

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208341Orig1s000**

**OFFICE DIRECTOR MEMO**

Deputy Office Director Decisional Memo

<b>Date</b>	(electronic stamp)
<b>From</b>	John Farley, MD, MPH
<b>Subject</b>	Deputy Office Director Decisional Memo
<b>NDA#</b>	208341
<b>Applicant Name</b>	Gilead Sciences
<b>Date of Submission</b>	October 28, 2015
<b>PDUFA Goal Date</b>	June 28, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Epclusa / [sofosbuvir (SOF) and velpatasvir (VEL)]
<b>Dosage Forms / Strength</b>	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
<b>Applicant Proposed Indication(s)/Populations</b>	Treatment of adult patients with chronic hepatitis C virus infection
<b>Action:</b>	Approval
<b>Approved Indication(s)/Populations</b>	Indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection: <ul style="list-style-type: none"> <li>• without cirrhosis or with compensated cirrhosis</li> <li>• with decompensated cirrhosis for use in combination with ribavirin</li> </ul>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
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; Dr. Fang Li supervised by Dr. Jeffrey Florian
DDMAC	Dr. Kemi Asante
OSI	Dr. Antoine El Hage
OSE/DMEPA	Dr. Mónica Calderón
OPM/DMPP	Dr. Morgan Walker
OSE/DRISK	Dr. Erin Hachey
CDTL Review	Dr. Kim Struble
Division Director Review	Dr. Debra Birnkrant

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

## 1. Benefit-Risk Assessment

### Benefit-Risk Summary and Assessment

This New Drug Application, submitted by Gilead Sciences (the applicant), contains information to support the approval of Epclusa for the treatment of chronic hepatitis C virus (HCV) infection genotypes (GTs) 1,2,3,4,5, and 6 in adults. Epclusa is comprised of sofosbuvir (SOF), a previously approved NS5B nucleotide analog polymerase inhibitor, and velpatasvir (VEL), a new HCV NS5A inhibitor, co-formulated as a fixed dose combination tablet to be taken once daily. For patients with decompensated cirrhosis, Epclusa is to be administered with ribavirin (RBV).

Chronic HCV infection is a serious disease that causes debilitating symptoms and is life-threatening. Direct acting antivirals (DAA) are a major clinical advance, and all oral, interferon-free regimens are now standard of care for chronic HCV. All patients with chronic HCV would benefit from new therapeutic options that are efficacious and well-tolerated. This is particularly the case for patients with GT2, 5, and 6, as there is only one DAA regimen currently approved. Patients with decompensated cirrhosis and GT 2, 4, 5, and 6 represent an unmet need population as there are no DAA regimens currently approved.

The applicant provided four adequate and well-controlled trials as evidence of efficacy. The trial populations varied by HCV GT and cirrhosis status. The primary efficacy endpoint for all trials was sustained virologic response 12 weeks after the end of treatment (SVR12) considered a virologic cure. I concur with the review team, CDTL, and Division Director that the ASTRAL- 1, 2, and 3 trials provide substantial evidence of efficacy of SOF/VEL for 12 weeks for the treatment of chronic HCV in patients with GTs 1-6 without cirrhosis or with compensated cirrhosis. I concur with the review team, CDTL, and Division Director that the ASTRAL-4 trial provides substantial evidence of efficacy of SOF/VEL for 12 weeks in combination with RBV for the treatment of chronic HCV in patients with GTs 1-6 with decompensated cirrhosis. I agree with their conclusion that the SOF/VEL 12 week regimen in combination with RBV resulted in the highest SVR12 rate among the regimens studied in ASTRAL-4 and should be recommended for this difficult to treat population regardless of GT.

I concur with the Division Director and CDTL that SOF/VEL with or without RBV demonstrated an overall favorable safety profile and there was no evidence in the clinical trials that the known RBV associated safety issues are exacerbated by SOF/VEL. Risks can be adequately addressed in labeling. Labeling will include a statement in Dosage and Administration that no dosage recommendation can be given for patients with severe renal impairment or ESRD due to high exposures of a SOF metabolite. The SOF/VEL + RBV regimen will be contraindicated in patients for whom RBV is contraindicated. The SOF/VEL label will include a Warning regarding amiodarone co-administration. The label describes potential drug interactions and recommends against co-administration when appropriate.

