CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 1, 2016
From	Kimberly Struble, PharmD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208341
Applicant	Gilead Sciences
Date of Submission	October 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Non-Proprietary Name	Epclusa [(sofosbuvir (SOF) and velpatasvir (VEL)]
Dosage form(s) / Strength(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic hepatitis C virus infection
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	SOF/VEL: Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis SOF/VEL/ribavirin (RBV): Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection with decompensated cirrhosis

1. Benefit-Risk Assessment

I am in agreement with the Risk-Benefit Assessment as provided in the Clinical Review by Dr. Prabha Viswanathan and Dr. Sarah Connelly; therefore this section closely mirrors that found in the Clinical Review with the exception of relatively minor revisions that do not substantively impact the overall risk-benefit assessment.

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 dates 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 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 SVR12 rate in these GT3 subpopulations remains unclear. A PMR is recommended 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. • Globally, an estimated 170 million people are infected with HCV, including approximately 3 to 5 million people in the United States (US). • 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. • 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 • 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%.	HCV infection is a significant and growing public health concern. If untreated, chronic HCV infection is a life-threatening condition, one that affects a large population in the US and worldwide. Patients can experience symptoms that are severe and debilitating.
Current Treatment Options	• The current standard-of-care treatments for CHC are interferon-free, all-oral DAA regimens. Treatment options vary based on HCV GT: ○ GT1: ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir + sofosbuvir; and simeprevir + sofosbuvir ○ GT2: sofosbuvir + ribavirin ○ GT3: daclatasvir + sofosbuvir; sofosbuvir + ribavirin ○ GT4: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir + RBV ○ GT5: ledipasvir/sofosbuvir ○ GT6: ledipasvir/sofosbuvir • Treatment with DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in	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. Only one approved regimen for subjects with GT2, 5 and 6 HCV is available. These subjects would benefit from a treatment alternative. RBV-free regimens with shorter treatment durations (< 16 weeks) are needed for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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. • 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: ○ 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. ○ Treatment with daclatasvir + sofosbuvir + RBV for 12 weeks resulted in SVR12 rates 92% for CPT B subjects and 50% of CPT C subjects with GT1; 83% of subjects with GT3 achieved SVR12. • 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.	populations that are traditionally harder to treat; such regimens may improve treatment adherence and minimize safety and tolerability issues associated with RBV. 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.
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. ○ 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. ○ 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. ○ 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. ○ 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 • 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	Four clinical trials provide substantial evidence of effectiveness of SOF/VEL for treatment of CHC GT1-6. • The recommended regimen for subjects with compensated liver disease is SOF/VEL for 12 weeks irrespective of HCV GT or prior treatment experience. • The recommended regimen for subjects with decompensated cirrhosis is SOF/VEL + RBV for 12 weeks, irrespective of HCV GT or prior treatment status. The lower SVR12 rates observed among GT3 subjects, particularly those with cirrhosis, merit consideration of 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 GT3 infected subjects with cirrhosis.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
GT 1, 2, 3, and 4 subjects with decompensated cirrhosis was 85-100%.

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

• 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.
• Overall, demographic factors did not impact SVR12 rates.
</td><td>
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.

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>
• The safety database for SOF/VEL includes 1302 subjects from the four aforementioned clinical trials and is considered adequate.
• ASTRAL-1 included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo.
• 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.
• No major safety issues were identified during this review.
• Headache, fatigue, and nausea were the three most commonly reported adverse drug reactions reported across trials.
• Subjects who received RBV with SOF/VEL experienced higher rates of
</td><td>
SOF/VEL with or without RBV demonstrated an overall favorable safety profile.

The safety issues with RBV are well known and are not exacerbated by SOF/VEL.
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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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: ○ 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. ○ Rash and depression are recommended for inclusion in Section 6 of the SOF/VEL label. • 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.

2. Background

Chronic hepatitis C virus (HCV) infection is a serious and life-threatening condition and can lead to cirrhosis and hepatocellular carcinoma. Chronic HCV infection is a global health problem with an estimated 170 million individuals infected worldwide. In the United States, approximately 3 to 5 million people have chronic HCV infection (http://www.epidemic.org/theFacts/theEpidemic/worldPrevalence/).

The majority of cases of chronic HCV infection in the United States are HCV genotype (GT) 1 (70-75%, predominately GT 1a). Approximately 20% are infected with HCV GT 2 or 3, approximately 5% with HCV GT 4, and less than 1% with HCV GT 5 or 6.

The treatment of HCV infection has rapidly evolved since the approval of the first direct acting agents (DAAs) in 2011, boceprevir and telaprevir, both NS3/4A protease inhibitors, followed by the approvals of simeprevir (NS3/4A protease inhibitor) and sofosbuvir, an NS5B nucleotide analog polymerase inhibitor, in 2013. Boceprevir, telaprevir, sofosbuvir and simeprevir required the use of interferon (IFN) and ribavirin (RBV) for HCV GT1. Since 2013 several other interferon-free DAA regimens were approved for GTs 1-6, many of which offer SVR12 rates in excess of 90% for most GTs and exceeding 95% for certain populations and GTs. Recommended regimens for CHC treatment for all GTs no longer require the use of IFN; however, RBV is still recommended for certain GTs or subpopulations.
Approved interferon-free regimens for specific GTs include:

- Sofosbuvir/ledipasvir (GT 1,4,5,6)
- Sofosbuvir+daclatasvir (GT 1,3)
- Sofosbuvir+simeprevir (GT 1)
- Sofosbuvir+ribavirin (GT 2,3)
- Dasabuvir, ombitasvir, paritaprevir/ritonavir (GT1)
- Ombitasvir, paritaprevir/ritonavir (GT4)
- Elbasvir/grazoprevir (GT1,4)

This New Drug Application (NDA), submitted by Gilead Sciences, contains information to support the approval of Epclusa, an interferon-free, complete regimen proposed for the treatment of chronic HCV infection GTs 1, 2, 3, 4, 5, and 6 in adults. Epclusa is comprised of sofosbuvir (SOF), an NS5B nucleotide analog polymerase inhibitor, and velpatasvir (VEL), an HCV NS5A inhibitor, coformulated as a fixed dose combination (FDC) tablet and administered with or without RBV. SOF is an approved product and if approved VEL would represent the 5th approved HCV NS5A inhibitor to date.

The regulatory history was also notable for fast track designation for HCV GT 1, 2, 3, 4, 5 and 6 in September 2013. Breakthrough designation was granted in April 2014 for HCV GT 1, 3, 4, 5, and 6 infection in treatment-naïve (TN) patients. The Breakthrough Therapy Designation was rescinded on April 1, 2015 due to approval of treatment regimens demonstrating high SVR rates and favorable safety profiles for HCV GT 1 infection. A new Breakthrough Therapy Designation was granted in May 2015 for HCV GT 3, 4, 5 and 6 infection in TN patients.

This NDA received a priority review under PDUFA V and was not presented at the Antimicrobial Advisory Committee because SOF/VEL received breakthrough designation and the benefit/risk

assessment did not appear controversial based on the review team's preliminary assessment of the top line trial results.

SOF/VEL FDC tablet has not been marketed outside the United States to date; a marketing application is currently under consideration by the EMA.

21 CFR 300.50 describes FDA's policy for the approval of fixed combination prescription drugs for humans. The Federal Food, Drug and Cosmetics Act states in part, "Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug". The regulations are interpreted to require a factorial analysis of proposed combination ingredients to demonstrate the combination is more effective than each component of the combination alone. For HCV drugs, however, studying the efficacy of an FDC in a clinical study with a factorial design in which the entire combination would be compared to its individual components is not feasible or ethical. This type of study design requires HCV-infected individuals to be exposed to suboptimal regimens that could quickly result in drug resistance not only to the drug or drugs under study, but in many cases to other drugs from within the same class. Suboptimal therapy may jeopardize the success of future therapeutic options for those patients exposed to single treatment or risk disease progression.

