CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209195Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	209195
Priority or Standard	Priority
Submit Date(s)	December 8, 2016
Received Date(s)	December 8, 2016
PDUFA Goal Date	August 8, 2017
Division/Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Kirk Chan-Tack, MD
Review Completion Date	May 5, 2017
Established Name	sofosbuvir and velpatasvir and voxilaprevir
(Proposed) Trade Name	Vosevi®
Applicant	Gilead Sciences, Inc.
Formulation(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir and 100 mg voxilaprevir
Dosing Regimen	One tablet orally once daily
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 infection

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Glossary

AE	adverse event
APRI	aspartate aminotransferase: platelet ratio index
AUC	area under the concentration-time curve
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHC	Chronic Hepatitis C
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CPT	Child-Pugh-Turcotte score
CSR	clinical study report
CYP	cytochrome P450
DAA	direct acting antiviral
DAIDS	Division of AIDS
DMC	data monitoring committee
DDI	drug-drug interaction
DILI	drug-induced liver injury
ECG	electrocardiogram
ECI	event of clinical interest
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FU	follow up
GT	genotype
HCV	hepatitis C virus
IAC	Independent Adjudication Committee
ICH	International Conference on Harmonization
IND	Investigational New Drug
IFN	interferon alfa
ITG	immediate treatment group
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease score
NC	noncirrhotic

NDA	new drug application
NME	new molecular entity
OSI	Office of Scientific Investigation
PBO	placebo
PD	pharmacodynamics
PI	protease inhibitor
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPI	patient package insert
PR	pegylated interferon alfa and ribavirin
PREA	Pediatric Research Equity Act
PT	Preferred Term (aka Dictionary Derived Term)
RAP	resistance associated polymorphism
RAS	resistance associated substitution
RBV	ribavirin
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOF	sofosbuvir
SVR	sustained virologic response
TE	treatment experienced
TEAE	treatment emergent adverse event
TN	treatment naïve
TW	treatment week
VEL	velpatasvir
VOX	voxilaprevir
US	United States

1 Executive Summary

1.1. Product Introduction

Vosevi® (SOF/VEL/VOX) is a fixed dose combination (FDC) tablet containing three direct acting antiviral (DAA) agents that interfere with critical steps in the replication cycle of hepatitis C virus (HCV). Sofosbuvir (SOF) is a nucleotide analog inhibitor of HCV nonstructural protein 5B (NS5B) polymerase, which is essential for viral replication. SOF is currently approved for use in combination with other agents for the treatment of chronic HCV infection in adults and is commercially available as a single entity (tradename Sovaldi®; NDA 204671) and in combination with ledipasvir (LDV) in an FDC tablet (LDV/SOF, tradename Harvoni®; NDA 205834) and in combination with velpatasvir (VEL) in an FDC tablet (SOF/VEL, tradename Epclusa®; NDA 208341). Velpatasvir (VEL) inhibits activity of the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. VEL is commercially available as Epclusa. Voxilaprevir (VOX) is an HCV NS3/4A protease inhibitor (PI). VOX is a new molecular entity (NME) that will be available only in the FDC product currently under review.

The Applicant's proposed indication is treatment of patients with chronic HCV infection (b) (4) The Applicant's recommended dosage for noncirrhotic subjects and subjects with compensated cirrhosis is one tablet by mouth once daily for 12 weeks. The Applicant has not proposed a different dose or duration based on HCV genotype (GT).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from the POLARIS-1 and POLARIS-4 Phase 3 trials included in this application provide substantial evidence of effectiveness as required by law 21 CFR 314.126(a)(b) to support approval of SOF/VEL/VOX x 12 weeks for treatment of chronic HCV infection without cirrhosis or with compensated cirrhosis (Child Pugh Turcotte [CPT] A) in the following populations:

- Genotype 1, 2, 3, 4, 5, or 6 in NS5A inhibitor treatment-experienced adults
- Genotype 1a or 3 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve

The overall sustained virologic response rates at post-treatment week 12 (SVR12), considered a virologic cure, were 96% among subjects treated with SOF/VEL/VOX for 12 weeks in POLARIS-1; and 97% for subjects treated with SOF/VEL/VOX for 12 weeks in POLARIS-4.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Sofosbuvir (SOF) is a hepatitis C virus (HCV) NS5B 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 subpopulations include DAA-experienced patients 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 (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 have been approved that confer SVR12 rates greater than 93% for HCV GT 1, 2, 3, 4, 5, or 6-infected patients (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 NS5B polymerase inhibitor-containing regimens. In NS5A inhibitor treatment-experienced adults, SOF/VEL/VOX demonstrated SVR12 rates ranging from 91-100% depending on the HCV GT. In NS5B polymerase inhibitor treatment-experienced and NS5A inhibitor treatment-naïve adults, SOF/VEL/VOX demonstrated SVR12 rates ranging from 94-98% in HCV GT1a and GT3; these SVR12 rates were numerically higher than SOF/VEL SVR12 rates in HCVT GT1a and GT3. For these DAA-experienced patients with compensated liver disease, SOF/VEL/VOX is a highly 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 Boxed 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 DAA drugs for CHC coinfection. 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 in NS5A inhibitor treatment-experienced adults
(2) Genotype 1a or 3 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve

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, it is estimated that over 130 million people are infected with HCV, including approximately 3 million people in the United States (US). • There are at least seven distinct HCV genotypes (GTs). 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 (in combination with sofosbuvir); simeprevir (in combination with sofosbuvir); sofosbuvir/velpatasvir (+ ribavirin in CPT B and C)	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ GT2: sofosbuvir + ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ GT3: daclatasvir + sofosbuvir; sofosbuvir + ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ GT4: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir with ribavirin; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ GT5: ledipasvir/sofosbuvir; sofosbuvir/velpatasvir (+ ribavirin in CPT B and C) ○ GT6: 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. For treatment-experienced patient populations, such as NS5A inhibitor treatment-experienced patients (evaluated in POLARIS-1), as well as nucleotide analog NS5B polymerase inhibitor treatment-experienced patients who are NS5A inhibitor treatment-naïve (evaluated in POLARIS-4), a limited amount of data exists about options not currently in approved labels and strategies that failed. Most of these other options are 24 week, RBV-containing regimens with a wide range of SVR12 rates (70-97% in GT1; 93% in GT2; 76% in GT3) and SVR12 rates are impacted by baseline RAS.	options. 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 prior DAA treatment because no approved regimens are available.
Benefit	• The efficacy of SOF/VEL/VOX was established in two Phase 3 clinical trials which cumulatively evaluated 445 subjects in the SOF/VEL/VOX treatment arms. 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 GT 1, 2, 3, 4, 5, or 6. Subjects received SOF/VEL/VOX x 12 weeks or placebo x 12 weeks.	Two clinical trials provide substantial evidence of effectiveness of SOF/VEL/VOX x 12 weeks in subjects with compensated liver disease for treatment of the following

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>

POLARIS-4: DAA-experienced subjects who have not previously received NS5A inhibitors with compensated liver disease and HCV GT 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 GT.

POLARIS-1: SVR12 by HCV 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>
POLARIS-4: SVR12 by Treatment Arm and HCV GT n (%)
<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>51/54 (94%)</td><td>19/19 (100%)</td><td>177/182 (97%)</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 GT5 or GT6 subjects were enrolled in POLARIS-4

In POLARIS-1, SVR12 rates were comparable across GTs. Subgroup analyses demonstrated that cirrhosis, prior DAA treatment failure, and baseline RAS (NS5A, NS3, NS5B) did not impact SVR12 rates. HCV GT1 and GT3 comprise the majority of subjects in POLARIS-1. Subjects with HCV GT1 and GT3 had 95-97% SVR12, confirming robust efficacy. SOF/VEL/VOX is also recommended for HCV GT 2, 4, 5, and 6 NS5A inhibitor treatment-experienced adults, recognizing the limited number of enrolled subjects in these HCV GT subgroups. Based on high SVR12 results in GT1 and GT3, the most difficult to treat GTs, it is reasonable to extend the indication to other GTs for these difficult to treat populations with unmet medical need.

</td><td>patient populations:
- CHC GT1-6 (NS5A inhibitor treatment-experienced adults)
- CHC GT1a or 3 (nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve)

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In POLARIS-4, the contribution of VOX is established in HCV GT1a and GT3 (94-98% 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 GT1a (98% vs. 89%) and HCVT GT3 (94% vs. 85%) infection. • In POLARIS-4, the contribution of VOX has not been established for HCV GT1b, 2, 4, 5 and 6. Comparable SVR12 rates were seen with SOF/VEL/VOX and SOF/VEL in subjects with HCV GT1b and GT2. No comparison data are available for HCV GT 4, 5, and 6. Given these data, no additional benefit of SOF/VEL/VOX has been established over SOF/VEL for HCV GT 1b, 2, 4, 5, and 6 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve. Therefore SOF/VEL/VOX is (b) (4) indicated for nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve with HCV GT 1a or 3. • Overall, demographic factors did not impact SVR12 rates in either trial.	
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. • Headache, fatigue, and diarrhea were the three most commonly reported adverse drug reactions reported across trials.	SOF/VEL/VOX demonstrated an overall favorable safety profile.
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 occurred rarely	Safety concerns associated with SOF or VEL or VOX are adequately addressed in product

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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 Boxed 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.	labeling.

2 Therapeutic Context

2.1. Analysis of Condition

Chronic infection with hepatitis C virus (HCV) is a global health problem affecting an estimated 130-150 million people worldwide, including approximately 3 to 5 million people in the United States (US). At least seven different HCV GTs have been identified, numbered 1 to 7, with further breakdown into subtypes for several of the known GTs (e.g., GT 1 subtypes 1a and 1b).[1] In the US, GT 1 is the most common (70-75%; mostly subtype 1a), 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.[1-3]

HCV is a leading cause of chronic liver disease and is currently the most common reason for liver transplantation in the US. The natural history of chronic HCV (CHC) typically involves an asymptomatic period in the early stages with progression to cirrhosis, hepatocellular carcinoma (HCC), liver failure, or death, if left untreated. 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%.[4, 5]

The ultimate goal of HCV treatment is to reduce the occurrence of end-stage liver disease and its related complications by achieving a sustained virologic response (SVR), typically defined as unquantifiable HCV RNA 12 weeks following the completion of treatment (SVR12). SVR12 is generally considered a virologic cure. Achieving sustained HCV viral eradication through successful HCV treatment is associated with improvements in clinical outcomes such as decreased development of HCC, hepatic events, fibrosis, and all-cause mortality.[6-8]

Over the past five years, numerous direct acting antiviral (DAA) agents have been approved for the treatment of chronic HCV infection, initially in combination with pegylated interferon and ribavirin (PR). Treatment with these early regimens resulted in substantially higher SVR rates than PR alone, but the toxicity of PR, particularly the interferon component, made these regimens suboptimal. More recently approved all-oral DAA regimens have demonstrated high SVR12 rates without use of interferon, and in many cases, without ribavirin (RBV).

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 (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, there is a need for treatment options for patients who have failed DAA-only treatment, such as NS5A inhibitor-containing regimens or NS5B polymerase inhibitor-containing regimens. At the time of this review, a limited amount of data exists about options not currently in approved labels and

strategies that failed. Most of these other options are 24 week, RBV-containing regimens with a wide range of SVR12 rates (70-97% in GT1; 93% in GT2; 76% in GT3) and SVR12 rates are impacted by baseline RAS.[9-20]

Currently, there no FDA approved treatment options for patients who have failed DAA-only treatment, such as NS5A inhibitor-containing regimens or NS5B polymerase inhibitor-containing regimens. Consequently, an unmet need exists for new therapeutic options that can be used across HCV GTs and for patients with advanced stages of DAA treatment experience.

In the current NDA, the Applicant seeks approval for SOF/VEL/VOX for the treatment of HCV GT 1-6 in subjects without cirrhosis or with compensated cirrhosis (CPT A) in the following patient populations:

- NS5A inhibitor treatment-experienced adults
- nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve

2.2. Analysis of Current Treatment Options

Treatment with interferon (IFN)-sparing DAA regimens is the current standard-of-care for all HCV GTs. Table 1 provides a brief synopsis of single agents and fixed-dose combination products that are approved for use without IFN. For additional details regarding the specific populations that are indicated (e.g. patients with cirrhosis or undergoing liver transplant), please refer to the complete prescribing information for the product of interest.

Table 1. Summary of Currently Approved Interferon-Free Treatment for Chronic HCV Infection

Product (s) Name	Product Class	HCV GT	Year of Approval	Dosing/ Administration	Efficacy	TE population studied	Important Safety and Tolerability Issues
Sofosbuvir and velpatasvir (Epclusa®)	NS5B inhibitor (nucleotide)/ NS5A inhibitor	1, 2, 3, 4, 5, 6	2016	1 tablet orally once daily with or without RBV for 12 weeks	SVR 94-100%	Failed prior therapy with Peg-IFN + RBV ± NS3/4 PI*	No serious drug-specific toxicity identified
Elbasvir and grazoprevir (Zepatier®)	NS5A inhibitor, NS3/4A protease inhibitor (PI)	1, 4	2016	1 tablet orally once daily with or without RBV for 12 or 16 weeks	SVR 94-97%	Failed prior therapy with Peg-IFN + RBV ± NS3/4 PI*	Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients
Ombitasvir, paritaprevir and ritonavir (Technivie®)	NS5A inhibitor, NS3/4A PI, PK enhancer	4	2015	2 tablets orally once daily with RBV for 12 weeks	SVR 97-100%	Failed prior therapy with Peg-IFN + RBV	Hepatic decompensation and hepatic failure in cirrhotics; ALT elevation in all patients

Daclatasvir (Daklinza®)	NS5A inhibitor	1, 3	2015	1 tablet orally with sofosbuvir and with or without RBV for 12 weeks	SVR 82-97%	Failed prior therapy with Peg-IFN + RBV	No serious drug-specific toxicity identified
Ledipasvir and sofosbuvir (Harvoni®)	NS5A inhibitor/ NS5B inhibitor (nucleotide)	1, 4, 5, 6	2014	1 tablet orally once daily with or without RBV for 8, 12, or 24 weeks	SVR 93-99%	1) Failed prior therapy with Peg-IFN + RBV ± NS3/4 PI* 2) Failed prior therapy with Peg-IFN + RBV followed by subsequent Peg-IFN + RBV + NS3/4 PI*therapy	Serious symptomatic bradycardia when coadministered with amiodarone and another DAA (daclatasvir, ledipasvir or simeprevir)
Dasabuvir, ombitasvir, paritaprevir and ritonavir (Viekira Pak®)	NS5B inhibitor (non-nucleoside), NS5A inhibitor, NS3/4A PI	1	2014	2 FDC tablets once daily + 1 dasabuvir tablet twice daily (+/- RBV) for 12 or 24 weeks	SVR 95-99%	Failed prior therapy with Peg-IFN + RBV	Contraindicated for patients with decompensated liver disease; Risk of ALT elevations in all patients
Sofosbuvir† (Sovaldi®)	NS5B inhibitor (nucleotide)	2, 3	2013	One tablet orally once daily with RBV for 12 or 24 weeks	SVR 82-95%	Failed prior IFN-based therapy	Serious symptomatic bradycardia when coadministered with amiodarone and another DAA (daclatasvir, ledipasvir or simeprevir)
Simeprevir (Olysio®)	NS3/4 PI	1	2013	1 capsule orally once daily (with sofosbuvir) for 12 or 24 weeks	SVR 93-97%	Failed prior therapy with IFN (Peg-IFN or IFN) + RBV	Hepatic decompensation and hepatic failure; photosensitivity; rash

*Boceprevir, telaprevir, or simeprevir
†Excludes FDC containing sofosbuvir

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The SOF/VEL/VOX FDC tablet contains three distinct chemical entities. SOF was first approved as a single entity in 2013 and is currently approved for the treatment of chronic HCV GT 1, 2, 3

or 4 infection as a component of a combination antiviral treatment regimen. It was subsequently approved as a component of a FDC with ledipasvir (LDV/SOF, Harvoni) in 2014, and as a component of a FDC with velpatasvir (SOF/VEL, Epclusa) in 2016. The single entity, the LDV/SOF formulation, and the SOF/VEL formulation are commercially available in the US.

This is the first marketing application for any product containing VOX, a new molecular entity. At present, the Applicant does not plan to pursue marketing of a single-entity VOX formulation.

3.2. Summary of Presubmission/Submission Regulatory Activity

This section will summarize and focus only on the notable events which directly impacted the current SOF/VEL/VOX NDA.

An Investigational New Drug application (IND) for the SOF/VEL/VOX FDC was submitted on May 22, 2015 by Gilead Sciences, Inc. Clinical protocols and the development plan were reviewed by the Division throughout the SOF/VEL/VOX development program, with feedback provided regarding issues of dose selection, treatment duration, treatment regimen, and trial population.

An End of Phase 2 meeting was held on September 30, 2015 to discuss the SOF/VEL/VOX Phase 3 development program and the proposed registration plan to support a pangenotypic indication. The final Phase 3 POLARIS-1, -2, -3, and -4 protocol designs later submitted to the Division were determined to be acceptable.

A pre-NDA meeting (teleconference) was held on June 2, 2016 to discuss the NDA preparation and submission strategy. One agreement resulting from the pre-NDA meeting was involvement of an Independent Adjudication Committee (IAC) to screen for potential cases of drug-induced liver injury (DILI) in the POLARIS -1, POLARIS -2, POLARIS -3, POLARIS -4 Phase 3 trials and four supportive Phase 2 trials.

A Type B meeting (teleconference) was held on October 26, 2016 to discuss the top-line phase 3 results in support of the NDA submission as well as the contribution of VOX for the other HCV genotypes in the NS5A-naïve population.

The details of the milestone meetings can be found in the official meeting minutes archived in the Document Archiving, Reporting and Regulatory Tracking System (DARRTS). All previous reviews can also be accessed in DARRTS for additional information.

Fast track designation for SOF/VEL/VOX FDC treatment of chronic HCV GT 1 to 6 infection was granted on June 12, 2015. Breakthrough Therapy Designation for treatment of HCV GT 1 infection in patients who have previously failed an NS5A inhibitor containing DAA regimen was granted on February 19, 2016.

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, neither SOF/VEL/VOX nor VOX have been marketed in any country. SOF, LDV/SOF, and SOF/VEL are commercially available in the US, Canada, the European Union, and in over 20 other countries worldwide.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspection sites were selected from POLARIS-1 and POLARIS-4 as these contributed to the proposed indication. A total of 4 sites, 2 from each trial, were selected from the large number of sites per study based on enrollment. Both domestic and foreign sites were selected because this would be the first approval of VOX and for this FDC, and because a substantial amount of the clinical trial experience with this drug has been at foreign sites, particularly in Europe and Australia/New Zealand. Multinational studies were necessary because the prevalence of HCV GTs varies between geographic regions, and including trial sites around the world enables greater accrual of subjects with HCV GTs that are uncommon in the US. It is desirable to include foreign sites in the OSI inspections to verify the quality of conduct of the studies.

The final reports from the clinical site inspections were pending at the time this review was finalized.

4.2. Clinical Microbiology

This section includes a brief summary of key SOF, VEL and VOX nonclinical virology characteristics to support clinical trials evaluating this combination regimen. Specific discussions of clinical virology assessments conducted during the pivotal trials, development of resistance, impact of baseline NS5A resistance associated polymorphisms, and consequences of virologic failure, are provided in Sections 6 and 7 (clinical efficacy).

Hepatitis C virus is a small, positive-strand RNA virus belonging to the Flaviviridae family. At least seven HCV genotypes have been identified, numbered 1 to 7, with further breakdown into subtypes for several of the known GTs (e.g. GT1 subtypes 1a and 1b). DAAs act by inhibiting viral proteins involved in RNA replication. Despite having similar targets, various DAAs of the same class (e.g. NS3/4 PIs, NS5A inhibitors), may have differential degrees of activity across HCV GTs.

SOF is a prodrug which undergoes intracellular triphosphorylation to become the active compound, GS-461203, which acts as a uridine nucleotide analog. HCV NS5B RNA-dependent RNA polymerase incorporates GS-461203 into the growing RNA strand during transcription, resulting in premature chain termination. VEL inhibits NS5A, which has no known enzymatic activity but postulated activity in multiple aspects of the replication cycle. VOX inhibits NS3/4A

protease. SOF, VEL and VOX demonstrate activity across HCV GT 1-6 in cell-based replicon assays.