In summary, I agree with the review team, the CDTL, and the Division Director that the approval of Epclusa for treatment of adults with chronic

HCV GT 1,2,3,4,5,and 6 infection is fully supported by the available evidence of safety and efficacy. I agree that the appropriate regimens to recommend in labeling are as follows:

Patients without cirrhosis or with compensated cirrhosis (Child-Pugh A): Epclusa for 12 weeks

Patients with decompensated cirrhosis (Child-Pugh B or C): Epclusa + ribavirin for 12 weeks

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<b>Analysis of Condition</b>	<ul style="list-style-type: none"> <li>Chronic HCV causes chronic inflammation of the liver. While HCV is initially asymptomatic, untreated HCV infection can lead to cirrhosis, hepatocellular carcinoma, liver failure, and death. Once cirrhosis occurs, the 5 year survival is approximately 50%.</li> <li>3-5 million people in the U.S. are chronically infected with HCV, and 170 million people are infected world-wide. There are at least seven distinct HCV GTs. The major GTs among U.S. patients are GT1, 2, 3, and 4, with GT1 being the most common (72%).</li> </ul>	<p>Chronic HCV infection is a serious disease that causes debilitating symptoms and is life-threatening.</p> <p>Chronic HCV infection is a major public health concern in the U.S. and world-wide.</p>
<b>Current Treatment Options</b>	<ul style="list-style-type: none"> <li>DAA's are a major clinical advance, and all oral, interferon-free regimens are now standard of care for chronic HCV. Treatment can result in SVR12, considered a virologic cure, in greater than 90% of patients without cirrhosis or with compensated cirrhosis. SVR12 rates are lower for patients with decompensated cirrhosis and/or other risk factors, and regimens for higher risk patients may be of longer duration or require the addition of ribavirin (RBV).</li> <li>Only one DAA regimen is approved for treatment of HCV GT2, 5, and 6.</li> <li>For patients with decompensated cirrhosis, there are newly approved DAA regimens for GT1 and 3, but no approved DAA regimens for GT 2, 4, 5, and 6.</li> </ul>	<p>All patients with chronic HCV would benefit from new therapeutic options that are efficacious and well-tolerated. This is particularly the case for patients with GT2, 5, and 6, as there is only one DAA regimen currently approved.</p> <p>Patients with decompensated cirrhosis and GT 2, 4, 5, and 6 represent an unmet need population as there are no DAA regimens currently approved.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<p>The applicant provided four adequate and well-controlled trials as evidence of efficacy. The trial populations varied by HCV GT and cirrhosis status. Patients with prior NS5A or NS5B inhibitor exposure were excluded. The primary efficacy endpoint for all trials was SVR12 or virologic cure.</p> <ul style="list-style-type: none"> <li>• <u>ASTRAL-1</u> randomized HCV GT1, 2, 4, and 6 subjects with and without compensated cirrhosis to receive either 12 weeks of SOF/VEL or placebo. Subjects infected with HCV GT5 were assigned 12 weeks of SOF/VEL. The SVR12 rate for 12 weeks of SOF/VEL was as high as 99% in subjects infected with HCV GT1, 2, 4, 5 and 6 which was statistically superior to the pre-specified threshold of 85% (p&lt;0.001).</li> <li>• <u>ASTRAL-2</u> was an active-controlled trial conducted in HCV GT2 subjects with and without compensated cirrhosis to compare 12 weeks of SOF/VEL with the standard of care of SOF plus RBV for 12 weeks. Twelve weeks of SOF/VEL resulted in a statistically higher SVR12 rate than 12 weeks of SOF + RBV in subjects with HCV GT2 infection (99% vs. 94%, p=0.018).</li> <li>• <u>ASTRAL-3</u> was conducted in HCV GT3 subjects with and without compensated cirrhosis. The trial compared 12 weeks of SOF/VEL against an approved regimen of 24 weeks of SOF plus RBV. The 12-week SOF/VEL treatment was statistically superior to the 24-week SOF + RBV treatment in SVR12 rate among subjects infected with HCV GT3 (95% vs. 80%, p&lt;0.001).