In this scenario where components of the combination cannot be administered individually (more than few days) due to rapid development of resistance, other evidence to show the contribution of each agent to the combination is needed. The evidence to show the contribution of each agent to the combination comes from (1) monotherapy and dose ranging trial results for VEL, (2) the comparison of SVR rates between SOF+IFN+RBV or SOF+RBV and SOF/VEL and (3) the approval of SOF 400 mg QD as part of a combination regimen for HCV GT 1 subjects (NDA 204671).

<u>VEL monotherapy and dose ranging</u>

- VEL proof-of-concept was established in a 3-day dose-ranging monotherapy trial in HCV GT1, 2, 3 and 4 infection evaluating VEL doses 5 to 150 mg once daily. The median maximal decline in HCV RNA across all HCV GTs for all VEL doses evaluated was greater than 3 log10 IU/mL.
- The Phase 2 trials (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 and VEL in subjects with HCV GT 1 to 6 infection. Based on results from the 8 week and 12 week regimens, a duration response was observed. Therefore, the 12 week regimen was considered the preferred regimen for all genotypes for the Phase 3 trials.

  Specifically, two treatment durations (8 and 12 weeks), two VEL doses (25 and 100 mg), and the contribution of RBV to efficacy and safety were evaluated in GS-US-342-0102.
  - Treatment groups 7-14 evaluated SOF/VEL with or without RBV for 8 weeks in HCV GT 1 and 2 infected subjects. SVR12 rates in this group ranged from 77% to 89%.
  - In contrast, the 12 week regimens resulted in higher SVR12 rates compared to the 8 week regimens. The SVR12 rates were 91-96% for HCV GT 1 and GT2, 93% for HCV GT3, 88-100% for HCV GT4, and 100% for HCV GT 5 and 6.

- Trial GS-US-342-0109 evaluated SOF/VEL 400/25 mg and SOF/VEL 400/100 mg with or without RBV, administered for 12 weeks in HCV GT 1 and 3 treatment-experienced (TE) subjects with or without cirrhosis. Results from Trial GS-US-342-0109 show a dose response in HCV GT 3 subjects. Therefore, the 100 mg VEL dose was selected for the Phase 3 trials.
    - For HCV GT 3 subjects, SVR12 rates were higher for the groups treated with 100mg VEL, regardless of RBV.
    - For cirrhotics and noncirrhotics combined the SVR12 was 71% for the 25 mg VEL group without RBV (37/52) and 96% for the 100mg VEL group without RBV (50/52).

Overall, the Phase 2 data show the contribution of VEL to the regimen via dose response (GT3 SOF/VEL 400/25 mg vs 400/100 mg in TE subjects) and duration response (8 vs 12 weeks). The Phase 2 data were used to select one dosage regimen (SOF/VEL 400/100 mg) and one duration (12 weeks) for all HCV GTs.

SVR rates for SOF-containing regimens

- The SVR rate for SOF + IFN and RBV for 12 weeks in HCV GT 1 TN subjects is 90%. In comparison, the SVR rate for VEL/SOF for 12 weeks in TN and TE HCV GT 1 subjects in the ASTRAL-1 trial is 98%.
- The SVR rates for SOF/RBV for 12 weeks in HCV GT 2 TN + TE subjects range from 82-95% and the SVR rates for SOF/RBV for 24 weeks in HCV GT3 TN + TE subjects with SOF/RBV is 84%. In comparison the SVR rate for SOF/VEL for 12 weeks in HCV GT2 and GT3 TN + TE subjects is 99-100% and 95%, respectively.

Collectively these data (monotherapy, dose ranging and Phase 3 cross-trial comparison results) show the contribution of VEL to the SOF/VEL FDC and satisfy 21 CFR 300.50. Based on cross trial comparison, SVR rates are numerically improved when VEL is combined with SOF compared to SOF+IFN and RBV or SOF+RBV and eliminates the need for an IFN and RBV based regimen.

This cross-discipline team leader review presents the major findings from the NDA review. For a more comprehensive assessment, please refer to the specific discipline reviews.

3. Product Quality

At this time evaluation of all manufacturing facilities is not complete. Additionally, the acceptance criteria for VEL impurities in the drug substance and product specifications were under discussion with Gilead when the initial review was finalized. That issue was resolved with the April 6, 2016 amendment. The recommendation from the Product Quality perspective is PENDING at this time because of the on-going final inspection (May 16-20, 2016).

- **General product quality considerations**

SOF/VEL is for oral administration and each tablet contains 400 mg of SOF and 100 mg of VEL.

According to the product quality reviewers, Dr. George Lunn and Mouli Chandramouli, the data presented in the NDA and amendments are adequate to assure composition, manufacturing process, and specifications for SOF/VEL FDC are appropriate, with the exception of the ongoing

review discussion about drug substance and drug product specifications for VEL impurity acceptance criteria. The expiration dating period of 24 months when stored below 30 degrees Celsius is supported by adequate data. No product quality microbiology issues were identified by Dr. Ying Wang. The proposed labeling is adequate pending minor revisions. Adequate data were provided to support the discriminating ability of the dissolution method. The dissolution method and dissolution acceptance criteria, as amended, were found to be acceptable for both SOF and VEL by Dr. Ge Bai.

- **Facilities review/inspection**

The facilities review and inspections are pending.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology evaluation of SOF was conducted during the review for NDA 204671. Please refer to previous reviews and SOF product labeling for details. This review focuses on the nonclinical evaluation of VEL. The nonclinical evaluation includes over 58 studies to assess the safety, pharmacology, pharmacokinetics, general toxicity, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and local tolerance, in mice, rats, dogs, rabbits and monkeys. Repeat dose studies were conducted in mice (4 weeks), rats (26 weeks), and dogs (39 weeks). Dr. John Dubinion recommended approval for this NDA based on the nonclinical pharmacology/toxicology findings.

- **General nonclinical pharmacology/toxicology considerations**

According to Dr. Dubinion's assessment, 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. No specific overlapping toxicity of clinical concern was identified in animals administered VEL or SOF alone. VEL related effects were limited to the highest dose examined in rats and dogs and were not considered adverse. No significant neurological, cardiovascular, or pulmonary findings in the safety pharmacology studies of VEL were observed.

- **Genetic toxicology and carcinogenicity**

VEL is not mutagenic or clastogenic following testing in bacterial mutagenicity, chromosome aberration and in vivo rat micronucleus assays.

Carcinogenicity studies of VEL in mice and rats are ongoing

- **Reproductive toxicology**

VEL is not associated with effects on fertility or on embryo-fetal development. At the highest dose tested, VEL exposure was approximately 6 times the exposure in humans at the recommended human dose.

VEL maternal exposure was not associated with effects on pre-and postnatal development. Maternal systemic exposure (AUC) to VEL was approximately 5 times the exposure in humans at the recommended human dose.

5. Clinical Pharmacology

Approval is recommended from the clinical pharmacology and pharmacometrics review team (Drs. Jenny Zheng, Abhay Joshi, Shirley Seo, Fang Li and Jeffry Florian). Specific labeling for use with proton pump inhibitors is ongoing (see below for further discussion). This section focuses predominantly on VEL. Please refer to previous reviews (NDA 204671) and SOF product labeling for details.

- **General clinical pharmacology considerations**

The pharmacokinetic properties of SOF and the predominant circulating metabolite GS-331007 and VEL were evaluated in healthy and HCV infected subjects. Mean peak concentrations of SOF and VEL were observed at 0.5-1 hour and 3 hours, respectively.

