CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209195Orig1s000

SUMMARY REVIEW

Combined Division Director and Cross-Discipline Team Leader Review

Date	July 13, 2017
From	Debra Birnkrant, M.D. Kimberly Struble, Pharm.D.
Subject	Combined Division Director and Cross-Discipline Team Leader Review
NDA/BLA #	209195
Applicant	Gilead Sciences, Inc. (referred to as Gilead)
Date of Submission	December 8, 2016
PDUFA Goal Date	August 8, 2017
Proprietary Name / Non-Proprietary Name	Vosevi ®
Dosage form(s) / Strength(s)	Fixed-dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir and 100 mg voxilaprevir
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)	Treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have: • Genotype 1,2,3,4,5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor • Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

Material Reviewed/Consulted OND Action Package, including	Names of Discipline Reviewers
Medical Officer Review	Dr. Kirk Chan-Tack
Statistical Review	Drs. Karen Qi and Thamban Valappil supervised by Dr. Dionne Price
Pharmacology Toxicology Review	Dr. Mark Powley supervised by Dr. Hanan Ghantous
CMC Review Team	Drug Product: Dr. Shrikant Pagay (Primary); Dr. Balajee Shanmugam (Secondary) Drug Substance: Dr. Sithamalli Chandramouli Process & Micro: Dr. Ying Wang(Primary); Dr. Arwa El Hagrasy (Secondary) Biopharm: Dr. Min Li (Primary); Dr. Raines Kimberly (Secondary) Facilities: Dr. Christina Capacci-Daniel Environmental Assessment: Dr. James Laurenson
Virology Review	Drs. Lisa Naeger and Eric Donaldson supervised by Dr. Jules O'Rear
Clinical Pharmacology/Pharmacometrics	Drs. Qin Sun, Jenny Zheng supervised by Dr. Shirley Seo; Dr. Fang Li supervised by Dr. Jeffry Florian
OMP/DMPP/PLT	Dr. Morgan Walker supervised by Barbara Fuller
OPDP (DDMAC)	Dr. Wendy Lubarsky supervised by Sam Skariah
OSE/DMEPA	Dr. Valerie Wilson supervised by Vicky Borders-Hemphill
OSE/DRISK (REMS)	Dr. Elizabeth Everhart supervised by Naomi Redd

OMP/DMPP/PLT = Office of Medical Policy/ Division of Medical Policy Programs/Patient Labeling Team
OPDP/ DDMAC=Office of Prescription Drug Promotion/Division of Drug Marketing, Advertising and Communication
OSE/ DMEPA = Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Benefit-Risk Assessment

We are in agreement with the benefit-risk assessment provided in the Clinical Review by Dr. Kirk Chan-Tack and recommend approval of NDA 209195. This section is aligned with the Clinical Review with the exception of relatively minor clarifications that do not substantively impact the overall benefit-risk assessment.

Benefit-Risk Summary and Assessment

Sofosbuvir (SOF) is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, velpatasvir (VEL) is an HCV NS5A inhibitor, and voxilaprevir (VOX) is an HCV NS3/4A protease inhibitor. SOF/VEL/VOX is a fixed-dose combination tablet with a proposed indication for treatment of patients with chronic HCV infection (b) (4) Intended populations include adults with (1) HCV genotype 1,2,3,4,5 or 6 infection who have previously been treated with an HCV regimen containing an NS5A inhibitor and (2) those with HCV genotype 1a or 3 infection who have previously been treated with an HCV regimen containing sofosbuvir without an NS5A. The indicated patient population includes those with compensated liver disease, defined as the absence of cirrhosis or with compensated (Child Pugh Turcotte [CPT] A) cirrhosis.

HCV infection is a serious disease, affecting an estimated 3-5 million people in the US and 130-150 million people worldwide. 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 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 cure. Several DAA regimens have been approved that confer SVR12 rates greater than 93% for HCV GT 1, 2, 3, 4, 5, or 6-infected patients (treatment-naïve (TN), IFN/RBV-experienced, or NS3/4A PI-experienced) with compensated liver disease.

While great progress has been made in improving SVR12 rates among TN, IFN/RBV-experienced patients, and NS3/4A PI-experienced patients, treatment options are needed for patients who have failed DAA-only treatment, such as NS5A inhibitor-containing regimens or nucleotide analog NS5B polymerase inhibitor (sofosbuvir)-containing regimens. In HCV genotypes 1-6 infected patients who have previously been treated with an HCV regimen containing an NS5A inhibitor, SOF/VEL/VOX demonstrated SVR12 rates ranging from 91-100% depending on the HCV genotype. In HCV genotype 1a and 3 infected patients who have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor, SOF/VEL/VOX demonstrated SVR12 rates ranging from 96-98%. Based on the SVR12 rates for the patient populations stated above, SOF/VEL/VOX is an effective, RBV-free, single tablet, once-daily treatment option.

No major safety issues unique to SOF/VEL/VOX were identified in this review. The most frequent adverse drug reactions were headache, fatigue, and diarrhea. SOF has been associated with serious bradycardia when co-administered with amiodarone; amiodarone treatment was prohibited in the phase 3 trials, and no cases of serious bradycardia were observed. Current SOF-containing labels include a Box Warning and a Warning and Precaution regarding the risk of hepatitis B virus (HBV) reactivation, resulting in fulminant hepatitis, hepatic failure and death in HCV/HBV coinfected patients who received treatment with DAAs. HBV coinfection was prohibited in the phase 3 trials and therefore no cases of HBV reactivation were observed.

Approval of SOF/VEL/VOX for treatment of adult patients with CHC infection is fully supported by the available evidence of efficacy and safety. Based on thorough analysis of efficacy, safety, and virology data overall, and in each subpopulation, SOF/VEL/VOX for 12 weeks recommended for the following patient populations:

(1) Genotype 1,2,3,4,5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor
(2) Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

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, over 170 million people are infected with HCV, including approximately 3 million people in the United States (US). • At least seven distinct HCV genotypes exist. Genotype 1 is the most common among US patients (72%), followed by Genotype 2 (11%), Genotype 3 (9%), and Genotype 4 (6%). Genotypes 5 and 6 occur uncommonly (≤ 1%) in the US but may predominate in other parts of the world. Genotype 7 is found only in the Democratic Republic of Congo. • HCV infection is typically asymptomatic in the 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 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 gentoype: ○ **Genotype 1**: ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir (in combination with sofosbuvir); simeprevir (in combination with sofosbuvir); sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ **Genotype 2**: sofosbuvir + ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ **Genotype 3**: daclatasvir + sofosbuvir; sofosbuvir + ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ **Genotype 4**: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir with ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ **Genotype 5:** ledipasvir/sofosbuvir; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ **Genotype 6:** ledipasvir/sofosbuvir; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) • Treatment with DAAs in TN, IFN/RBV-experienced patients, and NS3/4A PI-experienced patients can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in > 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. • At the time of this review, no DAA regimens are approved for patients who have failed DAA-only treatment, specifically an NS5A inhibitor or sofosbuvir containing regimen	RBV-free regimens with shorter treatment durations (< 16 weeks) are needed for populations that are traditionally harder to treat; such regimens may improve treatment adherence and minimize safety and tolerability issues associated with RBV. A specific unmet medical need exists for highly effective DAA regimens for subjects who have failed a prior NS5A inhibitor containing regimen or who have failed a prior sofosbuvir containing regimen because no approved regimens are

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>(without an NS5A inhibitor). For treatment-experienced patient populations, such as those who have previously received an NS5A inhibitor (evaluated in POLARIS-1), as those who have previously received sofosbuvir but have not received an NS5A inhibitor (evaluated in POLARIS-4), a limited amount of data exists about options not currently in approved labels. Most of these other options are 24 week, RBV-containing regimens with a wide range of SVR12 rates (70-97% in Genotype 1; 93% in Genotype 2; 76% in Genotype 3) and SVR12 rates are impacted by baseline RAS.</td><td>available.</td></tr>
<tr><td>Benefit</td><td>

The efficacy of SOF/VEL/VOX was established in two Phase 3 clinical trials that included 445 subjects treated with SOF/VEL/VOX for 12 weeks. The trial populations varied based on DAA experience.

POLARIS-1: DAA-experienced subjects who have previously received NS5A inhibitors with compensated liver disease and HCV Genotype 1, 2, 3, 4, 5, or 6. Genotype 1 subjects received SOF/VEL/VOX x 12 weeks or placebo x 12 weeks; subjects with Genotypes 2-6 received SOF/VEL/VOX.
POLARIS-4: DAA-experienced subjects who have not previously received NS5A inhibitors with compensated liver disease and HCV Genotype 1, 2, 3, 4, 5, or 6. Subjects received SOF/VEL/VOX x 12 weeks or SOF/VEL x 12 weeks.

The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 results overall ranged from 91-100% depending on the HCV genotype.