</li> <li>• A pooled analysis of ASTRAL-1,2, and 3 shows an adequate number of patients with the six major GTs: GT1- 328, GT2-238, GT3-277, GT4-116, GT5-35, and GT6-41. SVR12 rates ranged from 95% (GT3) to 100% (GT4 and 6). Prior interferon/RBV treatment experience did not impact SVR12 rates. For GT3 patients in ASTRAL-3, compensated cirrhosis, PR treatment experience, and</li> </ul>	<p>I concur with the review team, CDTL, and Division Director that the ASTRAL- 1, 2, and 3 trials provide substantial evidence of efficacy of SOF/VEL for 12 weeks for the treatment of chronic HCV in patients with GTs 1-6 without cirrhosis or with compensated cirrhosis. While the numbers of patients in some subgroups were low, an adequate number of patients from each of the six GTs were included in the clinical trials to support this conclusion. SVR12 rates for GT1,2,4,5,and 6 were similar for patients with compensated cirrhosis and without cirrhosis at baseline. In ASTRAL-3, SVR12 rates for GT3 patients with compensated cirrhosis were numerically lower than for patients without cirrhosis, but I have concluded that the SOF/VEL for 12 week regimen is appropriate for GT3 patients with compensated cirrhosis. I discuss this further below.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>baseline resistance associated polymorphisms were associated with lower SVR12 point estimates.</p> <ul style="list-style-type: none"> <li>• Compensated cirrhotics in ASTRAL-1, 2, and 3: <ul style="list-style-type: none"> <li>○ In ASTRAL-1, 19% of patients had compensated cirrhosis at baseline. SVR12 rates were similar compared with patients without cirrhosis for all GTs. The number of patients with compensated cirrhosis was small for a number of GTs: GT1-73, GT2-10, GT4-27, GT5-5, GT6-6.</li> <li>○ In ASTRAL-2, 34 patients (14%) had compensated cirrhosis at baseline. SVR12 rates for the SOF/VEL 12 week arm were similar compared with patients without cirrhosis.</li> <li>○ In ASTRAL-3, 163 patients (30%) had compensated cirrhosis at baseline. For the SOF/VEL 12 week arm, the SVR12 rate was 91% compared with 97% for patients without cirrhosis. The review team considered a recommendation by the Clinical Virology Reviewer to add a footnote in the Dosage and Administration section of the Prescribing Information stating “SOF/VEL + RBV for 12 weeks can be considered for GT3 patients with compensated cirrhosis”. The rationale was that relapse rates may be reduced for GT3 patients with compensated cirrhosis who could take RBV. The justification was a Phase 2 trial (GS-US-342-0109) that enrolled 52 patients and reported a higher SVR12 rate for patients treated with SOV/VEL plus RBV that was not statistically significant. In addition, as cirrhosis is a continuum, the Reviewer opined that data from ASTRAL-4 should be considered. ASTRAL-4 reported higher SVR12 rates for GT1 and GT3 patients with decompensated cirrhosis treated with RBV, but there was not statistical superiority for RBV containing arms compared with the SOF/VEL alone</li> </ul> </li> </ul>	<p>I concur with the Clinical Reviewer, Statistical Reviewer, CDTL, and Division Director that the SOF/VEL for 12 week regimen is appropriate for GT3 patients with compensated cirrhosis, and the data are insufficient at this time to recommend in labeling the addition of RBV to 12 weeks of SOF/VEL for GT3 patients with compensated cirrhosis. While SVR12 rates for GT3 patients with compensated cirrhosis were numerically lower than for patients without cirrhosis, the Phase 2 trial and ASTRAL-4 data cited as justification by the Clinical Virology Reviewer do not demonstrate a statistically significant difference in SVR12 rates for patients treated with SOF/VEL plus RBV. From a risk/benefit perspective, over 90% of GT3 patients with compensated cirrhosis achieved SVR12 treated with a 12 week SOF/VEL regimen without RBV. Adding RBV would carry with it the risks of RBV associated adverse effects that would be unnecessary for the majority of patients. However, I agree with all that further data would be very helpful to inform this challenging risk benefit issue in the future. I concur with the review team decision to issue a PMR to conduct a trial to determine if the</p>

