent adverse drug reactions were headache, fatigue, and nausea. SOF has been associated with serious bradycardia when co-administered with amiodarone and another DAA; 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 serious risks, but these safety issues are well known and are not exacerbated by concomitant administration with SOF/VEL.

Approval of SOF/VEL for treatment of adult patients with CHC infection is fully supported by the available evidence of efficacy and safety. The following regimens are recommended based on thorough analysis of efficacy, safety, and virology data overall, and in each subpopulation:

(1) SOF/VEL for 12 weeks: Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and without cirrhosis or with compensated cirrhosis
(2) SOF/VEL + RBV for 12 weeks: Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and decompensated cirrhosis

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Chronic infection with hepatitis C virus (HCV) causes inflammation of the liver that can lead to long-term health problems or death.<br>• Globally, an estimated 170 million people are infected with HCV, including approximately 3 to 5 million people in the United States (US) (Edlin, et al, Hepatology, 2015 .<br>• At least seven distinct HCV genotypes (GTs) exist. GT 1 is the most common among US patients (72%), followed by GT 2 (11%), GT 3 (9%), and GT 4 (6%). GTs 5 and 6 occur uncommonly (≤ 1%) in the US but may predominate in other parts of the world.<br>• HCV infection is typically asymptomatic in its early stages. However, if left untreated, HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. HCV infection is a leading cause of chronic liver disease in the US. | HCV monoinfection and HCV/HIV-1 coinfection are a significant and growing public health concern. CDC reported an increase in new cases of hepatitis C in Appalachia and Scott County, Indiana related to injection drug use (CDC.gov).<br><br>If untreated, chronic HCV infection is a life-threatening condition that affects a large population in the US and worldwide. Patients can experience symptoms that are severe and debilitating. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • Once cirrhosis is established, complications such as jaundice, ascites, variceal hemorrhage, and encephalopathy may develop which defines decompensated cirrhosis, or end-stage liver disease. In patients with decompensated cirrhosis, the 5-year survival rate is approximately 50%. | |
| **Current Treatment Options** | • The current standard-of-care treatments for CHC are interferon-free, all-oral DAA regimens (AASLD Treatment Guidelines, April 2016). Treatment options vary based on HCV GT:<br>○ GT1: ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir + sofosbuvir; and simeprevir + sofosbuvir<br>○ GT2: sofosbuvir + ribavirin<br>○ GT3: daclatasvir + sofosbuvir; sofosbuvir + ribavirin<br>○ GT4: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir + RBV<br>○ GT5: ledipasvir/sofosbuvir<br>○ GT6: ledipasvir/sofosbuvir<br>• Treatment with DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in greater than 93% of CHC patients with compensated liver disease. However, SVR12 rates were lower for certain subpopulations, and some of these regimens require the addition of RBV or longer treatment durations for subjects with cirrhosis and/or prior treatment failure.<br>• During this NDA review cycle, two regimens were approved for treatment of HCV GT 1 or GT 3-infected subjects with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] score B or C) or liver transplant:<br>○ Treatment with ledipasvir/sofosbuvir + RBV for 12 weeks resulted in SVR12 rates of 87-88% among GT1-infected pre-transplant subjects with decompensated cirrhosis and SVR12 rates of 89% and 57% for post-transplant CPT B and C subjects, respectively.<br>○ Treatment with daclatasvir + sofosbuvir + RBV for 12 weeks resulted in SVR12 rates 92% for CPT B subjects and 50% of CPT | Patients with chronic HCV infection would greatly benefit from new therapeutic options that are well tolerated and equally or more efficacious than current interferon-free DAA options.<br><br>Only one approved regimen for subjects with GT 2, 5 and 6 HCV is available. These subjects would benefit from a treatment alternative.<br><br>RBV-free regimens with shorter treatment durations (< 16 weeks) are needed for populations that are traditionally harder to treat; such regimens may improve treatment adherence and minimize safety and tolerability issues associated with RBV.<br><br>DAA regimens for subjects with decompensated cirrhosis, particularly for those infected with HCV GT 2, 4, 5, or 6 is an unmet medical need population because no approved regimens are available. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | C subjects with GT1; 83% of subjects with GT3 achieved SVR12.<br>• At the time of this review, no DAA regimens are approved for patients with decompensated cirrhosis and HCV GT 2, 4, 5, or 6 infection. | |
| Benefit | • The efficacy of SOF/VEL was established in four Phase 3 clinical trials which cumulatively evaluated 1302 subjects in the SOF/VEL treatment arms. The trial populations varied based on HCV GT and cirrhosis status.<br>○ ASTRAL-1: TN and TE subjects with compensated liver disease and HCV GT 1, 2, 4, 5, or 6. Subjects received SOF/VEL x 12 weeks or placebo x 12 weeks.<br>○ ASTRAL-2: TN and TE subjects with compensated liver disease and HCV GT2. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 12 weeks.<br>○ ASTRAL-3: TN and TE subjects with compensated liver disease and HCV GT3. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 24 weeks.<br>○ ASTRAL-4: TN and TE subjects with decompensated liver disease (CPT B at screening) with HCV GT 1-6. Subjects received SOF/VEL x 12 weeks, SOF/VEL+RBV x 12 weeks, or SOF/VEL x 24 weeks<br>• The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 results for SOF/VEL for 12 weeks in HCV GT 1, 2, 3, 4, 5, and 6 subjects without cirrhosis or with compensated cirrhosis were 95-100%. The SVR12 rates for SOF/VEL+RBV for 12 weeks in HCV GT 1, 2, 3, and 4 subjects with decompensated cirrhosis were 85-100%. | Four clinical trials provide substantial evidence of effectiveness of SOF/VEL for treatment of CHC GT1-6.<br>• The recommended regimen for subjects with compensated liver disease is SOF/VEL for 12 weeks irrespective of HCV GT or prior treatment experience.<br>• The recommended regimen for subjects with decompensated cirrhosis is SOF/VEL + RBV for 12 weeks, irrespective of HCV GT or prior treatment status.<br><br>The lower SVR12 rates observed among GT 3 subjects, particularly those with cirrhosis, merit consideration of the utility of adding RBV to optimize treatment success. A PMR is recommended to obtain the results from Trial GS-US-342-2097 to assess the role of RBV in HCV GT 3 infected subjects with cirrhosis.<br><br>SOF/VEL fills an important unmet medical need for a 12 week, RBV-free regimen for subjects with GT 1-6 infection and compensated liver disease, irrespective of prior treatment status. |