TABLE 1: POLARIS-1: SVR12 by HCV Genotype (GT) Among Subjects Treated with SOF/VEL/VOX 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>146/150 (97%)</td><td>5/5 (100%)</td><td>74/78 (95%)</td><td>20/22 (91%)</td><td>1/1 (100%)</td><td>6/6 (100%)</td><td>253/263 (96%)</td></tr>
</table>
TABLE 2: POLARIS-4: SVR12 by Treatment Arm and HCV GT n (%) for those subjects with prior exposure to SOF containing regimen
<table>
<tr><th></th><th colspan="3">GT1</th><th>GT2</th><th>GT3</th><th>GT4</th><th>Total</th></tr>
<tr><th></th><th>Total</th><th>GT1a</th><th>GT1b</th><th></th><th></th><th></th><th></th></tr>
<tr><td>SOF/VEL/VOX x 12 weeks</td><td>76/78 (97%)</td><td>53/54 (98%)</td><td>23/24 (96%)</td><td>31/31 (100%)</td><td>52/54 (96%)</td><td>19/19 (100%)</td><td>178/182 (98%)</td></tr>
<tr><td>SOF/ VEL x 12 weeks</td><td>60/66 (91%)</td><td>39/44 (89%)</td><td>21/22 (95%)</td><td>32/33 (97%)</td><td>44/52 (85%)</td><td>Not enrolled</td><td>136/151 (90%)</td></tr>
</table>
No subjects with HCV genotype 5 or 6 infection were enrolled in POLARIS-4</td><td>The two phase 3 clinical trials provide substantial evidence of effectiveness of SOF/VEL/VOX x 12 weeks in adult patients with chronic hepatitis C virus infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have

• genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor .
• genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

In these patient populations, SOF/VEL/VOX fills an important unmet medical need.
- No effect of baseline resistance-associated substitutions (RAS),</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In POLARIS-1, SVR12 rates were comparable across genotypes. Subgroup analyses demonstrated that cirrhosis, prior DAA treatment failure, and baseline resistance-associated substitutions (RAS) (NS5A, NS3, NS5B) did not impact SVR12 rates. Adults with HCV genotype 1 and genotype 3 infection comprise the majority of subjects in POLARIS-1. SVR12 rates were 95-97% among subjects with HCV genotype 1 and genotype 3 infection, confirming robust efficacy. SOF/VEL/VOX is also recommended for adults with HCV genotype 2, 4, 5, and 6 infection who previously received an NS5A inhibitor based regimen, recognizing the limited number of enrolled subjects in these HCV genotype subgroups. Based on high SVR12 results in genotype 1 and 3, the most difficult to treat genotypes, it is reasonable to extend the indication to other genotypes for these difficult to treat populations with unmet medical need. • In POLARIS-4, the contribution of VOX is established for subjects who previously received a sofosbuvir containing regimen without an NS5A inhibitor in HCV genotype 1a and 3 (96-97% SVR12, similar SVR12 rates across subgroup analyses, no effect of baseline RAS [NS3, NS5B] on SVR12). Treatment with SOF/VEL/VOX resulted in numerically higher SVR12 rates than treatment with SOF/VEL in subjects with HCV genotype1a (97% vs. 89%) and HCV genotype 3 (96% vs. 85%) infection. • In POLARIS-4, the contribution of VOX has not been established for HCV genotype 1b, 2, 4, 5 and 6. Comparable SVR12 rates were seen with SOF/VEL/VOX and SOF/VEL in subjects with HCV genotype 1b and 2. No comparison data are available for HCV genotype 4, 5, and 6. Given these data, the benefit of adding VOX to SOF/VEL for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in adults previously treated with SOF-without an NS5A inhibitor was not shown when compared to SOF/VEL. Therefore SOF/VEL/VOX is only indicated for in subjects with HCV genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor • Overall, demographic factors did not impact SVR12 rates in either trial.	cirrhosis, or prior treatment failure on SVR12. - Shorter duration (12 weeks) compared to off-label use of other drugs (most are 24 weeks and some include RBV).
Risk	• The safety database for SOF/VEL/VOX includes 445 subjects from the two aforementioned clinical trials and is considered adequate. • POLARIS-1 included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo. • POLARIS-4 included an active-controlled comparison for safety. • The hepatic safety pool included additional subjects who received SOF/VEL/VOX at doses of at least SOF/VEL 400/100 mg and VOX 100 mg in Phase 2 trials. • No major safety issues were encountered during this review.	SOF/VEL/VOX demonstrated an overall favorable safety profile; however, SOF/VEL/VOX is not recommended for use in patients with moderate or severe hepatic impairment. Also several potentially

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Headache, fatigue, and diarrhea were the three most commonly reported adverse drug reactions reported across trials. • SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment due to higher exposures of VOX in these patients • There is the potential of other drugs to affect SOF/VEL/VOX exposures and the potential for SOF/VEL/VOX to affect other drugs. For components of SOF/VEL/VOX have the potential to affect other drugs or other drugs can affect SOF/VEL/VOX. For example use of inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., St. John's wort, carbamazepine) may significantly decrease plasma concentrations of SOF, VEL, and/or VOX leading to reduced therapeutic effect of SOF/VEL/VOX. The use of OATP inhibitors which may substantially increase exposure of VOX (e.g., cyclosporine) with VOSEVI is not recommended. VEL and VOX are inhibitors of drug transporters P-gp, BCRP, OATP1B1, and OATP1B3. VEL is also an inhibitor of OATP2B1. Coadministration of SOF/VEL/VOX with drugs that are substrates of these transporters may alter the exposure of such drugs. Coadministration of SOF/VEL/VOX with BCRP substrates (e.g., methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) is not recommended	significant drug interactions can occur resulting in contraindications, not recommended for use or alteration of dose or regimen recommendations
Risk Management	• Although no significant safety signals were detected in this review, the SOF/VEL/VOX prescribing information will include safety information contained in the current SOF, LDV/SOF and SOF/VEL labels, even if the events haven't occurred or occurred rarely in the SOF/VEL/VOX trials: ○ Although no cases were reported in the Phase 3 SOF/VEL/VOX trials, Section 5 of the SOF/VEL/VOX label will include a warning regarding the risk of HBV reactivation in subjects receiving DAAs. ○ Although no cases were reported in the Phase 3 SOF/VEL/VOX trials, Section 5 of the SOF/VEL/VOX 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 being considered for inclusion in Section 6 of the SOF/VEL/VOX label. ○ LDV/SOF is labeled for angioedema based on postmarketing experience. Although no clear signal is identified for angioedema with SOF/VEL/VOX use, product labeling similar to LDV/SOF is recommended. • A Box Warning about the risk of HBV reactivation will also be included for consistency with safety labeling for all approved DAAs. • A Contraindication about the drug-drug interaction with rifampin will also be included.	Safety concerns associated with SOF or VEL or VOX are adequately addressed in product labeling.

2. Background

Chronic hepatitis C virus (HCV) infection is a serious and life-threatening condition that 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 1 (70-75%, predominately genotype 1a). Approximately 20% are infected with HCV genotype 2 or 3, approximately 5% with HCV genotype 4, and less than 1% with HCV genotype 5 or 6.

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. These approvals were followed by the approvals of simeprevir (NS3/4A protease inhibitor) and sofosbuvir, an NS5B nucleotide analog polymerase inhibitor, both in 2013. Boceprevir, telaprevir, sofosbuvir and simeprevir required the use of interferon (IFN) and ribavirin (RBV) for treatment of HCV genotype 1. Since 2013 several other interferon-free DAA regimens were approved for genotypes 1-6, many of which have SVR12 rates in excess of 90% for most genotypes and exceed 95% for certain populations and genotypes. Recommended regimens for CHC treatment for all genotypes no longer require the use of IFN; however, RBV is still recommended for certain subpopulations.

Approved interferon-free regimens for specific genotypes include:

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

Despite the high efficacy reported in clinical trials for the HCV DAAs, some patients will not achieve a sustained virologic response (SVR) or cure. Patients who failed treatment with an NS3/4A protease inhibitor with pegylated interferon and ribavirin were included in several clinical trials of the currently approved HCV DAAs. These patients can be successfully retreated as noted in the respective product labeling. To date, no regimens are currently approved for patients who previously received an NS5A inhibitor-containing regimen or NS5B polymerase inhibitor-containing regimen. In part, to address DAA failures, Gilead developed voxilaprevir (VOX), an HCV NS3/4A protease inhibitor with activity across all HCV genotypes. VOX is part of a fixed-dose combination tablet with sofosbuvir (SOF) (approved in 2011) and velpatasvir (VEL) (approved in 2016). Two phase 3 clinical trials contained in this applicationspecifically evaluated safety and efficacy in DAA-experienced patients and were used as the basis to support NDA 209195.

This New Drug Application (NDA), submitted by Gilead Sciences, contains information to support the approval of Vosevi (FDC containing SOF/VEL/VOX), an interferon-free, complete regimen proposed for adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have:

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor; and
- genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.