- SOF has EC50 values ranging from 15-264 nM against GT 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a in stable replicon cell lines. Replicons containing the S282T mutation displayed a reduced susceptibility to SOF with EC50 values across all 8 genotypes tested with the fold increase in EC50 for S282T ranging from 2.4 to 18.1 compared with the wild type from the corresponding genotypes. To determine the role of the other NS5B substitutions observed in SOF clinical studies, an expanded panel of HCV replicons bearing NS5B resistance-associated substitutions (RAS) in GT 1-6 was tested in a transient transfection assay for susceptibility to SOF. The substitutions examined included those observed in clinical studies in > 1 subject who failed a SOF-containing regimen or in vitro resistance selection assays with SOF in GT 1 to 6 replicons. Only S282T alone, or in combination with other NS5B substitutions, showed > 2.5-fold change in SOF EC50 in these studies.
- VEL has EC50 values ranging from 0.002-0.13 nM in GT 1a, 1b, 2a, 2b, 3a, 4a, 4d, 5a, 6a, and 6e in full length chimeric replicon assays. A transient chimeric replicon assay assessing the activity of VEL against replicons from 256 treatment-naïve HCV-infected subjects (GT1-6 from Phase 2 and 3 clinical studies) yielded similar results, with median EC50 values of 0.002 to 0.024. Replicon-based in vitro selection assays performed to characterize VEL resistance demonstrated variants at positions 24, 28, 31, 32, 58, 92, and 93; the most prevalent RAS were at positions 28, 31, and 93.
- VOX has EC50 values ranging from 0.33-6.6 nM in GT 1a, 1b, 2a, 2b, 3a, 4a, 4d, 5a, 6a, 6e, and 6n in full length chimeric replicon assays. Replicon-based in vitro selection assays performed to characterize VOX resistance demonstrated variants at positions 41, 156, and 168; the RAS selected in 2 or more genotypes were Q41H, A156V/T/L, and D168E/H/Y.
- SOF/VEL/VOX combination therapy: In vitro combination studies demonstrated additive antiviral effect and no antiviral antagonism. Assays assessing cross-resistance for SOF and VEL and VOX (SOF and VOX against NS5A mutant replicons; SOF and VEL against NS3mutant replicons; VEL and VOX against S282T mutant replicons) demonstrated no cross-resistance.

Please refer to Dr. Lisa Naeger's Clinical Virology review for additional details.

4.3. Product Quality

The commercial SOF/VEL/VOX drug product is an immediate-release FDC tablet containing 400 mg SOF and 100 mg VEL and 100 mg VOX. Each tablet contains 400 mg sofosbuvir, 100 mg velpatasvir, and 100 mg of voxilaprevir. The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: ferrosoferric oxide, iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide. No changes were made to the SOF/VEL 400/100/100 mg tablet formulation over the entirety of its clinical development. SOF/VEL/VOX tablet clinical supplies and stability lots were manufactured at the designated commercial manufacturing site, Gilead Cork.

The container closure system was selected based on the drug product attributes required to ensure a physicochemically stable dosage form during storage and shipment. The bottle size was selected based on a volume to accommodate tablets and polyester coil. The polyester coil type was chosen based on (b) (4) properties. The long-term and accelerated stability data demonstrate that the packaging is appropriate to maintain the quality of the drug product.

Please refer to the CMC Reviews by Dr. Shrikant Pagay, Dr. Min Li, Dr. Sithamalli Chandramouli, and Dr. Ying Wang for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity, and quality for SOF/VEL/VOX. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.4. Nonclinical Pharmacology/Toxicology

This section summarizes the key outcomes of the pharmacology/toxicology discipline review. Please see the Pharmacology/Toxicology review by Dr. Mark Powley for full details.

SOF: Nonclinical SOF safety studies to support the SOF/VEL/VOX FDC were reviewed previously: please refer to the Pharmacology/Toxicology reviews for NDA 204671 and NDA 205834 for detailed summary of SOF nonclinical data.

VEL: Nonclinical VEL safety studies to support the SOF/VEL/VOX FDC were reviewed previously: please refer to the Pharmacology/Toxicology reviews for NDA 208341 for detailed summary of VEL nonclinical data.

VOX: The oral bioavailability of VOX was 83% in rat and 27% in dog. *In vitro* protein binding was >99% in all species, including human. Following an oral dose of ^{14}C-VOX in rat, radioactivity was widely distributed with the highest concentrations found in liver, GI tissues, and kidney. VOX did not readily cross the blood:brain barrier, blood:eye barrier, blood:testis barrier, or bind to melanin. Although VOX metabolites were not detected in plasma from rats or dogs, multiple minor metabolites were detected in urine and/or feces. A similar metabolite profile was observed in human. There were no significant circulating clinical metabolites (e.g., >10% of total drug-related exposure) requiring non-clinical safety assessment. Elimination primarily occurred through the biliary route in rats, dogs, and humans. VOX was transferred to rat pups during lactation.

VOX was not associated with clinically relevant adverse effects on cardiovascular, neurological, or respiratory endpoints evaluated in safety pharmacology studies. In addition, there were no clinically relevant adverse effects observed in pivotal repeat-dose general toxicology studies, a male and female fertility study, embryofetal development studies, or a pre/post-natal development study. VOX was not considered genotoxic based on negative results in the *in vitro*

bacterial mutation assay, *in vitro* mammalian chromosome aberration assay, and *in vivo* rat micronucleus assay. As VOX was not genotoxic and will be administered to humans for only 12 weeks, carcinogenicity studies were not required. Non-adverse increases in bilirubin parameters, consistent with expected organic anion transporting polypeptide (OATP) inhibition by VOX, were observed both nonclinically and clinically.

Neither SOF or VEL were associated with clinically relevant adverse effects. Because there were no specific safety concerns with the individual SOF/VEL/VOX components, nonclinical studies with the combination were not warranted.

4.5. Clinical Pharmacology

This section summarizes the key outcomes of the clinical pharmacology discipline review, including highlights of pharmacokinetics (PK), pharmacodynamics (PD), and dose-response relationships that support dose selection. Please see the Clinical Pharmacology review by Drs. Qin Sun and Fang Li for full details.

4.5.1. Mechanism of Action

VOX is an HCV NS3/4A protease inhibitor, VEL is an HCV NS5A inhibitor, and SOF is a nucleotide HCV NS5B inhibitor.

4.5.2. Pharmacodynamics

The results from the Phase 1 study GS-US-338-1121, Phase 2 studies GS-US-337-1468, GS-US-367-1168, GS-US-367-1169 and GS-US-367-1871 formed the basis for selecting the 100 mg VOX dose for the SOF/VEL/VOX FDC as well as the 12 week treatment duration studied in POLARIS-1 and POLARIS-4.

- Study 1121 evaluated VOX 50 100, or 300 mg administered once daily as monotherapy for 3 days in subjects with genotype 1 to 4 HCV infection. An E_{max} model was able to characterize the relationship between antiviral response (change from baseline HCV RNA on Day 4) and VOX $AUC_{tau.}$ The pharmacodynamics of VOX indicated that near maximal antiviral response (≥ 90% of E_{max}) will be achieved at a VOX dose of 100 mg, and doses > 100 mg are unlikely to achieve further meaningful reduction in HCV RNA.
- Study 1468, Study 1168, and Study 1169 evaluated VOX 100 mg combined with SOF/VEL (400/100 mg), administered over 4, 6, 8 or 12 weeks. SVR12 rates ranged from 27% to 100% in <12 week regimens. SVR12 rates were consistently near 100% in the 12 week regimen, regardless of genotype, cirrhosis, or DAA-experience:
    - SVR12 in the 4 week group was 27%.
    - SVR12 rates in the 6 week groups ranged from 67% to 93%.
    - SVR12 rates in the 8 week groups (with or without RBV) ranged from 81% to 100%; of note, most of the 8 week groups were DAA-naïve.
    - SVR12 rates in the 12 week, DAA-experienced groups (with or without cirrhosis) were 99-100%.

- Study 1871 evaluated SOF/VEL/VOX FDC (400/100/100 mg), administered for 12 weeks, with or without RBV, in DAA-experienced subjects with or without cirrhosis and GT 1 HCV infection. SVR12 rates ranged from 94% (with RBV) to 100% (without RBV).
- These studies also showed no benefit with RBV use. Therefore, the 12 week, RBV-free regimen was considered the preferred regimen for all genotypes for POLARIS-1 and POLARIS-4.

No exposure-response relationships for efficacy were identified across exposure ranges for VOX, VEL, SOF, and GS-331007 observed in Phase 3 studies.

There was no evident exposure-response relationship between exposure of VOX, VEL, or SOF and the incidence of the most frequently reported AEs (occurring in > 10% of subjects: headache, fatigue, diarrhea, and nausea). There was no association between exposure of SOF or VEL and laboratory measures such as lipase, creatine kinase, or total bilirubin. However, there was a clear linear relationship between higher VOX AUC_{tau} and maximum change from baseline in total bilirubin (mg/dL). The magnitude of increase in total bilirubin was modest and not considered as clinically significant, given the low grade of total bilirubin elevation (predominantly Grade 1) and return to baseline total bilirubin levels after completion of treatment.

4.5.3. Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic properties of SOF, GS-331007 (primary circulating metabolite of SOF), VEL, and VOX have been evaluated in healthy subjects and in HCV patients. Following oral administration of SOF/VEL/VOX FDC at 400/100/100 mg under fed conditions, SOF, GS-331007, VEL and VOX reached peak plasma concentrations at about 2, 4, 4, 4 hours post-dose, respectively. SOF/VEL/VOX FDC tablets are recommended to be administered under fed conditions, and food increases SOF exposure by 64% to 144%, increases VEL exposure by 40% to 166%, and increases VOX exposure by 112% to 435%.

Sofosbuvir and GS-331007 AUC_{0-24} and C_{max} were similar in healthy adult subjects and subjects with HCV infection. Relative to healthy subjects (N=137), velpatasvir AUC_{0-24} and C_{max} were 41% lower and 39% lower, respectively, in HCV-infected subjects. Relative to healthy subjects (N=63), voxilaprevir AUC_{0-24} and C_{max} were both 260% higher in HCV-infected subjects.

Sofosbuvir and GS-331007 AUCs are near dose-proportional over the dose range of 200 mg to 1200 mg. Velpatasvir AUC increases in a greater than proportional manner from 5 to 50 mg and in a less than proportional manner from 50 to 450 mg in healthy volunteers. However, velpatasvir exhibited near dose-proportional increase in exposures 25 mg to 150 mg in HCV-infected patients. Voxilaprevir AUC increases in a greater than proportional manner over the dose range of 100 to 900 mg when administered with food.

SOF is approximately 61–65% bound to human plasma proteins, while GS-331007 binds minimally in human plasma. VEL and VOX are > 99% bound to human plasma proteins. The blood to plasma ratios for SOF (GS-331007), VEL, VOX were 0.7, 0.5 to 0.7, and 0.5 to 0.8, respectively, indicating all the components in SOF/VEL/VOX FDC were predominantly distributed to plasma rather than the cellular components of blood.

SOF is extensively metabolized in the liver to form the pharmacologically active nucleoside analog triphosphate GS-461203. Dephosphorylation results in the formation of nucleoside metabolite GS-331007 that cannot be efficiently rephosphorylated and lacks anti-HCV activity *in vitro*. VEL is a substrate of CYP2B6, CYP2C8, and CYP3A4 with slow turnover, and VOX is a substrate of CYP2C8, CYP3A4, and CYP1A2 with slow turnover.

Renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of SOF and GS-331007 are 0.5 and 29 hours, respectively. Biliary excretion is the major route of elimination for both VEL and VOX (77% and 40% as parent in feces for VEL and VOX, respectively). The median terminal half-lives of VEL and VOX are approximately 17 and 33 hours, respectively.

Intrinsic Factors

- Renal Impairment

The PK of SOF was studied in HCV negative subjects with mild, moderate, and severe renal impairment following a single dose of SOF 400 mg, and in subjects with ESRD requiring hemodialysis following a single dose of SOF 400 mg prior to dialysis and following a single dose of SOF 400 mg after dialysis. Compared with subjects with normal renal function, the SOF AUC_{inf} was approximately 61%, 107%, and 171% higher and the GS-331007 AUC_{inf} was approximately 55%, 88% and 451% higher in subjects with mild, moderate, and severe renal impairment, respectively. In subjects with ESRD, compared with subjects with normal renal function, SOF and GS-331007 AUC_{inf} was approximately 28% and 1283% higher when SOF was dosed 1 hour before hemodialysis compared with 60% and 2072% higher when SOF was dosed 1 hour after hemodialysis, respectively.

The PK of VEL was studied with a single dose of 100 mg VEL in HCV negative subjects with severe renal impairment. No clinically relevant differences in VEL PK were observed between healthy subjects and subjects with severe renal impairment.

The PK of VOX was studied with a single dose of 100 mg VOX in HCV negative subjects with severe renal impairment. No clinically relevant differences in VOX PK were observed between healthy subjects and subjects with severe renal impairment.

The recommendation for use of SOF/VEL/VOX in subjects with renal impairment is guided by its most restrictive component in the setting of renal impairment, SOF (specifically GS-331007). No dose adjustment of SOF/VEL/VOX is warranted for subjects with mild or moderate renal impairment (GFR ≥ 30 ml/min/1.73m^2). No dosage recommendations can be made for patients

with severe or end stage renal disease (GFR < 30 ml/min/1.73 m^2), due to the unestablished safety and efficacy of SOF/VEL/VOX in those patients.

- Hepatic Impairment

The PK of SOF was studied following 7-day dosing of 400 mg SOF in HCV-infected subjects with moderate and severe hepatic impairment (CPT B and C). Relative to subjects with normal hepatic function, the SOF AUC_{0-24} were 126% and 143% higher in moderate and severe hepatic impairment, while the GS-331007 AUC_{0-24} were 18% and 9% higher, respectively. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (CPT A) had no clinically relevant effect on the exposure of SOF and GS-331007.

The PK of VEL was studied with a single dose of 100 mg VEL in HCV negative subjects with moderate and severe hepatic impairment (CPT B and C). VEL plasma exposure (AUC_{inf}) was similar in subjects with moderate hepatic impairment, severe hepatic impairment, and control subjects with normal hepatic function. Population pharmacokinetics analysis in HCV-infected subjects indicated that cirrhosis (CPT A) had no clinically relevant effect on the exposure of VEL.

The PK of VOX was studied with a single dose of 100 mg VOX in HCV-negative subjects with moderate and severe hepatic impairment (CPT B and C). Relative to subjects with normal hepatic function, VOX plasma exposure (AUC_{inf}) was 299% and 500% higher in subjects with moderate and severe hepatic impairment, respectively. Population pharmacokinetic analysis in HCV-infected subjects indicated that subjects with cirrhosis (CPT A) had 74% higher exposure of VOX than those without cirrhosis.

The recommendation for use of SOF/VEL/VOX in subjects with hepatic impairment is guided by its most restrictive component in the setting of hepatic impairment, VOX. SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (CPT B and C).

- Demographic Factors

Several demographic factors, such as age, gender, race, and body mass index (BMI), have been evaluated to determine if these factors have an effect on the PK of SOF, GS-331007, VEL and VOX. No clinically relevant effect has been found for age, race, gender, or BMI. Cirrhosis was identified as the most influential covariate in population PK analysis, resulting in 74% higher VOX AUC_{tau} in subjects with compensated cirrhosis compared to subjects without cirrhosis. Higher VOX AUC_{tau} was associated with a greater maximum change in total bilirubin and correlates with the findings that increased total bilirubin was more common in cirrhotic versus non-cirrhotic subjects (14% versus 6%). Of note, most elevations were Grade 1 and none of the bilirubin elevations were associated with jaundice (see Section 8.4.6 and Section 8.5.8).

Extrinsic Factors: Drug Interactions

SOF, VEL, and VOX are substrates of drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), while GS-331007 is not. VOX, and to a lesser extent VEL, are also substrates of OATP1B1 and OATP1B3. In addition, VEL is a substrate of CYP2B6, CYP2C8 and

CYP3A4 with slow turnover, and VOX is a substrate of CYP2C8, CYP3A4, and CYP1A2 with slow turnover. Drugs that are inducers of P-gp, and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 may decrease plasma concentrations of SOF, VEL, and/or VOX leading to reduced therapeutic effect of SOF/VEL/VOX. Co-administration with drugs that inhibit P-gp and/or BCRP may increase SOF, VEL, and/or VOX exposure without increasing GS-331007 exposure. Co-administration with drugs that inhibit OATP may increase VOX exposure. Drugs that inhibit CYP2B6, CYP2C8, and CYP3A4 may increase plasma exposure of VEL and/or VOX.

VEL and VOX are inhibitors of drug transporters P-gp, BCRP, OATP1B1 and OATP1B3, and co-administration of SOF/VEL/VOX with drugs that are substrates of these transporters may increase the exposure of such drugs.

An extensive battery of DDI studies has been conducted to evaluate possible drug interactions with SOF/VEL/VOX as perpetrator or victim of interactions with frequently co-administered drugs in the HCV population, including HIV antiretroviral drugs, gastric acid blockers (particularly proton-pump inhibitors), immunosuppressive agents, methadone, oral contraceptives and statins (pravastatin, rosuvastatin). Please see Section 10 of this review (Labeling) and the clinical pharmacology review for complete details.

(b) (4)

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2 contains a summary of the four Phase 3 trials and pertinent Phase 2 trials that were submitted with this application.

Table 2. Summary of Relevant Clinical Trials

Trial Identity	Phase	Trial Design	HCV GT	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
Studies to Support Efficacy and Safety								
POLARIS-1	3	Randomized, double-blind, placebo-controlled trial with 1:1 randomization for GT1; all other subjects received SOF/VEL/VOX	1, 2, 3, 4, 5, 6	SOF/VEL/VOX 12 weeks or placebo (PBO) 12 weeks	TE (received prior NS5A) ± cirrhosis (CPT A)	415 in total: 263 SOF/VEL/VOX 152 PBO	SVR12 and Safety	108 sites, 7 countries
POLARIS-4	3	Randomized, open-label, active controlled trial with 1:1 randomization for GT1-3; all other subjects received SOF/VEL/VOX	1, 2, 3, 4, 5, 6	SOF/VEL/VOX 12 weeks or SOF/VEL 12 weeks	TE (not received prior NS5A) ± cirrhosis (CPT A)	333 in total: 182 SOF/VEL/VOX 151 SOF/VEL	SVR12 and Safety	101 sites, 7 countries
Other Studies Pertinent to the Review of Efficacy and Safety								
POLARIS-2*	3	Randomized, open-label, active controlled trial with 1:1 randomization for GT1-4; all other subjects received SOF/VEL/VOX	1, 2, 3, 4, 5, 6	SOF/VEL/VOX 8 weeks or SOF/VEL 12 weeks	TN or TE (not received prior DAA) ± cirrhosis (CPT A)	941 in total: 501 SOF/VEL/VOX 440 SOF/VEL	Safety and SVR12	117 sites, 7 countries
POLARIS-3*	3	Randomized, open-label trial with 1:1:1 randomization	3	SOF/VEL/VOX 8 weeks or SOF/VEL 12 weeks	TN or TE (not received prior DAA) cirrhosis (CPT A)	219 in total: 110 SOF/VEL/VOX 109 SOF/VEL	Safety and SVR12	84 sites, 7 countries
GS-US-337-1468 (Cohorts 4 and 5)*	2	Randomized, open-label, dose-ranging trial	1, 3	SOF/VEL + VOX for 4, 6, or 8 weeks	TN or TE (not received prior DAA) ± cirrhosis (CPT A)	161	Safety and SVR12	2 sites (both ex-US)

Trial Identity	Phase	Trial Design	HCV GT	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
GS-US-367-1168*	2	Randomized, open-label, dose-ranging trial	1	SOF/VEL + VOX for 6, 8, or 12 weeks *OR* SOF/VEL + VOX + RBV 8 weeks	TN or TE (including prior DAA) ± cirrhosis (CPT A)	205	Safety and SVR12	34 sites in 2 countries
GS-US-367-1169*	2	Randomized, open-label, dose-ranging trial	2, 3, 4, 6	SOF/VEL + VOX for 6, 8, or 12 weeks	TN or TE (including prior DAA) ± cirrhosis (CPT A)	128	Safety and SVR12	34 sites in 2 countries
GS-US-367-1871*	2	Randomized, open-label	1	SOF/VEL/VOX 12 weeks *or* SOF/VEL/VOX + RBV 12 weeks	TE (received prior DAA) ± cirrhosis (CPT A)	49	Safety and SVR12	1 site (in US)
GS-US-367-1171[§]	3	Single-arm, open-label trial of subjects who received placebo in POLARIS-1	1, 2, 3, 4, 5, 6	SOF/VEL/VOX 12 weeks	TE (received prior NS5A) ± cirrhosis (CPT A)	147	Safety	*Unavailable*
CO-US-367-2082[§]	2	Randomized, open-label	1	SOF/VEL/VOX 12 weeks *or* SOF/VEL/VOX + RBV 12 weeks	TE (received prior DAA) ± cirrhosis (CPT A)	49	Safety	1 site (in US)

*These studies were used to support the 100mg VOX dose for the SOF/VEL/VOX FDC and were incorporated in the hepatic safety database for the SOF/VEL/VOX development program

[§]In the Safety Update Report, the Applicant provided summaries of key safety events, narratives, and case report forms for these ongoing studies. Datasets were not provided.