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
Pooled Analysis of ASTRAL-1, ASTRAL-2, and ASTRAL-3: SVR12 by HCV GT Among Subjects Treated with SOF/VEL Subjects for 12 Weeks n (%)
<table>
<tr><th>GT1</th><th>GT2</th><th>GT3</th><th>GT4</th><th>GT5</th><th>GT6</th><th>Total</th></tr>
<tr><td>323/328 (99%)</td><td>237/238 (99%)</td><td>264/277 (95%)</td><td>116/116 (100%)</td><td>34/35 (97%)</td><td>41/41 (100%)</td><td>1015/1035 (98%)</td></tr>
</table>
ASTRAL-4: SVR12 by Treatment Arm and HCV GT n (%)
<table>
<tr><th></th><th>GT1</th><th>GT2</th><th>GT3</th><th>GT4</th><th>GT6</th><th>Total</th></tr>
<tr><td>SOF/ VEL x 12 wks</td><td>60/68 (88%)</td><td>4/4 (100%)</td><td>7/14 (50%)</td><td>4/4 (100%)</td><td>-</td><td>75/90 (83%)</td></tr>
<tr><td>SOF/ VEL+RBV x 12 wks</td><td>65/68 (96%)</td><td>4/4 (100%)</td><td>11/13 (85%)</td><td>2/2 (100%)</td><td>-</td><td>82/87 (94%)</td></tr>
<tr><td>SOF/ VEL x 24 wks</td><td>65/71 (92%)</td><td>3/4 (75%)</td><td>6/12 (50%)</td><td>2/2 (100%)</td><td>1/1 (100%)</td><td>77/90 (86%)</td></tr>
</table>
No GT5 subjects were enrolled in ASTRAL-4
<ul>
<li>SVR12 rates were comparable across GT with the exception of GT3; subjects with GT 3 in ASTRAL-3 and ASTRAL-4 had higher rates of virologic failure relative to other GTs. Subgroup analyses demonstrated cirrhosis, prior treatment failure, and the presence of baseline NS5A resistance-associated polymorphisms were associated with numerically higher rates of treatment failure.</li>
</ul>
<ul>
<li>Overall, demographic factors did not impact SVR12 rates.</li>
</ul>
</td><td>SOF/VEL + RBV fills an important unmet medical need for subjects with decompensated cirrhosis who have few or no treatment options.</td></tr>
<tr><td>Risk</td><td>
<ul>
<li>The safety database for SOF/VEL includes 1302 subjects from the four aforementioned clinical trials and is considered adequate.</li>
<li>ASTRAL-1 included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo.</li>
<li>Additional safety data included subjects who received SOF/VEL at doses of at least SOF 400 mg and VEL 25 mg in Phase 2 trials.</li>
<li>No major safety issues were identified during this review.</li>
</ul>
</td><td>SOF/VEL with or without RBV demonstrated an overall favorable safety profile.<br><br>The safety issues with RBV are well known and are not exacerbated by SOF/VEL.</td></tr>
</table>

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | • Headache, fatigue, and nausea were the three most commonly reported adverse drug reactions reported across trials.<br>• Subjects who received RBV with SOF/VEL experienced higher rates of RBV-associated adverse events, at rates consistent with prior HCV DAA trials. | |
| **Risk Management** | • Although no significant safety signals were detected in this review, the SOF/VEL prescribing information will include safety information contained in the current SOF label, even if the events occurred rarely in the SOF/VEL trials:<br>  ○ Though no cases were reported in the Phase 3 SOF/VEL trials, Section 5 of the SOF/VEL label will include a warning regarding the risk of serious symptomatic bradycardia related to co-administration of sofosbuvir with amiodarone and another DAA.<br>  ○ Rash and depression are recommended for inclusion in Section 6 of the SOF/VEL label.<br>• Section 5 will also include a warning regarding risks associated with RBV therapy. | Safety concerns associated with SOF or RBV are adequately addressed in product labeling. |

This Division Director's memorandum provides a topline summary of NDA 208341 for Gilead Sciences, Inc.'s New Drug Application (NDA) for the fixed-dose combination of of two direct-acting antivirals (DAAs), sofosbuvir (SOF), a nucleotide analog NS5B polymerase inhibitor and velpatasavir (VEL) a hepatitis C virus (HCV) NS5A inhibitor indicated for the treatment of adults with genotypes 1- 6 chronic hepatitis C viral infection. This decisional review summarizes pertinent findings from the NDA submission, FDA's multidisciplinary reviews, and product labeling.

## 2. Background

Chronic hepatitis C (CHC) viral infection remains a public health challenge despite recent approvals of highly potent direct-acting antivirals. CHC affects millions domestically of whom almost 50% are unaware of their infection (Yehia, et al, PLoS One, 2014). Recent death rate estimates with hepatitis C as an underlying or contributing cause have surpassed those related to 60 nationally notifiable infections reported to CDC (LY, et al, CID, 2016).

Hepatitis C virus is classified into at least seven distinct genotypes and many subtypes. Hepatitis C genotype 1 is responsible for approximately 70-75% of HCV infections domestically; whereas GT 2 comprises approximately 11%, GT 3, 9%, and GT 4, 6% of infections. GTs 5 and 6 occur uncommonly ($\leq$ 1%) in the US but predominate in other parts of the world. (Gower et al, J. Hepatology, 2014; Messina et al, Hepatology, 2015).

Sustained virologic response (SVR), a measure of virologic cure used as an endpoint in clinical trials and in clinical practice is a validated surrogate endpoint that is measured 12 weeks after treatment. SVR correlates with clinically important outcomes such as histologic benefit, a decrease in all-cause and liver-related mortality, and decreases in rates of HCC and hepatic decompensation (Backus, et al, Clin. Gastroenterol Hepatol 2011; Singal, et al, Clin Gastroenterol Hepatol, 2010; van der Meer, et al JAMA, 2012; Veldt, et al, Ann Intern Med, 2007; Mishra, et al, Hepatology, 2015).

Treatment of CHC has improved over the years, especially with the approval of potent direct-acting antivirals (DAA). Treatment regimens are well tolerated and yield cure rates of at least 90% for most genotypes with 8-12 week interferon-free regimens. See table 1 excerpted from the clinical NDA review:

**Table 1. Summary of Approved Interferon-Free Treatments for Chronic HCV Infection**

| Product (s) Name | Product Class | HCV GT | Year of Approval | Dosing/ Administration | Efficacy Information | Important Safety and Tolerability Issues |
|---|---|---|---|---|---|---|
| Elbas ir and grazoprevir (Zepatier®) | NS5A inhibitor, NS3/4A protease inhibitor (PI) | 1, 4 | 2016 | 1 tablet orally once daily with or without RBV for 12 or 16 weeks | SVR 94-97% | Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients |
| Ombitasvir, paritaprevir and ritonavir (Technivie®) | NS5A inhibitor, NS3/4A PI, PK enhancer | 4 | 2015 | 2 tablets orally once daily with RBV for 12 weeks | SVR 100% | Hepatic decompensation and hepatic failure in cirrhotics; ALT elevation in all patients |
| Daclatasvir (Daklinza®) | NS5A inhibitor | 1, 3 | 2015 | 1 tablet orally with sofosbuvir and with or without RBV for 12 weeks | SVR 82-97% | No serious drug-specific toxicity identified |
| Ledipasvir and sofosbuvir (Harvoni®) | NS5A inhibitor/ NS5B inhibitor (nucleotide) | 1, 4, 5, 6 | 2014 | 1 tablet orally once daily with or without RBV for 8, 12, or 24 weeks | SVR 93-99% | Serious symptomatic bradycardia when coadministered with amiodarone and another DAA (daclatasvir, ledipasvir or simeprevir) |
| Dasabuvir, ombitasvir, paritaprevir and ritonavir (Viekira Pak®) | NS5B inhibitor (non-nucleoside), NS5A inhibitor, NS3/4A PI | 1 | 2014 | 2 FDC tablets once daily + 1 dasabuvir tablet twice daily (+/- RBV) for 12 or 24 weeks | SVR 95-99% | Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients |
| Sofosbuvir* (Sovaldi®) | NS5B inhibitor (nucleotide) | 2, 3 | 2013 | One tablet orally once daily with RBV for 12 or 24 weeks | SVR 82-95% | Serious symptomatic bradycardia when coadministered with amiodarone and another DAA (daclatasvir, ledipasvir or simeprevir) |
| Simeprevir (Olysio®) | NS3/4 PI | 1 | 2013 | 1 capsule orally once daily (with sofosbuvir) for 12 or 24 weeks | SVR 93-97% | Hepatic decompensation and hepatic failure; photosensitivity; rash |