The regulatory history was also notable for Fast Track Designation for HCV GT 1, 2, 3, 4, 5 and 6 on June 12, 2015 because CHC is a serious condition and the fixed-dose combination demonstrated the potential to address an unmet medical need. Breakthrough designation was granted in February 19, 2016 for the treatment of CHC due to HCV genotype 1 infection based on preliminary evidence that indicated that the fixed-dose combination demonstrated activity in patients for whom there was no approved therapy who previously failed an NS5A-inhibitor containing DAA regimen.

This NDA received a priority review under PDUFA V and was not presented at the Antimicrobial Advisory Committee because SOF/VEL/VOX 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/VOX 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". A clinical trial with a factorial design is one approach to evaluating two or more drugs to assess the contribution of each component. For HCV drugs, however, studying the efficacy of a fixed-dose combination in a clinical study with a factorial design in which the entire combination would be compared to its individual components is neither feasible nor 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 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 (for more than few days) due to rapid development of resistance, other evidence is needed to show the contribution of each agent to the combination. Determining the contribution of VOX for certain genotypes was the primary efficacy review issue. As discussed in section 7, the contribution of VOX was established in patients with HCV genotypes 1-6 who previously received an NS5A inhibitor; whereas in patients who previously received SOF without an NS5A inhibitor the added benefit of VOX as part of SOF/VEL/VOX versus SOF/VEL was not evident for certain genotypes. The review team's analyses and recommendations are further summarized in section 7. Other evidence to show the contribution of each agent to the combination comes from monotherapy trial results for VEL and VOX (see below), dose-ranging trial results for SOF, VEL and VOX, the approval of SOF 400 mg QD as part of a combination regimen, and the recent approval of SOF/VEL (NDA 208341). (b) (4)

VOX Monotherapy and Dose-Ranging

- VOX proof-of-concept was established in a 3-day dose-ranging monotherapy trial (GS-US-338-1121) in HCV genotype1-4 infection. On average, mean reductions in HCV RNA of > 2 $\log_{10}$ IU/mL and > 3 $\log_{10}$ IU/mL were observed within 24 and 60 hours, respectively. An Emax model was able to show that near maximal antiviral response (≥ 90% of Emax) will be achieved at a VOX dose of 100 mg and doses > 100 mg are unlikely to achieve further meaningful reduction in HCV RNA.

- Based on the collective data from trials 1468, 1168, 1169 and 1871 a duration response was observed. SOF/VEL (400/100 mg) plus VOX 100 mg was given to HCV treatment-experienced patients and improved SVR12 rates were seen for the 12-week regimen (94-100%) compared to the SVR12 rates for the 6-week (67%) and 8-week (89%) regimens.

  This combined Division Director/Cross-Discipline Team Leader review presents the major findings from the multidisciplinary NDA review. For a more comprehensive assessment, please refer to the specific discipline reviews.

3. Product Quality

- General product quality considerations

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

According to the product quality reviewers, the data presented in the NDA and amendments are adequate to assure that composition, manufacturing processes, and the specifications for SOF/VEL/VOX fixed-dose combination are appropriate. 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. The proposed labeling is adequate pending minor revisions. Adequate data were also 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 SOF, VEL and VOX.

- Facilities review/inspection

The facilities review and inspections are pending.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology evaluation of SOF and VEL was conducted during the review for NDA 204671 and NDA 208341. Please refer to previous reviews and SOF/VEL product labeling for details. This review focuses on the nonclinical evaluation of VOX. The nonclinical evaluation includes over 40 studies to assess the safety pharmacology, pharmacokinetics/ADME, general toxicity, carcinogenicity, reproductive and developmental toxicology, genetic toxicology and special toxicology, in mice, rats, dogs, and rabbits as well as in vitro. Dr. Mark Powley recommended approval for this NDA based on the nonclinical pharmacology/toxicology findings.

- General nonclinical pharmacology/toxicology considerations

According to Dr. Powley's assessment, no clinically relevant target organs of toxicity were identified in repeat-dose toxicology studies in rats (up to 100 mg/kg/day) and dogs (up to 20 mg/kg/day) administered VOX orally for up to 26 and 39 weeks, respectively. Increases in bilirubin were noted in nonclinical studies and the increases in bilirubin are associated with OATP inhibition. No specific overlapping toxicity of clinical concern was identified in animals administered SOF, VEL or VOX alone. VOX related effects were generally limited to the highest dose examined in rats and dogs and were not considered clinically relevant. No significant neurological, cardiovascular, or pulmonary findings in the safety pharmacology studies of VOX were observed.

- Genetic toxicology and carcinogenicity

VOX is not genotoxic following testing in bacterial mutagenicity, chromosome aberration and in vivo rat micronucleus assays.

Clinical administration of VOX is only for 12 weeks; therefore, carcinogenicity studies were not required.

- Reproductive and developmental toxicology

VOX was administered orally to pregnant rats (up to 100 mg/kg/day) and rabbits (up to 600 mg/kg/day) from gestation days 6 to 17, and 7 to 19, respectively, and also to rats (up to 100 mg/kg) on gestation day 6 to lactation day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. AUCs of VOX during gestation were approximately 141 (rats), and 4 (rabbits) times the exposure in humans at the recommended human dose.

In rat pre/postnatal development studies, maternal systemic exposure (AUC) for VOX was approximately 238 times the exposure in humans at the recommended human dose, with exposure of approximately 58% that of maternal exposure observed in nursing pups on lactation day 10.

VOX was administered orally to male and female rats (up to 100 mg/kg/day) for 28 days before cohabitation through mating and 14 days before cohabitation until gestation day 6, respectively. No significant effects on male fertility, female fertility, or early embryonic development occurred at the highest doses tested. AUC values for VOX were approximately 149 times the exposure in humans at the recommended human dose.

5. Clinical Pharmacology

Approval is recommended from the clinical pharmacology and pharmacometrics review teams (Drs. Qin Sun, Jenny Zheng, Jeffrey Froude, Shirley Seo, Fang Li and Jeffry Florian). This section focuses predominantly on VOX. Please refer to previous reviews (NDA 208341) and SOF product labeling for details.

- General clinical pharmacology considerations

The pharmacokinetic properties of SOF and the predominant circulating metabolite GS-331007, VEL and VOX were evaluated in healthy and HCV infected subjects. Mean peak concentrations of SOF, VEL and VOX were observed at 2 hours and 4 hours (both VEL and VOX), respectively.

Following administration of SOF/VEL/VOX, the median terminal half-lives of SOF, GS-331007, VEL and VOX were 0.5 hours, 29 hours, 17 hours and 33 hours, respectively. Ninety-four percent of VOX (40% as parent) is excreted in feces and is not is excreted in urine. The major route of elimination for VOX is biliary excretion.

The impact of food (including meal type) and additional considerations for drug-drug interactions (DDI) based on exposure changes with type of meal administered were reviewed in detail. The clinical pharmacology review notes in trial GS-US-338-1130, a DDI was seen between SOF/VEL and VOX in the fasted state which resulted in lower VOX exposures compared to VOX alone. However administration of SOF/VEL plus VOX or SOF/VEL/VOX with a range of meal types mitigated this interaction. As a result, the recommendation for SOF/VEL/VOX is one tablet, once daily with food. Of note, SOF/VEL/VOX was given with food in the phase 2 and 3 trials.

A high fat meal results in higher VOX exposures compared to a moderate fat meal (435% vs 185% increase in AUC, 680% vs 259% increase in Cmax). Dr. Sun noted this could be a concern when interpreting results from DDI trials with SOF/VEL/VOX as perpetrator drugs because these DDI trials were conducted with a moderate-fat meal in healthy subjects. Also of note, VOX exposures are 3 to 4 times higher in HCV infected patients than healthy subjects. Therefore to cover the higher VOX exposures in HCV infected patients, the DDI perpetrator trials were conducted with SOF/VEL/VOX 400/100/100 mg plus an additional 100 mg of VOX, which resulted in much higher VOX exposure ranging from 4000 to 6000 h*ng/mL in healthy subjects than clinical efficacious exposure at 2577

h*ng/mL in HCV patients. As summarized in the clinical pharmacology review the higher VOX exposures in DDI perpetrator studies mitigate the concern for how a high-fat meal could impact DDI data interpretation.

- Critical intrinsic factors: age, race, gender, body mass index (BMI), hepatic impairment, and renal impairment

Age, Race, Gender, BMI:

No clinically relevant effects on the exposure of SOF, GS-331007, VEL or VOX were found for age, race or BMI. Based on the population PK analyses, gender was a statistically significant covariate for SOF, GS-331007, VEL and VOX PK (17-65% higher exposure in females). Based on the favorable safety profile (see Section 8), the noted differences in PK between females and males were not considered clinically relevant.

Hepatic Impairment:

No dosage adjustment is needed for patients with mild hepatic impairment. SOF/VEL/VOX is not recommended for subjects with moderate or severe hepatic impairment because VOX exposures were up to 5 fold higher in subjects with moderate or severe hepatic impairment relative to subjects with normal hepatic function and the safety and efficacy have not been established in moderate or severe hepatic impairment. This finding is based on a single dose of VOX 100 mg in HCV-negative subjects with moderate or severe hepatic impairment.