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	<p>arm.</p> <ul style="list-style-type: none"> <li>• With respect to baseline NS5A polymorphisms, there were two virologic failures in GT1 patients and the impact of baseline NS5A polymorphisms could not be assessed. For GT2, 4, 5, and 6, the SVR12 rates were 100% regardless of baseline NS5A polymorphisms. For GT3 patients in ASTRAL-3, the presence of baseline NS5A resistance associated polymorphisms increased the relapse rate and the relapse rate was highest in the small number of GT-3 patients with decompensated cirrhosis and baseline NS5A resistance associated polymorphisms. However, the other regimens approved to treat patients with HCV GT3 would also be impacted by baseline NS5A resistance associated polymorphisms, therefore, the results from baseline NS5A resistance testing would not be clinically actionable (e.g. treatment with a different regimen).</li> <li>• <u>ASTRAL-4</u> investigated three SOF/VEL-containing regimens in HCV subjects with decompensated cirrhosis. The three regimens in the trial included 12 weeks of SOF/VEL, 12 weeks of SOF/VEL plus RBV, and 24 weeks of SOF/VEL. The regimen of SOF/VEL + RBV for 12 weeks had the highest SVR12 rate (94%) compared with SOF/VEL for 12 weeks (83%) and SOF/VEL for 24 weeks (86%). The SVR12 rates of all three treatment groups were clearly superior to the assumed spontaneous rate of 1%. Pairwise comparisons in SVR12 rate among the three treatment groups were not pre-specified. However, the Statistical Reviewer’s exploratory analyses showed that the 12-week SOF/VEL + RBV arm had a nominally significantly higher SVR12 rate than 12-week SOF/VEL arm (p=0.031 Fisher’s exact test) and was not significantly different compared to the 24-week SOF/VEL arm (p=0.056 Fisher’s exact test). <ul style="list-style-type: none"> <li>○ The majority of the patients in the trial had GT1 (207</li> </ul> </li> </ul>	<p>addition of RBV improves the efficacy (SVR rate) of SOF/VEL for HCV GT3 patients with cirrhosis. The applicant has agreed to conduct this trial.</p> <p>I concur with the review team that the results of screening for NS5A resistance associated polymorphisms at baseline for patients without cirrhosis or with compensated cirrhosis would not be clinically actionable and should not be recommended in labeling.</p> <p>I concur with the review team, CDTL, and Division Director that the ASTRAL-4 trial provides substantial evidence of efficacy of SOF/VEL for 12 weeks in combination with RBV for the treatment of chronic HCV in patients with GTs 1-6 with decompensated cirrhosis. I agree with their conclusion that the SOF/VEL 12 week regimen in combination with RBV resulted in the highest SVR12 rate among the regimens studied in ASTRAL-4 and should be recommended for this difficult to treat population regardless of GT.</p> <p>Although there were very few patients with GT 2, 4, and 6 and no patients with GT5 enrolled in ASTRAL-4, I agree with the review team that</p>