Following administration of SOF/VEL, the median terminal half-lives of SOF, GS-331007 and VEL were 0.5 hours, 25 hours and 15 hours, respectively. Ninety-four percent of VEL is excreted in feces and 0.4% is excreted in urine compared to 14% and 80% for SOF, respectively. The major route of elimination for VEL is biliary excretion (77%).

Administration of SOF/VEL with a high-fat/high-calorie or a moderate-fat/moderate-calorie meal resulted in a 21% and 34% increase in VEL AUC, with no change to 31% increases in VEL Cmax. Food slowed the rate of absorption of SOF within SOF/VEL, with only modest alterations in bioavailability, as evidenced by less than 2-fold higher mean AUC and no change in mean Cmax. For GS-331007, an approximately 25% to 37% lower Cmax was observed following SOF/VEL administration with food, with no change in AUC (Study GS-US-342-0104). These changes in exposure are not considered clinically significant for any moiety. Accordingly, SOF/VEL can be administered without regard to food.

SOF and GS-331007 AUC0-24 and Cmax were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=331), VEL AUC0-24 and Cmax were 37% lower and 41% lower, respectively in HCV-infected subjects.

- Critical intrinsic factors: age, race, gender, hepatic impairment, and renal impairment

Age, race, gender:

No clinically relevant effects on the exposure of SOF, GS-331007 or VEL were found for age, race or BMI. Based on the population PK analyses, gender was a statistically significant covariate for SOF, GS-331007 and VEL PK. Female subjects had 27-28% higher AUC and Cmax for GS-331007 compared to male subjects. Female subjects also had 47%, 43% and 69% higher AUC, Cmax and Ctau, respectively, for VEL compared to male subjects. Based on the favorable safety profile (see Section 8), the noted differences in PK between females and males for GS-331007 and VEL were not considered clinically relevant.

Hepatic impairment:

No clinically relevant effect on the exposure of SOF, GS-331007 or VEL was seen in subjects with severe hepatic impairment. SOF/VEL can be given to patients with mild, moderate and severe hepatic impairment.

Renal impairment:

The effect of renal impairment was evaluated for SOF and VEL as individual agents. No clinically relevant differences in VEL pharmacokinetics were seen between healthy subjects and subjects with severe renal impairment, thus supporting that VEL can be given to patients with mild, moderate or severe renal impairment. However, the SOF component of the FDC cannot be given to patients with severe renal impairment. Higher exposures (up to 20 fold) for GS-331007 were seen in subjects with severe renal impairment. Safety and efficacy have not been established for GS-331007 exposures; therefore, dosing recommendations in patients with severe renal impairment cannot be made for SOF/VEL.

- Drug-drug interactions

SOF/VEL has the potential for drug interactions both as a perpetrator and victim.

VEL solubility decreases as pH increases; therefore, drugs that increase gastric pH are expected to decrease systemic exposures of VEL. As a result coadministration of SOF/VEL and antacids must be separated by four hours. Coadministration of H2-receptor antagonists can be given simultaneously or 12 hours apart from SOF/VEL at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.

Currently, the Division concluded coadministration of SOF/VEL and proton pump inhibitors is not recommended; whereas, Gilead recommended (b) (4)

Relative to healthy subjects, VEL AUC(0-24) and Cmax are 37% lower and 41% lower, respectively in HCV-infected subjects. The finding of lower VEL exposures in HCV infected subjects is important to assess the clinical relevance of an interaction with proton pump inhibitors. The VEL exposures observed in Phase 3 would not cover the lower range of VEL exposures that would be produced by a concomitant proton pump inhibitor. In order to support that proton pump inhibitor coadministration is acceptable with SOF/VEL, the Division needs dose/exposure-response data showing that a 50% decrease in VEL exposure will have minimal impact on SOF/VEL efficacy. Of note, the reference in the DDI study was under fasted conditions, while Phase 2/3 trials were under either fasted or fed conditions and thus the effect of omeprazole may be more substantial in patients. Additional discussions are ongoing. Please refer to the Clinical Pharmacology review addendum for further details and resolution of this labeling issue.

SOF and VEL are substrates of drug transporters P-gp and BCRP. GS- 331007 (the predominant circulating metabolite of sofosbuvir) is not a substrate for P-gp or BCRP. In vitro, slow metabolic turnover of VEL by CYP2B6, CYP2C8, and CYP3A4 was 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 and/or VEL leading to reduced therapeutic effect. Coadministration of SOF/VEL with of inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8 or CYP3A4 is not recommended. This information is included in Section 5 Warnings and Precautions and in Section 7: Drug Interactions of the product labeling. SOF/VEL may be coadministered with P-gp, BCRP, and CYP inhibitors.

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.

Drug interaction trials were conducted with VEL as a single agent, SOF as a single agent or LDV/SOF in combination with several antiretrovirals, H2 receptor antagonists, proton pump inhibitors, oral contraceptives, cyclosporine, ketoconazole, methadone, pravastatin, rosuvastatin, rifampin and tacrolimus. Some potentially clinically significant interactions were noted. Please refer to Dr. Jenny Zheng's review for full details and rationale for recommendations despite changes in VEL, SOF or concomitant medication exposures. Below is the proposed table for the package insert and still under discussion. As mentioned above, one outstanding issue remains regarding SOF/VEL use with proton pump inhibitors. Safety data from ASTRAL-5 in HIV-1/HCV co-infected patients was reviewed to support the clinical recommendations for use with tenofovir. Please refer to addendum by Dr. Prabha Viswanathan for details.

Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	**Effect on Concentration[b]**	**Clinical Effect/Recommendation**
Acid Reducing Agents:	↓ velpatasvir	Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir.
Antacids (e.g., aluminum and magnesium hydroxide)		Separate antacid and EPCLUSA administration by 4 hours.
H_2-receptor antagonists[c] (e.g., famotidine)		H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from EPCLUSA at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Proton-pump inhibitors[c] (e.g., omeprazole)		Under discussion
Antiarrhythmics: amiodarone	Effect on amiodarone, sofosbuvir, and velpatasvir concentrations unknown	Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended; if coadministration is required, cardiac monitoring is recommended *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)].*
digoxin[c]	↑ digoxin	Therapeutic concentration monitoring of digoxin is recommended when coadministered with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentration increases of less than 50%.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.
Anticonvulsants: carbamazepine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.

phenytoin phenobarbital oxcarbazepine		
Antimycobacterials: rifabutin rifampin[c] rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HIV Antiretrovirals:		
efavirenz[c]	↓ velpatasvir	Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir DF	↑ tenofovir	Monitor for tenofovir-associated adverse reactions in patients receiving EPCLUSA concomitantly with a regimen containing tenofovir DF. Refer to (b) (4) prescribing information for recommendations on renal monitoring.
tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort *(Hypericum perforatum)*	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
HMG-CoA Reductase Inhibitors: rosuvastatin[c]	↑ rosuvastatin	Coadministration of EPCLUSA with rosuvastatin may significantly increase the concentration of rosuvastatin which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg.
atorvastatin	↑ atorvastatin	Coadministration of EPCLUSA with atorvastatin is expected to increase the concentrations of atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy.

DF = Disoproxil fumarate
a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase
c. These interactions have been studied in healthy adults.

- Thorough QT trial or other QT assessment

A thorough QT trial was not conducted for SOF/VEL FDC. The individual products were evaluated in a thorough QT trial. SOF or VEL did not prolong QTc to any clinically relevant extent compared to an active control (moxifloxacin 400 mg).

- Formulation

The pivotal clinical trials were performed with the to-be-marketed fixed-dose formulation; therefore bridging information between formulations is not required.