Renal Impairment:

The effect of renal impairment was evaluated for SOF, VEL and VOX as individual agents and with population PK analysis in the Phase 2 and 3 trials. No clinically relevant differences in VEL or VOX pharmacokinetics were seen between healthy subjects and subjects with severe renal impairment, thus supporting that VEL or VOX 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 or with end stage renal disease (ESRD). Higher exposures (up to 20 fold) of GS-331007 were seen in subjects with severe renal impairment or with ESRD. Safety and efficacy have not been established for SOF/VEL/VOX in patients with severe renal impairment or with ESRD; therefore, dosing recommendations cannot be made in these patients.

- Drug-drug interactions

SOF/VEL/VOX has the potential for drug interactions both as a perpetrator and as a victim. The table below summarizes the substrate and inhibition profiles of VOX, VEL, SOF and GS-331007 for enzymes and transporters. SOF, GS-331007, VEL and VOX are not inducers of CYP or UGT1A1 enzymes.

TABLE 3: Drug Interactions

		Substrate	Inhibition
VOX	Enzyme	CYP1A2, CYP2C8, CYP3A4	None
	Transporter	P-gp, BCRP, OATP1B1/3	P-gp, BCRP, BSEP, OATP1B1/3
VEL	Enzyme	CYP2B6, CYP2C8, CYP3A4	None
	Transporter	P-gp, BCRP, OATP1B1/3	P-gp, BCRP, BSEP, OATP1B1/3, OATP2B1
SOF	Enzyme	CatA/CES1, HINT1*	None
	Transporter	P-gp, BCRP	None
GS-331007	Enzyme	None	None
	Transporter	None	None

CatA: cathepsin A; CES1: carboxylesterase 1; HINT1: histidine triad nucleotide-binding protein 1
Source: Clinical Pharmacology review

Numerous DDI trials were conducted to evaluate possible drug interactions with SOF/VEL/VOX as a perpetrator or victim of interactions with frequently co-administered drugs in the HCV population, including acid reducing agents, antiarrhythmics, anticoagulants, anticonvulsants, antimycobacterials, antiretrovirals, herbal supplements, HMG-CoA reductase inhibitors, immunosuppressants, and oral contraceptives. Knowledge from SOF/VEL DDIs was leveraged and included in section 7 of the package insert.

Gilead is in agreement with the review team's recommendation to contraindicate rifampin because rifampin can significantly decrease SOF, VEL and VOX exposures after multiple doses and therefore could adversely affect efficacy. This is especially concerning because the indication is for patients who have already failed a prior DAA and some of these patients may not have future treatment options.

DDI trials were conducted with pravastatin and rosuvastatin. Based on the observed DDI results and the ADME profile of the other approved statins, Gilead proposed use of the lowest necessary dose for fluvastatin, lovastatin, pitavastatin and simvastatin; 20 mg for atorvastatin was proposed when coadministered with SOF/VEL/VOX. However, the clinical pharmacology review team did not agree with the recommendation. For pitavastatin, coadministration is not recommended due to an increased risk of severe myopathy at > 4 mg in premarketing clinical studies. For other unstudied statins, including atorvastatin, fluvastatin, lovastatin, and simvastatin, use of the lowest approved statin dose oruse of the lowest necessary statin dose based on a risk/benefit assessment , if higher doses are needed is recommended due to the potential for increased risk of myopathy, including rhabdomyolysis associated with higher exposure of statins.

Originally, the review team recommended the clinical comment for dabigatran etexilate specifically mention the dose adjustment for dabigatran (reduce dose of dabigatran to 75 mg twice daily) in the setting of moderate renal impairment. Instead Gilead proposed to "Clinical monitoring of dabigatran is recommended when coadministered with VOSEVI. Refer to dabigatran etexilate prescribing information for dose modification recommendations." The review team accepts this change because the dose adjustment for dabigatran could change in the future; however, the statement must include "in the setting of moderate renal impairment".

- Thorough QT trial or other QT assessment

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

- 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 Virology

Please refer to the review by Dr. Lisa Naeger for a detailed assessment of the cell culture and in vivo virology data. An approval action was recommended by Dr. Naeger. The results from the effect of baseline NS5A inhibitor and nucleotide analog NS5B inhibitor resistance-associated substitutions/ polymorphisms (RAPs) and outcome (SVR12 and relapse rate) and virologic failures from POLARIS-1 and POLARIS-4 are summarized in this section.

Overall, in both POLARIS-1 and POLARIS-4, the presence of NS5A inhibitor, nucleotide analog NS5B inhibitor or NS3 protease inhibitor resistance-associated substitutions, did not affect SVR12 rates. SVR12 rates in subjects with or without baseline NS3 and NS5A resistance-associated substitutions in the POLARIS-1 and POLARIS-4 trials were all greater than or equal to 97%. Additionally previous duration of DAAs, time since DAA exposure or number of DAAs received in the past did not have an effect on SVR12 rates.

Few subjects receiving SOF/VEL/VOX experienced virologic failure in POLARIS-1 and POLARIS-4. Seven subjects (3%) experienced virologic failure in POLARIS-1, on treatment (1) or relapse (6): two with HCV genotype 1a, four with HCV genotype 3a and one with HCV genotype 4d. All subjects were cirrhotic and all had previous exposure to a SOF containing regimen. Six had a baseline NS5A inhibitor resistance-associated substitution at either position 30 or 90. All seven subjects had NS5A resistance-associated substitutions at failure. Two subjects had an NS3 resistance-associated substitution at the time of virologic failure; whereas no subjects had nucleotide analog NS5B resistance-associated substitutions at the time of virologic failure.

In POLARIS-4, one subject relapsed in the SOF/VEL/VOX group. No NS3 or NS5B resistance-associated substitutions emerged at relapse; however the M28T substitution was present at relapse.

Dr. Donaldson concluded good agreement between his independent analysis of the next generation sequencing (NGS) data and the analysis done by Gilead, with few exceptions. One RAS in the subject infected with HCV GT4d from POLARIS-1 contained an NS5A H54R RAS at 99% frequency at the post-treatment time point. As a result a PMR will be issued to determine the phenotype of NS5A H54R in the GT4d replicon.

7. Clinical/Statistical- Efficacy

This section focuses on the POLARIS-1 and -4 efficacy analyses conducted by the review team. Please refer to the Clinical Review by Dr. Kirk Chan-Tack, 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 Gileads' primary and secondary efficacy findings for the pivotal trials; however, the interpretation of the contribution of VOX in POLARIS-4 differed between FDA and Gilead. Each reviewer recommended approval for this NDA.

The primary endpoint for POLARIS-1 and -4 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 (Backus LI, et al and van der Meer AJ, et al).

Cirrhosis status was the stratification factor at randomization in POLARIS 1 and one of the two stratification factors in POLARIS 4. The methods for determining cirrhosis (liver biopsy, Fibroscan and FibroTest +APRI) were acceptable. In POLARIS-1 and -4, Fibroscan accounted for the majority of cirrhosis determination (72-73%) whereas FibroTest + APRI and liver biopsy accounted for 16-17% and 11-29% of the cirrhosis determination, respectively.

Please refer to Table 4 below for a summary of the clinical trial designs. No approved treatment options are available for NS5A inhibitor treatment-experienced patients; thus an active or historical control was not feasible. A placebo control was included primarily for safety comparison for GT1 (GT2-6 only received SOF/VEL/VOX). POLARIS-1 was designed to show superiority over an 85% performance goal based on the lower bound of the 95% confidence interval for the observed SVR12 rate in the study exceeding 85%. As stated in protocol, the basis for the 85% benchmark includes the overall trend toward increasing SVR rates in recent years and the general appeal of using a fixed clinically relevant threshold as a measure of treatment benefit of SOF/VEL/VOX for this population.

Per the review team's recommendation a SOF/VEL control arm was included in POLARIS-4 in order to assess the clinical benefit of SOF/VEL/VOX versus SOF/VEL in DAA-experienced subjects who have not previously received an NS5A inhibitor. The draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment states that if multiple genotypes are included in a single trial, then efficacy analyses should be conducted separately within each genotype. However, for uncommon HCV genotypes (genotype 5, 6 or 7) with potentially limited data, collective evidence of efficacy and safety will be assessed to determine the strength of evidence. The review team advised Gilead that a subset analysis by genotype was important and the results needed to be sufficiently compelling to support the contribution of VOX for each genotype. Nevertheless, Gilead designed POLARIS-4 to include two primary efficacy endpoint tests; the SVR12 rate for SOF/VEL/VOX and SOF/VEL groups were each separately compared with the performance goal of 85%.