5.2. Review Strategy

The clinical efficacy review is based on the two pivotal Phase 3 trials POLARIS-1 and POLARIS-4. The clinical reviewer along with the statistical and virology reviewers collaborated extensively during the review process, and a number of analyses included in this review were performed by the statistical reviewer, Dr. Karen Qi, and the virology reviewer, Dr. Lisa Naeger. In addition, there were significant interactions with the clinical pharmacology, pharmacometrics, pharmacology/toxicology, and chemistry manufacturing and controls reviewers. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

Only the primary efficacy endpoint, SVR12, will be discussed in detail in this review, accompanied by a discussion regarding virologic status of subjects who did not achieve SVR12 in the POLARIS-1 and POLARIS-4 trials and accompanied by a discussion regarding efficacy outcomes by HCV genotype and baseline RAS. Detailed analyses of secondary endpoints such as SVR4, percentage of subjects with HCV RNA < LLOQ while on treatment, and change from baseline in HCV RNA (log10 IU/mL) through end of treatment (EOT), will not be discussed here but are presented in Dr. Qi's statistics review. SVR24 data are not available for a significant proportion of Phase 3 subjects, and therefore cannot be discussed this review.

The clinical safety review was primarily based on POLARIS-1 and POLARIS-4. In addition, data from the four Phase 3 trials (POLARIS-1, -2, -3, and -4) were pooled to form the integrated safety (ISS) population; given that the majority of safety events 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 ISS population, is reasonable. Data from the four Phase 2 trials highlighted in the summary table (Table 2) were also reviewed for key safety analyses, including hepatic safety, as described in Section 8. These supportive Phase 2 trials include subjects who were treated at the dose and duration of the proposed to-be-marketed SOF/VEL/VOX regimen, but also included subjects who received shorter durations of treatment. Serious adverse events and Grade 3 and 4 adverse events in these lower-dose/duration populations were considered to be significant predictors of potential drug-related toxicity and were therefore reviewed but were not pooled with other trials. JMP software was used to conduct the safety analyses presented in this review; any analyses performed by the Applicant or other members of the FDA review team will be labeled as such.

6 Review of Relevant Individual Trials Used to Support Efficacy

Compliance with Good Clinical Practices
Each of the two pivotal Phase 3 trials was conducted under a US IND application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization (ICH) guideline for Good Clinical

Practice (GCP) and the original principles embodied in the Declaration of Helsinki. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), and the European Community Directive 2001/20/EC.

The trial protocols, amendments and informed consent forms were reviewed and approved by independent ethics committees (IEC) or institutional review boards (IRB) before trial initiation. Investigators (or designees) were responsible for obtaining written informed consent from each individual prior to undertaking any study-related procedures. The FDA OSI inspected selected clinical sites but the inspection reports were not available at the time this review was finalized (See Section 4.1). A detailed discussion of the OSI audit will be available in the Clinical Inspection Summary by Dr. Antoine El-Hage.

Data Quality and Integrity: Sponsor's Assurance
The review team considered the Applicant's methods for assuring data quality and integrity to be adequate. These methods included investigator and study center staff training on the trial protocols and study-specific procedures, study site monitoring in accordance with ICH GCP guidelines, compliance audits of investigative sites, use of electronic case report forms (eCRFs), and use of data validation specifications along with manual data review. The Applicant reviewed eCRF data to verify protocol and GCP adherence, and to verify the data against source documentation. The Applicant confirmed that missing data, selected protocol deviations and other data inconsistencies were addressed prior to database finalization. Clinical laboratory data were transferred electronically to the Applicant using defined transfer specifications. The Applicant's lead clinical data associate completed the database.

6.1. POLARIS-1

6.1.1. Study Design

Overview and Objectives
POLARIS-1 (GS-US-367-1171) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter, trial assessing the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of placebo treatment in DAA-Experienced subjects with chronic infection with HCV GT 1, 2, 3, 4, 5, or 6 who have previously received NS5A inhibitors. The primary objectives of the trial are to evaluate the efficacy and safety of treatment with 12 weeks of SOF/VEL/VOX in subjects with CHC.

The trial began on November 11, 2015 and is ongoing at this time. The last subject observation included in the NDA submission was made on October 14, 2016, at which point the database was finalized for SVR12 analysis. Subjects were enrolled across 108 study sites in the US, Canada, Great Britain, France, Germany, Australia, and New Zealand.

Trial Design
Subjects with HCV GT1 infection (with a target of at least 30% with cirrhosis) were randomized

in a 1:1 ratio in a double-blind manner to receive either SOF/VEL/VOX or matching placebo for 12 weeks. A placebo-controlled trial design was chosen because no approved regimens exist for this patient population. Randomization was stratified by the presence or absence of cirrhosis at screening.

Subjects with HCV GT3 or HCV GT4 infection (with a target of at least 30% with cirrhosis) were enrolled in the SOF/VEL/VOX 12 Week group. Due to small size of the GT2, GT5, or indeterminate populations, all of these subjects were enrolled into the SOF/VEL/VOX 12 Week group in order to maximize the number of these subjects treated with SOF/VEL/VOX.

Men and non-pregnant/non-lactating women $\geq$ 18 years of age with evidence of chronic HCV GT 1, 2, 3, 4, 5, 6, or indeterminate infection (at least 6 months in duration) and HCV RNA $\geq 10^4$ IU/mL at screening were eligible for participation. Treatment experienced (TE) was defined as prior treatment failure to a NS5A inhibitor-containing regimen that was completed at least 8 weeks prior to screening. Subjects with HIV or HBV coinfection, significant cardiac, pulmonary or psychiatric disease, solid organ transplantation, or with malignancy in the past 5 years were also ineligible.

Noncirrhotic subjects as well as subjects with compensated cirrhosis (CPT A) were eligible for the trial. These two groups together will hereafter be described as subjects with compensated liver disease. Cirrhosis was defined as any one of the following: 1) liver biopsy showing cirrhosis (e.g., Metavir score = 4 or Ishak score ≥ 5); 2) FibroTest® score > 0.75 and an aspartate aminotransferase: platelet ratio index (APRI) > 2 during screening; 3) Fibroscan® result > 12.5 kPa. Subjects with any of the following were considered noncirrhotics: 1) liver biopsy showing absence of cirrhosis; 2) FibroTest score ≤ 0.48 and APRI ≤ 1 performed during screening; 3) Fibroscan with a result of ≤ 12.5 kPa within ≤ 6 months of baseline/Day 1. In the absence of a definitive diagnosis of presence or absence of cirrhosis by FibroTest/APRI using the above criteria, a liver biopsy or Fibroscan was required. Liver biopsy results superseded FibroTest/APRI or Fibroscan results and were considered definitive. Subjects with clinical or laboratory evidence of decompensated liver disease were excluded. Enrollment for cirrhotics was targeted for at least 30% of the accrual for HCV GT1, GT3, and GT4.

Study Endpoints

The primary efficacy endpoint was SVR12, defined as HCV RNA < lower limit of quantitation (LLOQ) 12 weeks after discontinuation of the study drug. The primary efficacy analysis was performed using the full analysis set (FAS), which included all subjects who received at least one dose of study medication. Secondary efficacy endpoints include SVR4 and SVR24, HCV RNA absolute values and changes from baseline, and the proportion of subjects with virologic failure. The COBAS®AmpliPrep®/COBAS® TaqMan® HCV Quantitative Test, v2.0 was used to quantify HCV RNA in this study. The LLOQ of the assay was 15 IU/mL.

Statistical Analysis Plan

The primary hypothesis was that subjects in the SOF/VEL/VOX group would achieve an SVR12 rate superior to the performance goal of 85%, calculated using the 2-sided exact 1-sample binomial test at the 0.05 significance level. It is difficult to characterize a historical control rate for all HCV genotypes included in this study because no approved regimens exist for this patient population. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary endpoint, a performance goal was defined as a benchmark against which the efficacy of SOF/VEL/VOX will be evaluated. 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. The point estimate and the 2-sided 95% exact CIs for SVR12 were determined using the Clopper-Pearson method for the SOF/VEL 12 Week and Placebo 12 Week groups. The analysis population is the FAS, and the missing data approach is missing=failure.

Subgroup analyses of the primary endpoint were planned for exploratory purposes only. Subgroups included age, sex, race, ethnicity, region, baseline BMI, cirrhosis status, IL28B genotype, baseline HCV RNA, baseline ALT, prior treatment experience, treatment completion and adherence to study regimen.

Please refer to Dr. Karen Qi's statistics review for complete details.

6.1.2. Study Results

Patient Disposition
Of the 416 enrolled subjects, 415 were randomized to treatment groups and received at least one dose of study medication and were included in the FAS: 263 in the SOF/VEL/VOX group and 152 in the placebo group. Five subjects (1.2%) prematurely discontinued study treatment. Two of the 5 subjects were in the SOF/VEL/VOX group, and the reasons for premature discontinuation were AE (1 subject) and lost to follow up (1 subject). Three subjects in the placebo group discontinued due to AEs.

Protocol Violations/Deviations
A total of 36 important protocol deviations occurred in 33 subjects during the study. Three subjects had 2 deviations and the remainder had a single deviation. Violations of inclusion/exclusion criteria were the most common deviations (n=27), followed by receipt of prohibited concomitant medications (n=4), management not according to protocol (n=3), study medication dosing (n=1), and improper informed consent (n=1). These protocol violations had no bearing on the interpretability of the trial results.

Baseline Characteristics
Tables 3 and 4 summarize the baseline demographic and disease characteristics.

Table 3. POLARIS-1 Baseline Demographic Characteristics, FAS

Demographic Parameters	**SOF/VEL/VOX** (N=263) n (%)	**Placebo** (N=152) n (%)	**Total** (N=415) n (%)
Sex			
Male	200 (76%)	121 (80%)	321 (77%)
Female	63 (24%)	31 (20%)	94 (23%)
Age			
Mean years (SD)	58 (8.5)	59 (8.0)	58 (8.3)
Median (years)	59	60	59
Min, max (years)	27, 84	29, 80	27, 84
Age Group			
< 65 years	222 (84%)	121 (80%)	343 (83%)
≥ 65 years	41 (16%)	31 (20%)	72 (17%)
Race			
White	211 (80%)	124 (82%)	335 (81%)
Black or African American	38 (14%)	22 (14%)	60 (14%)
Asian	8 (3%)	6 (4%)	14 (3%)
Other[1]	5 (2%)	0	5 (1%)
Not disclosed	1 (<1%)	0	1 (<1%)
Ethnicity: Hispanic/Latino			
Yes	15 (6%)	10 (7%)	25 (6%)
No	247 (94%)	142 (93%)	389 (94%)
Not disclosed	1 (<1%)	0	1 (<1%)
Region			
United States	135 (51%)	101 (66%)	236 (57%)
Non-US	128 (49%)	51 (34%)	179 (43%)

[1] Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: ADSL, POLARIS-1 dataset

Reviewer Comment: The two treatment arms are well balanced with respect to age, race, sex, and region. A sizable proportion of the study population is from the US, which makes the data readily applicable to the US population. However, the multinational nature of the study enables recruitment of greater numbers of subjects with non-GT1 HCV genotypes, which are present but less prevalent in US, thereby providing valuable data to inform treatment for those US subjects that may otherwise not be adequately represented.

The preponderance of younger white men in the study population reflect the epidemiology of HCV in sites where the trial was conducted. The impact of the lower representation among older subjects and non-white racial groups will be explored throughout this review.

Table 4. POLARIS-1 Baseline HCV Disease Characteristics

Baseline Disease Characteristics	SOF/VEL/VOX (N=263) n (%)	Placebo (N=152) n (%)	Total (N=415) n (%)
Genotype			
GT1	150 (57.0%)	150 (98.7%)	300 (72.3%)
GT1a	101 (38.4%)	117 (77.0%)	218 (52.5%)
GT1b	45 (17.1%)	31 (20.4%)	76 (18.3%)
GT1 other	4 (1.5%)	2 (1.3%)	6 (1.4%)
GT2	5 (1.9%)	0	5 (1.2%)
GT3	78 (29.7%)	0	78 (18.8%)
GT4	22 (8.4%)	0	22 (5.3%)
GT5	1 (0.4%)	0	1 (0.2%)
GT6	6 (2.3%)	2 (1.3%)	8 (1.9%)
Unknown	1 (0.4%)	0	1 (0.2%)
Cirrhosis			
Yes	121 (46.0%)	51 (33.6%)	172 (41.4%)
No	142 (54.0%)	101 (66.4%)	243 (58.6%)
IL28B			
CC	47 (17.9%)	27 (17.8%)	74 (17.8%)
Non-CC	216 (82.1%)	125 (82.2%)	341 (82.2%)
CT	165 (62.7%)	93 (61.2%)	258 (62.2%)
TT	51 (19.4%)	32 (21.1%)	83 (20.0%)
Baseline HCV RNA (log_{10}IU/mL)			
Mean (SD)	6.3 (0.68)	6.3 (0.63)	6.3 (0.66)
Median	6.3	6.4	6.3
Q1, Q3	5.8, 6.7	5.9, 6.7	5.9, 6.7
Min, Max	1.6, 7.7	3.7, 7.6	1.6, 7.7
< 800,000 IU/mL	73 (27.8%)	36 (23.7%)	100 (26.3%)
≥ 800,000 IU/mL	190 (72.2%)	116 (76.3%)	306 (73.7%)
Baseline ALT			
≤ 1.5 x ULN	120 (45.6%)	93 (61.2%)	213 (51.3%)
> 1.5 x ULN	143 (54.4%)	59 (38.8%)	202 (48.7%)
Prior DAA(s) history			
NS5A + NS5B	161 (61.2%)	81 (53.3%)	242 (58.3%)
NS5A + NS3 ± NS5B	83 (31.6%)	61 (40.1%)	144 (34.7%)
NS5A ± Other(s)	18 (6.8%)	9 (5.9%)	27 (6.5%)
Other(s)	1 (0.4%)	1 (0.7%)	2 (0.5%)

Source: Table created by Dr. Karen Qi, Statistics Reviewer

The determination of cirrhosis status was made by Fibroscan for 73% of subjects (305/415), by Fibrotest + APRI in 16% of subjects (65/415), and by biopsy in 11% of subjects (45/415). A numerically higher proportion of subjects in the SOF/VEL/VOX group were diagnosed by biopsy (13% versus 7% for SOF/VEL/VOX and placebo, respectively); accordingly, a higher proportion of

subjects in the placebo group were diagnosed using Fibrotest + APRI (13% versus 21% for SOF/VEL/VOX and placebo, respectively).

Reviewer Comment: Baseline prognostic indicators of treatment success include absence of cirrhosis, IL28B CC genotype, and low baseline HCV viral load. The SOF/VEL/VOX group had higher proportions of cirrhotics, comparable proportions of IL28B CC genotype, and slightly higher proportions of subjects with low baseline HCV viral load compared to the placebo group.

In the SOF/VEL/VOX group, most subjects had HCV GT1 (57%) or GT3 (30%) infection. There were few subjects with HCV GT2 (2%), GT4 (8%), GT5 (<1%) or GT6 (2%). Approximately 46% of the SOF/VEL/VOX group had cirrhosis at baseline.

The majority of SOF/VEL/VOX subjects had non-CC IL28B (82%), baseline HCV RNA ≥ 800,000 IU/mL (72%), and DAA-experience with NS5A + NS5B (61%). These factors are all indicative of a clinically difficult-to-treat patient population.

Of the 263 subjects in the SOF/VEL/VOX group, the most common prior NS5A inhibitors that had been previously received were ledipasvir (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasivir (3%). This information is clinically relevant and will be described in labeling.

Efficacy Results – Primary Endpoint
The trial met its primary endpoint with an overall SVR12 rate higher than 85%. As expected, no subjects in the placebo group achieved SVR as a result of spontaneous viral clearance. Table 5 provides a summary of overall SVR12 rates in the SOF/VEL/VOX group.

Table 5. POLARIS-1 Primary Efficacy Results, SOF/VEL/VOX Subjects

	SOF/VEL/VOX 12 Weeks (N=263)
SVR12 Achieved	
SVR12 rate [95% CI] p-value (compared to 85%)	96.2% (253/263) [93.1%, 98.2%] <0.001
SVR12 Not Achieved	
On-treatment Virologic Failure	0.4% (1/263)
Relapse*	2.3% (6/261)
Other†	1.1% (3/263)

*The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.
†Other includes subjects with missing data and those who discontinued treatment prior to virologic suppression.
Source: Analysis performed by Dr. Karen Qi, Statistics Reviewer

Outcomes of Subjects who did not Achieve SVR12

Missing Data/Other

Three subjects did not achieve SVR12 because of missing data. These subjects were counted as failures for the overall SVR12 rate but are not true virologic failures. These cases are briefly summarized below.

- Subject 02019-24348 (HCV GT4, with cirrhosis) discontinued SOF/VEL/VOX on Day 12 due to adverse event and then withdrew consent for further follow-up (see Section 8.4.3).
- Subject 05663-24309 (HCV GT1a, NC) had no HCV RNA detected at Weeks 2, 4, and 8, but was lost to follow-up at the posttreatment Week 4 visit.
- Subject 04001-24394 (HCV GT1a, NC) completed 12 weeks of SOF/VEL/VOX and achieved SVR4, but withdrew consent before the posttreatment Week 12 visit.

On-treatment Virologic Failure

One subject had on-treatment virologic failure:

- Subject 02140-24070 (60-year-old cirrhotic black male with HCV GT1a) who had previously relapsed following LDV/SOF for 12 weeks. He had baseline HCV RNA level of 1,870,000 IU/mL, no HCV RNA detected at Weeks 2, 4, and 8, and HCV RNA level of 1180 IU/mL at Week 12. Plasma concentrations of GS-331007 (the predominant SOF metabolite), VEL, and/or VOX were lower at Weeks 8 and 12 than had been observed at Weeks 1, 2, and 4; the Applicant suggested these findings were consistent with non-adherence. Although review of the records of study drug dispensed and returned showed no returned pills over the 12 week treatment period, I agree the lower drug exposures at Weeks 8 and 12 suggest non-adherence (likely intermittent study drug administration) as the cause of virologic breakthrough in this subject.

Relapses

There were 6 relapses:

- Subjects 01057-24090, 01386-24385, and 03060-24009 all had HCV GT3 and cirrhosis; these 3 subjects had relapse determined at the posttreatment Week 4 visit.
- Subjects 00407-24286 (HCV GT1a, with cirrhosis), 01065-24344 (HCV GT3, with cirrhosis), and 04021-24246 (HCV GT4, with cirrhosis) achieved SVR4, but had relapse determined at the posttreatment Week 12 visit.