*Excludes FDC containing sofosbuvir

SOF was first approved for GTs 2 and 3 with ribavirin in 2013. More recently, SOF in a FDC with ledipasavir (LDV) as Harvoni, with or without ribavirin was approved for GTs 1, 4, 5 and 6 in 2014. SOF/VEL is a FDC that was studied in four phase 3 clinical trials, ASTRAL 1-4 in multiple patient populations. SOF is a nucleotide analog inhibitor of HCV NS5B polymerase and VEL is a NS5A inhibitor. The pangenotypic combination received fast track designation on September 30, 2013. Breakthrough Therapy Designation was originally granted April 22, 2014 for SOF/VEL FDC treatment of chronic HCV GT 1, 3, 4, 5, and 6 infection in TN patients. However, due to the approval and availability of other safe and effective therapies to treat HCV GT 1 infection, the Agency rescinded Breakthrough Therapy Designation April 1, 2015, and the Applicant submitted a new request for Breakthrough Therapy for the treatment of GTs 3, 4, 5, and 6 infection in TN patients. This request was granted May 15, 2015.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), FDA inspected eight clinical sites, both domestic and foreign. Two sites were selected from each phase 3 clinical trial based on enrollment, number of protocol deviations, or results that were dissimilar from overall trends. Based on the inspection findings, the data generated were found to be reliable and acceptable in support of this application.

The application was not presented before the Antimicrobial Drugs Advisory Committee because a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion. In addition, SOF was previously approved and VEL is the fifth NS5A inhibitor in its class.

**3. CMC**

CMC reviewers were Dr. Larry Bai, Dr. George Lunn, Dr. Sithamalli Chandramouli, and Dr. Ying Wang; Dr. Stephen Miller served as CMC Lead. The CMC team reviewed data to assure the identity, strength, purity, and quality of SOF/VEL. The commercial product is an immediate-release FDC containing SOF 400 mg and VEL 100 mg. (b) (4) Long-term and accelerated stability data demonstrate that the packaging is appropriate to maintain the quality of the drug product.

An overall recommendation of Acceptable has been made by the Office of Process and Facilities. Therefore, from a CMC perspective, NDA 208341 is recommended for approval.

**4. Nonclinical Pharmacology/Toxicology**

Please see review of submitted nonclinical toxicology studies by Dr. John Dubinion, supervised by Dr. Hanan Ghantous. Nonclinical SOF safety studies to support the SOF/VEL FDC were reviewed previously: please refer to the

Pharmacology/Toxicology reviews for NDA 204671 and NDA 205834 for detailed summary of SOF nonclinical data.

Per Dr. Dubinion's review, the nonclinical safety profile of VEL has been satisfactorily evaluated in the following studies: safety pharmacology, PK/ADME, single-dose and repeat-dose toxicity, phototoxicity, genotoxicity, and reproductive toxicity. No significant safety pharmacology signals were detected in studies evaluating cardiotoxicity (including effects on the hERG channel), CNS toxicity, and respiratory toxicity. No clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats, and dogs administered VEL doses up to 1500, 200, and 100 mg/kg/day for 1, 6 and 9 months, respectively. Specifications for impurities were deemed acceptable, see review by Dr. Mark Powley.

VEL was rapidly eliminated from most tissues and mainly excreted in the bile within 24 hours, except from the eye which maintained VEL exposure at 168 hours postdose. Additional studies in rats and rabbits suggested VEL was not an ocular irritant. Several minor metabolites were identified; however, unchanged parent drug was the predominant circulating component (in mice, rats, dogs, and human subjects) as well as the primary drug component in feces.

Per Dr. Dubinion's review, VEL was not genotoxic in standard testing. Further, VEL had no effects on reproduction or development in multiple species. Carcinogenicity studies in rats and transgenic mice are ongoing.

There are no adequate and well-controlled trials of SOF/VEL in pregnant women to inform a drug-associated risk. Therefore, the benefits and risks of SOF/VEL should be considered when prescribing SOF/VEL to a pregnant woman.

**5. Clinical Pharmacology**

Drs. Jenny Zheng and Fang Li reviewed dedicated in vitro and clinical pharmacology trials that were conducted in healthy volunteers and HCV-infected subjects to characterize the pharmacokinetics (PK) of SOF, its principal metabolite, GS-331007 and VEL. The following table from their review characterizes the absorption, distribution, metabolism, and excretion (ADME) of the components of SOF/VEL.

**Table 2. ADME Components of SOF/VEL**

| | Sofosbuvir | Velpatasvir |
|---|---|---|
| **Absorption** | | |
| Tmax (h) | 0.5-1 | 3 |
| Effect of moderate meal (relative to fasting)[a] | ↑ 60% | ↑ 34% |
| Effect of high fat meal (relative to fasting)[a] | ↑ 78% | ↑ 21% |
| **Distribution** | | |
| % Bound to human plasma proteins | 61-65% | >99.5% |
| Blood-to-plasma ratio | 0.7 | 0.52-0.67 |
| **Metabolism** | | |
| Metabolism | Cathepsin A<br>CES1<br>HINT1 | CYP2B6 (minor)<br>CYP2C8 (minor)<br>CYP3A4 (minor) |
| **Elimination** | | |
| Major route of elimination | SOF: metabolism<br>GS-331007[b]: glomerular filtration and active tubular secretion | Biliary excretion as parent (77%) |
| t1/2 (h)[c] | SOF: 0.5<br>GS-331007[b]: 25 | 15 |
| % Of dose excreted in urine[d] | 80%[e] | 0.4% |
| % Of dose excreted in feces[d] | 14% | 94% |

CES1 = carboxylesterase 1; HINT1 = histidine triad nucleotide-binding protein 1
[a] Values refer to mean systemic exposure. Moderate meal = ~600 kcal, 30% fat; high fat meal = ~800 kcal, 50% fat. SOF/VEL can be taken with or without food.
[b] GS-331007 is the primary circulating nucleoside metabolite of SOF.
[c] $t_{1/2}$ values refer to median terminal plasma half-life.
[d] Single dose administration of [$^{14}$C] SOF or [$^{14}$C] VEL in mass balance studies.
[e] Predominantly as GS-331007.

Dose exploration for SOF had been previously conducted and SOF 400 mg is the marketed dose. VEL dose selection was based on a phase 1b Study GS-US-281-0102 that evaluated the antiviral activity and safety of VEL for 3 days at doses ranging from 5 to 150 mg in subjects with GTs 1, 2, 3, or 4 HCV viral infection. The median maximal decline in HCV RNA across all HCV genotypes at all VEL doses evaluated was > 3 log10 IU/mL. Phase 2 studies (Studies GS-US-342-0102, GS-US-342-0109, and GS-US-337-0122 [ELECTRON-2, Cohort 4]) evaluated the efficacy and safety of coadministration of SOF/VEL in subjects with GTs 1 to 6 HCV viral infection. Two treatment durations (8 and 12 weeks), two VEL doses (25 and 100 mg), and the contribution of RBV to efficacy and safety were also assessed. A regimen of SOF 400 mg with VEL 25 mg for 12 weeks resulted in a lower SVR12 rate for treatment-experienced subjects with genotype 3 compared to regimen with VEL at 100 mg (71% compared to 94%).