Table 4: Key Efficacy Trials

Trial	Population	Study Arms and Comparator Groups (Number of Subjects Treated)
POLARIS-1	Genotype 1, 2, 3, 4, 5, and 6 NS5A inhibitor treatment-experienced*, without cirrhosis or with compensated cirrhosis	SOF/VEL/VOX 12 weeks (263) Placebo 12 weeks (152)
POLARIS-4	Genotype 1, 2, 3, and 4 DAA-experienced† who have not received an NS5A inhibitor, without cirrhosis or with compensated cirrhosis	SOF/VEL/VOX 12 weeks (182) SOF/VEL 12 weeks (151)

DAA: direct-acting antiviral; SOF: sofosbuvir; VEL: velpatasvir
*In clinical trials, prior NS5A inhibitor experience included daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir.
†In clinical trials, prior treatment experience included sofosbuvir, with or without prior experience with any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir).

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

POLARIS-1

POLARIS-1 is an ongoing randomized, double-blind, placebo-controlled, multicenter trial. The trial population consisted of adult subjects with genotype 1, 2, 3, 4, 5, or 6 HCV infection who previously failed a regimen containing an NS5A inhibitor. Randomization was stratified by the presence or absence of compensated cirrhosis. Only subjects with HCV genotype 1 were randomized. Due to the anticipated limited sample size, subjects with less common genotypes 2, 3, 4, 5, or 6, were not randomized and all received SOF/VEL/VOX.

Demographics and baseline characteristics were generally balanced across treatment groups. Almost half of the subjects enrolled had compensated cirrhosis. Of the 263 subjects treated with SOF/VEL/VOX the most common prior NS5A inhibitors were ledipasvir (LDV) (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasvir (3%).

The key efficacy findings are summarized in Table 5 below. Overall, 96% of subjects achieved SVR12. No subjects in the placebo group achieved SVR12. The SVR12 rates for SOF/VEL/VOX for 12 weeks also exceeded the protocol specified threshold of 85%. Six patients (2%) experienced virologic relapse. The majority (n=4) of the relapsers were infected with HCV genotype 3. The details of these patients are discussed in Section 6: Clinical Virology above.

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Table 5 POLARIS-1 Trial: Virologic Outcomes (12 Weeks after treatment) by HCV

	[TRADENAME] 12 Weeks (N=263)								
	Total (all GTs)[a] (N=263)	GT-1			GT-2 (N=5)	GT-3 (N=78)	GT-4 (N=22)	GT-5 (N=1)	GT-6 (N=6)
		GT-1a (N=101)	GT-1b (N=45)	Total[b] (N=150)					
SVR12	96% (253/263)	96% (97/101)	100% (45/45)	97% (146/150)	100% (5/5)	95% (74/78)	91% (20/22)	100% (1/1)	100% (6/6)
Outcome for Subjects without SVR									
On-Treatment Virologic Failure	<1% (1/263)	1% (1/101)	0/45	1% (1/150)	0/5	0/78	0/22	0/1	0/6
Relapse[c]	2% (6/261)	1% (1/100)	0/45	1% (1/149)	0/5	5% (4/78)	5% (1/21)	0/1	0/6
Other[d]	1% (3/263)	2% (2/101)	0/45	1% (2/150)	0/5	0/78	5% (1/22)	0/1	0/6

a. One subject with undetermined genotype achieved SVR12.
b. Four subjects had GT-1 subtypes other than GT-1a or GT-1b; all 4 subjects achieved SVR12.

c. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.
d. Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

In order to assess the contribution and benefit of adding VOX to SOF/VEL for patients previously treated with an NS5A inhibitor, we also reviewed published data (literature, abstracts and treatment guidelines) to assess the various retreatment strategies and SVR12 rates.

Limited data are available on retreatment of patients with HCV genotype 1 or 3 infection who have previously been treated with an HCV regimen containing an NS5A inhibitor. Published retreatment data are not available for patients with HCV genotypes 2, 4, 5 or 6 infection for whom prior treatment with an NS5A inhibitor has failed. According to AASLD treatment guidelines, the recommendation for HCV genotype 1 NS5A inhibitor treatment-experienced patients is deferral of treatment pending availability of data for patients with HCV genotype 1, regardless of subtype, in whom previous treatment with any HCV NS5A inhibitor has failed, who do not have cirrhosis, and do not have reasons for urgent retreatment. When using nucleotide-based (e.g., SOF) dual DAA therapy, a 24 week treatment duration is recommended, and weight-based ribavirin (RBV), unless contraindicated, should be added. Further, if available, nucleotide-based (e.g., SOF) triple or quadruple DAA regimens may be considered. In these settings, treatment duration ranges from 12 weeks to 24 weeks and weight-based ribavirin, unless contraindicated, is also recommended.(18) Table 2 summarizes the published treatment options that exist for subjects who previously received an NS5A inhibitor, along with the retreatment SVR12 results from various published retreatment strategies, and the SVR12 results from POLARIS-1 for comparison.

Although the evidence is generated across different trials, the SVR12 rate was higher for SOF/VEL/VOX compared with retreatment regimens cited in the literature for gentotype 1 and 3 patients. Overall, SVR12 rates ranged from 70-71% in HCV genotype 1 infected subjects previously treated with LDV/SOF and who were retreated with LDV/SOF for 12-24 weeks. In comparison, in POLARIS-1 the SVR12 rate was 97% for HCV genotype 1 infected subjects who previously received an NS5A inhibitor-based regimen. Also numerically higher SVR12 rates were seen in POLARIS-1 (95%) compared to published data from HCV genotype 3 infected patients who previously received SOF/VEL and who were retreated with SOF/VEL+RBV for 24 weeks (76%).

While some regimens administered to HCV genotype 1 infected subjects had similar SVR12 rates compared with patients treated with SOF VEL VOX in POLARIS-1, these regimens included either three or four DAAs with RBV and were administered for a longer duration of treatment (24 weeks). One trial noted that the SVR12 rates for retreatment with LDV/SOF for 24 weeks were affected by the presence of baseline NS5A resistance associated substitutions (60% with baseline NS5A resistance associated substitutions compared to 100% with no baseline NS5A resistance associated substitutions) (21). Whereas, in POLARIS-1 SVR12 rates were not impacted by baseline resistance associated substitutions. These differences highlight the benefits of SOF/VEL/VOX which is a RBV-free, 12-week regimen that is not impacted by baseline RAS.

The review team acknowledged the limited number of subjects with HCV genotypes 2, 4, 5 and 6 enrolled in POLARIS-1 and lack of published data for these genotypes in patients previously treated with an NS5A inhibitor. Given the strength of the evidence of SOF/VEL/VOX in HCV genotypes 1 and 3, noting that HCV genotype 3 is considered the “hardest to treat” genotype, the lack of currently approved treatment options for any patient previously treated with an NS5A inhibitor, the limitations of currently recommended retreatment options, and the favorable efficacy results in the less common genotypes, the review team recommended that the indication be extended to all HCV genotypes for patients previously treated with an NS5A inhibitor. Another factor in our decision was the reasonable safety profile demonstrated in both POLARIS-1 and POLARIS-4. The overall safety risks, including drug-drug interaction risks were acceptable for these patients with limited treatment options. Therefore we concluded the benefits of SOF/VEL/VOX outweigh the risks for adults who have HCV genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.

Table 6 Summary of Potential Retreatment Options and SVR12 rates for subjects who previously received an NS5A inhibitor

GT	Potential Retreatment Options Per AASLD Guidelines and Other Sources	Published Retreatment Results	POLARIS-1 results
1	LDV/SOF x 24 weeks SOF/VEL + RBV x 24 weeks SIM + SOF + RBV x 24 weeks ELB/GRZ + SOF + RBV x 12 weeks PrOD + SOF+ RBV x 24 weeks	- LDV/SOF failures/retreated with LDV/SOF x 24 weeks: 71% SVR12 (29/41, Lawitz, of note for patients with baseline NS5A RAS SVR12 is 60% (18/30) compared to 100% (11/11) if no baseline NS5A RAS) DCV/ASV failures/retreated with LDV/SOF x 12 weeks: (70% SVR12 (38/54, Akuta) - Short course ELB/GRZ + SOF failure/retreated with ELB/GRZ +SOF+ RBV: 100% SVR12 (23/23, Lawitz) - SOF/VEL based regimen failures/retreated with SOF/VEL + RBV: 97% SVR12 (33/34, Gane) - PrOD failures/retreated with PrOD + SOF+ RBV: 88% SVR12 (14/15, Poordad)	97% (146/150)
2	SOF/VEL + RBV x 24 weeks (recommended for prior SOF+RBV failures, no published data for NS5A failures aside from POLARIS 1)	Prior SOF/RBV failures/retreated with SOF/VEL + RBV: 93% SVR12 (13/14, Gane)	100% (5/5)
3	SOF/VEL + RBV x 12- 24 weeks, (add RBV and extend duration to 24 weeks especially if Y93H substitution is present)	SOF/VEL, SOF/VEL+RBV and SOF/VEL/VOX failures/retreated with SOF/VEL + RBV x 24 weeks: 78% SVR12 (14/18, Gane)	95% (74/78)
4	No available data		91% (20/22)
5	No available data		100% (1/1)
6	No available data		100% (6/6)

POLARIS-4

POLARIS-4 is an ongoing, randomized, open-label, active controlled trial. The patient population consists of subjects who previously failed a HCV DAA-containing regimen that did not include an NS5A inhibitor. Subjects with genotype 1, 2, or 3 HCV infection were randomized 1:1 to either SOF/VEL/VOX or SOF/VEL. Randomization was stratified by HCV genotype and by the presence or absence of cirrhosis. Subjects with genotype 4 HCV infection received SOF/VEL/VOX. No subjects with genotype 5 or 6 were enrolled.