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	<p>patients, 78%) and GT3 (39 patients, 15%) infections. The trial included 12 GT2, 8 GT4, 0 GT5 and 1 GT6 patients. In the SOF/VEL + RBV for 12 weeks arm, the SVR12 rates were similar for GT1-4, with small numbers for GT2 and GT4 and no GT5 or GT6 patients:</p> <p style="padding-left: 40px;">GT1: 65/68 (96%)  GT2: 4/4 (100%)  GT3: 11/13 (85%)  GT4: 2/2 (100%)  GT5: -  GT6: -</p> <ul style="list-style-type: none"> <li>○ The majority of patients (240, 90%) were classified as Child-Pugh (CPT) class B cirrhosis at baseline. In the SOF/VEL + RBV 12 week arm, the SVR12 rates were similar regardless of CPT class, but small numbers for CPT class A and CPT class C: <p style="padding-left: 40px;">CPT A: 6/6 (100%)  CPT B: 72/77 (93.5%)  CPT C: 4/4 (100%)</p> <p>With respect to baseline MELD score, the majority of patients in the SOF/VEL + RBV for 12 weeks arm had a MELD score of 10-15 and SVR12 rates were similar regardless of MELD score:</p> </li> </ul>	<p>the SOF/VEL for 12 weeks in combination with RBV regimen should be recommended in labeling for the treatment of decompensated cirrhotics in these subgroups. My rationale is as follows:</p> <ul style="list-style-type: none"> <li>- The ASTRAL-1 trial demonstrated similar SVR12 rates for GT2, 4, 5, and 6 compared with GT1 among patients without cirrhosis or with compensated cirrhosis.</li> <li>- In the SOF/VEL for 12 week and SOF/VEL for 24 week arms of the ASTRAL-4 trial, GT2,4, and 6 patients had SVR12 rates similar to patients with GT1.</li> <li>-This is an unmet need population, as there are presently no approved treatment regimens for GT2,4,5, or 6 decompensated cirrhotics.</li> </ul> <p>Although the number of patients with baseline CPT class C was small, the review team supported extending the SOF/VEL plus RBV 12 week dosing recommendation to all decompensated cirrhotics and I agree. My rationale is as follows:</p> <ul style="list-style-type: none"> <li>-The SVR12 rate in the CPT class C subgroup in ASTRAL-4 was similar to the CPT class B subgroup in all study arms.</li> <li>-There are no exposure or unique safety issues identified for this subgroup.</li> <li>-Decompensated cirrhosis should be considered as a single population. Frequent shifts between</li> </ul>

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	<p>&lt;10: 29/29 (100%)  10-15: 49/54 (90.7%)  16-20: 4/4 (100%)</p> <p>○ In the ASTRAL-4 SOF/VEL + RBV for 12 weeks arm, the presence of baseline NS5A polymorphisms did not impact SVR rates or relapse rates.</p>	<p>Class B and C have been observed in trials and were observed among patients enrolled in ASTRAL-4.</p> <p>- MELD score is also considered by clinicians to be clinically meaningful. There were an adequate number of patients in ASTRAL-4 with MELD scores between 10-15. This is an important population as these patients are considered to be approaching eligibility for liver transplant.</p> <p>Additional safety data for this regimen in decompensated cirrhotics will be obtained in a PMR study.</p> <p>I concur with the review team that there is not a rationale to recommend screening for baseline NS5A polymorphisms for decompensated cirrhotics.</p>
<b>Risk</b>	<p>• Overall, 1,035 patients received at least one dose of SOF/VEL in the pooled safety population from ASTRAL-1, 2, and 3, and 267 patients received SOF/VEL+RBV in ASTRAL-4. Assessments of causality for deaths and evaluation of SAEs did not raise safety concerns. Discontinuations were more common in RBV containing arms and were assessed as likely related to AEs which are known to be associated with RBV. The most common AEs (&gt;10%) observed with treatment with SOF/VEL for 12 weeks were headache and fatigue. The common AEs (&gt;10%) observed with treatment with SOF/VEL + RBV for 12 weeks were fatigue, anemia, headache, insomnia, and diarrhea.</p>	<p>The safety population was adequate to perform a thorough safety review. I concur with the Clinical Reviewers, Division Director and CDTL that SOF/VEL with or without RBV demonstrated an overall favorable safety profile and there was no evidence in the clinical trials that the known RBV associated safety issues are exacerbated by SOF/VEL.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• A comprehensive hepatic safety review was conducted by the Clinical Reviewers, the applicant, and an independent adjudication committee (IAC) commissioned by the applicant. The IAC and the Clinical Reviewers reviewed potential drug induced liver injury cases and identified one potential case in a patient with compensated cirrhosis, a second potential case in a patient with decompensated cirrhosis who discontinued SOF/VEL and recovered, and a third potential case in a patient with decompensated cirrhosis and unexplained total bilirubin elevation to 4.2 mg/dL who completed SOF/VEL treatment and recovered. The first two cases had alternative etiologies.</li> <li>• Based on the history of a serious cardiac safety signal in a development program for another NS5B inhibitor and post-marketing cases of serious bradycardia when SOF is co-administered with amiodarone, the review team conducted an analysis of potential cardiac safety in the ASTRAL-1-4 trials. No cardiac safety signal was apparent.</li> <li>• The review team also focused on rash events and depression events and concluded that the data were supportive of including these as “Less Common Adverse Reactions Reported in Clinical Trials” in labeling.</li> </ul>	<p>I concur with the assessment of the Division Director, CDTL, and review team that there is not clear evidence of drug induced liver injury associated with SOF/VEL. Post-marketing surveillance will be important.</p>
<p><b>Risk Management</b></p>	<ul style="list-style-type: none"> <li>• The pharmacokinetics of SOF was previously studied in healthy subjects with renal impairment (mild, moderate, severe, and ESRD receiving hemodialysis). In patients with eGFR &lt; 30 mL/min/1.73m<sup>2</sup>, there were higher exposures (20 fold) of the predominant SOF metabolite, similar to other SOF-containing products.</li> </ul>	<p>Labeling will include a statement in Dosage and Administration that no dosage recommendation can be given for patients with severe renal impairment or ESRD and provide the rationale.</p> <p>The SOF/VEL + RBV regimen will be contraindicated in patients for whom RBV is contraindicated.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<ul style="list-style-type: none"> <li>• There is a known risk of bradycardia when amiodarone is co-administered with SOF and other direct acting antivirals. Amiodarone co-administration was not permitted in the ASTRAL-1-4 trials.</li> <li>• Drug interaction studies demonstrated that P-gp inducers and moderate to potent CYP inducers may decrease concentrations of SOF and/or VEL.</li> </ul>	<p>The SOF/VEL label will include a Warning regarding amiodarone co-administration.</p> <p>The label describes potential drug interactions and recommends against co-administration when appropriate.</p>