6. Clinical Microbiology

Please refer to the reviews by Drs. Lisa Naeger and Eric Donaldson for a detailed assessment of the cell culture and in vivo virology data. An approval action was recommended by the virology team. The results from baseline NS5A resistance-associated polymorphism (RAPs) and outcome (SVR12 and relapse rate) are presented in Section 7 Clinical/Statistical Efficacy. This section focuses on the virologic failures from the Phase 3 trials. Additionally a brief summary is presented from the next generation sequencing (NGS) analyses.

Overall, few subjects experienced virologic failure throughout the SOF/VEL Phase 3 program. Thirteen subjects (1%) experienced virologic failure in ASTRAL 1-3; two with HCV GT1 infection and 11 with HCV GT3 infection. Of the two HCV GT1 subjects who experienced virologic failure, one subject had virus with emergent NS5A resistance substitution Y93N and one subject had emergent Y93N along with low-level NS5A resistance substitutions K24M/T and L31I/V. The latter subject had baseline NS5A RAPs (Q30R, L31M, H58P). No sofosbuvir-associated substitutions were observed at the time of virologic failure.

Of the ten HCV GT3 subjects with available resistance testing, all ten subjects had the Y93H at failure (seven had Y93H emerge post-treatment and three had Y93H at baseline and post treatment). Sofosbuvir associated substitutions were seen in one subject.

Among subjects in ASTRAL-4 who received SOF/VEL + RBV for 12 weeks, three subjects experienced virologic failure (one with HCV GT1 and two with HCV GT3). The one HCV GT1 subject did not develop any NS5A or NS5B resistance-associated substitutions at failure. Both HCV GT3 subjects had the Y93H resistance substitution emerge at failure along with either low-level M28V or S38P. One HCV GT3 subjects had low level NS5B nucleoside analog inhibitor resistance substitutions N142T and E237G at failure.

Dr. Donaldson concluded good agreement between his independent analysis of the NGS data and the analysis done by Gilead, with few exceptions. Based on the NGS analyses, the NS5B L314F/I sofosbuvir resistance-associated substitution will be added to the label. A PMC to submit a phenotypic assessment of NS5B_L314F, NS5B_L314I, and NS5B_L314P in the HCV genotype 3 replicon is recommended.

7. Clinical/Statistical- Efficacy

This section summarizes the efficacy analyses conducted by the review team for the pivotal trials supporting the use of SOF/VEL for the treatment of adult patients with chronic HCV GT 1, 2, 3, 4, 5, and 6 infection without cirrhosis or with compensated cirrhosis and with decompensated cirrhosis for use in combination with RBV. This section focuses on the ASTRAL 1, 2, 3, and 4 trials. Please refer to the Clinical Review by Drs. Prabha Viswanathan and Sarah Connelly, the Virology Review by Dr. Lisa Naeger and the Statistical Review by Dr. Karen Qi for complete details. Overall, the FDA reviewers' independent analyses confirmed Gilead's primary and secondary efficacy findings for the pivotal trials. Each reviewer recommended approval for this NDA.

The primary endpoint for the four pivotal clinical trials was SVR (HCV RNA analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v 2.0 assay with lower limit of quantitation (LLOQ) < 15 IU/mL) measured 12 weeks after the end of therapy and deemed acceptable. SVR12 is the currently recommended primary endpoint in the revised draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral

Agents for Treatment, published in 2016. Sustained virologic response (HCV RNA < LLOQ at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a cure for hepatitis C virus infection; and recent studies have shown that achievement of SVR is associated with halting the progression of liver disease and decreasing the frequency of chronic hepatitis C complications, including cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related mortality.

In ASTRAL 1, 2 and 3 subjects were stratified by cirrhosis status. The method for determining cirrhosis (liver biopsy, Fibroscan and FibroTest +APRI) was acceptable. In ASTRAL 1, 2, and 3 Fibroscan accounted for the majority of cirrhosis determination (36-67%) whereas liver biopsy accounted for 15-29% of the cirrhosis determination.

Please refer to Table 1 below for a summary of the clinical trial designs. Please also refer to the statistical review for the justification of the non-inferiority margins for ASTRAL 2 and 3. At the time ASTRAL-4 was initiated, no approved treatment options were available; thus an active control was not feasible. The trial was designed to show superiority over an assumed spontaneous HCV clearance rate of 1%. The review team was in agreement with the statistical plans during review of the Phase 3 trials.

Table 1: Key Efficacy Trials

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

The trial designs, key demographics, and key efficacy results from each of the trials outlined above are reviewed, followed by a discussion of sub-group analyses of interest and by conclusions on effectiveness based on the totality of evidence from the clinical trials.

Trial designs, key demographics, and key efficacy results

ASTRAL-1

ASTRAL-1 is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter trial. The patient population consisted of TN and TE subjects without cirrhosis or with compensated cirrhosis and HCV GT 1, 2, 4, 5, and 6 infection. The regimen was SOF/VEL for 12 weeks versus placebo. Randomization was stratified by HCV genotype and cirrhosis status. All subjects with HCV GT5 received SOF/VEL for 12 weeks and were not randomized because of the small size of the HCV GT5 population, especially in the US. Nineteen percent of subjects were classified as cirrhotic and 32% were treatment-experienced. The key efficacy findings are summarized in Table 2 below. 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. Only two HCV GT1 subjects relapsed. The details of these subjects are discussed in Section 6 above.

Table 2 - ASTRAL-1: Virologic Outcomes by HCV Genotype

	SOF/VEL x 12 Weeks (N=624)							
	Total (all GTs) (N=624)	**GT-1**			**GT-2 (N=104)**	**GT-4 (N=116)**	**GT-5 (N=35)**	**GT-6 (N=41)**
		GT-1a (N=210)	**GT-1b (N=118)**	**Total (N=328)**				
SVR12	99% (618/624)	98% (206/210)	99% (117/118)	98% (323/328)	100% (104/104)	100% (116/116)	97% (34/35)	100% (41/41)
Outcome for Subjects without SVR								
On-Treatment Virologic Failure	0/624	0/210	0/118	0/328	0/104	0/116	0/35	0/41
Relapse[a]	<1% (2/623)	<1% (1/209)	1% (1/118)	1% (2/327)	0/104	0/116	0/35	0/41
Other[b]	1% (4/624)	1% (3/210)	0/118	1% (3/328)	0/104	0/116	3% (1/35)	0/41

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

ASTRAL-2

ASTRAL-2 is an ongoing Phase 3, randomized, open-label, active-controlled trial. The patient population consisted of TN and TE subjects without cirrhosis or with compensated cirrhosis and HCV GT 2 infection. Randomization was stratified by presence or absence of compensated cirrhosis and prior treatment experience. The regimens studied were SOF/VEL for 12 weeks versus SOF/RBV for 12 weeks. Fourteen percent of subjects were classified as cirrhotic and 15% were treatment-experienced. The key efficacy findings are summarized in Table 3 below.

SOF/VEL was superior to SOF/RBV. In the SOF/VEL treatment group, no subjects experienced virologic failure or relapse; therefore, results by stratification are not presented.

Table 3 ASTRAL-2: Virologic Outcomes in HCV GT2 Subjects

	EPCLUSA 12 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

ASTRAL-3 is an ongoing Phase 3, randomized, open-label, active-controlled trial. The patient population consisted of TN and TE subjects without cirrhosis or with compensated cirrhosis and HCV GT 3 infection. Randomization was stratified by presence or absence of compensated cirrhosis and prior treatment experience. The regimens studied were SOF/VEL for 12 weeks versus SOF/RBV for 24 weeks. Thirty percent of subjects were classified as cirrhotic and 26% were treatment-experienced. The key efficacy findings are summarized in Table 4 below.