No exposure-response relationships for safety were identified for either of the components of SOF/VEL at the recommended dosage. Neither SOF nor VEL prolonged the QTc to a clinically relevant extent at a dose three times the maximum recommended dose for SOF and five times the maximum recommended dose for VEL. Please see the review conducted by Interdisciplinary Review Team for QT Studies Consultation (IND 115670 dated 4/15/2015) for details.

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

- No dosage adjustment of SOF/VEL is required for patients with mild or moderate renal impairment, however the safety and efficacy of SOF/VEL have not been established in patients with severe renal impairment (eGFR less than 30 mL/min/1.73m$^2$) or ESRD requiring hemodialysis. Healthcare providers are referred to ribavirin prescribing information regarding use of ribavirin in patients with renal impairment.

- No dosage adjustment of SOF/VEL is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C), however clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with SOF/VEL and ribavirin.

- SOF/VEL can be dosed without regard to food.

- Based on population pharmacokinetic analyses in HCV-infected subjects, gender had no clinically relevant effect on exposure of SOF, GS-331007 or VEL.

- Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposure of SOF, GS-331007 or VEL.

- Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (18 to 82 years) analyzed, age did not have a clinically relevant effect on exposure of SOF, GS-331007 or VEL.

SOF and VEL are substrates of drug transporters P-gp and BCRP. In vitro, slow metabolic turnover of VEL by CYP2B6, CYP2C8, and CYP3A4 was also observed. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of SOF/VEL leading to reduced therapeutic effect. The use of these agents with SOF/VEL is not recommended in labeling*[see Warnings and Precautions (5.2), Drug Interactions (7) and Clinical Pharmacology (12.3)]*; however, SOF/VEL may be coadministered with P-gp, BCRP, and CYP inhibitors.

There is also potential for SOF/VEL to affect other drugs. Labeling contains wording that VEL is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Coadministration of SOF/VEL with drugs that are substrates of these transporters may increase the exposure of such drugs. Table 3 in labeling highlights potentially significant drug interactions. Since VEL solubility decreases as pH increases, specific recommendations for dosing of acid-reducing agents is detailed in labeling. For example, antacids and SOF/VEL should be seprated by 4 hours. $H_2$-receptor antagonists may be administered simultaneously with or 12 hours apart from SOF/VEL at a dose that does not exceed doses comparable to famotidine 40 mg twice daily, whereas coadministration of proton-pump inhibitors is not recommended unless it is medically necessary. FDA and the Applicant agreed to the following wording: Coadministration of omeprazole or other proton pump inhibitors is not recommended. If it is considered medically necessary to coadminister, SOF/VEL should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump inhibitors has not been studied.

Other important drug interactions include use of amiodarone with SOF/VEL which could result in symptomatic bradycardia and coadministration of HMG-CoA reductase inhibitors that may increase the risk of myopathy. See table 3 in labeling for a complete list.

Review of limited ASTRAL-5 safety data in HIV-1/HCV coinfected patients supports the clinical recommendations for concomitant use of SOF/VEL with tenofovir and with boosted atazanavir.

**6. Clinical Microbiology**

Please see extensive reviews by Drs. Lisa Naeger and Eric Donaldson who conducted the review of virology and resistance data, with supervisory concurrence by Dr. Jules O'Rear. Our virology review staff concluded that SOF/VEL is approvable with respect to virology for the treatment of GTs 1-6.

SOF is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase and acts as a chain terminator. The pharmacologically active uridine analog triphosphate (GS-461203) is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase. VEL targets NS5A as its mode of action.

Activity of SOF/VEL against full length or chimeric laboratory replicons is presented as $EC_{50}$ values in Table 8 in labeling. SOF/VEL demonstrates $EC_{50}$ values in the nanomolar range:

**Table 3(8) Activity of SOF/VEL Against Full Length or Chimeric Laboratory Replicons**

| Replicon Genotype | Sofosbuvir $EC_{50}$, nM[a] | Velpatasvir $EC_{50}$, nM[a] |
|---|---|---|
| 1a | 40 | 0.014 |
| 1b | 110 | 0.016 |
| 2a | 50 | 0.005-0.016[c] |
| 2b | 15[b] | 0.002-0.006[c] |
| 3a | 50 | 0.004 |
| 4a | 40 | 0.009 |
| 4d | 33.4 | 0.004 |
| 5a | 15[b] | 0.021-0.054[d] |
| 6a | 14-25[b] | 0.006-0.009 |
| 6e | NA | 0.130[d] |

NA=Not available
a. Mean value from multiple experiments of same laboratory replicon.
b. Stable chimeric 1b replicons carrying NS5B genes from genotype 2b, 5a or 6a were used for testing.
c. Data from various strains of full length NS5A replicons or chimeric NS5A replicons carrying full-length NS5A genes that contain L31 or M31 polymorphisms.
d. Data from a chimeric NS5A replicon carrying NS5A amino acids 9-184.

Against clinical isolates, median $EC_{50}$ values range from 29 - 102 nM and 0.002 – 0.024 nM for SOF and VEL, respectively.

The following information is excerpted from the virology review:

In cell culture, reduced susceptibility to SOF was associated with the NS5B substitution S282T in all replicon genotypes examined. HCV genotypes 1a, 1b, 2a, 3a, 4a, 5a, and 6a replicon variants with reduced susceptibility to VEL were also selected in cell culture. Selected viruses developed amino acid substitutions at NS5A resistance-associated positions 24, 28, 30, 31, 32, 58, 92, and 93. Phenotypic analysis of site-directed mutagenesis mutant replicons of the selected NS5A substitutions showed that single and double combinations of L31V and Y93H/N in genotype 1a, the combination of L31V +Y93H in genotype 1b, Y93H/S in genotype 3a, and L31V and P32A/L/Q/R in genotype 6 conferred greater than 100-fold reduction in VEL susceptibility. In the genotype 2a replicon, the single mutants F28S and Y93H showed 91-fold and 46-fold reduced susceptibility to VEL, respectively. The single mutant Y93H conferred 3-fold reduced susceptibility to VEL in genotype 4a replicons. Combinations of these NS5A substitutions often showed greater reductions in susceptibility to VEL than single substitutions alone.

In the overall development program, virologic failures were limited. There were only two GT1 virologic failures in ASTRAL 1; both patients who failed had the emergence of the NS5A resistance substitutionY93H. There were no virologic failures in ASTRAL 2. SVR12 rates were 100% with or without the presence of baseline NS5A resistance-associated polymorphisms (RAPs) for GT2, GT4, GT5 and GT6 subjects.