## **2. Further discussion to support regulatory action**

### **Background**

The SOF component of Epclusa is a previously approved drug. Sovaldi (SOF 400 mg tablets) was approved under NDA 204671 on December 6, 2013. Harvoni (SOF 400 mg + ledipasvir 90 mg FDC tablet) was approved under NDA 205834 on October 10, 2014. Relevant data and reviews from these NDAs (also owned by the applicant) were considered as part of the review of this NDA. The SOF/VEL FDC tablet has not been marketed outside the U.S. to date.

The SOF/VEL FDC tablet received Fast Track designation in September 2013 and has a current Breakthrough Therapy Designation for HCV GT 3, 4,5,and 6 in treatment naïve patients.

### **Product Quality**

From the Product Quality perspective, NDA 208341 was recommended for approval. All manufacturing facilities were determined to be in acceptable status.

### **Nonclinical Pharmacology/Toxicology**

The Pharmacology Toxicology Reviewer recommended approval. The Pharmacology Toxicology of VEL was reviewed; SOF had been previously reviewed as part of the review of NDA 204671. The Reviewer noted that the oral FDC of SOF/VEL doubled the clinical exposure of SOF (and its main circulating metabolite, GS-331007) which appears to be the result of increased intestinal absorption of SOF due to VEL inhibition of intestinal efflux transporters, but the increase in SOF exposure due to this effect did not significantly alter the safety margins associated with SOF. No clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats and dogs administered VEL doses of up to 1500, 200 and 100 mg/kg/day for 1, 6 and 9 months, respectively. VEL was not mutagenic or clastogenic. VEL exposure was not associated with effects on fertility or embryo-fetal development. VEL maternal exposure was not associated with effects on pre- and postnatal development.