Table 4 - Study ASTRAL-3: Virologic 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.
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

SVR12 rates for the pre-specified randomization stratification factors are presented in Table 5.

Table 5- Study 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.

I agree with Dr. Viswanathan's assessment that the SVR12 rates observed in ASTRAL-3 are the highest rates seen to date for HCV GT3 subjects. Overall, 95% of HCV GT 3 subjects receiving SOF/VEL for 12 weeks achieved SVR12. Treatment with SOF/VEL for GT3 provides superior SVR12 rates compared to SOF/RBV for 24 weeks. However, the need to optimize treatment and improve SVR12 rates particularly for HCV GT3 cirrhotics is acknowledged. The consequence of virologic failure is the development of the NS5A resistance substitution specifically, Y93H, and the potential loss of subsequent treatment options. (b) (4)

A numeric difference in SVR12 rates was observed between HCV GT3 subjects treated with SOF/VEL with compensated cirrhosis (91%) and HCV GT3 subjects without cirrhosis (97%). As a result much of the review discussions centered on results from additional analyses regarding the impact of baseline factors on higher relapse rates and if the addition of RBV could minimize the risk of relapse based on data from other trial populations.

Dr. Qi conducted numerous subgroup analyses by demographic and baseline disease characteristics. No apparent treatment difference by subgroup interaction was identified. Additionally, the baseline demographic and disease characteristics of those GT3 subjects who relapsed were analyzed to help identify factors most likely to predict treatment failure (please refer to the clinical review for details). No significant trends were observed to determine which subgroup(s) of patients were at the highest risk for virologic failure.

The effects of baseline NS5A RAPs on relapse rates were examined. The overall relapse rate for the SOF/VEL group was 4% (11/275). In the SOF/VEL group the relapse rate was 7% (4/56) for HCV GT 3 subjects with baseline NS5A RAPs compared to 3% (7/218) for HCV GT 3 subjects without baseline NS5A RAPs. Relapse rates were also higher in HCV GT 3 subjects with cirrhosis and baseline NS5A RAPs (33%; 3/9) compared to subjects with cirrhosis and no baseline NS5A RAPs (6%; 4/71). Given the numeric differences in relapse rates among those with and without baseline NS5A RAPs, the team discussed the possibility of baseline resistance screening to help minimize relapse rates. However, as noted in Dr. Viswanathan's review such

strategies are only helpful if the test result guides a change in management strategy for subjects with RAPs (e.g. treatment with a different regimen). The only approved regimens for HCV GT3 are SOF/RBV and DCV/SOF, both of which have significantly lower SVR12 rates compared to SOF/VEL based on ASTRAL-3 and cross trial comparison with ALLY-3 for DCV/SOF. As Dr. Naeger noted in the virology review, insufficient data are currently available to support screening all patients for NS5A RAPs before treatment with SOF/VEL.

Next the review team considered the totality of evidence to determine if the addition of RBV could minimize relapse rates. Data from the Phase 2 trial GS-US-342-0109, and the Phase 3 trials ASTRAL 1 and 4 were further examined to estimate the potential benefit of adding RBV for HCV GT3 subjects with compensated cirrhosis. Whether or not to consider the use of RBV in HCV GT3 subjects with compensated cirrhosis as a footnote to the Dosage and Administration table was challenging for the review team. Different perspectives from the review disciplines were discussed at several meetings and included the strength of evidence from the Phase 2 trial GS-US-342-0109, the applicability of leveraging data from other populations in ASTRAL-1 and ASTRAL-4 and the clinical safety considerations for use of RBV in the setting of > 90% efficacy without RBV.

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.

- Although the SVR12 rates were higher in the SOF/VEL+RBV group [96% (25/26)] compared to the SOF/VEL [89% (23/26)] in trial GS-US-342-0109, the sample size was small and the difference was not statistically significant [treatment difference -8% and 95% CI: -28%, 10%].
- In ASTRAL-4, SVR12 rates were numerically higher in the SOF/VEL + RBV group compared to the SOF/VEL for 12 or 24 weeks; however, the difference was not statistically significant. The more conservative approach to include RBV in decompensated subjects may not apply to all compensated cirrhotics.
- 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 RBV label includes a box warning for hemolytic anemia and includes several Warnings and Precautions including risk of hepatic failure and death, severe hypersensitivity reactions and pulmonary disorders. In 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 trial GS-US-342-0109, the single subject who relapsed in the SOF/VEL + RBV group and two of the three subjects who relapsed in the SOF/VEL group developed an Y93H resistance substitution.
    - In ASTRAL-4, three subjects who experienced virologic failure also had resistance testing available. The HCV GT1 failure had no NS5A resistance

substitutions at failure. The two HCV GT3 failures had the NS5A resistance substitution Y93H and either M28V or S38P at failure.

In sum, from the clinical perspective, the available data do not conclusively demonstrate the benefit of adding RBV outweighs the risk for developing serious RBV-associated toxicities in GT3 patients with compensated cirrhosis. Data from a trial that definitively shows the benefit of adding RBV to SOF/VEL in this population are not available. Despite numeric differences noted, the sample size in the Phase 2 trial GS-US-342-0109 was limited and the results were not conclusive as noted by the treatment difference and 95% CIs. The ability to leverage data from ASTRAL-4 in HCV GT 1 and 3 decompensated cirrhotics to HCV GT3 compensated cirrhotics is challenging. In my opinion, data from ASTRAL-4 in decompensated patients did not offer additional support because the benefit/risk assessment is different between those with compensated cirrhosis compared to decompensated cirrhosis.

The addition of RBV may have a role in HCV GT3 subjects with compensated cirrhosis; however, additional data are needed prior to a recommendation in labeling. I support the decision to issue a PMR to determine if the addition of RBV improves SVR12 rates in HCV GT3 subjects with compensated cirrhosis. In my opinion 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

ASTRAL-4 is an ongoing Phase 3, open-label trial. The patient population consisted of 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. Randomization was by HCV GT. Although all subjects had Child-Pugh B cirrhosis at screening, 6% and 4% of subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively, on the first day of treatment. The key efficacy findings are summarized in Table 6 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 6 - ASTRAL-4 Efficacy Results, 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. High SVR12 rates were seen for SOF/VEL 12 or 24 weeks for HCV GT 2, 4, 5 and 6 subjects and the possibility exists RBV is not needed for some of these subjects. However, given the small sample sizes and wide 95% CI the review team agreed with Gilead's conservative approach and dosage recommendation: SOF/ VEL + RBV for 12 weeks in HCV GTs 2, 4, 5, and 6. The feasibility of conducting a larger trial in HCV GTs 2, 4, 5 and 6 with decompensated cirrhosis to determine if RBV is needed for all GT 2, 4, 5 and 6 subjects with decompensated cirrhosis is not likely given the limited numbers of subjects in these subgroups.

Based on the Phase 2 data, the intent of ASTRAL-4 was to enrich for HCV GT3 subjects because of the concern that longer treatment or addition of RBV may be needed to optimize SVR rates; however, only 15% enrolled had HCV GT3 infection. Given the limited number of HCV GT3 subjects in total (n=39), the 95% CIs of the SVR12 rates overlapped across all treatment groups. Despite this the SOF/VEL + RBV group had the highest SVR12 rate (85%)

compared to the SOF/VEL 12 or 24 week groups (50%). Extending the treatment from 12 to 24 weeks did not improve SVR12 rates. The treatment difference in SVR12 rates (+35%) and treatment difference in relapse rates (-32% to -35%) between SOF/VEL + RBV compared to SOF/VEL for 12 or 24 weeks was considered clinically relevant to support to use of RBV in HCV GT3 decompensated cirrhotics. Additionally the safety profile and few treatment discontinuations with the RBV containing regimen provided additional support for SOF/VEL + RBV for 12 weeks.