Reviewer Comment: POLARIS-1 is the most treatment experienced patient population compared to the registrational trials for currently approved HCV antivirals. The overall 96% SVR12 rate far exceeds the pre-specified rate of 85% and is comparable to the efficacy rates for other recently approved DAA regimens, even in treatment-naïve populations. With 6 relapsers (2%) and 1 on-treatment virologic failure (<1%) among 263 SOF/VEL-treated subjects, these results strongly support the efficacy of SOF/VEL/VOX for the populations studied. Furthermore, this is the first trial to demonstrate uniform efficacy of a single drug combination with the same dose and duration of treatment regardless of prior DAA treatment experience, cirrhosis status, or HCV GT for GT 1-6 in NS5A inhibitor treatment-experienced patients. Although there were smaller numbers of GT2 (n=5), GT4 (n=22), GT5 (n=1), and GT6 (n=6), these GTs had an overall 94%

SVR12 (32/34) and baseline RAS did not affect SVR12 in GT4. The low percentage of NS5A inhibitor treatment-experienced patients with HCV GT 2, 4, 5 or 6 infections in the US make a larger and/or comparative trial not feasible to conduct in addition to likely delaying access to HCV treatment options with established in vitro and clinical efficacy data. Recognizing the limited number of enrolled subjects in these HCV GT subgroups, the lack of approved options in GT 2, 4-6 NS5A inhibitor treatment-experienced patients make these populations ones with an unmet medical need.

Subgroup Analyses

Table 6 describes SVR12 by HCV GT and other baseline prognostic indicators. As previously stated, there were no virologic successes among placebo subjects. The remainder of this section presents results from the SOF/VEL/VOX group exclusively. These subgroup analyses should be interpreted with caution because no adjustments were made for multiple comparisons and the sample size in some of the subgroups was small.

Table 6. POLARIS-1 Subgroup Analysis: SVR12 by selected baseline disease characteristics, SOF/VEL/VOX Subjects

Baseline Disease Characteristics	SOF/VEL/VOX 12 Weeks (N=263)	95% CI
Genotype		
GT1	97.3% (146/150)	93.3%, 99.3%
GT1a	96.0% (97/101)	90.2%, 98.9%
GT1b	100% (45/45)	92.1%, 100.0%
GT2	100% (5/5)	47.8%, 100.0%
GT3	94.9% (74/78)	87.4%, 98.6%
GT4	90.9% (20/22)	70.8%, 98.9%
GT5	100% (1/1)	2.5%, 100.0%
GT6	100% (6/6)	54.1%, 100.0%
Cirrhosis		
Yes	93.4% (113/121)	87.4%, 97.1%
No	98.6% (140/142)	95.0%, 99.8%
IL28B		
CC	97.9% (46/47)	88.7%, 99.9%
Non-CC	95.8% (207/216)	92.2%, 98.1%
CT	96.4% (159/165)	92.3%, 98.7%
TT	94.1% (48/51)	83.8%, 98.8%
Baseline HCV RNA (log_{10}IU/mL)		
< 800,000 IU/mL	94.5% (69/73)	86.6%, 98.5%
≥ 800,000 IU/mL	96.8% (184/190)	93.3%, 98.8%
Baseline ALT		
≤ 1.5 x ULN	97.5% (117/120)	92.9%, 99.5%
> 1.5 x ULN	95.1% (136/143)	90.2%, 98.0%
Prior DAA(s) history		
NS5A + NS5B	93.8% (151/161)	88.9%, 97.0%

NS5A + NS3/4A ± NS5B	100% (83/83)	95.7%, 100%
NS5A + Other(s)	100% (18/18)	81.5%, 100%

Source: Analysis performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: This analysis by GT confirms the activity of SOF/VEL/VOX against HCV GT 1, 2, 3, 4, 5, and 6. The high efficacy rate across all baseline disease subgroups also supports uniform dosing recommendations for all subjects with compensated liver disease regardless of prior DAA failure, cirrhosis status, IL28B non CC, high baseline HCV RNA.

An additional subgroup analysis was performed to examine the relationship between baseline demographic factors and treatment success (Table 7).

Table 7. POLARIS-1 Subgroup Analysis: SVR12 by Baseline Demographic Characteristics

	SOF/VEL/VOX 12 Weeks (N=263)	95% CI
Age		
< 65 years	95.9% (213/222)	92.4%, 98.1%
≥ 65 years	97.6% (40/41)	87.1%, 99.9%
Sex		
Male	96.0% (192/200)	92.3%, 98.3%
Female	96.8% (61/63)	89.0%, 99.6%
Race		
Black/African American	92.1% (35/38)	78.6%, 98.3%
Non Black/African American	96.9% (217/224)	93.7%, 98.7%
Ethnicity		
Hispanic or Latino	100% (15/15)	78.2%, 100.0%
Not Hispanic or Latino	96.0% (237/247)	92.7%, 98.0%
Region		
US	96.3% (130/135)	91.6%, 98.8%
Non-US	96.1% (123/128)	91.1%, 98.7%
Baseline BMI		
< 30 kg/m^2	97.8% (175/179)	94.4%, 99.4%
≥ 30 kg/m^2	92.9% (78/84)	85.1%, 97.3%

Source: Analysis performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: The SVR12 rates were high in nearly every demographic subgroup evaluated. The SVR12 rates in subjects with BMI ≥ 30 kg/m^2 (93% [78 of 84]), and of Black/African Americans (92% [35 of 38]) are likely a result of these subgroups being too small to make reliable conclusions. Overall, these results support the efficacy of SOF/VEL/VOX for 12 weeks in all demographic subgroups evaluated.

Impact of Baseline NS5A Resistance Associated Substitutions (RAS)

Among the 263 SOF/VEL/VOX subjects with baseline NS5A deep sequence data, 78% of subjects (206/263) had baseline NS5A RAS. A single NS5A RAS was identified in 111 subjects, 2 were

detected in 66 subjects, and >2 were detected in 29 subjects. Overall prevalence of NS3 RAS and NS5B RAS across all genotypes was 34% (85/247) and 8% (22/260), respectively.

SVR12 rates for GT1a, GT1b, GT3a and GT4 subjects with NS5A RAS was comparable to subjects without baseline NS5A RAS: 98% (85/87), 100% (41/41), 94% 42/45), and 95% (18/19), respectively. In addition, SVR12 rates were not affected by the presence of NS3 RAS or NS5B RAS at baseline. All 7 virologic failures had NS5A RAS at failure, which confer resistance to VEL; three had emergent NS5A RAS (L31M, E92K or Y93H), two had enrichment of NS5A RAS Y93H, and two had baseline NS5A RAS (A30K or Y93N) with no additional detectable substitutions at failure.

Please refer to Dr. Lisa Naeger's virology review for additional details regarding the types and frequencies of NS5A, NS3 and NS5B RAS observed in the trial and the implications of these RAS for treatment success.

Reviewer Comment: Treatment with SOF/VEL/VOX is highly effective in subjects with and without baseline NS5A, NS3 and NS5B RAS. Hence, screening for baseline RAS will not be recommended in product labeling because SVR12 rates are already maximized for this population.

6.2. POLARIS-4

6.2.1. Study Design

Overview and Objectives
POLARIS-4 (GS-US-367-1170) is an ongoing Phase 3, randomized, open-label, active-controlled, multicenter, trial assessing the antiviral efficacy, safety, and tolerability of 12 weeks of SOF/VEL/VOX treatment compared with 12 weeks of SOF/VEL treatment in DAA-Experienced subjects with chronic infection with HCV GT 1, 2, 3, 4, 5, or 6 who have not previously received NS5A inhibitors. Of note, subjects whose only DAA exposure was an NS3/4A protease inhibitor were excluded. The primary objectives of the trial are to evaluate the efficacy and safety of treatment with 12 weeks of SOF/VEL/VOX in subjects with CHC.

The trial began on December 23, 2015 and is ongoing at this time. The last subject observation included in the NDA submission was made on October 17, 2016, at which point the database was finalized for SVR12 analysis. Subjects were enrolled across 101 study sites in the US, Canada, Great Britain, France, Germany, Australia, and New Zealand.

Trial Design
Subjects with HCV GT1, HCV GT2, or HCV GT3 infection (with a target of at least 30% with cirrhosis) were randomized in a 1:1 ratio in a double-blind manner to receive either SOF/VEL/VOX or SOF/VEL for 12 weeks. An active-controlled trial design with SOF/VEL as the comparator was chosen to evaluate the contribution of VOX in this patient population.

Randomization was stratified by HCV genotype and by the presence or absence of cirrhosis at screening.

Due to small size of the GT4, GT5, or indeterminate populations, all of these subjects were enrolled into the SOF/VEL/VOX 12 Week group in order to maximize the number of these subjects treated with SOF/VEL/VOX.

Study Endpoints
The primary efficacy endpoint is SVR12 and utilized the same definition as POLARIS-1, as described in Section 6.1.1.

Statistical Analysis Plan
The primary hypothesis was that subjects in the SOF/VEL/VOX group would achieve an SVR12 rate superior to the performance goal of 85%, calculated using the 2-sided exact 1-sample binomial test at the 0.025 significance level. It is difficult to characterize a historical control rate for all HCV genotypes included in this study because no approved regimens exist for this patient population. Given these difficulties, rather than use a historical control rate as the basis for assessing the primary endpoint, a performance goal was defined as a benchmark against which the efficacy of SOF/VEL/VOX or SOF/VEL will be evaluated. 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 or SOF/VEL for this population. The point estimate and the 2-sided 95% exact CIs for SVR12 were determined using the Clopper-Pearson method for the SOF/VEL/VOX 12 Week and SOF/VEL 12 Week groups. The analysis population is the FAS, and the missing data approach is missing=failure.

Subgroup analyses of the primary endpoint were planned for exploratory purposes only. Subgroups included age, sex, race, ethnicity, region, baseline BMI, cirrhosis status, IL28B genotype, baseline HCV RNA, baseline ALT, prior treatment experience, treatment completion and adherence to study regimen.

Please refer to Dr. Karen Qi's statistics review for complete details.

Protocol Amendments
Two protocol amendments have been made thus far, neither of which significantly impact the conduct of the trial.

6.2.2. Study Results

Patient Disposition
A total of 397 subjects were screened for participation, of which 333 were randomized: 182 subjects in the SOF/VEL/VOX group and 151 subjects in the SOF/VEL group. All 333 randomized subjects received at least one dose of study medication and were included in the FAS. Two

subjects (1%), both in SOF/VEL/VOX group, prematurely discontinued study treatment. The reasons for premature discontinuation were AE (1 subject) and lack of efficacy (1 subject).

Protocol Violations/Deviations

A total of 36 important protocol deviations occurred among 34 subjects during the study through post-treatment Week 12. Two subjects had 2 deviations and the remainder had a single deviation. Violations of inclusion/exclusion criteria were the most common deviations (n=23), followed by management not according to protocol (n=9), receipt of prohibited concomitant medications (n=2), and improper informed consent (n=2). These protocol violations had no bearing on the interpretability of the trial results.

Baseline Characteristics

Tables 8 and 9 summarize the baseline demographic and disease characteristics for subjects in the FAS.

Table 8. POLARIS-4 Baseline Demographic Characteristics

Demographic Parameters	**SOF/VEL/VOX 12 Weeks** (N=182) n (%)	**SOF/VEL 12 Weeks** (N=151) n (%)	**Total** (N=333) n (%)
Sex			
Male	143 (79%)	114 (75%)	257 (77%)
Female	39 (21%)	37 (25%)	76 (23%)
Age			
Mean years (SD)	57 (9.0)	57 (7.3)	57 (8.3)
Median (years)	58	58	58
Min, max (years)	24, 85	24, 80	24, 85
Age Group			
< 65 years	149 (82%)	135 (89%)	284 (85%)
≥ 65 years	33 (18%)	16 (11%)	49 (15%)
Race			
White	160 (88%)	131 (87%)	291 (88%)
Black or African American	16 (9%)	13 (9%)	29 (9%)
Asian	2 (1%)	4 (3%)	6 (2%)
Other[1]	4 (2%)	3 (2%)	7 (2%)
Ethnicity: Hispanic/Latino			
Yes	19 (10%)	8 (5%)	27 (8%)
No	163 (90%)	143 (95%)	306 (92%)
Region			
United States	101 (55%)	87 (58%)	188 (56%)
Non-US	81 (45%)	64 (42%)	179 (44%)

[1] Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: ADSL, POLARIS-4 dataset

Reviewer Comment: The two treatment arms are adequately balanced with respect to baseline demographics. A sizable proportion of the study population is from the US, which makes the data readily applicable to the US population. However, the multinational nature of the study enables recruitment of greater numbers of subjects with non-GT1 HCV genotypes, which are present but less prevalent in US, thereby providing valuable data to inform treatment for those US subjects that may otherwise not be adequately represented.

The preponderance of younger white men in the study population reflect the epidemiology of HCV in sites where the trial was conducted. The impact of the lower representation among older subjects and non-white racial groups will be explored throughout this review.

Table 9. POLARIS-4 Baseline HCV Disease Characteristics

Baseline Disease Characteristics	**SOF/VEL/VOX 12 Weeks** (N=182) n (%)	**SOF/VEL 12 Weeks** (N=151) n (%)	**Total** (N=333) n (%)
Genotype			
GT1	78 (42.9%)	66 (43.7%)	144 (43.2%)
GT1a	54 (29.7%)	44 (29.1%)	98 (29.4%)
GT1b	24 (13.2%)	22 (14.6%)	46 (13.8%)
GT2	31 (17.0%)	33 (21.9%)	64 (19.2%)
GT3	54 (29.7%)	52 (34.4%)	106 (31.8%)
GT4	19 (10.4%)	Not enrolled	19 (5.7%)
Cirrhosis			
Yes	84 (46.2%)	69 (45.7%)	153 (45.9%)
No	98 (53.8%)	82 (54.3%)	180 (54.1%)
IL28B			
CC	33 (18.1%)	29 (19.2%)	62 (18.6%)
Non-CC	149 (81.9%)	122 (80.8%)	271 (81.4%)
CT	107 (58.8%)	95 (62.9%)	202 (60.7%)
TT	42 (23.1%)	27 (17.9%)	69 (20.7%)
Baseline HCV RNA (log_{10}IU/mL)			
Mean (SD)	6.3 (0.56)	6.3 (0.66)	6.3 (0.61)
Median	6.4	6.4	6.4
Q1, Q3	5.9, 6.7	5.9, 6.7	5.9, 6.7
Min, Max	5.0, 7.5	3.6, 7.3	3.6, 7.5
< 800,000 IU/mL	46 (25.3%)	38 (25.2%)	84 (25.2%)
≥ 800,000 IU/mL	136 (74.7%)	113 (74.8%)	249 (74.8%)
Baseline ALT			
≤ 1.5 x ULN	88 (48.4%)	72 (47.7%)	160 (48.0%)
> 1.5 x ULN	94 (51.6%)	79 (52.3%)	173 (52.0%)
Prior DAA(s) history			
DAA-naïve	0	1 (0.7%)	1 (0.3%)
DAA-experienced	182 (100%)	150 (99.3%)	332 (99.7%)
NS5B only	134 (73.6%)	109 (72.2%)	243 (73.0%)

NS5B + NS3	46 (25.3%)	38 (25.2%)	84 (25.2%)
NS3 only	2 (1.1%)	3 (2.0%)	5 (1.5%)
Sofosbuvir-experienced[1]			
Yes	157 (86.3%)	125 (82.8%)	282 (84.7%)
Sofosbuvir only	127 (69.8%)	104 (68.9%)	231 (69.4%)
Sofosbuvir + NS3	28 (15.4%)	21 (13.1%)	49 (14.7%)
Sofosbuvir + other investigational agents	2 (1.1%)	0	2 (0.6%)
No			
NS3 only	2 (1.1%)	3 (2.0%)	5 (1.5%)
NS3 + investigational agents	3 (1.7%)	3 (2.0%)	6 (1.8%)
Investigational agents only	20 (11.0%)	19 (12.6%)	39 (11.7%)
DAA-naïve	0 (0%)	1 (0.7%)	1 (0.3%)

Source: Table created by Dr. Karen Qi, Statistics Reviewer

The determination of cirrhosis status was made by Fibroscan for 72% of subjects (239/333), by Fibrotest + APRI in 17% of subjects (56/333), and by biopsy in 29% of subjects (37/333). A numerically higher proportion of subjects in the SOF/VEL/VOX group were diagnosed by biopsy (14% versus 7% for SOF/VEL/VOX and SOF/VEL, respectively).

Reviewer Comment: Due to the study design, no GT4 subjects were enrolled in the SOF/VEL group. Otherwise, the two trial arms are overall well matched with respect to baseline prognostic indicators of treatment response. Treatment experience information is clinically relevant and will be described in labeling.

Efficacy Results - Primary Endpoint

Table 10 summarizes overall primary endpoint results and key subgroup analyses evaluating the differences in virologic outcomes (SVR12, relapse, on-treatment virologic failure) by HCV GT.

Table 10. POLARIS-4 Overall Primary Efficacy Results and Subgroup Analysis of Virologic Outcomes at Post-Treatment Week 12 by HCV Genotype

	SOF/VEL/VOX 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)
SVR12 Achieved (Overall)		
SVR12 rate (number of responders/N) [95% CI] P-value (compared to 85%)	97.3% (177/182) [93.7%, 99.1%] <0.001	90.1% (136/151) [84.1%, 94.3%] 0.092
SVR12 Not Achieved (Overall)		
On-treatment Virologic Failure	0% (0/182)	0.7% (1/151)
Relapse	0.5% (1/182)	9.3% (14/150)

Other	2.2% (4/182)	0% (0/151)
Virologic outcome by GT	**SOF/VEL/VOX 12 Weeks (N=182)**	**SOF/VEL 12 Weeks (N=151)**
GT1		
SVR12 rate	97.4% (76/78)	90.9% (60/66)
Not achieving SVR12		
On-treatment virologic failure	0% (0/78)	0% (0/66)
Relapse	1.3% (1/78)	9.1% (6/66)
Other	1.3% (1/78)	0% (0/66)
GT1a		
SVR12 rate	98.1% (53/54)	88.6% (39/44)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/44)
Relapse	1.9% (1/54)	11.4% (5/44)
Other	0% (0/54)	0% (0/44)
GT1b		
SVR12 rate	95.8% (23/24)	95.5% (21/22)
Not achieving SVR12		
On-treatment virologic failure	0% (0/24)	0% (0/22)
Relapse	0% (0/24)	0% (0/22)
Other	4.2% (1/24)	4.6% (1/22)
GT2		
SVR12 rate	100% (31/31)	97.0% (32/33)
Not achieving SVR12		
On-treatment virologic failure	0% (0/31)	3.0% (1/33)
Relapse	0% (0/31)	0% (0/32)
Other	0% (0/31)	0% (0/33)
GT3		
SVR12 rate	94.4% (51/54)	84.6% (44/52)
Not achieving SVR12		
On-treatment virologic failure	0% (0/54)	0% (0/52)
Relapse	0% (0/54)	15.4% (8/52)
Other	5.6% (3/54)	0% (0/52)
GT4		
SVR12 rate	100% (19/19)	Not enrolled
Not achieving SVR12		
On-treatment virologic failure	0% (0/19)	Not enrolled
Relapse	0% (0/19)	Not enrolled
Other	0% (0/19)	Not enrolled

The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment. Other includes subjects with missing data and those who discontinued treatment prior to virologic suppression.
Source: Analysis performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: Treatment with SOF/VEL/VOX had a 97% SVR12 rate which was statistically significantly higher than the pre-specified 85% performance goal. However, treatment with

SOF/VEL resulted in a 90% SVR12 rate which was not statistically significantly higher than the pre-specified criteria.

FDA statistical reviewer conducted a post-hoc analysis to compare SVR12 rates between groups. These exploratory analyses showed a 7% treatment difference in favor of SOF/VEL/VOX (95% CI of [1.9%, 12.5%], and p = 0.006 based on Chi-square test). The lower relapse rate between SOF/VEL/VOX and SOF/VEL (1% versus 9%) was the driving factor behind higher SVR12 in the SOF/VEL/VOX group. These findings are further delineated in subgroup analyses that are presented above. The differences in SVR12 and relapse rates between treatment groups were most clearly established in HCV GT1 and GT3 subjects. For GT1b subjects, SOF/VEL/VOX and SOF/VEL had almost identical SVR12 rates and no relapse was observed in either group. Among HCV GT2 subjects, both groups had similar SVR12 rates and no relapse was observed in either group. All GT4 subjects received SOF/VEL/VOX. POLARIS-4 did not enroll any subjects with HCV GT5 or 6. Therefore, no comparison data are available for HCV GT 4, 5, and 6.

Outcomes of Subjects who did not Achieve SVR12

Missing Data/Other

Five subjects (four in the SOF/VEL/VOX group and one in the SOF/VEL group), had missing data in the post-treatment Week 12 window and were therefore considered failures. These subjects were counted as failures for the overall SVR12 rate but are not true virologic failures. These cases are briefly summarized below.