### **Clinical Pharmacology**

The Clinical Pharmacology Reviewer recommended approval. The increased SOF exposure observed in animal studies was also observed in human trials, but there were not exposure-response relationships for safety or efficacy identified for either SOF or VEL at the recommended dosage. Drug interaction studies demonstrated that P-gp inducers and moderate to potent CYP inducers may decrease concentrations of SOF and/or VEL. Interactions and recommendations to avoid co-administration when appropriate are provided in labeling. Thorough QT studies have been conducted for SOF and VEL. Neither prolonged the QT<sub>c</sub> interval to any clinically relevant extent. Post-marketing cases of serious rhabdomyolysis have been reported in patients receiving SOF in combination with another DAA and concomitant

atorvastatin. A PMR will be issued for a drug-drug interaction trial between SOF/VEL and atorvastatin to determine the magnitude of interactions and inform labeling recommendations.

### **Clinical Virology**

Both Virology Reviewers recommended approval. The review team considered a recommendation by the Clinical Virology Reviewer to add a footnote in the Dosage and Administration section of the Prescribing Information stating “SOF/VEL + RBV for 12 weeks can be considered for GT3 patients with compensated cirrhosis”. This is discussed in the Benefit-Risk Assessment section of this memo. An independent assessment of next generation sequencing (NGS) data was conducted. Resistance-associated substitutions L314F/I were detected in the NS5B polymerase protein of HCV viruses from <sup>(b) (4)</sup> subjects infected with HCV GT3a who relapsed after treatment ended. This was described in labeling and the applicant agreed to a PMC to characterize this further.

### **Clinical/Statistical – Efficacy**

The Statistical Reviewer, Clinical Reviewers, CDTL, and Division Director all concluded that substantial evidence of efficacy had been provided. The adequate and well-controlled trials supporting this conclusion are summarized in the Benefit-Risk Assessment section of this memo.

The CDTL review summarizes the data supporting the contribution of each component of this FDC tablet to the claimed effect. These data include: monotherapy and dose ranging trials for VEL, a numerically higher SVR rate for SOF/VEL in a cross-study comparison of SOF+RBV+interferon, SOF+RBV, and SOF/VEL, and clinical data regarding the activity of SOF as part of a combination regimen in NDA 204671.

### **Safety**

The Clinical Reviewers, CDTL, and Division Director all concluded that SOF/VEL with or without RBV demonstrated an overall favorable safety profile and that safety concerns are adequately address in labeling. Safety review issues are summarized in the Benefit-Risk Assessment section of this memo.

### **Advisory Committee Meeting**

As there were no efficacy or safety issues that would benefit from an Advisory Committee discussion, an Advisory Committee was not convened to discuss this application.

### **Pediatrics**

At this time, no trials in patients < 18 years of age were conducted or are ongoing. As vertically infected children often spontaneously clear the virus by 24 months of age and guidelines do not recommend early treatment in younger vertically infected children, the PeRC

agreed to a PREA waiver for children < 3 years of age. This is consistent with other previously approved DAAs. The applicant submitted a Pediatric Study Plan to study SOF/VEL in children  $\geq$  3 years of age that was acceptable.

### **Other Relevant Regulatory Issues**

Eight clinical sites were inspected and considered acceptable.

### **Labeling**

Labeling issues discussed in the course of the review are highlighted in the Benefit-Risk Assessment section of this memo. Final labeling has been agreed to with the applicant.

### **Risk Evaluation and Mitigation Strategies**

I concur with the review team that the safety profile does not warrant a Risk Evaluation and Management Strategy.

### **Postmarketing Requirements and Commitments**

The applicant and the Agency have agreed to the following:

PMRs:

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus infection.
2. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C virus infection.
3. Conduct a drug interaction trial to evaluate the interaction between sofosbuvir and velpatasvir and atorvastatin.
4. Submit the final clinical study report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5) to provide safety data in HIV-1/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy.
5. Conduct a trial in hepatitis C virus genotype 3 infected subjects with cirrhosis treated with sofosbuvir and velpatasvir to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) and reduces the rate of virologic failure.
6. Collect, analyze, and submit data from the HCV infected subjects with decompensated Child-Pugh Turcotte (CPT) C cirrhosis treated with sofosbuvir/velpatasvir regimen to

obtain safety data in a broader decompensated cirrhosis population (genotype 1-6 HCV infection).

PMCs:

7. Collect, analyze, and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir/velpatasvir-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.
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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/s/

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JOHN J FARLEY  
06/27/2016