A similar rationale as described in the clinical review was used to support the SOF/VEL + RBV 12 week regimen in HCV GT1 decompensated subjects.

Twenty seven subjects had Child-Pugh A or C subjects at baseline. None experienced virologic failure or relapse. All achieved SVR12 with the exception of one subject with missing SVR12 data (achieved SVR4) and one subject who discontinued due to an AE. SOF/VEL+RBV for 12 week dosing recommendation were extended to the Child-Pugh C population. We consider decompensated cirrhosis as a single population rather than two discreet decompensated cirrhosis sub-populations of Child-Pugh B and C. No exposure or unique safety issues were identified to preclude the use of SOF/VEL + RBV in subjects with Child-Pugh C cirrhosis. We note from ASTRAL-4 and SOLAR 1, SOLAR 2 and ALLY-1 trials patients shift Child-Pugh class between screening and baseline, providing further support to consider decompensated cirrhosis as a single population.

Conclusions on the Substantial Evidence of Effectiveness:

Gilead Sciences provided substantial evidence of effectiveness as required by law [see 21 CFR 314.126(a)(b)] to support approval for HCV GT 1, 2, 3, 4, 5 and 6 infected adult patients. Efficacy was demonstrated in TN and TE subjects 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. Lower SVR12 rates observed among HCV GT3 subjects, particularly those with compensated cirrhosis, warrant additional exploration to optimize treatment success and minimize relapse rates. A PMR trial to evaluate the utility of adding RBV to SOF/VEL in HCV GT3 subjects with compensated cirrhosis is recommended. SOF/VEL fills an important unmet medical need for a 12 week, RBV-free regimen for subjects with HCV GTs 1-6 without cirrhosis and with compensated cirrhosis irrespective of treatment history. Similarly, SOF/VEL + RBV for 12 weeks fills an important unmet medical need for HCV GT 1-6 subjects with decompensated cirrhosis who have few or no treatment options.

8. Safety

This section provides a focused summary of the safety data from the four Phase 3 clinical trials, ASTRAL 1, 2, 3, and 4. Data from ASTRAL 1, 2, and 3 were pooled because the overall trial designs and trial populations were comparable in terms of underlying disease severity. Data from ASTRAL-4 were reviewed separately because subjects with decompensated cirrhotisis were expected to have different frequency and severity of AEs and laboratory abnormalities compared to subjects with compensated liver disease in ASTRAL 1,2,and 3. For a complete description of these data and the Agency's independent safety analyses, please refer to the joint Clinical Review performed by Drs. Prabha Viswanathan and Sarah Connelly.

<u>Adequacy of the safety database, Applicant's safety assessments, and submission quality</u>

The safety database for SOF/VEL is adequate to assess safety for the proposed indication, dosage regimen, duration of treatment and patient populations. The safety database was consistent with the safety considerations as outlined in the Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment. Overall 1035 subjects received at least one dose of SOF/VEL in the pooled phase 3 safety population and 267 subjects received SOF/VEL + RBV in ASTRAL-4.

Gilead performed a comprehensive assessment of safety, including but not limited to a detailed analysis of hepatotoxicity. The submission quality was adequate to perform a thorough safety review and no substantive issues with data integrity were identified.

Key safety results, including deaths, serious adverse events (SAEs), discontinuations due to AEs, results of laboratory tests, and immunogenicity

Deaths

Three treatment-emergent and three non-treatment emergent deaths were reported in ASTRAL 1, 2, and 3. Three deaths occurred in SOF/VEL treated subjects and three deaths occurred in SOF/RBV treated subjects. The three deaths occurring in SOF/VEL treated subjects all occurred post 12 weeks of treatment and were considered not related. The cause of deaths included metastatic lung cancer, drug overdose, and died in sleep due to unknown causes. For the subject who died in his sleep due to unknown causes, an autopsy report could not be obtained due to legal reasons. No notable adverse events or laboratory abnormalities were noted; however, he was undergoing current treatment for dyslipidemia. The final assessment was likely due to cardiovascular risk factors.

In ASTRAL-4 ten deaths were reported (nine in the original applications and one in the safety update report). None were considered treatment-related. Two treatment-emergent deaths were reported: sepsis following duodenal ulcer perforation (SOF/VEL+RBV x 12 weeks) and MI in a subject with ongoing tobacco use (SOF/VEL 24 weeks).

I concur with the clinical reviewers' assessment of causality in all the cases presented in the NDA.

SAEs

The rates of non-fatal serious AEs (SAEs) in ASTRAL 1, 2, and 3 were low. Two percent of subjects (n=23) receiving SOF/VEL experienced an SAE compared to 2%, 5% and 0% in the SOF + RBV 12 week, SOF + RBV 24 week and placebo, respectively. The only SAE occurring in more than one SOF/VEL treated subject was acute MI (0.2%, 2 subjects). Both events occurred in subjects with underlying risk factors for coronary artery disease. The remaining SAEs in the SOF/VEL groups were unrelated. The majority of events (1%, n=7) were related to acute infections and not related to study medication.

In ASTRAL-4, 16-19% of subjects experienced a non-fatal SAE. Only two SAEs were considered related to treatment and included dyspnea (specifically RBV related) and hepatorenal syndrome/hypertension/peritonitis/sepsis. In general SAEs were similar between SOF/VEL 12 and 24 week regimens and SOF/VEL + RBV. No consistent pattern regarding the types of SAEs reported were seen across the three treatment arms.

Discontinuations

Overall only two subjects prematurely discontinued SOF/VEL in ASTRAL 1, 2 and 3 trials. One event was Grade 3 anxiety and considered unrelated. The second event was related to Grade 3 AEs of difficulty concentrating, headache and anxiety. In comparison two subjects (1.7%) in the placebo group prematurely discontinued drug due to prespecified stopping criteria for ALT or AST. Nine subjects in the SOF+RBV 24 group prematurely discontinued study drugs due mainly to RBV-associated AEs or insomnia.

In ASTRAL-4, nine subjects (3%) prematurely discontinued SOF/VEL containing treatment due to an AE. No AE leading to SOF/VEL discontinuation occurred in more than one subject. The majority of AEs leading to SOF/VEL discontinuation were also considered an SAE. In the SOF/VEL + RBV group, four subjects (5%) discontinued the entire regimen. Nine subjects (10%) permanently discontinued RBV due to a RBV-related AE but continued SOF/VEL treatment.

Common AEs and Laboratory Abnormalities

The most commonly reported adverse events in ASTRAL 1, 2, and 3 (at least 10%, all grade, all causality) for SOF/VEL were headache (29%), fatigue (21%), nausea (13%), insomnia (8%), and nasopharyngitis (12%). The majority of events were Grade 1 in severity. Review of adverse reactions (ADRs) (all grades, related) in ASTRAL 1, 2, and 3 for SOF/VEL showed similar results. Headache, fatigue, nausea and insomnia were the most commonly reported ADRs. The type and frequency of AEs and ADRs observed in ASTRAL-4 were consistent with those observed in ASTRAL 1-3.

Laboratory abnormalities in ASTRAL 1, 2, and 3 were infrequent. Data for four laboratory abnormalities are proposed for labeling and include lipase, creatine kinase, indirect bilirubin and hemoglobin (ASTRAL-4 only). No new or unexpected findings were seen. Elevated CK values were seen across all SOF-containing regimens and likely due to SOF. Elevated CK values are a known SOF related laboratory abnormality and included in labeling for SOF and LDV/SOF.

Grade 3 elevated lipase was seen more frequently in SOF/VEL groups. 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, 2% of subjects treated with SOF/VEL + RBV had isolated, asymptomatic lipase elevations (> 3x ULN).