- SOF/VEL/VOX: Subject 00380-27734 (HCV GT1b, NC) died of illicit drug overdose 2 days after the last dose of SOF/VEL/VOX (see Section 8.4.1). He had no detected HCV RNA at the Week 8 visit, the last visit prior to death.
- SOF/VEL/VOX: Subjects 02024-27777 (HCV GT3, NC), 02024-27810 (HCV GT3, with cirrhosis), and 05969-27808 (HCV GT3, with cirrhosis) did not have a posttreatment Week 12 assessment. One of these subjects (Subject 02024-27777) achieved SVR4; the other 2 subjects had no detected HCV RNA at the last available HCV RNA assessment at Week 8.
- SOF/VEL: Subject 00407-27557 (HCV GT1b, NC) discontinued on Day 56 due to Grade 2 headache (see Section 8.4.3); HCV RNA was < 15 IU/mL at the Week 4 visit, the last visit prior to study drug discontinuation.

Reviewer Comment: Although the Applicant defined Subject 00407-27557 as a relapse with SOF/VEL, the review team believes this GT1b subject should be classified as "Other" since this subject discontinued to an AE and did not complete the 12 week treatment course.

On-treatment Virologic Failure

There was one on-treatment virologic failure, Subject 00632-27709 (58-year-old NC black male, HCV GT2), occurring in the SOF/VEL group. This subject represents the difference in SVR12 rates (100% versus 97%) among GT2 subjects in POLARIS-4. Our evaluation of Subject 00632-27709 identified the following:

- Baseline HCV RNA level of 230,000 IU/mL, with GT2a/2d/2j; NS5A T24S and L31M substitutions at baseline

- HCV RNA was < 15 IU/mL at Weeks 2 and 4, respectively
- Viral breakthrough at Week 8 with HCV RNA level of 80,500 IU/mL:
    - Emergent Y93H and low-level F28C (4%), L31V (5%), P58Q (1%), and Y93N (1%) in NS5A
    - Emergent S282T and M289I in NS5B
- Review of the records of study drug dispensed and returned showed 100% adherence
    - Day 1 (03/31/2016): 2 bottles with 28 tablets were dispensed
    - Day 29 (04/28/2016, Week 4 study visit): Zero tablets from bottle #1 were returned, and bottle #3 with 28 tablets was dispensed;
    - Day 57 (05/26/2016, Week 8 study visit): HCV RNA was 80,500 IU/mL; patient instructed to return to site for confirmation of virologic breakthrough
    - Day 69 (06/07/ 2016): HCV RNA was 53,800 IU/mL confirming virologic breakthrough; patient instructed to discontinue study drug
    - Day 75 (06/13/2016): Discontinued study drug
    - Post-treatment Day 1 (06/14/2016, Early Termination Visit): Returned zero tablets from bottle #2 and 9 tables from bottle #3

Reviewer Comment: At this time, a single case of viral breakthrough is not sufficient to establish the contribution of VOX for GT2.

To support the contribution of VOX for GT2, the Applicant also submitted a summary of SOF/VEL results in DAA-naïve subjects from ASTRAL-1, ASTRAL-2 and POLARIS-2 studies, an abstract with observational data (Curry et al. Utilization of sofosbuvir/velpatasvir in genotype 2-6 HCV: Real-world experience from the TRIO Network, EASL 2017), and a top-line summary of the ongoing non-IND study GS-US-342-3921 (Phase 3 randomized, open-label study assessing SOF/VEL+RBV for 12 or 24 weeks in DAA-experienced subjects with HCV GT 1 or 2) showing 7 out of 10 subjects (70%) with GT2 achieved SVR12. The abstract and Study 3921 data cannot be fully assessed without reviewing in detail all the baseline characteristics for these subjects. In the absence of a clinical study report and individual patient level data, Trial GS-US-342-3941 does not provide sufficient supportive information to extend the indication to GT2. These data are needed to understand the difference in SVR12 rates reported with SOF/VEL (97%) in POLARIS-4 compared to this trial (70%). Trial GS-US-342-3941 also does not include a SOF/VEL/VOX comparator arm to further assess the contribution of VOX, and this represents another review issue requiring further delineation. The Applicant can consider an sNDA to include Trial GS-US-342-3941 and other data to support extending the indication to GT2. Based on the totality of the available data, including the additional GT2 data, we conclude that the data does not provide sufficient evidence for VOX's contribution for GT2 in the POLARIS-4 study population.

<u>Relapses</u>

There was 1 relapse in the SOF/VEL/VOX group:

- Subject 00071-27790 (HCV GT1a, with cirrhosis), relapsed at posttreatment Week 4 visit.

There were 13 relapses in the SOF/VEL group and all occurred in GT1a and GT3 subjects:

- Five subjects had HCV GT1: 3 subjects with HCV GT1a with cirrhosis, 2 subjects with HCV

GT1a without cirrhosis.

- Three subjects had relapse determined at the posttreatment Week 4 visit. Two subjects achieved SVR4, but had relapse determined at posttreatment Week 12 visit.

- Eight subjects had HCV GT3, and 7 of these subjects also had cirrhosis. All 8 subjects had relapse determined at the posttreatment Week 4 visit.

Subgroup Analyses

Subgroup analyses were also conducted to evaluate differences in treatment response based on baseline disease characteristics (Table 11).

Table 11: POLARIS-4 Subgroup Analysis: SVR12 by selected baseline disease characteristics

Baseline Disease Characteristics	SOF/VEL/VOX 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)	Difference in SVR12 Rate (95% CI)
Genotype			
GT1 [95% CI]	97.4% (76/78) [91.0%, 99.7%]	90.9% (60/66) [81.3%, 96.6%]	6.5% (-1.2%, 16.6%)
GT1a [95% CI]	98.1% (53/54) [90.1%, 100%]	88.6% (39/44) [75.4%, 96.2%]	5.7% (-0.4%, 23.3%)
GT1b [95% CI]	95.8% (23/24) [78.9%, 99.9%]	95.5% (21/22) [77.2%, 99.9%]	0.4% (-17.6%, 19.3%)
GT2 [95% CI]	100% (31/31) [88.8%, 100.0%]	97.0% (32/33) [84.2%, 99.9%]	3.0% (-8.3%, 16.5%)
GT3 [95% CI]	94.4% (51/54) [84.6%, 98.8%]	84.6% (44/52) [71.9%, 93.1%]	9.8% (-2.3%, 23.1%)
GT4 [95% CI]	100% (19/19) [82.4%, 100.0%]	Not enrolled	n/a
Cirrhosis			
Yes [95% CI]	96.4% (81/84) [89.9%, 99.3%]	85.5% (59/69) [75.0%, 92.8%]	10.9% (1.9%, 21.9%)
No [95% CI]	98.0% (96/98) [92.8%, 99.8%]	93.9% (77/82) [86.3%, 98.0%]	4.1% (-2.1%, 11.9%)
IL28B			
CC [95% CI]	93.9% (31/33) [79.8%, 99.3%]	86.2% (25/29) [68.3%, 96.1%]	7.7% (-8.6%, 26.2%)
Non-CC [95% CI]	98.0% (146/149) [94.2%, 99.6%]	91.0% (111/122) [84.4%, 95.4%]	7.0% (1.7%, 13.8%)
CT	97.2% (104/107)	91.6% (87/95)	5.6% (-0.8%, 13.8%)

[95% CI]	[92.0%, 99.4%]	[84.1%, 96.3%]	
TT	100% (42/42)	88.9% (24/27)	11.1% (1.8%, 29.7%)
[95% CI]	[91.6%, 100%]	[70.8%, 97.6%]	
Baseline HCV RNA (log_{10}IU/mL)			
< 800,000 IU/mL	95.7% (44/46)	92.1% (35/38)	3.6% (-8.0%, 17.4%)
[95% CI]	[85.2%, 99.5%]	[78.6%, 98.3%]	
≥ 800,000 IU/mL	97.8% (133/136)	89.4% (101/113)	8.4% (2.5%, 16.0%)
[95% CI]	[93.7%, 99.5%]	[82.2%, 94.4%]	
Baseline ALT			
≤ 1.5 x ULN	100% (88/88)	91.7% (66/72)	8.3% (3.4%, 17.4%)
[95% CI]	[95.9%, 100.0%]	[82.7%, 96.9%]	
> 1.5 x ULN	94.7% (89/94)	88.6% (70/79)	6.1% (-2.3%, 15.9%)
[95% CI]	[88.0%, 98.3%]	[79.5%, 94.7%]	
Prior DAA(s) history			
NS5B Only	97.0% (130/134)	90.8% (99/109)	6.2% (2.8%, 13.6%)
[95% CI]	[92.5%, 99.2%]	[83.8%, 95.5%]	
NS5B + NS3	97.8% (45/46)	86.8% (33/38)	11.0% (-0.3%, 25.6%)
[95% CI]	[88.5%, 99.9%]	[71.9%, 95.6%]	

Source: Analysis performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: This analysis confirms the differences between treatment groups are primarily driven by GT1a and GT3 subjects. Although an overall treatment difference was observed in cirrhotics, this treatment difference also only occurs in GT1a and GT3 subjects.

An additional subgroup analysis was performed to examine the relationship between baseline demographic factors and treatment success (Table 12).

Table 12: POLARIS-4 Subgroup Analysis: SVR12 by Baseline Demographic Characteristics

	SOF/VEL/VOX 12 weeks (N=182)	SOF/VEL 12 weeks (N=151)	Diff in SVR12 rate (95% CI)
Age at baseline (years)			
< 65 years	96.6% (144/149)	88.9% (120/135)	7.8% (1.9%, 14.7%)
[95% CI]	[92.3%, 98.9%]	[82.3%, 93.6%]	
≥ 65 years	100% (33/33)	100% (16/16)	0% (-11.1%, 21.9%)
[95% CI]	[89.4%, 100.0%]	[79.4%, 100.0%]	
Sex			
Male	96.5% (138/143)	89.5% (102/114)	7.0% (0.9%, 14.6%)
[95% CI]	[92.0%, 98.9%]	[82.3%, 94.4%]	
Female	100% (39/39)	91.9% (34/37)	8.1% (-1.5%, 21.7%)
[95% CI]	[91.0%, 100.0%]	[78.1%, 98.3%]	

Race			
Black or African American [95% CI]	93.8% (15/16) [69.8%, 99.8%]	69.2% (9/13) [38.6%, 90.9%]	24.5% (-5.3%, 55.3%)
Non Black or African American [95% CI]	97.6% (162/166) [93.9%, 99.3%]	92.0% (127/138) [86.2%, 96.0%]	5.6% (0.7%, 11.7%)
Ethnicity			
Hispanic or Latino [95% CI]	100% (19/19) [82.4%, 100.0%]	75.0% (6/8) [34.9%, 96.8%]	25% (3.0%, 62.6%)
Not Hispanic or Latino [95% CI]	96.9% (158/163) [93.0%, 99.0%]	90.9% (130/143) [85.0%, 95.1%]	6.0% (0.7%, 12.3%)
Region			
US [95% CI]	98.0% (99/101) [93.0%, 99.8%]	87.4% (76/87) [78.5%, 93.5%]	10.7% (3.5%, 19.6%)
Non-US [95% CI]	96.3% (78/81) [89.6%, 99.2%]	93.8% (60/64) [84.8%, 98.3%]	2.5% (-5.1%, 12.1%)
Body mass index (kg/m^2) at baseline			
< 30 kg/m^2 [95% CI]	95.8% (115/120) [90.5%, 98.6%]	92.9% (91/98) [85.8%, 97.1%]	2.9% (-3.5%, 10.4%)
≥ 30 kg/m^2 [95% CI]	100% (62/62) [94.2%, 100.0%]	84.9% (45/53) [72.4%, 93.3%]	15.1% (7.5%, 27.4%)

Source: Analysis Performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: For most demographic subgroups evaluated, SVR12 rates were higher in SOF/VEL/VOX compared to SOF/VEL. For several subgroups (such as Black/African Americans and Hispanic), the sample sizes are too small to make reliable conclusions. Overall, these results support the efficacy of SOF/VEL/VOX for 12 weeks in all demographic subgroups evaluated. However, when GT is factored into these analyses, the differences between treatment groups are primarily driven by GT1a and GT3 subjects.

During the March 21, 2017 Mid-Cycle meeting, the Applicant proposed that the difference in SVR12 rates between the SOF/VEL/VOX and SOF/VEL groups is due to the cumulative negative host factors associated with lower response rates rather than viral factors. The Applicant's post hoc analyses did not clearly specify how the five negative host factors (cirrhosis, non-CC IL28B, male, baseline HCV RNA≥ 800,000 IU/mL, BMI ≥30 kg/m^2) were identified. These negative host factors are historically associated poorer response with interferon based regimens. For approved non-interferon containing DAA regimens, gender, BMI and IL28B do not appear to be predictive for negative virologic outcomes. Cirrhosis status has been predictive for negative virologic outcomes and is included in labeling for currently approved DAAs. To date, Harvoni is the only DAA label that defines a population for whom treatment is guided by a baseline HCV viral load cut-off.

Even with the uncertainty about the selection of host factors and this reviewer's differing perspective from the Applicant on the clinical significance of each of these host factors, the distribution of the number of these negative host factors was overall balanced between the two groups, as would be expected due to randomization.

The Applicant's analysis suggested that the contribution of VOX was not evident in subjects with 1 or 2 negative host factors and therefore SOF/VEL was sufficient for these subjects. However, this subset included some cirrhotic subjects, including subjects with HCV GT3 infection and cirrhosis who are generally considered the most difficult to treat with DAA regimen (Table 13).

Table 13. SVR12 rates by HCV genotype and cirrhosis status among subjects with 1 or 2 negative host factors in POLARIS-4

Virologic outcome	SOF/VEL/VOX 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)
GT1a		
Cirrhosis		
No	100% (10/10)	92.9% (13/14)
Yes	100% (1/1)	n/a
GT1b		
Cirrhosis		
No	87.5% (7/8)	90% (9/10)
Yes	100% (1/1)	n/a
GT2		
Cirrhosis		
No	100% (8/8)	100% (7/7)
Yes	100% (1/1)	n/a
GT3		
Cirrhosis		
No	100% (8/8)	100% (9/9)
Yes	66.7% (2/3)	n/a
GT4		
Cirrhosis		
No	100% (2/2)	n/a
Yes	100% (1/1)	n/a

Source: Analysis Performed by Dr. Karen Qi, Statistics Reviewer

Although the Applicant's analysis indicated the contribution of VOX was more evident among subjects with 3-5 negative host factors, when these subjects were evaluated in FDA analyses, the differences between treatment groups remain primarily driven by GT1a and GT3 subjects (Table 14).

Table 14. SVR12 rates by HCV genotype and cirrhosis status among subjects with 3, 4 or 5 negative host factors in POLARIS-4

Virologic outcome	SOF/VEL/VOX 12 Weeks (N=182)	SOF/VEL 12 Weeks (N=151)
GT1a		
Cirrhosis		
No	100% (27/27)	92.9% (13/14)
Yes	93.8% (15/16)	81.3% (13/16)
GT1b		
Cirrhosis		
No	100% (5/5)	100% (5/5)
Yes	100% (10/10)	100% (7/7)
GT2		
Cirrhosis		
No	100% (10/10)	90% (9/10)
Yes	100% (10/10)	100% (15/15)
GT3		
Cirrhosis		
No	93.3% (14/15)	92.3% (12/13)
Yes	96.4% (27/28)	76.7% (23/30)
GT4		
Cirrhosis		
No	100% (5/5)	n/a
Yes	100% (11/11)	n/a

Source: Analysis Performed by Dr. Karen Qi, Statistics Reviewer

Reviewer Comment: The Applicant's additional data and rationale (provided in the March 24 and March 30, 2017 submissions) (b) (4) [redacted]

Impact of Baseline NS5A Resistance Associated Substitutions (RAS)

Among the 133 subjects in POLARIS-4 with baseline NS5A deep sequence data, 29% of subjects (97/329) had baseline NS5A RAS. A single RAS was identified in 72 subjects and 2 or more were detected in 25 subjects. SVR12 was 100% in each group. Overall prevalence of baseline NS3 RAS and NS5B RAS was 26% (85/323) and 8% (27/320), respectively. In addition, SVR12 rates were not affected by the presence of NS3 RAS or NS5B RAS at baseline.

Please refer to Dr. Lisa Naeger's virology review for additional details regarding the types and frequencies of baseline NS5A RAS observed in the trial.

Reviewer Comment: Screening for baseline RAS will not be recommended in product labeling because baseline NS5A, NS3 and NS5B RAS did not have an effect on SVR12 rates for SOF/VEL/VOX.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Results from POLARIS-1 are summarized describing SVR12 rates by HCV genotype (Table 15). A 12 week course of SOF/VEL/VOX is effective across all 6 evaluated HCV GTs in subjects who are NS5A inhibitor treatment-experienced. No placebo subjects achieved SVR12.

Table 15. POLARIS-1: SVR12 by HCV GT Among Subjects Treated with SOF/VEL/VOX n (%)

GT1	GT2	GT3	GT4	GT5	GT6	Total
146/150 (97%)	5/5 (100%)	74/78 (95%)	20/22 (91%)	1/1 (100%)	6/6 (100%)	253/263 (96%)

Source: ADEFF dataset, POLARIS-1

Results from POLARIS-4 are summarized describing SVR12 rates by treatment arm and HCV genotype (Table 16). For nucleotide analog NS5B inhibitor treatment-experienced subjects who are NS5A inhibitor treatment-naïve, the contribution of VOX is most clearly established in HCV GT1a and 3. The added benefit of SOF/VEL/VOX over SOF/VEL is not evident for HCV GT1b, 2, 4, 5 and 6.

Table 16. POLARIS-4: SVR12 by Treatment Arm and HCV GT n (%)

	GT1			GT2	GT3	GT4	Total
	Total	GT1a	GT1b				
SOF/VEL/VOX x 12 weeks	76/78 (97%)	53/54 (98%)	23/24 (96%)	31/31 (100%)	51/54 (94%)	19/19 (100%)	177/182 (97%)
SOF/ VEL x 12 weeks	60/66 (91%)	39/44 (89%)	21/22 (95%)	32/33 (97%)	44/52 (85%)	Not enrolled	136/151 (90%)

Source: ADEFF dataset, POLARIS-4

7.1.2. Subpopulations

SVR12 results in POLARIS-1 and -4 did not vary substantially based on age, race, or sex. As previously noted, there were very few treatment failures across the trials, and the small numbers complicated attempts to identify meaningful trends based on age, race, or sex.

7.1.3. Dose and Dose-Response

Dose-ranging studies were not conducted as part of the Phase 3 development program. In Phase 2, VOX 100 mg combined with SOF/VEL (400/100 mg) or given as SOF/VEL/VOX FDC

(400/100/100 mg), was evaluated for different durations.

7.1.4. Onset, Duration, and Durability of Efficacy Effects

The goal of HCV treatment is total viral eradication, as measured by SVR. Therefore the duration of therapy needed before HCV viral load becomes undetectable therapy (the onset of efficacy) is less important than maintenance of an undetectable viral load off therapy, which is measured as SVR 12 and 24. Historically, SVR24 was considered a cure but data from DAA trials demonstrated high correlation between SVR12 and 24, thereby prompting DAVP to use SVR12 as the primary endpoint for marketing applications rather than SVR24.[21] However, relapse has occurred between weeks 12 and 24 in other DAA development programs, which serves as reminder that the SVR24 analysis is necessary to evaluate the durability of efficacy, particularly in populations at higher risk of treatment failure. Complete SVR24 data were not available for the Phase 3 trials but these data will be submitted upon trial completion.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

For NS5A inhibitor treatment-experienced adults with compensated liver disease, SOF/VEL/VOX would be the first HCV treatment regimen that yields high SVR rates across HCV GT 1-6.

For nucleotide analog NS5B inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve, with compensated liver disease, SOF/VEL/VOX would be the first HCV treatment regimen that yields high SVR rates in HCV GT1a and GT3.

7.2.2. Other Relevant Benefits

SOF/VEL/VOX is a fixed dose combination tablet that is administered once daily (b) (4) to food. The convenience of a once daily regimen requiring only a single tablet may facilitate treatment adherence, thereby improving the likelihood of achieving SVR.