Demographics and baseline characteristics were generally balanced across treatment groups. Overall 46% had compensated cirrhosis. The majority (85%) of subjects were previously treated with a nucleotide analog NS5B polymerase inhibitor (sofosbuvir): 69% had prior exposure to sofosbuvir with or without peginterferon alfa/ribavirin or ribavirin, 15% had prior exposure to sofosbuvir + HCV NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir) with or without peginterferon alfa/ribavirin, and <1% had prior exposure to sofosbuvir + an investigational HCV DAA. The remaining 15% of subjects without prior nucleotide analog NS5B polymerase inhibitor (sofosbuvir) exposure received investigational HCV DAAs or an approved HCV NS3/4A protease inhibitor, with or without peginterferon alfa/ribavirin.

The key efficacy findings are summarized in Table 7 below. Overall, 98% of subjects achieved SVR12. Only one subject treated with SOF/VEL/VOX experienced virologic relapse. During the review an issue arose regarding the classification of subject 00407-27557 who was infected with HCV genotype 1 infection and randomized to the SOF/VEL arm. This subject discontinued on Day 56 due to Grade 2 headache; HCV RNA was < 15 IU/mL at the Week 4 visit, the last visit prior to study drug discontinuation. Gilead classified this subject as relapse according to their statistical analysis plan definition “HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at end of treatment, confirmed with 2 consecutive values or last available posttreatment measurement”. Gilead notes this is consistent with other SOF-based statistical analysis plans. The review team’s interpretation of end of treatment is pre-specified or assigned treatment duration. Additionally, to be classified as a relapse, the subject must have completed the assigned treatment and had undetectable HCV viral load (VL) at the end of such treatment. If a subject prematurely discontinues while on assigned treatment, then there is no chance of him/her being categorized as a relapse. Unless subjects prematurely discontinued due to having an increasing VL, then they are placed into the “Other” category for failing to achieve SVR12. After further discussions with Gilead, the “other” classification was accepted and clarifying footnotes were included in labeling.

Table 7 POLARIS-4 Trial: Virologic Outcomes (12 Weeks After Treatment) by HCV Genotype

	VOSEVI 12 Weeks (N=(b) (4))	SOF/VEL 12 Weeks (N=(b) (4))
Genotype 1	[redacted]	
SVR12 rate		
Not achieving SVR12		
On-treatment virologic failure		
Relapse[a]		
Other[b]		
Genotype 1a		
SVR12 rate		
Not achieving SVR12		
On-treatment virologic failure		
Relapse[a]		
Other[b]		
Genotype 1b		
SVR12 rate		
Not achieving SVR12		
On-treatment virologic failure		
Relapse[a]		
Other[b]		
Genotype 2		
SVR12 rate	100% (31/31)	97% (32/33)
Not achieving SVR12		
On-treatment virologic failure	0% (0/31)	3% (1/33)
Relapse[a]	0% (0/31)	0% (0/33)
Other[b]	0% (0/31)	0% (0/33)
Genotype 3		
SVR12 rate	96% (52/54)	85% (44/52)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/52)
Relapse[a]	0% (0/54)	15% (8/52)
Other[b]	4% (2/54)	0% (0/52)
[redacted]		

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.
b. Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

The key review issue was to determine the contribution of VOX for the different genotypes. During Phase 3 development the review team recommended conducting efficacy analyses by genotype and advised Gilead that the data would need to be sufficiently compelling to support the contribution of VOX for each genotype.

In this trial, the additional benefit of SOF/VEL/VOX over SOF/VEL was not shown for all DAA-experienced patients for each genotype. The SVR12 rates are numerically higher for SOF/VEL/VOX compared to SOF/VEL in subjects with HCV genotypes 1a and 3, thereby demonstrating the added benefit of SOF/VEL/VOX over SOF/VEL only in these genotypes as required by the regulations pertaining to the combination rule. The additional benefit SOF/VEL/VOX over SOF/VEL was not shown

in adults with HCV genotype 1b, 2, 4, 5, or 6 infection previously treated with SOF without an NS5A inhibitor. Specifically, for HCV genotype 1b, the SVR12 rates were almost identical (96 and 95%) with no virologic failures or relapses. For HCV genotype 2, the SVR12 rates were similar (100% and 97%). Notably, one on-treatment virologic failure was reported in an SOF/VEL treated subject with HCV genotype 2. SOF/VEL/VOX is likely to be effective in HCV genotypes 4, 5, and 6; however, without comparative data for HCV genotypes 4, 5, and 6 (noting no data are available for genotype 5 and 6) we are not able to determine if VOX is needed for these genotypes in DAA-experienced subjects who are NS5A inhibitor treatment-naïve. SVR12 rates in NS5A treatment-naïve subjects with HCV genotype 4, 5 or 6 infection are likely similar for those receiving either a two-drug regimen containing SOF/VEL or a three-drug regimen containing SOF/VEL/VOX; (b) (4)

Gilead submitted additional analyses to show that the difference in SVR12 rates between SOF/VEL/VOX and SOF/VEL is due to cumulative negative host factors (cirrhosis, non-CC IL28B, male, baseline HCV RNA≥ 800,000 IU/mL, BMI ≥30 kg/m^2) and the contribution of VOX is demonstrated for all HCV genotypes. Please refer to Drs. Qi and Chan-Tack's reviews for details regarding the analyses performed by FDA and Gilead. In the analyses presented the differences between treatment groups were driven by HCV genotype 1a and 3 subjects. Gilead also submitted top line data from 10 HCV genotype 2 infected subjects receiving SOF/VEL +/- RBV for 12-24 weeks in a non-IND trial (b) (4). However, the review team does not have sufficient details from the trial to understand the reason(s) why the SVR12 rate in the non IND-trial was 70% compared to 97% in POLARIS-4 among NS5A treatment-naïve subjects who were also SOF experienced. (b) (4)

(b) (4)

Our rationale for defining the POLARIS-4 patient population as having previously been treated with an HCV regimen containing SOF without an NS5A inhibitor in the proposed labeling is based on the findings that the majority of subjects had failed a SOF-containing regimen (85%) and the contribution of VOX was not evident in those whose prior HCV treatment regimen did not contain SOF, including genotype 1a. Therefore, section 14 of the label will only include the SVR12 rates for those subjects who previously received SOF. See tables 8a and 8b below. Table 8b appears in the product labeling.

(b) (4)

Table 8b **POLARIS-4 Trial: Virologic Outcomes by HCV Genotype in VOSEVI-Treated Subjects* and SOF/VEL-Treated Subjects* Without Cirrhosis or With Compensated Cirrhosis (12 Weeks After Treatment)**

*Subjects with prior exposure to a SOF-containing regimen	VOSEVI 12 Weeks (N=139)	SOF/VEL 12 Weeks (N=125)
Overall (Genotypes 1, 2, and 3)		
SVR12	97% (135/139)	88% (110/125)
Not achieving SVR12		
On-treatment virologic failure	0% (0/139)	1% (1/125)
Relapse[a]	1% (1/139)	10% (13/124)
Other[b]	2% (3/139)	1% (1/125)
Genotype 1		
SVR12	96% (52/54)	85% (34/40)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/40)
Relapse[a]	2% (1/54)	13% (5/40)
Other[b]	2% (1/54)	3% (1/40)
Genotype 1a		
SVR12	97% (35/36)	82% (23/28)
Not achieving SVR12		
On-treatment virologic failure	0% (0/36)	0% (0/28)
Relapse[a]	3% (1/36)	18% (5/28)
Other[b]	0% (0/36)	0% (0/28)
Genotype 1b		
SVR12	94% (17/18)	92% (11/12)
Not achieving SVR12		
On-treatment virologic failure	0% (0/18)	0% (0/12)
Relapse[a]	0% (0/18)	0% (0/12)
Other[b]	6% (1/18)	8% (1/12)
Genotype 2		
SVR12	100% (31/31)	97% (32/33)
Not achieving SVR12		
On-treatment virologic failure	0% (0/31)	3% (1/33)
Relapse[a]	0% (0/31)	0% (0/32)
Other[b]	0% (0/31)	0% (0/33)
Genotype 3		
SVR12	96% (52/54)	85% (44/52)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/52)
Relapse[a]	0% (0/54)	15% (8/52)
Other[b]	4% (2/54)	0% (0/52)

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the end-of-treatment assessment.
b. Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

For adults previously treated with an HCV regimen containing SOF without an NS5A inhibitor, our approach to the benefit-risk assessment in the decision to only indicate SOF/VEL/VOX for adults with HCV genotype 1a or 3 infection and not for adults with HCV genotype 1b, 2, 4, 5, or 6 infection was based on the benefits as discussed above along with the potential risks. Because the additional benefit of SOF/VELVOX over SOF/VEL was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor, in our view the potential risks outweighed the benefits. (b) (4)

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. Efficacy was demonstrated in adult patients with HCV genotypes 1,2,3,4,5, or 6 infection who have previously been treated with an HCV regimen containing an NS5A inhibitor.