In ASTRAL-1, creatine kinase elevations ($\geq$ 10xULN) were seen in 1% and 0% of subjects treated with SOF/VEL and placebo, respectively. Overall, 2% and 2% of subjects treated with SOF/VEL in ASTRAL 2 and 3, respectively had creatine kinase elevations (> 10xULN). Similar results were seen in ASTRAL-4 (1% of subjects treated with SOF/VEL + RBV).

Review of the ASTRAL-5 data in HIV-1/HCV co-infected subjects to support recommendations for use with antiretroviral agents showed increases in indirect bilirubin up to 3 mg/dL above baseline among those 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 without dose adjustment or treatment interruption of either SOF/VEL or HIV antiretroviral agents.

In ASTRAL-4 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 with ribavirin for 12 weeks, respectively. Decreases in hemoglobin are a known RBV-related laboratory abnormality. Additionally, AEs occurred with similar frequency and severity across demographic groups (age, gender and race). No patterns were identified to suggest a higher risk for specific events in any population.

Special safety concerns

Drs. Viswanathan and Connelly conducted detailed reviews to address safety concerns for HCV DAAs in general, such as hepatotoxicity and safety issues based on SOF and LDV/SOF labeling or preclinical data including cardiac events, rash, neuropsychiatric events.

Hepatotoxicity

A comprehensive safety evaluation was conducted by Drs. Viswanathan and Connelly, Gilead, and an independent adjudication committee (IAC) commissioned by Gilead comprised of drug-induced liver injury (DILI) experts to assess the overall hepatic safety profile. These evaluations were conducted at the request of FDA because both the review of data in subjects with decompensated cirrhosis and the ability to discern if observed safety events were related to the SOF/VEL regimen or underlying advanced cirrhosis are challenging. A similar evaluation was done for subjects with compensated liver disease. Please refer to clinical review for review criteria and further details.

In summary, 56 cases met at least one of the six criteria for IAC review from ASTRAL 1-3 and Phase 2 trials. The IAC found their criteria were not optimal for subjects with compensated liver disease because many of the cases were isolated and asymptomatic elevations of ALT or AST. Therefore the IAC used conventional biochemical screening criteria for possible DILI. As a result, only one case was identified where DILI could not be excluded. In a phase 2 trial GS-US-342-0109 a subject had unexplained increase in ALT and AST. The increase in ALT and AST was temporally associated with new antihypertensive medication and antibiotics/steroids. Study medication and antihypertensive medication were discontinued and the ALT and AST subsequently normalized. Dr. Viswanathan reviewed all the case narratives and agreed with the IAC's assessment that an alternative etiology existed for each remaining case and no clear evidence of DILI with SOF/VEL in subjects with compensated liver disease.

In ASTRAL-4, ten cases met the IAC criteria, of which nine were deemed unlikely related to SOF/VEL due to confounding events and/or isolated laboratory elevations which improved while HCV treatment continued. Dr. Connelly found another case during her review for further evaluation of possible DILI. The IAC subsequently reviewed this case. DILI could not be excluded due to temporal association with SOF/VEL therapy and improvement in bilirubin off therapy. However, alternative etiologies are possible given clinical presentation in setting of cholelithiasis, possible viral illness and concomitant use of ciprofloxacin. The subject experienced an increase in total bilirubin on Day 85 (> 3x baseline, 3.8 mg/dL) which subsequently increased to 14 mg/dL on Day 91. The subject had nausea, vomiting, back pain, clay colored stools, dark urine, jaundice and pruritus leading to discontinuation of SOF/VEL. A sick contact at home with URI was reported and concomitant medications included metronidazole (prescribed Day 1-13 for colitis), ciprofloxacin and Zofran. No evidence of hepatitis A, B or E infection, stool studies were negative. Liver biopsy showed cirrhosis, lobular hepatitis and moderate cholestasis. The subject recovered.

The other subject had a direct bilirubin increase to 2.1 mg/dL (baseline 0.8 mg/dL) at Week 6 which improved on subsequent visits (0.6 mg/dL at Week 20). Total bilirubin was also elevated and ranged from 1.6 mg/dL to 4.2 mg/dL on treatment. AST and CK elevations fluctuated during treatment; however, the subject was asymptomatic except for Grade 1 fatigue at the time of the bilirubin increases and completed SOF/VEL treatment. This subject has a history of bilirubin and AST fluctuations.

I agree with clinical assessment by the review team and IAC, the totality of the data in subjects with compensated and decompensated liver disease does not suggest clear evidence of DILI with SOF/VEL use. Additional analyses conducted by the clinical reviewers do not raise any hepatotoxicity safety concerns at this time. Ongoing post-marketing pharmacovigilance activities will be important to monitor for any safety signals.

Cardiac Disorders

During the original SOF NDA review, a detailed analysis of cardiac disorders including cardiac failure, cardiomyopathy and congestive heart failure cases was conducted. This targeted review was done because during the development of an investigational NS5B, BMS-986094, nine patients were hospitalized and one died due to heart failure. (b) (4) a detailed review of cardiac disorders was done. Based on the original SOF NDA review and subsequent SOF containing regimen NDA reviews, no obvious safety signal was noted for cardiac toxicity. Nevertheless, another review was undertaken with this NDA. Additionally, a targeted cardiac review was done because postmarketing cases of serious symptomatic bradycardia events were reported when amiodarone was coadministered with SOF in combination with another HCV DAA. Of note amiodarone was not permitted in all Phase 3 trials.

As shown in the clinical review cardiac events in ASTRAL 1-3 were infrequent (all cause, all grade). Numerically more events were seen in the SOF/RBV comparator groups (20% 56/407) compared to SOF/VEL (7%; 69/1035). Most events were mild or moderate in severity. Four SAEs occurred and included MI (2), palpitations and sudden death (discussed above). Adverse events suggestive of symptomatic bradycardia were infrequent and occurred at similar rates between subjects with or without coadministration of beta blockers or calcium channel blockers. Additionally no clinically relevant changes from baseline in heart rate were observed.

Similarly in ASTRAL-4 6% of subjects experienced a cardiac event. Most events were nonserious, Grade 1 or 2 in severity and did not result in discontinuation of treatment. Three subjects experienced a cardiac related SAE. Two MIs, including one fatal case, occurred in subjects with cardiac history or risk factors. Another SAE of transient atrial fibrillation occurred in subject with history of palpitations who completed 24 weeks of SOF/VEL treatment. No subjects receiving concomitant beta blockers or calcium channel blockers had events suggestive of symptomatic bradycardia and no clinically relevant changes in heart rate were observed.

Overall no cardiac signal was detected from the extensive analyses conducted for ASTRAL 1-4.

Rash and Depressive Events:

Rash and depressive events were reviewed in detail because these events may be related to SOF and are contained in Section 6 of the SOF and LDV/SOF label. For the reasons summarized below we recommend including rash and depression as Less Common Adverse

Reactions. Per Adverse Reactions guidance, serious, low-frequency AEs generally will be listed when there is reason to suspect the drug may have caused the event, in this case, plausibility in light of the drug's known pharmacology.

Rash Events (using pooled preferred terms under the MedDRA Skin and Soft Tissue Body SOC: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular)

Although rash events in SOF/VEL-treated subjects occur below the 5% ADR cutoff for the ASTRAL 1-3 and below the 10% ADR cutoff for the ASTRAL-4 population proposed in Section 6 of the label, the review team considers the totality of the data supportive to recommend inclusion of rash events in the Less Common Adverse Reactions Reported in Clinical Trials section. 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, (3) rash events reported in the current SOF and LDV/SOF labels which contain SOF.