7.3. Integrated Assessment of Effectiveness

The efficacy of SOF/VEL/VOX for the treatment of CHC infection in the following subjects with compensated liver disease has been established by the results from the two pivotal Phase 3 trials discussed in Section 6.

For NS5A inhibitor treatment-experienced adults (evaluated in POLARIS-1) and for NS5B polymerase inhibitor treatment-experienced and NS5A inhibitor treatment-naïve adults (evaluated in POLARIS-4), a limited amount of data exists about options not currently in approved labels. Additionally several treatment strategies led to high virologic failure rates. Most of these other options are 24 week, RBV-containing regimens with a wide range of SVR12 rates (70-97% in GT1; 93% in GT2; 76% in GT3) and SVR12 rates are impacted by baseline RAS.

Data from POLARIS-1 demonstrate that, for NS5A inhibitor treatment-experienced adults with compensated liver disease, 12 weeks of SOF/VEL/VOX yields high SVR rates for all subpopulations across the 6 HCV GTs studied. SOF/VEL/VOX would also be the first approved

regimen for NS5A inhibitor treatment-experienced adults. The rationale is based on the following:

- SVR12 rates were comparable across GTs. Subgroup analyses demonstrated that cirrhosis, prior DAA treatment failure, and baseline RAS (NS5A, NS3, NS5B) did not impact SVR12 rates.
- HCV GT1 and GT3 comprise the majority of subjects; these subjects had 95-97% SVR12, confirming robust efficacy. Subjects with HCV GT3 and cirrhosis are generally regarded the most difficult to treat with DAA regimens, and SOF/VEL/VOX achieved a 93% (52/56) SVR12 rate in this subgroup.
- Although there were limited numbers of subjects with GT2, 4, 5, or 6, these subjects had 94% SVR12 (32/34) and similar SVR12 rates across subgroup analyses. Baseline RAS did not affect SVR12 in GT4. All subjects with GT2, GT5, and GT6 achieved SVR12. Recognizing the limited number of enrolled subjects in these HCV GT subgroups, the totality of the data suggest that it is reasonable to extend the indication to other GTs for these difficult to treat populations with unmet medical need.

Data from POLARIS-4 demonstrate that, for nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve with compensated liver disease, the contribution of VOX is most apparent in GT1a and GT3 (94-98% 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 GT1a (98% vs. 89%) and HCVT GT3 (94% vs. 85%) infection. SOF/VEL/VOX would also be the first approved regimen for NS5B polymerase inhibitor treatment-experienced and NS5A inhibitor treatment-naïve subjects.

However, data from POLARIS-4 also show that the contribution of VOX has not been established for GT1b, 2, 4, 5 and 6. For GT1b and GT2, no relapse was observed with either SOF/VEL/VOX or SOF/VEL and both treatments had similar SVR12 rates. (b) (4)

(b) (4)

(b) (4) I recommend these limitations are described in labeling by including in the Indications section, as well as providing additional details in the Dosage & Administration section and the Clinical Trials section.

8 Review of Safety

8.1. Safety Review Approach

The safety review focused on POLARIS-1 and POLARIS-4 as these two studies will be described in labeling. Data from the four Phase 3 trials (POLARIS-1, -2, -3, and -4) were pooled to form the integrated safety (ISS) population. Pooling of these studies was appropriate because the trial design and conduct of these studies were similar and 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 ISS population, is reasonable.

Unless otherwise specified, the analyses presented in this section were performed using the analysis datasets for POLARIS-1, POLARIS-2, POLARIS-3, and POLARIS-4 as well as the ISS datasets. Data were analyzed with JMP software. Discrepancies between the FDA analyses and the Applicant's analyses were relatively minor and attributable to variable methods of pooling and subgroup analyses.

Hepatic safety signals can be difficult to detect in HCV trials, especially among subjects with advanced cirrhosis. To facilitate detection of possible safety concerns, the Applicant convened an Independent Adjudication Committee (IAC) to review possible cases of DILI. The panel reviewed all cases of pre-specified liver-related laboratory abnormalities, treatment-emergent deaths, liver transplants, hepatic failure events, and hepatic events leading to discontinuation of study drug. In addition, a thorough hepatic safety review was conducted by the clinical reviewers and the conclusions reached by FDA reviewers were compared to those of the IAC.

Cardiac events were a focus of scrutiny during the safety review, prompted by the emergence of post-marketing cases of serious symptomatic bradycardia among subjects receiving SOF with amiodarone in combination with another HCV DAA, as well as by the development of heart failure in a patient receiving an investigational nucleotide polymerase inhibitor. The safety review also focused on adverse drug reactions associated with nucleoside/nucleotide analogs in general and SOF in particular, including rash, rhabdomyolysis, and pancreatitis.

The Applicant submitted a Safety Update Report (SUR) two months after the original NDA submission. Trials included in the SUR include the four ongoing POLARIS trials and two additional ongoing trials that were not included previously:

- GS-US-367-1171 is evaluating the safety and efficacy of SOF/VEL/VOX for 12 weeks in subjects who received placebo in the POLARIS-1 study
- CO-US-367-2082 (non-Applicant sponsored study) is evaluating the safety and efficacy of SOF/VEL/VOX with or without RBV for 12 weeks in a retreatment study of subjects who failed prior DAA therapy

Deaths, SAEs, discontinuations due to AEs, and hepatic events of clinical interest (ECIs) reported in the SUR are included in the relevant safety sections. January 9, 2017 was the data cut date for all safety data included in this report.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 17 describes the overall exposure to SOF/VEL+VOX in the 16 studies that contribute to the primary safety database; additional subjects were exposed to SOF or VEL, but not in combination, in the Phase 1 VEL studies and in Phase 1, 2, and 3 SOF studies. The maximum duration of exposure to SOF/VEL/VOX was 12 weeks.

Table 17. Safety Population, Size and Denominators

Primary Safety Database for SOF/VEL/VOX Individuals exposed to SOF/VEL/VOX for the indication under review, either as SOF/VEL+VOX or in the fixed dose formulation (SOF/VEL/VOX) N= 2017			
Clinical Trial Groups	New Drug[a] (SOF/VEL+VOX) (n=2017)	Active Control[b] (SOF/VEL) (n=151)	Placebo (n=116)
Phase 1: Healthy Volunteers	418	N/A	N/A
Phase 2: HCV-infected[c]	543	N/A	N/A
Phase 3: HCV-infected	1056	151	152

[a] The total numbers include subjects who received 25mg VEL, which is lower than the to-be-marketed dose
[b] There is an overlap in SOF/VEL exposure between the New Drug group and the Active Control group
[c] The Phase 2 studies included in the primary safety database were all dose-ranging studies evaluating SOF/VEL+VOX or SOF/VEL/VOX, with or without RBV

8.2.2. Relevant characteristics of the safety population

Baseline characteristics for POLARIS-1 and POLARIS-4 are described individually in Section 6.

Reviewer Comment: The bulk of the safety database is comprised of white men less than 65 years of age. However, given the lack of any clear exposure-safety concerns in Phase 2 trials, the safety profile is not expected to differ based on demographic variables that may result in higher exposures to SOF, VEL or VOX. Subgroup analyses based on demographic factors will be presented in Section 8.6 of this review.

8.2.3. Adequacy of the safety database

The safety database for both products is adequate to assess the safety of SOF/VEL/VOX for the proposed indication, dosage regimen, duration of treatment, and patient population. POLARIS-1 and POLARIS-4 evaluated 445 subjects treated at the proposed dose and duration of SOF/VEL/VOX. Combined with supportive data from POLARIS-2 and POLARIS-3, and the similarity of the safety profile for the 8 week and 12 week treatment groups, these four phase 3 trials meet FDA's recommendation for a 1000-1500 subject safety database for treatment of patients with compensated liver disease.[12]

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

No data quality or data integrity issues were identified. For Phase 3 trials, all narratives for

deaths, SAEs, and treatment discontinuations were reviewed and compared to the Applicant's summary and assessment.

8.3.2. Categorization of Adverse Events

No issues were identified with respect to recording, coding, and categorizing AEs. The Applicant categorized AEs and SAEs in accordance with standard regulatory definitions.

AEs were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities, which is derived from the Division of AIDS (DAIDS) toxicity grading criteria. The clinical reviewer verified the Applicant's translation of verbatim terms to preferred terms for events reported in POLARIS-1, -2, -3, and -4.

8.3.3. Routine Clinical Tests

In POLARIS-1, -2, -3, and -4, routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Treatment Weeks (TW) 1, 2, 4, 8, and 12; Follow-Up weeks 4, 12, and 24. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included clinical evaluation of AEs, vital sign measurement, physical examinations, 12-lead ECGs, and standard laboratory safety tests. Additional testing occurred as indicated or deemed clinically necessary by the investigator during the trials.

8.4. Safety Results

Each subsection in this section presents the results from POLARIS-1 and POLARIS-4. Safety analyses were also performed for the ISS population (POLARIS-1, -2, -3, and -4). The safety results in POLARIS-1 and POLARIS-4 are overall comparable to the ISS population. Any notable findings from the ISS population (i.e. safety issues from POLARIS-2 and POLARIS-3 that were not observed in, or differed from, POLARIS-1 and POLARIS-4) are presented where applicable.

The Safety Analysis Set (SAS) was used for all analyses unless otherwise specified; all subjects who received at least one dose of study medication were included in the SAS. Treatment-emergent events were defined in the Phase 3 trials and in this review as any AE with onset date on or after study drug start date and no later than 30 days after permanent study drug discontinuation, or any AE leading to premature study drug discontinuation. For all analyses, subjects who experienced the same treatment-emergent AE on more than once occasion are counted only once, at the highest toxicity grade reported. When a "total" value is included for a column, it represents the total number of subjects included the analysis, rather than the total number of events. Use of the term "compensated liver disease" is used to encompass subjects without cirrhosis and with compensated cirrhosis (CPT A).

An overall summary of safety events in POLARIS-1 and POLARIS-4 is presented in Table 18. The reviewer assessments and conclusions are similar to those for the ISS population.

Table 18. Overview of Adverse Events, POLARIS-1 and POLARIS-4

Subjects Experiencing Event n (%)	SOF/VEL/VOX 12 Week N=445	SOF/VEL 12 Week N=151	PBO 12 Week N=152
Any AE	346 (78%)	111 (74%)	107 (70%)
Grade 2, 3, or 4 AE	120 (27%)	40 (27%)	42 (28%)
Grade 3 or 4 AE	7 (2%)	2 (1%)	4 (3%)
Related AE	251 (56%)	77 (51%)	63 (41%)
Related Grade 3 or 4 AE	1 (<1%)	0	0
SAE	9 (2%)	4 (3%)	7 (5%)
Related SAE	0	0	0
Discontinuation of study drug due to AE	1 (<1%)	1 (1%)	3 (2%)
Dose modification or interruption due to AE	1 (<1%)	0	1 (1%)
Death	1 (<1%)	0	0

Source: ISS ADSL and ADAE datasets

Reviewer Comment: Adverse events occurred at similar frequency across treatment groups. The majority of AEs were Grade 1 in severity. Serious adverse events (SAEs), AEs leading to study drug discontinuation, and Grade 3/4 AEs were infrequent across treatment groups. Related Grade 3/4 AEs were infrequent and there were no related SAEs.

8.4.1. Deaths

Overall 4 deaths were reported. One death occurred in POLARIS-1 and POLARIS-4 through the time of NDA submission. This event occurred in a SOF/VEL/VOX subject and is discussed briefly below.

Subject 00380-27734 was a 61 year old NC male of African descent with HCV GT1 who was randomized to receive 12 weeks of SOF/VEL/VOX in POLARIS-4. Past medical history was notable for hypertension, depression. Concomitant medications were amlodipine, lisinopril, quetiapine. During treatment, he reported Grade 1 headaches and received fioricet (acetaminophen/butalbital/caffeine). He did not attend his Week 12 visit on (b) (6); the study nurse attempted to contact the patient and was informed by a family member that the patient died (b) (6) at home. Last dose of study drug was (b) (6). The preliminary toxicology report indicated the presence of heroin and fentanyl. The AE of overdose was considered Grade 4, serious, and not related to study drug. The event was considered unrelated to study drug or procedures.

Reviewer Comment: The paucity of information regarding the subject's death complicates causality assessment. An information request was sent to the Applicant requesting additional details of the case, including an autopsy report if an autopsy was performed. The Applicant confirmed the details above and confirmed that no autopsy was performed. The Applicant concludes that the death was not treatment-related, but rather was likely related to drug overdose. Given the available information, most notably the lack of adverse events

(other than Grade 1 headache), vital sign/ECG abnormalities or laboratory abnormalities, I concur with this assessment.

In the ISS analyses, one additional death occurred and is discussed briefly below.

Subject 02111-27026 was a 61 year old, cirrhotic white male with HCV GT3 who was randomized to receive 8 weeks of SOF/VEL/VOX in POLARIS-3. Past medical history was notable for hypertension, tobacco use, anxiety, disc degeneration. Concomitant medications were atenolol, hydrochlorothiazide, oxycodone/acetaminophen, Xanax, Ambien. He completed 8 weeks of treatment on 17-APR-2016. No adverse events were reported during treatment. He was found unresponsive, apneic and pulseless at home (b) (6) transported via EMS and pronounced dead the Medical Center. According to the autopsy report, the patient was asystole during transport to the Medical Center and all attempts at life-saving rescue were unsuccessful. The autopsy report listed that the cause of death was "hypertension," which was reported as a Grade 4 SAE.

Reviewer Comment: I agree with the investigator's assessment that this death, that occurred on post-treatment Day (b) (6), was unrelated to study medication.

Safety Update Report

Two additional deaths occurred and are discussed briefly below.

Subject 5586-27542 was a 42-year-old, cirrhotic white female with HCV GT1 who was randomized to receive 12 weeks of SOF/VEL/VOX in POLARIS-4. Past medical history was notable for headaches, hyperlipidemia, and obesity. Concomitant medications were ranitidine and ibuprofen. She completed 12 weeks of SOF/VEL/VOX on 17 May 2016. No adverse events were reported during treatment. (b) (6) she experienced a brain intraparenchymal hemorrhage from a ruptured arteriovenous malformation (AVM). (b) (6) right frontal decompressive craniectomy and evacuation of hematoma was performed. (b) (6) she obtunded and did not respond to commands. A nuclear medicine brain death summary was obtained (b) (6) and the results were consistent with brain death. The patient was pronounced dead (b) (6) The death was assessed as unrelated to study drug by the investigator.

Reviewer Comment: I agree with the investigator's assessment that the findings (ruptured AVM identified by cerebral angiogram (b) (6) and the event occurring on posttreatment Day (b) (6) support the assessment of the death as unrelated to study medication. An information request was sent to the Applicant requesting additional details of the case, including an autopsy report if an autopsy was performed. The Applicant confirmed the details above and confirmed that no autopsy was performed.

Subject 2016-0230957 was a 64-year-old male with HCV GT1 who was randomized to receive 12 weeks of SOF/VEL/VOX in CO-US-367-2082. He had a history of CPT A cirrhosis

and diuretic-responsive ascites which was stable on furosemide. He had a liver ultrasound on 23 November 2015 which was negative for evidence of hepatocellular carcinoma, and began treatment with SOF/VEL/VOX on 13 June 2016. The subject was treated with doxycycline for Lyme disease at Week 5 of the study. On 15 August 2016 at the Week 8 visit, he reported abdominal fullness and had new elevations in ALT, AST, alkaline phosphatase, and total bilirubin. Study drug was discontinued due to the increased liver enzymes meeting a protocol-defined stopping criterion. Abdominal CT revealed esophageal varices, ascites and portal vein thrombosis. (b) (6) the subject was confused and fell. He was admitted to the hospital and treated for a gastrointestinal bleed. Repeat imaging demonstrated hepatocellular carcinoma with brain and spine metastases. The subject went home and died in hospice care (b) (6) The events were assessed as unrelated to SOF/VEL/VOX by the investigator.

Reviewer Comment: I agree with the investigator's assessment that these events (SAEs, death) were unrelated to study medication. While I agree with the investigator's assessment, this case is of interest given the prior internal multidisciplinary meetings that were held along with teleconferences with EMA to discuss potential HCC safety signal. FDA concluded no HCV DAA class labeling regarding HCC occurrence/recurrence was warranted at this time: current published observational studies do not provide epidemiologic evidence of an increased or decreased risk of HCC occurrence or recurrence in HCV patients treated with DAAs. Continued postmarketing pharmacovigilance in collaboration with DPV II is recommended.

8.4.2. Serious Adverse Events

SAEs were infrequent overall, occurring in 2% of subjects in the SOF/VEL/VOX group, 3% of subjects in the SOF/VEL group, and 5% of subjects in the placebo group. Table 19 provides a summary of SAEs by system organ class (SOC) that occurred in POLARIS-1 and POLARIS-4.

Table 19. Treatment-emergent SAEs by SOC, POLARIS-1 and POLARIS-4

Primary System Organ Class	SOF/VEL/VOX 12 Week N=445	SOF/VEL 12 Week N=151	PBO 12 Week N=152
Infections and infestations	1 (<1%)	0 (0%)	1 (1%)
Gastrointestinal disorders	1 (<1%)	0 (0%)	0 (0%)
Cardiac disorders	1 (<1%)	1 (1%)	2 (1%)
Nervous system disorders	1 (<1%)	1 (1%)	0 (0%)
Injury, poisoning and procedural complications	1 (<1%)	1 (1%)	1 (1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	0 (0%)	0 (0%)
Vascular disorders	1 (<1%)	0 (0%)	0 (0%)
Psychiatric disorders	0 (0%)	0 (0%)	1 (1%)
Musculoskeletal and connective tissue disorders	1 (<1%)	1 (1%)	0 (0%)
General disorders and administration site conditions	0 (0%)	0 (0%)	0 (0%)
Hepatobiliary disorders	0 (0%)	0 (0%)	1 (1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (<1%)	0 (0%)	1 (1%)
TOTAL SUBJECTS	9 (2%)	4 (3%)	7 (5%)

Source: ISS ADSL and ADAE datasets

These SAEs were assessed by investigators as not related to study drug.

Reviewer comment: The clinical narratives were reviewed and I agree with the investigators' assessments that these SAEs are unlikely to be related to study medication.

In the ISS analyses, the only SAE that occurred in more than one SOF/VEL/VOX subject was cerebral hemorrhage; all other SAEs occurred in a single subject. Both cases of cerebral hemorrhage occurred in subjects with pre-existing hypertension as a risk factor. Brief narratives are provided below.

- Subject 01081-24364 is a 75-year-old cirrhotic white female with HCV GT4 and a history of hypertension. She was randomized to receive 12 weeks of SOF/VEL/VOX in POLARIS-1 and completed 12 weeks of treatment. Baseline/Day 1 blood pressure was 180/90 mmHg and an AE of blood pressure fluctuation was reported on baseline/Day 1. Worsening blood pressure was noted (AE of blood pressure abnormal with a measurement of 190/110 mmHg on Day 29). The subject experienced a Grade 3 SAE of cerebral hemorrhage on study Day (b) (6) as well as Grade 2 AEs of dysphagia and hemiparesis and a Grade 3 AE of neurologic neglect syndrome. The SAE of cerebral hemorrhage resolved on study Day (b) (6). On Day 85, the subject had a Grade 4 SAE of seizure; the SAE of seizure resolved on study Day 85. The investigator assessed these events as not related to study treatment.

- Subject 04472-26730 is a 64 year old cirrhotic black female with HCV GT4 and a history of diabetes, hyperlipidemia and hypertension (baseline/Day 1 blood pressure of 150/71 mmHg). She was randomized to receive 8 weeks of SOF/VEL/VOX in POLARIS-2 and

completed 8 weeks of treatment. She experienced a Grade 3 AE of cerebral hemorrhage on study Day (b) (6) on admission to hospital, the subject was initially hypertensive with a blood pressure of 180/110 mmHg, had slurred speech and right-sided weakness, and she was diagnosed with a hemorrhagic stroke. Hypertension was initially managed with ramipril and amlodipine. Amlodipine was later discontinued due to postural hypotension. Her speech gradually improved within a few weeks and mobility improved over several months with ongoing rehabilitation. The SAE of cerebral hemorrhage has been updated to be resolved (with sequelae) on an unknown date in 2016. The investigator assessed the event as not related to study treatment.