In ASTRAL 3, the overall relapse rate for the SOF/VEL 12 week treatment arm was 4% (10/275) compared to 15% (40/260) for the comparator SOF/RBV 24 week treatment arm. The relapse rate for subjects in the SOF/VEL arm with baseline NS5A RAPs was 7% (4/56) compared to 3% (7/218) for subjects without RAPs. Relapse rates were higher for subjects with cirrhosis in both treatment arms; 9% (7/80) for the SOF/VEL arm and 29% (23/78) for the SOF+RBV arm. For subjects without cirrhosis, relapse rates were 2% for subjects with and without NS5A RAPs. However, for cirrhotic subjects treated with SOF/VEL for 12 weeks, relapse rates were higher for subjects with NS5A RAPs (33%; 3/9) than subjects without RAPs (6%; 4/71).

In decompensated cirrhosis patients in ASTRAL 4, no patients relapsed with GTs 2, 4 or 6. For GT1 patients, the overall relapse rates were lower for the 12-week SOF/VEL + RBV arm (2%; 1/66) compared to 8% (5/65) and 4% (3/68) for the SOF/VEL 12-week and 24-week treatment arms, respectively. For patients with baseline NS5A RAPs, relapse rates were 0% for the RBV containing arm compared to 17% and 11% for the 12-week and 24-week SOF/VEL regimens, respectively. For GT 3 patients, overall virologic failure rates were numerically lower for the 12-week SOF/VEL with ribavirin (15% (2/13) compared to SOF/VEL 12-week and 24-week treatment arms. There are insufficient data to determine the impact of HCV NS5A RAPs in genotype 3 subjects with decompensated cirrhosis.

Based on review of the data from the Phase 3 clinical trials, baseline screening for RAPs is not indicated.

Cross-resistance
Both SOF and VEL were fully active against substitutions associated with resistance to other classes of direct-acting antivirals with different mechanisms of action, such as NS5B non-nucleoside inhibitors and NS3 protease inhibitors. Efficacy of SOF/VEL has not been established in patients who have previously failed treatment with other regimens that include an NS5A inhibitor.

## 7. Clinical/Statistical-Efficacy

The clinical review was conducted by Drs. Prabha Viswanathan and Sarah Connelly with secondary review provided by Dr. Kim Struble who also served as the CDTL. The Biometrics review was conducted by Dr. Karen Qi with secondary review provided by Dr. Thamban Valappil and supervisory review provided by Dr. Dionne Price.

The primary endpoint for the four pivotal clinical trials, ASTRAL1- 4 was SVR using the COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0 (with a LLOQ < 15 IU/mL) measured at 12 weeks after completion of therapy. Clinical trial designs for the pivotal clinical trials are summarized below. Also refer to the statistical review for the justification of the non-inferiority margins for ASTRAL 2 and 3. Note that no approved treatment options were available for the ASTRAL 4 population at the time ASTRAL 4 was initiated; thus an active control was not feasible.

**Table 4 Pivotal Clinical Trials ASTRAL 1- 4**

| Trial | Population | SOF/VEL and Comparator Arms (Number of Subjects Treated) | Primary endpoint analyses |
|---|---|---|---|
| ASTRAL-1 | Genotype 1, 2, 4, 5, and 6<br>TN and TE, without cirrhosis or with compensated cirrhosis | SOF/VEL 12 weeks (624)<br>Placebo 12 weeks (116) | Superior to pre-specified threshold 85% |
| ASTRAL-2 | Genotype 2<br>TN and TE, without cirrhosis or with compensated cirrhosis | SOF/VEL 12 weeks (134)<br>SOF + RBV 12 weeks (132) | NI testing with 10% NI margin and superiority testing if NI is demonstrated |
| ASTRAL-3 | Genotype 3<br>TN and TE, without cirrhosis or with compensated cirrhosis | SOF/VEL 12 weeks (277)<br>SOF + RBV 24 weeks (275) | NI testing with 10% NI margin and superiority testing if NI is demonstrated |
| ASTRAL-4 | Genotype 1, 2, 3, 4, 5, and 6<br>TN and TE, with CP class B decompensated cirrhosis | SOF/VEL 12 weeks (90)<br>SOF/VEL + RBV 12 weeks (87)<br>SOF/VEL 24 weeks (90) | Superior to assumed spontaneous HCV clearance rate of 1% |

TN: treatment-naïve subjects; TE: Treatment-experienced subjects (including those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor); SOF=sofosbuvir, RBV=ribavirin, CP=Child-Pugh

ASTRAL 1 (n=740 randomized 5:1) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multinational trial of SOF/VEL for 12 weeks compared to placebo. The patient population consisted of TN and TE subjects without cirrhosis or with compensated cirrhosis and GTs 1, 2, 4, 5, and 6 infection. All subjects with GT5 received SOF/VEL for 12 weeks and were not randomized because of the small size of the HCV GT5 population. Nineteen percent of subjects were classified as cirrhotic and 32% were treatment-experienced (TE). TE was defined as prior treatment failure to a regimen containing IFN with or without RBV that was completed at least 8 weeks prior to baseline/Day 1. Subjects with prior exposure to SOF, other nucleotide

analogue HCV NS5B inhibitors, or any HCV NS5A inhibitor were excluded. Overall, 99% of subjects achieved SVR12. No subjects in the placebo group achieved SVR12.

The SVR12 rates for SOF/VEL for 12 weeks also exceeded the protocol specified threshold of 85%. No subjects with HCV GT2, 4, 5, or 6 experienced virologic failure or relapse and only two GT 1 patients relapsed as described above. The data support the efficacy of SOF/VEL for 12 weeks for all groups evaluated. Screening for baseline RAPs will not be recommended in product labeling because SVR12 rates are already maximized in this population.

ASTRAL 2 is an ongoing Phase 3, randomized, open-label, active-controlled trial of SOF/VEL for 12 weeks compared to SOF/ribavirin for 12 weeks conducted in the US and Puerto Rico. ASTRAL 2 is designed as a non-inferiority trial with a margin of 10%. The patient population consisted of TN and TE subjects, as described for ASTRAL 1 without cirrhosis or with compensated cirrhosis and GT 2 infection. Fourteen percent of subjects were classified as cirrhotic and 15% were treatment-experienced. The trial met its primary endpoint; key efficacy findings are summarized below and support use of SOF/VEL for 12 weeks in this population.

**Table 5 ASTRAL 2: SVR12 Outcomes in HCV GT2 Subjects**

| | **SOF/VEL12 Weeks (N=134)** | **SOF/RBV 12 Weeks (N=132)** |
|---|---|---|
| SVR12 | 99% (133/134) | 94% (124/132) |
| | Treatment difference +5.2%; 95% confidence interval: (+0.2% to +10.3%) | |
| Outcome for subjects without SVR | | |
| On-Treatment Virologic Failure | 0/134 | 0/132 |
| Relapse[a] | 0/133 | 5% (6/132) |
| Other[b] | 1% (1/134) | 2% (2/132) |

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the last on-treatment assessment.
b. Other includes subjects who did not achieve SVR12 and did not meet virologic failure criteria

ASTRAL 3 is an ongoing Phase 3, randomized, open-label, multinational, active-controlled trial, designed as a non-inferiority trial with a 10% margin comparing 12 weeks of SOF/VEL to 24 weeks of SOF/RBV. The patient population consisted of TN and TE subjects without cirrhosis or with compensated cirrhosis and GT 3 infection. Thirty percent of subjects were classified as cirrhotic and 26% were treatment-experienced. The key efficacy findings are summarized below.