Depression Events (using pooled preferred terms from the MedDRA High Level Group Terms "Depressed Mood Disorders and Disturbances" and "Suicidal and Self-Injurious Behaviours NEC")

Although depression events in SOF/VEL-treated subjects occur below the 2% ADR cutoff for the ASTRAL 1-3 population and below the 10% ADR cutoff for the ASTRAL-4 population proposed in Section 6 of the label, the review team considers 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 occurring in SOF-containing treatment arms, including SOF/VEL arm, of ASTRAL 1-3 population and none occurring in the placebo arm, (2) depression events reported in the current SOF and LDV/SOF labels which contain SOF.

Rhabdomyolysis and Pancreatitis

Because creatine kinase and lipase elevations are proposed for the SOF/VEL label and creatine kinase elevations is included in the SOF and LDV/SOF labels, analyses were performed to identify clinical cases of rhabdomyolysis and pancreatitis. Despite Grade 3 and 4 increases in creatine kinase no clinical cases of rhabdomyolysis were seen in ASTRAL1-3. One case of rhabdomyolysis was seen in ASTRAL-4 and likely due to anesthetic agents (succinylcholine and propofol) which are labeled for rhabdomyolysis.

No cases of clinical pancreatitis were observed in ASTRAL 1-4.

Given the lack of clinical cases the label will still include the creatine kinase and lipase laboratory abnormalities to alert clinicians of the potential risk.

9. Advisory Committee Meeting

This NDA was not presented at the Antimicrobial Drug Advisory Committee because SOF/VEL received breakthrough designation and the benefit/risk assessment did not appear controversial based on the review team's preliminary assessment of the top line trial results.

10. Pediatrics

To date, no trials in subjects < 18 years of age were conducted or are ongoing. The Applicant submitted a waiver for less than three years of age and a deferral for greater than or equal to three years of age. The requested waiver and deferral are consistent with other DAA NDAs. The Division has waived all trials in HCV infected children less than three years of age because infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection. Based on these data, the small number of patients in these age groups, and current practice guidelines, a waiver for children less than 3 years of age is deemed appropriate. The waiver and deferral were accepted by the PeRC.

The Applicant plans to conduct two trials as part of their SOF/VEL pediatric development plan for subjects with genotype 1, 2, 3, 4, 5, and 6 HCV infection. (b) (4) [redacted]. The Division is in agreement with the pediatric study plans.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation Inspections

Eight sites were inspected, two from each trial including domestic and foreign sites. The data submitted are considered acceptable. Please refer to the OSI Consult Review for further details.

Good Clinical Practice

The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines. No GCP issues were identified.

Financial Disclosures

Financial disclosures were reviewed for all investigators involved in Phase 3 trials used for assessment of efficacy and safety in the Division's review. See Dr. Viswanathan's review for full details. The likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

12. Labeling

Prescribing Information

- INDICATIONS AND USAGE section:

- Based on advice from the Labeling and Development Team, the indication was revised to provide specific language to clearly state when a drug is indicated for use in combination with other therapy. (b) (4) The final agreed indication is as follows:

  EPCLUSA is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5 and 6 infection [see Dosage and Administration (2.1) and Clinical Studies (14)]:
  - without cirrhosis or with compensated cirrhosis
  - with decompensated cirrhosis for use in combination with ribavirin

- DOSAGE AND ADMINISTRATION section:
  - As stated in Section 7, we agree with the proposed recommended dosage regimen(s) . The title for Table 1 in Section 2.1 was modified to show the recommended treatment regimens in patients with Genotype 1, 2, 3, 4, 5, and 6 HCV (b) (4)
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - No specific SOF/VEL contraindication was warranted. A contraindication for for patients for whom ribavirin is contraindicated was included.
  - Three specific Warnings and Precautions are included in Section 5.
    - All SOF-containing labels include statements about serious symptomatic bradycardia when sofosbuvir is coadministered with amiodarone and another HCV direct acting antiviral.
    - Drug interactions, specifically risk of reduced therapeutic effect due to concomitant use of SOF/VEL with inducers of P-gp and/or moderate to potent inducers of CYP is included. Coadministration is not recommended with rifampin, St. John's work, carbamazepine
    - A general reference (cross reference to ribavirin label) regarding risks associated with ribavirin is also included
- ADVERSE REACTIONS section
  - This section is still under discussion with Gilead. (b) (4) The current proposal is to (b) (4) state the following
    - (b) (4)
    - The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in

ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with EPCLUSA in ASTRAL 3.

- DRUG INTERACTION section
  - Please refer to Section 5 for discussion of outstanding issues
- CLINICAL STUDIES section:
  - The review team worked closely with Gilead to ensure the clinical trials of primary importance were displayed in clear, concise, and clinically meaningful a manner. This included the removal of data that were not directly relevant to dosing recommendations.
- Dispense only in Original Container language.
  - Based on previous communications with Gilead we note they are considering a [(b) (4)] The review team generally considers "dispense [(b) (4)] in original container" language as related to a specific product quality issues. The open-dish stress study at 40C/75% RH for 3 months had no change in assay, degradants or morphic form. [(b) (4)]. These data do not suggest a specific risk when dispensed in a pharmacy bottle. If a product has specific clinical risk (not shared by all drugs in a class or indication) then the "dispense [(b) (4)] in original container" language could be considered. Although FDA does not have specific guidance for these statements, we recommend Gilead does not include this statement in labeling. Gilead acknowledged our concern and stated inclusion of these statements were not related to physicochemical stability of the drug product. Rather, the statement is included in an effort to maintain the integrity of the product and to maximize patient adherence to the prescribed regimen. Permitting pharmacists to dispense Gilead product from unit-of-use bottles into new containers could lead to patients not receiving the full intended 4-weeks supply per bottle and potentially lead to deviation from the prescribed regimen. The recommendation to retain the statement in the USPI is to help maximize adherence by the patient to the prescribed dosing regimen and to protect product integrity and authenticity. In the absence of FDA guidance on use of "dispense [(b) (4)] in original container" statements, this statement will be retained in labeling. Internal discussion regarding future FDA guidance is being considered.

Other Labeling

- *Proprietary* name EPCLUSA was found acceptable by the Division of Medication Error Prevention and Analysis

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

Based on the safety profile of SOF/VEL FDC, the Division does not recommend a Risk Evaluation and Management Strategy (REMS).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Below is a recommended list of PMR/PMCs. The Applicant agreed to these during the April 19, 2016 late cycle meeting. Final dates for protocol and data submissions are forthcoming from Gilead.

1. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir/velpatasvir in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C.

2. Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir/velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C.

3. Conduct a drug interaction study to evaluate the interaction between sofosbuvir/velpatasvir and atorvastatin.

4. Collect, analyze, and submit data from the HCV population with decompensated Child-Pugh C cirrhosis treated with sofosbuvir/velpatasvir regimen to obtain safety data in a broader decompensated cirrhosis population.

5. Submit the final clinical study report and datasets for the ongoing trial GS-US-342-1202 (ASTRAL-5) to provide additional safety data in HIV/HCV co-infected subjects receiving sofosbuvir and velpatasvir concurrently with HIV antiretroviral therapy. These data will also be used to confirm dosing recommendations for co-infected subjects.

6. Conduct a trial to determine if the addition of ribavirin improves the efficacy (i.e., sustained virologic response rate) of sofosbuvir and velpatasvir for hepatitis C virus genotype 3 infected subjects with cirrhosis.

PMC:

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. Submit phenotypic assessment of NS5B_L314F, NS5B_L314I, and NS5B_L314P in the HCV genotype 3 replicon.

14. Recommended Comments to the Applicant

There are no additional comments to be conveyed to the Applicant at this time.

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/s/

KIMBERLY A STRUBLE
06/01/2016