Reviewer Comment: Both subjects had underlying hypertension as a risk factor for cerebral hemorrhage. I agree with the investigators that the events were unrelated to study medication. Cases of serious HTN and/or CVA events have occurred with SOF-containing regimens and generally occurred in patients with underlying risk factors for the events such as the above cases. Therefore, based upon the totality of the available information, I do not believe a clear causal associated between serious HTN events and/or CVA and SOF-containing treatment has been definitively established at this time and no labeling changes are recommended. Routine pharmacovigilance monitoring is recommended.

Safety Update Report

Seven new SAEs were reported in POLARIS-1 and POLARIS-4; six events occurred in subjects treated with SOF/VEL/VOX and one in a subject treated with SOF/VEL. All events occurred after more than 13 weeks off-treatment and were considered non-treatment emergent. Events in the SOF/VEL/VOX group were: 1) partial neuropraxia of left sciatic nerve, 2) urinary retention, 3) nausea, 4) amaurosis fugax, 5) epileptic episode, and 6) brain intraparenchymal hemorrhage (discussed in Section 8.4.1). The SOF/VEL subject had fractured hip. All events were considered unrelated to study medication.

Four new SAEs were reported POLARIS-2, all in subjects treated with SOF/VEL. All events occurred after more than 13 weeks off-treatment and were considered non-treatment emergent. Events in the SOF/VEL group were: 1) pancreatic neck mass, 2) chronic lymphocytic leukemia, 3) concussion, and 4) thyroid cancer. All events were considered unrelated to study medication.

No new SAEs were reported in POLARIS-3.

Seven SAEs were reported in GS-US-367-1171 Deferred Treatment Substudy. One subject had 2 events, all other SAEs occurred in single subjects: 1) acute myocardial infarction in a 57-year-old male with history of HTN, transient ischemic attack, pacemaker; 2) hepatocellular carcinoma in a subject with cirrhosis, 3) mesenteric vein thrombosis in a subject with cirrhosis, 4) generalized tonic-clonic seizure in 73-year-old male with a history of cerebral hemorrhage (resulted in a two day interruption in SOF/VEL/VOX administration); 5) traumatic wrist fracture; 6) and 7) nephrolithiasis and urosepsis in a subject with history of nephrolithiasis, renal impairment, and

renal colic. All events were deemed unrelated to study medication. Cases 1-4 were on-treatment events. Cases 5-7 occurred after more than 3 weeks off-treatment. Other than case 4, SOF/VEL/VOX dosing was not interrupted.

Eight SAEs was reported in 3 subjects in CO-US-367-2082: 1) aspiration pneumonia that occurred 4 weeks posttreatment; 2) 63-year-old female had a physical altercation which led to a fall and a subdural hematoma resulting in study drug discontinuation as subject was hospitalized, underwent emergent craniotomy and drain placement, followed by a prolonged hospitalization; 3) 64-year-old male with cirrhosis who died of hepatocellular carcinoma with brain and spine metastases, portal vein thrombosis, ascites, elevated liver function tests (see Section 8.4.1). All events were considered unrelated to study medication.

Reviewer Comment: The clinical narratives were reviewed and I agree with the investigators' assessments that these SAEs are not related to study medication.

Overall assessment of SAEs - Reviewer Comment: No specific drug-related safety concern has been identified from the broad range of SAEs reported with rare frequency in POLARIS-1 and POLARIS-4. There was no clustering of events to suggest a pattern. All narratives were reviewed and did not uncover new concerns. The reviewer assessments and conclusions are similar for the ISS population and for the Safety Update Report.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to AEs were infrequent, occurring in 1 subject in the SOF/VEL/VOX group, 1 subject in the SOF/VEL group, and 3 subjects in the placebo group (Table 20). The narratives were reviewed and are briefly summarized below.

SOF/VEL/VOX: One subject discontinued study drug on Day 12 (16 April 2016) due to a Grade 3 AE of angioedema. This AE was assessed by the investigator as unrelated to study drug. The investigator considered the angioedema as related to ramipril that the subject began on the day prior to the AE (15 April 2016). Ramipril was discontinued on 17 April 2016. The AE resolved on 20 April 2016.

SOF/VEL: One subject discontinued study drug on Day 56 (25 April 2016) due to a Grade 2 headache. The AE of headache was considered related to study drug by the investigator. The AE resolved on 25 April 2016 after the study drug was discontinued.

Placebo: Three subjects discontinued prematurely: 1 with increased hepatic enzymes, 1 with schizophrenia, and 1 with blurred vision, chest pain, dizziness, and confusional state. The investigators assessed these events as not related to study treatment.

Table 20. Adverse Events Leading to Study Drug Discontinuation, POLARIS-1 and POLARIS-4

Treatment Arm	Dictionary-Derived Term	Day, Start/End of AE	Last Day of study drug	SAE	Grade	Outcome	Related
SOF/VEL/VOX 12 Week							
GS-US-367-1171-02019-24348[a]	Angioedema	12/16	12	No	3	Resolved	No
SOF/VEL 12 Week							
GS-US-367-1170-00407-27557[b]	Headache	49/56	56	No	2	Resolved	Yes
PBO							
GS-US-367-1171-00334-24098[a]	Elevated hepatic enzymes	1/-	8	No	2	Ongoing	No
GS-US-367-1171-01657-24142[a]	Schizophrenia	58/88	57	Yes	3	Resolved	No
GS-US-367-1171-05505-24026[a]	Blurred vision	1/2	2	No	1	Resolved	No
	Chest pain	1/2	2	No	1	Resolved	No
	Dizziness	1/2	2	No	3	Resolved	No
	Confusional state	2/2	2	No	1	Resolved	No

Source: ADAE, ADSL datasets; [a]POLARIS-1; [b]POLARIS-4

Reviewer Comment: The narratives were reviewed and I agree with the investigators' assessments. In the SOF/VEL/VOX subject with angioedema, the close temporal relationship between the initiation of ramipril and the onset of the AE suggests that causality was due to ramipril. Headache is a commonly reported event that is described in SOF/VEL labeling. The other assessments that discontinuations due to AE were not related to HCV treatment are reasonable. 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 Harvoni is recommended for this adverse event of special interest. Routine pharmacovigilance will be in place to detect post-marketing signals.

Safety Update Report

There were no discontinuations due to AEs in GS-US-367-1171 Deferred Treatment Substudy. There were two discontinuations in CO-US-367-2082 (see Section 8.4.1 and Section 8.4.2) and both were assessed as unrelated to study medication.

Overall Assessment: No specific drug-related safety concern has been identified from the AEs prompting discontinuation.

8.4.4. Significant Adverse Events

This section describes Grade 3 and 4 events that occurred in the treatment emergent period. Adverse events (AEs) are treatment emergent and all cause. Adverse drug reactions (ADRs) are treatment emergent and at least possibly related by investigator. Some of these events were also considered SAEs; hence, there is some overlap between events reported in this section and 8.4.2.

Grade 3 and 4 AEs were infrequent, occurring in 2% of subjects in the SOF/VEL/VOX group, 1% of subjects in the SOF/VEL group, and 3% of subjects in the placebo group (Table 21). The majority of events occurred in a single subject and no clustering of similar events was observed. Both Grade 4 events in SOF/VEL/VOX subjects (illicit drug overdose, described in Section 8.4.1; seizure, described in Section 8.4.2) were also considered unrelated.

Table 21. Grade 3 and 4 AEs, POLARIS-1 and POLARIS-4

Subjects Experiencing Event n (%)	**SOF/VEL/VOX 12 Week N=445**	**SOF/VEL 12 Week N=151**	**PBO 12 Week N=152**
Number of Subjects with Grade 3/4 event	7 (2%)	2 (1%)	4 (3%)
Highest Grade 3	5 (1%)	2 (1%)	3 (2%)
Highest Grade 4	2 (<1%)	0 (0%)	1 (1%)
Dictionary Derived Term			
Headache	1 (<1%)	0 (0%)	0 (0%)
Cerebral hemorrhage	1 (<1%)	0 (0%)	0 (0%)
Cerebrovascular accident	0 (0%)	1 (1%)	0 (0%)
Dizziness	1 (<1%)	0 (0%)	1 (1%)
Neurologic neglect syndrome	1 (<1%)	0 (0%)	0 (0%)
Seizure	1* (<1%)	0 (0%)	0 (0%)
Schizophrenia	0 (0%)	0 (0%)	1 (1%)
Abdominal pain	0 (0%)	0 (0%)	1 (1%)
Atrial fibrillation	0 (0%)	0 (0%)	1 (1%)
Cardiac failure congestive	1 (<1%)	0 (0%)	0 (0%)
Ventricular fibrillation	0 (0%)	0 (0%)	1* (1%)
Illicit drug overdose	1* (<1%)	0 (0%)	0 (0%)
Lumbar spinal stenosis	0 (0%)	1 (1%)	0 (0%)
Ovarian cancer	1 (<1%)	0 (0%)	0 (0%)
Chronic obstructive pulmonary disease	1 (<1%)	0 (0%)	0 (0%)
Angioedema	1 (<1%)	0 (0%)	0 (0%)

Source: ISS ADSL and ADAE datasets; *Grade 4

Overall, ≥Grade 3 AEs considered related to study drug by the study investigators were:

- SOF/VEL/VOX: headache (n=1), dizziness (n=1) – these occurred in the same subject (GS-US-367-1171-0838-24304)

In the ISS analyses, the only event that occurred in more than one SOF/VEL/VOX subject was cerebral hemorrhage (n=2); both cases were deemed unrelated and the narratives for these events were described in Section 8.4.2.

Safety Update Report

The seven Grade 3 AEs reported in GS-US-367-1171 Deferred Treatment Substudy are the SAEs described in Section 8.4.2. There were no Grade 4 events.

Reviewer Comment: As noted, several of these events have been discussed in prior sections. No clear safety signal emerges from the review of Grade 3 and 4 events.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most common AEs reported were headache, fatigue, diarrhea, and nausea. Table 22 summarizes common AEs irrespective of severity and causality.

Table 22. Treatment-emergent AEs Reported in ≥ 5% of SOF/VEL/VOX Subjects, All Grade and All Causality, POLARIS-1 and POLARIS-4

Dictionary Derived Term	SOF/VEL/VOX 12 Week N=445	SOF/VEL 12 Week N=151	PBO 12 Week N=152
Headache	116 (28%)	43 (28%)	26 (17%)
Fatigue	99 (22%)	43 (28%)	30 (20%)
Diarrhea	83 (19%)	7 (5%)	19 (13%)
Nausea	59 (13%)	12 (8%)	12 (8%)
Insomnia	31 (7%)	3 (2%)	8 (5%)
Asthenia	30 (7%)	9 (6%)	9 (6%)
Back pain	23 (5%)	8 (5%)	8 (5%)
Total Subjects with AE	346 (78%)	111 (74%)	107 (70%)

Source: ISS ADSL and ADAE datasets

The majority of events were Grade 1 in severity. The three most commonly reported AEs in each group were:

- SOF/VEL/VOX: headache (28%), fatigue (22%), diarrhea (19%)
- SOF/VEL: headache (28%), fatigue (28%), nausea (8%)
- Placebo: fatigue (20%), headache (17%), diarrhea (13%)

Table 23 summarizes related adverse events (hereafter referred to adverse drug reactions [ADR]), irrespective of severity. The investigator's determination of causality is the basis for classification. The inaccuracies and biases of this type of classification are acknowledged.

Table 23. Treatment-emergent ADRs Reported in ≥ 2% of SOF/VEL/VOX Subjects, All Grade, POLARIS-1 and POLARIS-4

Dictionary Derived Term	SOF/VEL/VOX 12 Week N=445	SOF/VEL 12 Week N=151	PBO 12 Week N=152
Headache	97 (22%)	34 (23%)	21 (14%)
Fatigue	81 (18%)	34 (23%)	23 (15%)
Diarrhea	60 (13%)	4 (3%)	14 (9%)
Nausea	52 (12%)	5 (3%)	10 (7%)
Asthenia	24 (5%)	9 (6%)	6 (4%)
Insomnia	22 (5%)	1 (1%)	5 (3%)
Dizziness	12 (3%)	1 (1%)	5 (3%)
Arthralgia	12 (3%)	1 (1%)	2 (1%)
Irritability	9 (2%)	8 (5%)	3 (2%)
Myalgia	9 (2%)	0 (0%)	1 (1%)
Dyspepsia	7 (2%)	0 (0%)	4 (3%)
Decreased appetite	10 (2%)	4 (3%)	1 (1%)
Total subjects with ADR	251 (56%)	77 (51%)	63 (41%)

Source: ISS ADSL and ADAE datasets

Most ADRs were mild or moderate severity. The three most commonly reported ADRs in each group were:

- SOF/VEL/VOX 12 week: headache (22%), fatigue (18%), diarrhea (13%)
- SOF/VEL 12 Week: headache (23%), fatigue (23%), asthenia (6%)
- Placebo: fatigue (15%), headache (14%), diarrhea (13%)

Reviewer Comment: Both analyses (all AEs and ADRs) yield similar results, affirming that headache, fatigue, diarrhea, and nausea are the most frequently reported AEs with SOF/VEL/VOX. Adverse reactions in subjects receiving SOF/VEL/VOX 12 Week treatment with *≥5% greater frequency compared with SOF/VEL 12 Week treatment were diarrhea and nausea.*

Adverse reactions in subjects receiving SOF/VEL/VOX 12 Week treatment with ≥5% greater frequency compared with placebo were headache and nausea.

In ISS analyses, headache was the only treatment-emergent ADR with a ≥2% risk difference between SOF/VEL/VOX 8 Week versus 12 Week durations (19% versus 22%). The safety profile of SOF/VEL/VOX 8 Week versus 12 Week durations is overall comparable.

These results are also presented separately for POLARIS-1 and POLARIS-4 as non-pooled results are the preferred format for labeling (Table 24). Table 24 uses a ≥2% cut-off for completeness of the safety evaluation in this review. The label will present ADR data using a ≥5% cut-off for consistency with other DAA labels.

Table 24. Treatment-emergent ADRs Reported in ≥ 2% of SOF/VEL/VOX Subjects, All Grade, POLARIS-1 and POLARIS-4

Dictionary Derived Term	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
Headache	55 (21%)	21 (14%)	42 (23%)	34 (23%)
Fatigue	46 (18%)	23 (15%)	35 (19%)	34 (23%)
Diarrhea	35 (13%)	14 (9%)	25 (14%)	4 (3%)
Nausea	33 (13%)	10 (7%)	19 (10%)	5 (3%)
Asthenia	16 (6%)	6 (4%)	8 (4%)	9 (6%)
Insomnia	16 (6%)	5 (3%)	6 (3%)	1 (1%)
Dizziness	8 (3%)	5 (3%)	4 (2%)	1 (1%)
Arthralgia	7 (3%)	2 (1%)	5 (3%)	1 (1%)
Irritability	5 (2%)	3 (2%)	4 (2%)	8 (5%)
Myalgia	6 (2%)	1 (1%)	3 (2%)	0 (0%)
Dyspepsia	4 (2%)	4 (3%)	3 (2%)	0 (0%)
Decreased appetite	5 (2%)	1 (1%)	5 (3%)	4 (3%)
Total subjects with ADR	145 (55%)	63 (41%)	106 (58%)	77 (51%)

Source: ISS ADSL and ADAE datasets

Reviewer Comment: Product labeling will display ADR results for headache, fatigue, diarrhea, nausea, asthenia and insomnia from Table 24.

Safety Update Report

In GS-US-367-1171 Deferred Treatment Substudy, the most commonly reported treatment AEs (all grades, all causes) were fatigue (21%), headache (20%), diarrhea (18%), and nausea (14%). The majority of events were Grade 1 in severity.

Reviewer Comment: The adverse events reported in the Safety Update Report are consistent with the findings from the overall development program.

8.4.6. Laboratory Findings

The tables in this section display treatment-emergent graded laboratory abnormalities for chemistry and hematology parameters in POLARIS-1 and POLARIS-4. These analyses represent the worst change from baseline per subject.

Grade 3 and 4 abnormalities occurred infrequently and at a similar rate in subjects treated with SOF/VEL/VOX relative to the comparator arms. Laboratory analyses did not reveal any new significant safety concerns. Graded chemistry results are summarized in Table 25, and hematology results in Table 26.

Table 25. Liver Function Tests and Other Chemistry Lab Results, All Grade, POLARIS-1 and POLARIS-4

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
LIVER FUNCTION TESTS				
Increased Alanine Aminotransferase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	2 (1%)	24 (16%)	1 (1%)	1 (1%)
Grade 2 (2.5 to 5 × ULN)	2 (1%)	5 (3%)	2 (1%)	0 (0%)
Grade 3 (>5 to 10 × ULN)	0 (0%)	2 (1%)	1 (1%)	0 (0%)
Grade 4 (>10 × ULN)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Increased Aspartate Aminotransferase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	3 (1%)	24 (16%)	2 (1%)	2 (1%)
Grade 2 (>2.5 to 5 × ULN)	0 (0%)	7 (5%)	3 (2%)	0 (0%)
Grade 3 (>5 to 10 x ULN)	2 (1%)	7 (5%)	0 (0%)	0 (0%)
Grade 4 (>10 × ULN)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
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%)
Increased Alkaline Phosphatase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	3 (1%)	3 (2%)	4 (2%)	0 (0%)
Increased Prothrombin Intl. Normalized Ratio				
Grade 1 (1.1 to 1.5 x ULN)	5 (2%)	3 (2%)	1 (1%)	2 (1%)
Grade 2 (>1.5 to 2 x ULN)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (>2 to 3x ULN)	0 (0%)	2 (1%)	0 (0%)	1 (1%)
OTHER CHEMISTRY LABS				
Increased Creatinine (mg/dL)				
Grade 1 (>1.5 to 2 mg/dL)	1 (<1%)	1 (1%)	2 (1%)	1 (1%)
Grade 2 (>2 to 3 mg/dL)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased Creatine Kinase (U/L)				
Grade 1 (3 to <6x ULN)	4 (2%)	3 (2%)	2 (1%)	3 (2%)
Grade 2 (6 to <10x ULN)	2 (1%)	1 (1%)	3 (2%)	2 (1%)
Grade 3 (10 to <20x ULN)	2 (1%)	2 (1%)	1 (1%)	0 (0%)
Grade 4 (≥20 x ULN)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Increased Glucose (mg/dL)				
Grade 1 (116 to 160 mg/dL)	64 (24%)	38 (25%)	40 (22%)	29 (19%)
Grade 2 (>160 to 250 mg/dL)	25 (10%)	17 (11%)	23 (13%)	20 (13%)
Grade 3 (>250 to 500 mg/dL)	4 (2%)	7 (5%)	4 (2%)	3 (2%)
Increased Lipase (U/L)				
Grade 1 (>1 to 1.5 x ULN)	19 (7%)	5 (3%)	12 (7%)	7 (5%)

Grade 2 (>1.5 to 3 x ULN)	12 (5%)	4 (3%)	15 (8%)	5 (3%)
Grade 3 (>3 to 5 x ULN)	3 (1%)	3 (2%)	2 (1%)	0 (0%)
Grade 4 (>5 x ULN)	3 (1%)	1 (1%)	1 (1%)	1 (1%)

Source: ISS ADSL and ADLB datasets

Reviewer Comment: Grade 3 and 4 laboratory abnormalities were uncommon across treatment groups. ALT and AST trended down rapidly in the active treatment groups as HCV viral load decreased. Hence, it is not surprising that elevated ALT and AST were observed most frequently among subjects in the placebo group, who had ongoing HCV replication.

ALT and/or AST changes with concomitant SOF/VEL/VOX and estrogen use were also evaluated. Please see Section 8.5.1 of this review for complete details.

Similar to other NS3/4A PIs, VOX is an inhibitor of organic anion transporting polypeptide (OATP)1B1 and OATP1B3; this is likely responsible for the higher rate of Grade 1 total bilirubin elevations with SOF/VEL/VOX compared with SOF/VEL or placebo. None of the bilirubin elevations were associated with jaundice.

Elevated CK was observed at comparable rates across all groups and may be related to SOF exposure; VOX does not seem to contribute. Elevated CK was typically associated with exercise and there were no cases of rhabdomyolysis.

Grade 3/4 lipase elevations were infrequent across all groups, occurring in 2% of subjects in the SOF/VEL/VOX group, 1% of subjects in the SOF/VEL group, and 3% of subjects in the placebo group. None of the events were associated with clinical pancreatitis.