Efficacy was also demonstrated in adult patients with HCV genotype 1a and 3 infection who have previously been treated with an HCV regimen containing SOF without an NS5A inhibitor. The indication applies to patients without cirrhosis or with compensated cirrhosis. SOF/VEL/VOX is not recommended for patients with decompensated cirrhosis due to higher exposures of VOX in these patients and because the safety and efficacy have not been established in patients with decompensated cirrhosis. In POLARIS-1 and POLARIS-4, SVR12 rates ranged from 91-100% depending on patient population and HCV genotype. SOF/VEL/VOX fills an important unmet medical need for patients with HCV genotypes 1-6 who previously received an NS5A inhibitor-based treatment regimen.

8. Safety

This section provides a focused summary of the safety data from the two pivotal trials, POLARIS-1 and POLARIS-4. Additionally data from POLARIS-2 and POLARIS-3 were submitted as supportive safety data and included eight week data with SOF/VEL/VOX in DAA treatment-naïve subjects with HCV genotypes 2 and 3.

Data from POLARIS-1 and -4 were pooled and separately, data from POLARIS-1,-2,-3 and -4 were pooled (integrated safety population) because the trial populations were comparable in terms of underlying disease severity. Given that the majority of events (approximately 80%) occurred during the first 8 weeks of treatment in POLARIS-1 and -4, inclusion of SOF/VEL/VOX 8 week data (i.e. POLARIS-2 and -3) as part of the integrated safety population, is reasonable. Overall the safety findings from POLARIS-1 and POLARIS-4 are similar to the integrated safety population. For a complete description of these data and the Agency's independent safety analyses, please refer to the Clinical Review by Dr. Kirk Chan-Tack.

Adequacy of the safety database, Applicant's safety assessments, and submission quality

The safety database for SOF/VEL/VOX 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 1056 subjects received at least one dose of SOF/VEL/VOX in the pooled phase 3 integrated safety population, of which 445 subjects were enrolled in POLARIS-1 and POLARIS-4 and received SOF/VEL/VOX 400/100/100 mg for 12 weeks.

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, and results of laboratory tests

Deaths
In the database four deaths were reported, one in POLARIS-3 (post-treatment Day 78 due to hypertension), two in POLARIS-4 (post-treatment Day 133 due to brain intraparenchymal hemorrhage from a ruptured arteriovenous malformation and post-treatment Day 2 due to heroin and fentanyl overdose) and one in a non-Applicant sponsored trial (on-treatment death due to HCC with brain and spine metastases).

We concur with Dr. Chan-Tack's assessment that the deaths were unrelated to study medication.

Serious Adverse Events (SAEs)

The incidence of nonfatal SAEs was low (9 subjects: 2%) in POLARIS-1 and -4. In comparison, 3% of subjects in the SOF/VEL POLARIS-4 control group and 5% of subjects in the placebo POLARIS-1 control group experienced an SAE. Cerebral hemorrhage was the only SAE occurring in more than one SOF/VEL/VOX subject. Both subjects had pre-existing hypertension. Cerebral hemorrhage events have occurred with other SOF-containing regimens and generally in patients with underlying risk factors for cerebral hemorrhage. Labeling is not recommended at this time for SOF/VEL/VOX or any SOF-containing regimen; however, routine pharmacovigilance to assess cerebral hemorrhage is recommended for all SOF-containing regimens. No new or unexpected events were seen in the integrated safety summary population or in the safety update. All SAEs were considered not related to study medication.

Discontinuations due to AEs

One subject from the integrated safety population permanently discontinued SOF/VEL/VOX due to an adverse event. The patient in POLARIS-1 experienced a Grade 3 angioedema event one day after starting treatment with ramipril. Although the temporal relationship between ramipril initiation and the angioedema suggests the event maybe due to ramipril, angioedema-like swelling and angioedema events were recently included in the post-marketing section of the Harvoni label. Therefore, we recommended angioedema-like swelling and angioedema are included in the postmarketing subsection for all SOF and SOF-containing labels (Epclusa and Vosevi) for consistency. Additionally, three subjects did interrupt SOF/VEL/VOX treatment due to an adverse event. No subjects receiving SOF/VEL/VOX for 8 weeks discontinued SOF/VEL/VOX due to an adverse event.

Four subjects receiving SOF/VEL discontinued SOF/VEL due to an adverse event that included a Grade 2 headache, Grade 1 URI, Grade 3 *Clostridium difficile* colitis and Grade 2 pelvic fracture. Three subjects discontinued placebo due to an adverse event.

Common AEs and Laboratory Abnormalities

The most commonly reported adverse events in POLARIS-1 and -4 (at least 5%, all grade, all causality) for SOF/VEL/VOX were headache (28%), fatigue (28%), diarrhea (19%), nausea (13%), insomnia (7%), asthenia (7%) and back pain (5%). The majority of events were Grade 1 in severity. Review of adverse reactions (ADRs) (all grades, related) in POLARIS-1 and -4 for SOF/VEL/VOX showed similar results. Headache, fatigue, diarrhea and nausea were the most commonly reported ADRs. The clinical review team recommended Gilead revise section 6 to show ADRs separately by trial vs pooling the SOF/VEL/VOX arms in POLARIS 1 and 4 compared to placebo from POLARIS-1. The SOF/VEL comparison in POLARIS-4 provides important safety information regarding the contribution of VOX to the ADRs reported. Among subjects receiving SOF/VEL/VOX, the reported ADRs were consistent in POLARIS-1 and -4. Overall, more subjects in the SOF/VEL/VOX arm experienced ADRs compared to subjects receiving placebo in POLARIS-1. In POLARIS-4 diarrhea and nausea ADRs occurred more frequently in subjects receiving SOF/VEL/VOX compared to SOF/VEL.

Table 9: ADRs occurring in 5% or greater in any treatment arm

ADR	POLARIS-1		POLARIS-4	
	Placebo (n=152)	SOF/VEL/VOX (n=263)	SOF/VEL/VOX (n=182)	SOF/VEL (n=151)
Headache	14%	21%	23%	23%
Fatigue	15%	(b) (4)%	19%	23%
Diarrhea	9%	13%	14%	3%
Nausea	(b) (4)%	13%	10%	3%
Asthenia	4%	6%	4%	6%
Insomnia	3%	6%	3%	(b) (4)1%
				(b) (4)

The clinical review team recommends including a "Less Common Adverse Reaction" subsection of the label for consistency with other SOF and SOF-based labels (Harvoni and Epclusa). Rash and depression will be included.

Laboratory Abnormalities

Laboratory abnormalities in POLARIS-1 and -4 were infrequent. Also see section below on special safety concerns for further discussion regarding hepatotoxicity. No new safety signals were identified.

Data for three laboratory abnormalities are proposed for labeling and include lipase, creatine kinase (CK), and bilirubin. Elevated CK and lipase values are likely SOF-related laboratory abnormalities and are already included in labeling for Sovaldi, Harvoni and Epclusa. Even though numeric differences were not seen compared to placebo, the percent of subjects with CK and lipase abnormalities were generally consistent with that observed in the Sovaldi, Harvoni and Epclusa trials. For consistency, elevated CK and lipase values will be included in the Vosevi label. Of note no subjects developed rhabdomyolysis or pancreatitis. The CK and lipase elevations were transient and asymptomatic.

Total bilirubin is included in labeling due to inhibition of OATP1B1 and OATP1B3. Overall increases in total bilirubin (≤ 1.5 x ULN) were seen in 5% of subjects without cirrhosis and 9% of subjects with compensated cirrhosis. The table below summarizes the graded bilirubin changes during the trial. The majority of the bilirubin abnormalities were Grade 1. No cases of jaundice were reported.

Table 10: Bilirubin

Parameter and max Analysis Toxicity Grade	POLARIS-1		POLARIS-4	
	SOF/VEL/VOX 12 Week N=263	PBO 12 Week N=152	SOF/VEL/VOX 12 Week N=182	SOF/VEL 12 Week N=151
Increased Total Bilirubin (mg/dL)				
Grade 1 (>1 to 1.5 × ULN)	13 (5%)	6 (4%)	17 (9%)	3 (2%)
Grade 2 (>1.5 to 2.5 × ULN)	6 (2%)	4 (3%)	6 (3%)	2 (1%)
Grade 3 (>2.5 to 5 x ULN)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (>5 x ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Hematologic laboratory abnormalities are not recommended for labeling because the frequency of any hematologic laboratory abnormality was low and similar to placebo. Thrombocytopenia was the only laboratory abnormality reported in greater than 5%; however the proportion of subjects with decreased platelets was comparable across all treatment arms in POLARIS-1 and -4.