**Table 6: ASTRAL 3: SVR12 Outcomes in HCV GT 3 Subjects**

| | **SOF/VEL12 Weeks (N = 277)** | **SOF + RBV 24 Weeks (N = 275)** |
|---|---|---|
| SVR12 | 95% (264/277) | 80% (221/275) |
| | Treatment difference +14.8%; 95% confidence interval (+9.6% to +20.0%) | |
| Outcome for subjects without SVR | | |
| On-Treatment Virologic Failure | 0/277 | <1% (1/275) |
| Relapse[a+] | 4% (11/276) | 14% (38/272) |
| Other[b] | 1% (2/277) | 5% (15/275) |

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the last on-treatment assessment.
+ One relapser was a reinfection with GT1a
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

Per Dr. Viswanathan's review, there is no clear pattern among baseline disease characteristics which helps identify patients who are most likely to fail treatment. The only characteristic shared by nearly all of the 10 subjects is baseline viral load > 800,000 IU/mL, but 70% of ASTRAL-3 subjects overall had baseline viral load > 800,000 IU/mL and 94% went on to achieve SVR12 with SOF/VEL. None of the 10 subjects who relapsed had detectable NS5B RAPs at baseline or failure, however the development of the Y93H RAP in each of the 10 relapsers is a concern because Y93H confers high level resistance to other NS5A inhibitors.

Results by prior treatment and cirrhosis status are provided in the following table.

**Table 7 ASTRAL 3: SVR12 by Prior Treatment and Presence/Absence of Compensated Cirrhosis in Subjects with HCV GT3**

| | SOF/VEL12 Weeks | | SOF + RBV 24 Weeks[a] | |
|---|---|---|---|---|
| | Treatment-Naïve (N=206) | Treatment-Experienced (N=71) | Treatment-Naïve (N=201) | Treatment-Experienced (N=69) |
| Without cirrhosis | 98% (160/163) | 94% (31/33)[b] | 90% (141/156) | 71% (22/31) |
| With compensated cirrhosis | 93% (40/43) | 89% (33/37) | 73% (33/45) | 58% (22/38) |

a. Five subjects with missing cirrhosis status in the SOF + RBV 24 Week group were excluded from this subgroup analysis.
b. One treatment experienced subject without cirrhosis treated with EPCLUSA had genotype 1a HCV infection at failure indicating HCV re-infection and is therefore excluded from this analysis.

From the clinical perspective, the data reviewed were not sufficient to consider the addition of RBV to SOF/VEL 12 weeks in HCV GT3 subjects with compensated cirrhosis at this time. The clinical decision to not consider the addition of RBV in HCV GT3 subjects with compensated cirrhosis is based on the following assessments. Please also refer to the clinical, statistical and virology reviews for further details on the exploratory analyses conducted.

- Over 90% of subjects achieved SVR12 in ASTRAL 3 without RBV and a consideration to add RBV to all compensated cirrhotics introduces RBV-associated safety concerns that are likely unnecessary for the majority of subjects.
- The only available clinical trial data evaluating SOF/VEL + RBV compared to SOF/VEL come from a small cohort in Phase 2 trial GS-US-342-0109. Although the SVR12 rates were higher in the SOF/VEL+RBV group [96% (25/26)] compared to the SOF/VEL [89% (23/26)], the sample size was small and the difference was not statistically significant [treatment difference -8% and 95% CI: -28%, 10%].The RBV label includes a box warning for hemolytic anemia and several Warnings and Precautions including risk of hepatic failure and death, severe hypersensitivity reactions and pulmonary disorders. In Phase 2 trial GS-US-342-0109, more subjects in the SOF/VEL + RBV group had adverse drug reactions compared to the subjects in the SOF/VEL group (69% vs 46%) and more subjects in the SOF/VEL+ RBV group had adverse events (all cause, all grade) compared to subjects in the SOF/VEL group (88% vs 77%).
- Based on limited data the use of RBV does not prevent the emergence of the Y93H NS5A substitution

- In Phase 2 trial GS-US-342-0109, the single patient who relapsed in the SOF/VEL + RBV group and two of the three patients who relapsed in the SOF/VEL group developed an Y93H resistance substitution.
- In ASTRAL 4, two GT 3 failure patients also had the NS5A resistance substitution Y93H and either M28V or S38P at failure.

In sum, from a clinical perspective, the available data do not conclusively demonstrate the benefit of adding RBV to a 12-week regimen of SOF/VEL. In addition, the risk for developing serious RBV-associated toxicities in GT3 patients with compensated cirrhosis does not balance any theoretorical benefit at this time. A PMR to determine if the addition of RBV improves SVR12 rates in HCV GT3 subjects with compensated cirrhosis will be issued to address this situation. I agree with the review staff that these data are needed to determine if revisions to the Dosage and Administration section of the label are warranted following review of the PMR trial. Gilead agreed to conduct a trial in the HCV GT 3 compensated cirrhotic population to evaluate SOF/VEL + RBV versus SOF/VEL each for 12 weeks (b) (4)

ASTRAL 4 is an ongoing Phase 3, open-label trial in TN and TE subjects with HCV GT 1-6 and Child-Pugh B decompensated cirrhosis at screening. Subjects were randomized to receive SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks or SOF/VEL for 24 weeks. Key efficacy findings are summarized below. Overall, the SVR12 rate was 83%, 94% and 86% for the SOF/VEL 12 week, SOF/VEL + RBV 12 week and SOF/VEL 24 week regimens, respectively.

**Table 8: ASTRAL 4 Outcomes by HCV Genotype**

| | SOF/VEL 12 Weeks | SOF/VEL + RBV 12 Weeks | SOF/VEL 24 Weeks |
|---|---|---|---|
| **GT1** | | | |
| SVR12 rate [95% CI][1] | 88.2% (60/68) [78.1%, 94.8%] | 95.6% (65/68) [87.6%, 99.1%] | 91.5% (65/71) [82.5%, 96.8%] |
| Not achieving SVR12 | | | |
| On-trt virologic failure | 0% (0/68) | 0% (0/68) | 0% (0/71) |
| Relapse | 7.4% (5/68) | 1.5% (1/67) | 4.2% (3/71) |
| Other | 4.4% (3/68) | 2.9% (2/68) | 4.2% (3/71) |
| **GT2** | | | |
| SVR12 rate [95% CI][1] | 100% (4/4) [39.8%, 100%] | 100% (4/4) [39.8%, 100%] | 75.0% (3/4) [19.4%. 99.4%] |
| Not achieving SVR12 | | | |
| On-trt virologic failure | n/a | n/a | n/a |
| Relapse | n/a | n/a | n/a |
| Other | n/a | n/a | 25.0% (1/4) |
| **GT3** | | | |
| SVR12 rate [95% CI][1] | 50.0% (7/14) [23.0%, 77.0%] | 84.6% (11/13) [54.6%, 98.1%] | 50.0% (6/12) [21.1%, 78.9%] |
| Not achieving SVR12 | | | |
| On-trt virologic failure | 0% (0/14) | 7.7% (1/13) | 8.3% (1/12) |
| Relapse | 42.9% (6/14) | 8.3% (1/12) | 40.0% (4/10) |
| Other | 7.1% (1/14) | 0% (0/13) | 8.3% (1/12) |
| **GT4** | | | |
| SVR12 rate [95% CI][1] | 100% (4/4) [39.8%, 100%] | 100% (2/2) [15.8%, 100%] | 100% (2/2) [15.8%, 100%] |
| **GT6** | | | |
| SVR12 rate [95% CI][1] | n/a | n/a | 100% (1/1) [2.5%, 100%] |

[1]Based on Clopper-Pearson method
Source: Analysis Performed by Dr. Karen Qi, Statistics Reviewer

A limitation of ASTRAL 4 is the small sample size for HCV GTs 2, 4, 5 and 6. Although high SVR12 rates were seen for regimens without RBV for HCV GTs 2, 4, 5 and 6 and the possibility exists that RBV is not needed for some of these subjects, given the small sample sizes and wide 95% CI, the review team agreed with the Applicant's approach and dosage recommendations to include RBV for HCV GTs 2, 4, 5, and 6. The feasibility of conducting a larger pangenotypic trial in patients with decompensated cirrhosis to determine if RBV is needed for all genotypes is not likely given the limited numbers of subjects in these subgroups.

## 8. Safety

Over 3,000 subjects and patients were exposed to SOF/VEL in 12 studies/clinical trials that comprise the safety data base. The size of the safety data base for both products is adequate to assess the safety of SOF/VEL for the proposed indication, including the dosage regimen, duration of treatment, and patient populations. Phase 3 trials evaluated over 1300 patients treated at the proposed dose and duration of SOF/VEL, which meets FDA's recommendation for a 1000-1500 patient safety database for treatment of patients with compensated liver disease, with additional safety data to support treatment of patients with decompensated liver disease.

Safety analyses primarily focused on pooled data from ASTRAL 1, ASTRAL 2, and ASTRAL 3 to form the integrated summary of safety (ISS) population. Pooling of these studies was done because the trial design and conduct of these three studies were similar and the trial populations were comparable in terms of underlying disease severity. Data from ASTRAL 4 were analyzed separately because the review team anticipated that the frequency and severity of AEs may differ in this decompensated cirrhotic population.

Section 5 in product labeling, Warnings and Precautions, contains wording related to serious symptomatic bradycardia when SOF is coadministered with amiodarone and another HCV DAA such as daclatasvir or simeprevir. Although there were no cases of serious bradycardia with SOF/VEL, coadministration of amiodarone with SOF/VEL is not recommended.

Regarding hepatic safety, the Applicant convened an independent adjudication committee (IAC) to review possible cases of DILI. In addition, a thorough hepatic safety review was conducted by the clinical reviewers and the conclusions reached by FDA reviewers were comparable to those of the IAC.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates (adverse events assessed as causally related by the investigator) observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug in the same class and may not reflect the rates observed in practice. (b) (4):

Adverse reactions of all grades, observed in greater than or equal to 5% of patients receiving 12 weeks of treatment with SOF/VEL in ASTRAL 1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%); most had an adverse reaction of mild severity (Grade 1). With the exception of asthenia, each of these adverse reactions occurred more frequently in subjects treated with placebo compared to subjects treated with SOF/VEL (asthenia: 3% versus 5% for the placebo and SOF/VEL groups, respectively).

In ASTRAL 2 and ASTRAL 3, the adverse reactions observed in patients treated with SOF/VEL were consistent with those observed in ASTRAL 1. Irritability was also observed in greater than or equal to 5% of subjects treated with SOF/VEL in ASTRAL 3.

In ASTRAL 4, the most common adverse reactions, all grades with frequency of 10% or greater in patients who received SOF/VEL with RBV for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%); most of these adverse reactions were mild to moderate in severity.

Although rash events in SOF/VEL-treated patients occurred below the 5% ADR cutoff for the ASTRAL 1-3 ISS population and below the 10% ADR cutoff for the ASTRAL 4 population proposed in Section 6 of the label, the review team considered the totality of the data supportive to recommend inclusion of rash events in labeling. These data include: (1) treatment-related rash reported in a numerically higher percentage of SOF/VEL subjects (3%) compared to placebo subjects (1%) in the ISS population supporting a causal association between rash and SOF/VEL treatment, (2) treatment-related rash reported in 3% SOF/VEL-treated subjects in the absence of RBV and in 5% SOF/VEL+RBV-treated subjects in ASTRAL 4, and (3) rash events reported in the current Sovaldi and Harvoni labels which contain SOF.

Although depression events in SOF/VEL-treated patients occured below the 2% ADR cutoff for the ASTRAL 1-3 ISS population and below the 10% ADR cutoff for the ASTRAL 4 population proposed in Section 6 of the label, the review team considered the totality of the data supportive to recommend inclusion of depression events in the Less Common Adverse Reactions Reported in Clinical Trials section. These data include: (1) depression events only occuring in SOF-containing treatment arms, including SOF/VEL arm, of ASTRAL 1-3 ISS population and none occurring in the placebo arm, (2) depression events reported in the current Sovaldi and Harvoni labels which contain SOF.

Regarding SAEs in the ISS population, no specific drug-related safety concern has been identified from the range of SAEs reported with rare frequency in ASTRAL 1, 2, and 3. There was no clustering of events to suggest a pattern. All narratives were reviewed which did not uncover new concerns. In ASTRAL 4, SAEs considered related to study treatment by the investigator occurred in 2 subjects (0.7%): dyspnea related to RBV (01657-64124) and hepatorenal syndrome (HRS)/hypertension (HTN)/peritonitis/ sepsis related to SOF/VEL (03055-64017). Dyspnea is a known RBV-associated adverse reaction and our clinical team agrees with the investigator's assessment. Please see Section 8.5.1 Hepatotoxicity in the clinical review document for further discussion of Subject 03055-64017. This latter case was reviewed by the IAC and assessed as unlikely related to SOF/VEL-containing treatment.

Laboratory Abnormalities

*Hemoglobin:* Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% subjects treated with SOF/VEL + RBV for 12 weeks, respectively, in ASTRAL-4 (subjects with decompensated cirrhosis). RBV was permanently discontinued in 17% of subjects treated with SOF/VEL. One percent of subjects treated with SOF/VEL in ASTRAL 1-3 had decreases in hemoglobin to less than 10 g/dL.

*Lipase Elevations:* In ASTRAL 1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with SOF/VEL and placebo for 12 weeks, respectively; and in 6% and 3% of subjects treated with SOF/VEL in ASTRAL 2 and ASTRAL 3, respectively.

In ASTRAL 4, lipase was assessed when amylase values were ≥1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with SOF/VEL + RBV for 12 weeks.

*Creatine Kinase:* In ASTRAL 1, 2 and 3 clinical trials, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1-2%, of patients compared to none in the placebo arm of ASTRAL 1. In the Phase 3 trial with decompensated cirrhosis patients, (ASTRAL 4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of patients treated with SOF/VEL + RBV for 12 weeks.

*Indirect Bilirubin:* Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects in ASTRAL 5 treated with SOF/VEL 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 SOF/VEL.

**Deaths**

In the ISS population, a total of 6 deaths occurred through the time of NDA submission; 3 were on treatment and 3 occurred more than 3 months after completing treatment. Three of the events occurred in SOF/VEL arm and 3 in SOF+RBV arm. After review of the data, it was determined that the deaths were related to underlying medical conditions and one death was a result of a violent crime.

Ten total deaths were reported in ASTRAL 4. None of the 10 deaths were considered treatment-related by the investigator nor by the clinical reviewers and I concur with all the assessments. Causes of death were associated with underlying decompensated liver disease and other comorbidities and were not considered related to study treatment.