Other than numeric differences in bilirubin elevations in subjects without cirrhosis compared to subjects with compensated cirrhosis, no other safety differences were seen by age, sex or race.

Special safety concerns

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

Hepatotoxicity

A comprehensive safety evaluation was conducted by Dr. Chan-Tack, 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 for consistency with other SOF-containing NDA reviews and because this regimen includes an NS3/4A protease inhibitor which is not recommended in subjects with CPT B or CPT C cirrhosis. Please refer to the clinical review for review criteria and further details.

In summary, 46 cases met at least one of the five criteria for IAC review from POLARIS-1, -2, -3 and -4. The IAC identified one probable DILI case and one possible DILI case. The probable case occurred in a 50 year old woman with cirrhosis who started oral contraceptives one month prior to study initiation. She had an unexplained increase in ALT and AST in Week 2 of SOF/VEL+VOX+RBV. We agree with Dr. Chan-Tack's analysis that DILI cannot be excluded; however, the start of oral contraceptives one month prior may confound this case. The possible DILI case occurred in a 54 year old cirrhotic male whose ALT/AST increased at Week 8; however he had Grade 2 ALT and Grade 3 AST at baseline. Binge drinking was also reported but not confirmed; therefore the IAC determined DILI was possibly the cause of the ALT and AST elevations.

Dr. Chan-Tack also reviewed the hepatic AEs from the integrated safety summary population and 12 subjects reported a hepatic event, all were considered unrelated. An analysis to evaluate Grade 2 or higher ALT/AST in subjects receiving concomitant SOF/VEL/VOX and estrogen use was conducted by Dr. Chan-Tack. No significant drug-drug interaction was observed; however, a Grade 3 ALT elevation was observed in one subject in the drug-drug interaction trial. Additionally Grade 3 ALT increases were seen with Viekira Pak, another approved regimen containing an NS3/4A protease inhibitor. Two cases of Grade 3 ALT were identified (DILI case summarized above and subject in drug-drug interaction trial).

We agree with the assessment by Dr. Chan-Tack and the IAC that the totality of the data does not suggest clear evidence of DILI with SOF/VEL/VOX use. Additional analyses conducted by Dr. Chan-Tack do not raise any hepatotoxicity safety concerns at this time. Also specific labeling is not recommended for ALT increases in women receiving SOF/VEL/VOX and estrogens. 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. Although SOF is structurally different than BMS-986094, 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. Of note amiodarone was not permitted in all Phase 3 POLARIS trials.

As shown in the clinical review, cardiac events in POLARIS-1 and -4 were infrequent (all cause, all grade). Numerically more events were seen in the placebo arm (6%) compared to 3% in the SOF/VEL/VOX arm and 4% in the SOF/VEL arm. Most events were mild or moderate in severity. Three

SAEs occurred and included unstable angina, atrial fibrillation and ventricular fibrillation; none were considered related.

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.

In sum, no cardiac signal was detected in the extensive analyses conducted for POLARIS-1 and -4, the integrated safety population or the safety update report.

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, LDV/SOF and SOF/VEL 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/VOX-treated subjects occur below the 5% ADR cutoff for the POLARIS -1 and -4 trials, the clinical 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/VOX subjects (3%) compared to placebo subjects (1%) supporting a causal association between rash and SOF/VEL/VOX treatment, (2) rash events reported in the current SOF, LDV/SOF and SOF/VEL/VOX 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 Behaviors NEC")

No clear indication of increased risk of depressive events was seen compared to placebo. Depressive events were seen in 1% of subjects receiving SOF/VEL/VOX, SOF/VEL and placebo. For consistency with SOF, LDV/SOF and SOF/VEL product labeling, depressive events are recommended for inclusion in the package insert.

Rhabdomyolysis and Pancreatitis

No cases of clinical rhabdomyolysis and pancreatitis were observed in the integrated safety population.

Although no clinical cases were observed the label will still include the CK and lipase laboratory abnormalities to alert clinicians of the potential risk and provide consistency with the SOF, LDV/SOF and SOF/VEL labels.

9. Advisory Committee Meeting

This NDA was not presented at the Antimicrobial Drug Advisory Committee because SOF/VEL/VOX 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. An Agreed PSP was issued on April 29, 2016. (b) (4)

Based on the results of POLARIS-2 and -3, (b) (4) Gilead amended the Agreed PSP on December 6, 2016 and modified the plan to only evaluate a 12-week regimen in DAA-experienced children ages 12 to 17. Both the Division and PeRC agreed to the deferral for trials in DAA-experienced children 12-17 years of age and a waiver for trials in children < 12 years of age because:

- there is a high rate of spontaneous viral clearance and lack of significant disease progression in children < 3 years of age;
- DAAs are anticipated to be approved first for adolescents, therefore few children < 12 years of age will have been treated with a DAA; and
- as more women of childbearing age with HCV infection are diagnosed and treated with DAA regimens with high efficacy, the rate of maternal transmission is anticipated to decrease so that fewer new infections will be observed over time in younger children.

Please refer to Dr. Chan-Tack's review for details regarding the proposed pediatric development plan.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI) Inspections

Four 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. Chan-Tack'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:
  (b) (4) POLARIS-1 demonstrated efficacy for HCV genotypes 1-6 in patients who previously received an NS5A inhibitor. POLARIS-4 demonstrated efficacy in HCV genotypes 1a and 3 in patients who previously received SOF without an NS5A inhibitor. (b) (4)

Furthermore, Gilead accepted the following sub-bullet in the INDICATIONS and USAGE section of the label.

- Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

- DOSAGE AND ADMINISTRATION section:
  - This section was updated to reflect the indicated patient populations. Please refer to section 7 for full details regarding the rationale for the indicated patient population from POLARIS-4.

- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS sections:
  - All DAAs have a BOX WARNING for HBV reactivation and will be included in this label
  - A CONTRAINDICATION for rifampin is recommended and accepted by Gilead
  - All SOF-containing products have a WARNNG and PRECAUTION regarding use with amiodarone and bradycardia and will be included in this label

- ADVERSE REACTIONS section
  - Gilead agreed to the modified display of ADRs (display by trial with each comparator) and to include Rash and Depression as less common events

- DRUG INTERACTIONS section
  - Gilead agreed with the recommendations to contraindicate rifampin, to modify the clinical comment for pitavastatin (not recommended) and to include text regarding use of SOF/VEL/VOX and dabigatran in patients with moderate renal impairment

- CLINICAL STUDIES section:
  - Gilead agreed to the final description of POLARIS-4, tabular display and text regarding SVR12 results

Other Labeling

- The Division of Medication Error Prevention and Analysis concurred with the proprietary name, VOSEVI
- Patient Information is still under discussion
- Carton and container labeling are deemed acceptable

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

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

Postmarketing Requirements (PMRs) and Commitments (PMCs)

Two PMRs are proposed. No PMCs are recommended.

Below is a recommended list of PMRs.

PMR Description:	Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of VOSEVI in pediatric subjects 12 through less than 18 years of age with chronic hepatitis C virus (HCV) infection and who have been previously treated with HCV direct-acting antivirals (DAA-experienced).

PMR Schedule Milestones:	Final Protocol Submission:	March 2018
	Study/Trial Completion:	January 2021
	Final Report Submission:	July 2021

PMR/PMC Description:	Please determine the phenotype of NS5A H54R against velpatasvir in the GT4d replicon and report fold shifts in the EC_{50} value.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	N/A
	Study/Trial Completion:	N/A
	Final Report Submission:	01/15/2018

14. Summary Assessment

In summary, new and important populations of individuals with chronic hepatitis C viral infection who have failed prior DAA therapy now have a new treatment option with the fixed-dose combination (FDC) of SOF/VEL/VOX. Safety and efficacy in non-cirrhotic and compensated cirrhotic patients have been demonstrated in POLARIS-1 and -4 trials. The data showed substantial evidence of effectiveness to support approval. Based on the favorable benefit-risk assessment, SOF/VEL/VOX is recommended for approval in adults with HCV genotypes 1-6 infection who have previously been treated with an HCV regimen containing an NS5A inhibitor. The FDC is only recommended for those with HCV genotypes 1a and 3 infection who have previously been treated with an HCV regimen containing SOF without an NS5A inhibitor, because the benefit of adding VOX to SOF/VEL was not shown in HCV genotypes 1b, 3, 4, 5 or 6 in POLARIS-4. With this new FDC and other approved DAAs in the armamentarium, along with public health recommendations for testing and treatment, we are moving even closer to eradicating hepatitis C and its attendant morbidity and mortality.

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/s/

KIMBERLY A STRUBLE
07/13/2017

DEBRA B BIRNKRANT
07/13/2017
I agree with Dr. Chan-Tack's assessment along with the multidisciplinary team's assessments described in the combined Division Director and CDTL review.