Safety update reports were received two months after the NDA was submitted. All data were reviewed. New events in the ISS population were considered unrelated to study medication. No new events were reported in ASTRAL 4.

**9. Advisory Committee Meeting**

The application was not presented before the Antiviral Drugs Advisory Committee because SOF is already marketed and VEL is the fifth drug in the class of NS5A inhibitors. Further, a preliminary review of the NDA, including labeling did not reveal any significant clinical or safety issues that would benefit from an advisory committee discussion.

**10. Pediatrics**

The Applicant submitted a waiver for pediatric clinical trials for patients less than three years of age and a deferral for greater than or equal to three years of age. Their requests are consistent with other DAA NDAs and were accepted by the PeRC.

The Applicant plans to conduct two trials as part of their SOF/VEL pediatric development plan. (b) (4) The Division is in agreement with the pediatric study plans.

**11. Other Relevant Regulatory Issues**

Recommended Postmarketing Requirements include the following to which the Applicant agreed:

Required Pediatric Assessments under PREA

PMR

3092-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOF/VEL in pediatric patients 12 through less than 18 years of age with chronic hepatitis C infection

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| Final Protocol Submission: | 06/2016 |
| Study/Trial Completion: | 03/2019 |
| Final Report Submission: | 09/2019 |

3092-2 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of SOF/VEL in pediatric patients 3 through less than 12 years of age with chronic hepatitis C infection

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| Final Protocol Submission: | 06/2016 |
| Study/Trial Completion: | 10/2020 |
| Final Report Submission: | 04/2021 |

Additional PMRs

3092-3 Conduct a drug interaction study to evaluate the interaction between SOF/VEL and atorvastatin.

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| Final Protocol Submission: | 08/2016 |
| Trial Completion: | 12/2016 |
| Final Report Submission: | 05/2017 |

Results from the rosuvastatin drug interaction study indicate that VEL can significantly increase the concentration of substrates of organic anion transporting polypeptides (OATP) and breast cancer resistance protein (BCRP), such as atorvastatin. Although the results from the rosuvastatin drug interaction study cannot be directly extrapolated to atorvastatin, there is a mechanistic basis for a potentially clinically significant interaction with atorvastatin (a commonly used statin). Based on the evidence from *in vitro* studies, LDV and VEL may have similar drug interaction potential for inhibition of OATP1B and BCRP transport, so the potential exists for SOF/VEL FDC to increase atorvastatin exposures, leading to serious adverse events. Thus, a PMR is needed to study the interaction between sofosbuvir/velpatasvir and atorvastatin in order to derive appropriate dosing recommendations for concomitant use.

3092-4 Submit the final clinical study report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5), titled "A Phase 3, Open-label Study to Investigate the Efficacy and Safety of Sofosbuvir/GS-5816 Fixed Dose Combination for 12 weeks in Subjects with Chronic Hepatitis C Virus (HCV) and Human immunodeficiency Virus (HIV)-1 Coinfection," to provide safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.

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| Final Protocol Submission: | 04/2015 |
| Trial Completion: | 08/2016 |
| Final Report Submission: | 12/2016 |

Study GS-US-342-1202 (ASTRAL 5) is an ongoing trial evaluating the safety and efficacy of SOF/VEL in HCV/HIV coinfected subjects. Submission of the final study report and datasets are identified as a PMR in order to provide safety data in subjects receiving SOF/VEL concurrently with HIV antiretroviral therapy and to provide dosing recommendations for HCV/HIV-1 co-infected patients.

3092-5 Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with SOF/VEL to determine if the addition of RBV improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure.

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| Final Protocol Submission: | 03/2016 |
| Trial Completion: | 06/2017 |
| Final Report Submission: | 06/2018 |

Data from a clinical trial evaluating the SOF/VEL versus SOF/VEL + ribavirin will help inform whether the addition of ribavirin can mitigate the risk of treatment failure and the development of resistance-associated polymorphisms that limit future treatment options.

3092-6 Collect, analyze, and submit data from the HCV infected subjects with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with SOF/VEL regimen to obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

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| Final Protocol Submission: | 08/2016 |
| Trial Completion: | 05/2018 |
| Final Report Submission: | 05/2019 |

A SOF/VEL + RBV 12 week regimen is recommended for CHC treatment in patients with decompensated cirrhosis based on ASTRAL 4 data. Despite limited numbers of patients with baseline CPT C cirrhosis enrolled in the trial, the review team supported extending the SOF/VEL+ RBV 12 Week dosing recommendation to both the CPT B and C populations. This recommendation is based upon consideration of decompensated cirrhosis as a spectrum of disease progression. We are requiring data submission postapproval evaluating the safety of SOF/VEL-containing regimen in the population with decompensated CPT C cirrhosis because of the small overall number of subjects with baseline CPT C cirrhosis in ASTRAL 4.

PMC

3092-7 Collect, analyze, and submit data on subjects with cirrhosis including decompensated cirrhosis who achieved SVR following treatment with a SOF/VEL-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

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| Final Protocol Submission: | 08/2015 |
| Trial Completion: | 01/2022 |
| Final Report Submission: | 01/2023 |

The goal of the trial will be (1) obtain follow-up data in patients who have attained SVR12 in order to assess durability of response over 5 years, and (2) to evaluate the impact of SVR12 on important clinical endpoints such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation.

3092-8 Conduct site-directed mutant phenotypic analyses of sofosbuvir against an HCV genotype 3 replicon with the following substitutions: NS5B_L314F, NS5B_L314I, and NS5B_L314P.

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| Final Protocol Submission: | N/A |
| Trial Completion: | N/A |
| Final Report Submission: | 02/2017 |

## 12. Labeling

Final negotiations related to labeling have been completed.

## 13. Decision/Action/Risk Benefit Assessment

Gilead Sciences, Inc. provided substantial evidence of effectiveness as required by law under the FDC Act to support approval of SOF/VEL for HCV GTs 1, 2, 3, 4, 5 and 6 in adult patients with chronic hepatitis C viral infection. Efficacy was demonstrated in TN and TE patients without cirrhosis and with compensated and decompensated cirrhosis. SVR12 rates ranged from 83-100% depending on the Phase 3 trial regimen, HCV GT, and cirrhosis status. Due to lower rates of SVR in subjects with GT 3 compensated cirrhosis, the Applicant will be asked to conduct a post-marketing clinical trial to examine whether addition of RBV to SOF/VEL will improve SVR rates, which would reduce the risk of virologic failure and drug resistance emergence.

This combination of SOF/VEL was shown to be well-tolerated with a manageable safety profile. Although the safety data base did not have any cases of bradycardia, safety considerations related to bradycardia in the setting of administration of amiodarone will be described in warnings and precautions in labeling for SOF/VEL because of cases seen with other DAAs and amiodarone. Certain drug-drug interactions are complex, such as use of SOF/VEL with PPIs, but product labeling adequately conveys how to manage this issue.

In sum, I am in agreement with the conclusions of the multidisciplinary review team that the benefit-risk assessment favors approval of SOF/VEL for patients with CHC GTs 1- 6. I am confidant that with increased testing for chronic hepatitis C viral infection, along with wider access to highly efficacious, well-tolerated regimens that less morbidity, lower mortality and more cures of hepatitis C worldwide will be realized.

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/s/

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DEBRA B BIRNKRANT
06/16/2016