Increased glucose was observed at similar frequency in all groups; grade 3 elevations were primarily observed in diabetic subjects. Effect on serum creatinine was minimal in all groups.

Based on the observations above, total bilirubin is the chemistry laboratory parameter that merits inclusion in product labeling based solely on the results observed in the SOF/VEL/VOX development program. Please see Sections 8.5.5 and 8.5.6 for discussion about the Applicant's proposals about CK labeling and lipase labeling. Please see Section 8.5.1 for ISS summary of hepatic laboratory abnormalities.

Table 26. Hematology Laboratory Results, All Grade, POLARIS-1 and POLARIS-4

Parameter/ 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
Decreased Hemoglobin (g/dL)				
Grade 1 (10 to < 10.9 g/dL OR any decrease 2.5 to < 3.5 g/dL from baseline)	5 (2%)	1 (1%)	4 (2%)	0 (0%)
Grade 2 (9 to < 10 g/dL OR any decrease 3.5 to < 4.5 g/dL from baseline)	1 (<1%)	0 (0%)	1 (1%)	0 (0%)
Grade 3 (7 to < 9 g/dL OR any decrease ≥ 4.5 g/dL from baseline)	1 (<1%)	1 (1%)	0 (0%)	1 (1%)
Decreased Neutrophils, Segmented (cells/mm^3)				
Grade 1 (1000 to 1300/mm^3)	6 (2%)	4 (3%)	3 (2%)	2 (1%)
Grade 2 (750 to < 1000/mm^3)	2 (1%)	1 (1%)	2 (1%)	1 (1%)
Grade 3 (500 to < 750/mm^3)	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Grade 4 (<500/mm^3)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Decreased Lymphocytes (cells/mm^3)				
Grade 1 (600 to 650/mm^3)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Grade 2 (500 to < 600/mm^3)	2 (1%)	2 (1%)	2 (1%)	0 (0%)
Grade 3 (350 to < 500/mm^3)	0 (0%)	1 (1%)	1 (1%)	1 (1%)
Grade 4 (< 350/mm^3)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Decreased Platelets (cells/mm^3)				
Grade 1 (100,000 to < 125,000/mm^3)	12 (5%)	12 (8%)	14 (8%)	10 (7%)
Grade 2 (50,000 to < 100,000/mm^3)	13 (5%)	9 (6%)	6 (3%)	7 (5%)
Grade 3 (25,000 to < 50,000/mm^3)	2 (1%)	0 (0%)	3 (2%)	2 (1%)

Source: ISS ADSL and ADLB datasets

Reviewer Comment: Thrombocytopenia, which is observed in subjects with hepatitis, was the only laboratory abnormality reported in more than 5% of SOF/VEL/VOX subjects. The frequency of thrombocytopenia was overall comparable across all groups. Lymphopenia and neutropenia were uncommon in all groups. Given the low frequency of hematologic abnormalities and the similarities in laboratory profile between SOF/VEL/VOX and placebo, hematologic laboratory parameters are not recommended for inclusion in product labeling.

In ISS analyses, laboratory abnormalities with a ≥2% risk difference between SOF/VEL/VOX 8 Week versus 12 Week durations were observed for increased total bilirubin, increased lipase, increased glucose, and decreased platelets and are summarized below. These findings do not change the labeling recommendations that are discussed above.

Table 27. Laboratory abnormalities, All Grade, reported with ≥2% risk difference between SOF/VEL/VOX 8 Week versus 12 Week (ISS)

Parameter and max Analysis Toxicity Grade	SOF/VEL/VOX 8 Week N=611	SOF/VEL/VOX 12 Week N=445
Increased Total Bilirubin (mg/dL)		
Grade 1 (>1 to 1.5 × ULN)	34 (6%)	30 (7%)
Grade 2 (>1.5 to 2.5 × ULN)	6 (1%)	12 (3%)
Grade 3 (>2.5 to 5 x ULN)	0 (0%)	1 (<1%)
Grade 4 (>5 x ULN)	0 (0%)	0 (0%)
Increased Lipase (U/L)		
Grade 1 (>1 to 1.5 x ULN)	39 (6%)	31 (7%)
Grade 2 (>1.5 to 3 x ULN)	23 (4%)	27 (6%)
Grade 3 (>3 to 5 x ULN)	6 (1%)	5 (1%)
Grade 4 (>5 x ULN)	1 (<1%)	4 (1%)
Increased Glucose (mg/dL)		
Grade 1 (116 to 160 mg/dL)	135 (22%)	104 (23%)
Grade 2 (>160 to 250 mg/dL)	36 (6%)	48 (11%)
Grade 3 (>250 to 500 mg/dL)	15 (3%)	8 (2%)
Decreased Platelets (cells/mm^3)		
Grade 1 (100,000 to < 125,000/mm^3)	16 (3%)	26 (6%)
Grade 2 (50,000 to < 100,000/mm^3)	23 (4%)	19 (4%)
Grade 3 (25,000 to < 50,000/mm^3)	4 (1%)	5 (1%)

Reviewer Comment: Grade 3 and 4 laboratory abnormalities were uncommon and occurred at comparable rates in the SOF/VEL/VOX 8 Week versus 12 Week groups. Although platelet and glucose abnormalities occurred at higher rates in the SOF/VEL/VOX 12 Week versus 8 Week groups, the placebo group (see Tables 44 and 45) had comparable rates of these parameters compared to the SOF/VEL/VOX groups.

Safety Update Report

In GS-US-367-1171 Deferred Treatment Substudy, the following Grade 3/4 laboratory abnormalities were reported: increased lipase (6%), increased total bilirubin (1%), increased creatine kinase (1%), increased glucose (2%), decreased lymphocytes (1%). Of these, only two were Grade 4: lipase (n=1), creatine kinase (n=1, associated with exercise). There were no cases of pancreatitis or rhabdomyolysis.

Reviewer Comment: The laboratory abnormalities reported in the Safety Update Report are consistent with the findings from the overall development program.

8.4.7. Vital Signs

No notable changes from baseline systolic or diastolic blood pressure were noted during the treatment-emergent study period for subjects in POLARIS-1 and POLARIS-4. Please refer to Section 8.5.2 for a more specific discussion regarding changes in heart rate in subjects receiving SOF/VEL/VOX with or without concomitant beta blocker or calcium channel blocker at baseline.

8.4.8. Electrocardiograms (ECGs)

ECGs were assessed at screening, baseline, Week 1, and Week 12. The Applicant reports there were no subjects with treatment-emergent abnormal ECGs deemed clinically significant by the investigator. One subject developed a treatment-emergent abnormal ECG but was clinically asymptomatic; his narrative is briefly summarized:

Subject GS-US-367-1170- 04472-27560: 61-year-old male with hypertension had an AE of prolonged QTc at the Week 1 study visit (study Day 8). According to the investigator, there were no associated symptoms. The baseline/Day 1 ECG was assessed as normal; the Week 1 ECG on study Day 8 was assessed as abnormal, with prolonged QTc (> 450 ms), and not deemed clinically significant; the Week 12 ECG on study Day 85 was assessed as abnormal, with mildly prolonged QTc (457 ms), and not deemed clinically significant. The event was considered related to study drug by the investigator and resolved on study Day 85. The event did not result in any change in dosing.

Reviewer Comment: I agree with the investigator that the subject described above was asymptomatic at the time of abnormal ECG, had baseline cardiac risk factors that confounded assessment, and the abnormal ECG was not clinically significant. The primary review team concludes available reported ECG data do not support relevant labeling.

8.4.9. QT

A thorough QT (TQT) study was conducted to evaluate the potential of VOX to prolong the QT interval. Study GS-US-338-1123 was a randomized, partial-blinded placebo- and positive-controlled, 4-period, 8-treatment sequence, single-dose crossover study of 48 healthy subjects who received VOX 300 mg, VOX 900 mg, placebo, and moxifloxacin 400 mg. The results were reviewed by the Interdisciplinary Review Team, who concluded the following:

> No significant QTc prolongation effect of VOX (300 mg and 900 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between voxilaprevir (300 mg and 900 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines.

The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for VOX (300 mg and 900 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hours)	ΔΔQTcF (ms) (ms)	90% CI (ms)
VOX 300 mg	8	0.2	(-0.4, 4.1)
VOX 900 mg	12	1.0	(-0.8, 3.8)
Moxifloxacin 400 mg*	4	10.4	(9.2, 13.8)

*Multiple endpoint adjustment of 3 time points was applied.

> The supratherapeutic dose (500 mg) produces mean Cmax values of 12-fold the mean Cmax for the therapeutic dose (100 mg) when administered in combination with SOF and VEL to HCV-infected subjects. These concentrations are above those for the predicted worst case scenario and show that at these concentrations there are no

detectable prolongations of the QT-interval.

In conclusion, VOX does not prolong QTc to any clinically relevant extent. Please refer to the QT-IRT review by Huifang Chen for additional details (IND 119926, June 30, 2016)

8.4.10. Immunogenicity

Because SOF, VEL and VOX are small molecules and not peptides, immunogenicity was not anticipated and therefore not specifically evaluated in clinical trials.

8.5. Analysis of Submission-Specific Safety Issues

This section includes analyses conducted to address safety concerns for HCV DAAs in general, such as hepatotoxicity, as well as issues more specifically associated with antiviral nucleoside/nucleotide inhibitors, such as cardiac events, rash, neuropsychiatric events, and elevations of creatine kinase and lipase.

Analyses were conducted by organ system to identify possible safety concerns that were not apparent in the routine AE and laboratory analyses presented in prior sections. Analyses were performed using the relevant SOC or High Level Group Term (HLGT).

8.5.1. Hepatotoxicity

Detailed analyses of hepatic events were performed as SOF/VEL/VOX is being administered to subjects with underlying liver disease, including compensated cirrhosis. Based on review of the available data, we do not believe a definitive causal relationship between SOF/VEL/VOX use and hepatotoxicity is established at this time and thus do not believe Warnings and Precautions labeling for hepatotoxicity is supported. This conclusion incorporates the following considerations:

- In the ISS population and supportive Phase 2 safety population:
  - Of the 46 cases screened for DILI evaluation by the IAC, there were two cases in which DILI could not be definitively excluded; causality was confounded by concomitant medications and possible alcohol abuse in these subjects.
  - Reported hepatic events occurred in less than 1% of the population; the few events that occurred were mild (Grade 1) in intensity and were attributable to underlying hepatic disease.
  - Marked elevations in ALT or AST (> 5x ULN), or bilirubin (>2 x ULN) were reported in less than 2% of subjects treated with SOF/VEL/VOX and generally improved, rather than worsened, with treatment.

Language in the *Hepatic Impairment* Section 8.7 of the label includes that SOF/VEL/VOX is not recommended in patients with moderate or severe hepatic impairment (CPT B or C). Any potential signals of hepatotoxicity associated with SOF/VEL/VOX use will be closely monitored in the postmarketing setting.

Independent Adjudication Committee (IAC)

As requested by the Division, an IAC was instituted to identify cases of potential DILI in the principle Phase 2 and 3 trials. The IAC reviewed all cases of pre-specified liver-related laboratory abnormalities, treatment-emergent deaths, liver transplants, hepatic failure events, and hepatic events leading to discontinuation of study drug.

The IAC was composed of the following members:

(b) (4)

Using the above principles and incorporating recommendations from the Division, any subjects who met any of the following criteria were to be reviewed by the IAC for potential DILI.

All Principal Phase 2 and 3 Trials

1. Serious hepatic failure events, defined as SAEs with preferred terms of hepatic failure, acute hepatic failure, hepatotoxicity, liver injury, or DILI that occurred at any time after the first dose date of study drug and up to 30 days after last dose of study drug, in any subject group
2. Treatment-emergent deaths, defined as deaths occurring after the first dose of any study drug and within 30 days of the last dose of any study drug
3. Any subject requiring liver transplantation within 30 days of the last dose of any study drug
4. Any hepatic AEs (preferred terms of hepatic failure, acute hepatic failure, hepatotoxicity, liver injury, or DILI) leading to discontinuation of study drug
5. Pre-specified laboratory criteria for any subject during study treatment
   — ALT or AST > 3 x ULN and Total bilirubin (TB) >2x ULN; or
   — ALT > 5 × ULN; or
   — Total bilirubin (TB) >2x ULN

The IAC assessed the current drug-induced liver injury network (DILIN) causality scoring system (definite, very likely, probable, possible, and unlikely) was applicable to this subject population without cirrhosis and with compensated cirrhosis.

Reviewer Comment: The IAC criteria were reviewed by the Division prior to NDA submission and determined to be acceptable. The IAC criteria were also used in reviews of other HCV DAA products submitted by the Applicant.

Review of IAC Findings and FDA Analyses

Details supporting the review team's conclusions are based on the findings of the IAC as well as FDA review of hepatic events and laboratory abnormalities. This section presents data in the following format:

- IAC Assessment

- Hepatic and Hepatobiliary AEs
- Notable hepatic laboratory abnormalities

IAC Assessment

Forty-six cases met at least 1 of the 5 criteria for IAC review: 15 cases in POLARIS-1; 10 cases in POLARIS-4; 6 cases in POLARIS-2; 4 cases in POLARIS-3; and 11 cases in Phase 2 studies. DILI was unanimously excluded in 42 cases and the remaining 4 cases were discussed by the IAC during the meeting. Of these 4 cases, the IAC identified 2 cases as "Unlikely" DILI, 1 case as "Probably" DILI and 1 case as "Possibly" DILI; the cases of "Probably" DILI and "Possibly" DILI are described below.

Subject 02130-22194 (SOF/VEL+VOX+RBV 8 Week; Study GS-US-367-1168)

50-year-old treatment-naïve, cirrhotic, African American female with HCV GT1; her medical history included asthma, bursitis, and seasonal allergies. Concomitant medications included salbutamol, naproxen and anovlar (microestin) for contraception which was started in August 2015. She started open-label treatment with SOF/VEL+VOX+RBV for 8 weeks on 01 September 2015. Grade 3 ALT and Grade 2 AST were observed at the Week 2 visit and confirmed 7 days later. The subject was clinically asymptomatic and there were no new concomitant medications were ongoing at the time of the ALT/AST elevation. Per the investigator, the subject denied alcohol or drug use. Evaluation for the etiology of the laboratory abnormalities was unrevealing, including laboratory testing for hepatitis A, hepatitis B, hepatitis E, Epstein Barr virus and cytomegalovirus. Study drugs were discontinued on 24 September 2015 (Day 24) due to the increased liver enzymes meeting a protocol-specified stopping criterion. All other concomitant medications were continued. The ALT and AST values were decreased at the follow-up Week 4 visit on posttreatment Day 26. The ALT and AST values drawn from a local laboratory 4 months later were within the normal range.

IAC Assessment ("Probably DILI"): This was a case of a woman with cirrhosis taking oral contraceptives who had an unexplained increase in ALT and AST at Week 2 of treatment with SOF/VEL+VOX+RBV. The ALT and AST decreased when study drugs were discontinued after stopping criteria were met, and there was no alternative explanation for the laboratory abnormalities.

Reviewer Comment: Although I agree with the IAC that DILI cannot be excluded in this case, the patient started oral contraceptives one month prior to enrollment in the trial, and I believe this represents a potential confounder in this case.

Subject 05969-27808 (SOF/VEL/VOX 12 Week; Study GS-US-367-1170)

54-year-old cirrhotic, white, non-Hispanic male with HCV GT 3 who was randomized to receive 12 weeks of SOF/VEL/VOX in POLARIS-4. He completed 12 weeks of treatment. His medical history included hypertension, anxiety, seasonal allergy, insomnia, herniated lower back disk, and nausea. Concomitant medications included lisinopril, clonazepam,

fluticasone, trazodone, ibuprofen, gabapentin, vicodin, and ondansetron. He started open-label SOF/VEL/VOX on 13 April 2016; HCV RNA was undetectable at Week 4 and 8. Subject had Grade 3 total bilirubin at baseline and throughout the study; subject did not have jaundice. Subject had Grade 2 ALT and Grade 3 AST at baseline; Grade 1 ALT/AST at Week 4; Grade 2 ALT/AST at Week 8; and Grade 1 ALT/AST at the Week 4 follow-up visit on posttreatment Day 8. At the time of the Week 8 elevations in ALT/AST, subject reported Grade 1 lower respiratory tract congestion and Grade 1 oropharyngeal pain, as well as new concomitant medications (sucralfate for dyspepsia; azelastine hydrochloride for seasonal allergy). Per the investigator, the subject was evaluated in a local emergency department on (b) (6) for "binge drinking" due to new homelessness. The elevated ALT at screening/baseline and during Weeks 1 and 2 of treatment was considered by the investigator and the Applicant to be consistent with CHC. The transient Grade 2 ALT/AST elevation in the setting of HCV suppression may be related to concurrent alcohol use. The hyperbilirubinemia was considered to be consistent with pre-existing cirrhosis, as evidenced by the elevated total bilirubin at baseline.

IAC Assessment ("Possibly DILI"): This was a case of a man with cirrhosis who had increased ALT and AST at Week 8 with SOF/VEL/VOX which improved at posttreatment Week 4. Total bilirubin was elevated before and during treatment. Subject was documented as having heavy alcohol use after the posttreatment Week 4 visit. The IAC determined that DILI was possibly the cause of the ALT and AST elevation at Week 8 as there was no confirmation that alcohol use was ongoing at that time and the laboratory values improved at posttreatment Week 4.

Reviewer Comment: I agree with the IAC that DILI cannot be excluded in this case. Of note, as subject had baseline total bilirubin >2x ULN, this case does not meet the Hy's Law laboratory criteria as these criteria apply to treatment-emergent hepatic laboratory abnormalities.

Reviewer Comment: The IAC narratives were reviewed for each case and I agree with the IAC's assessment that there is an alternate etiology for each of the remaining cases.

Hepatic and Hepatobiliary AEs

Hepatic AEs were identified for the ISS Phase 3 Population using the MedDRA High Level Group Term *Hepatic and Hepatobiliary Disorders*. The overall occurrence of hepatic AEs was low with a total of 12 subjects reporting events, all of which were assessed as unrelated to study drug:

- SOF/VEL/VOX x 12 Weeks (n=1): 1 subject reported Grade 2 cholelithiasis
- SOF/VEL/VOX x 8 Weeks (n=4): 2 subjects reported Grade 1 hepatic pain; 1 subject reported Grade 2 cholelithiasis; 1 subject reported Grade 2 biliary colic
- SOF/VEL (n=5): 1 subject reported Grade 1 hepatic cirrhosis; 1 subject reported Grade 1 hepatic cyst; 1 subject reported Grade 1 hepatic pain; 1 subject reported Grade 1 hepatocellular injury; 1 subject reported Grade 2 alcoholic hepatitis
- Placebo (n=2): 1 subject reported Grade 2 hepatic failure; 1 subject reported Grade 1 hepatic lesion

There were no jaundice events. There were no discontinuations or treatment interruptions due to the events.

Hepatic Laboratory Abnormalities
Subjects meeting any one of the following three laboratory criteria were identified for further review (Table 28):

- AST or ALT > 3 x upper ULN and total bilirubin > 2 x ULN (Hy's Law)
- ALT > 5 x ULN
- Total bilirubin > 2 x ULN

Table 28: On-treatment Hepatic Lab Abnormalities, Integrated Phase 3 and Phase 2 Safety Population

	Criterion 1: (Hy's Law) AST or ALT > 3 x upper ULN and total bilirubin > 2 x ULN	Criterion 2: ALT > 5 x ULN	Criterion 3: Total bilirubin > 2 x ULN
Phase 3 Studies[1] (N=1908)	2 (<1%)	23 (1%)	11 (1%)
SOF/VEL/VOX 12 Weeks (N=445)	1* (<1%)	7 (2%)	8 (2%)
SOF/VEL/VOX 8 Weeks (N = 611)	0 (0%)	2 (<1%)	1 (<1%)
SOF/VEL 12 Weeks (N = 700)	0 (0%)	7 (1%)	1 (<1%)
Placebo 12 Weeks (N = 152)	1 (1%)	7 (2%)	1 (1%)
Phase 2 Studies[2] (N=543)	0 (0%)	3 (1%)	8 (1%)

[1]POLARIS-1, POLARIS-2, POLARIS -3, POLARIS-4
[2]337-1468, 367-1168, 367-1169, 367-1871
*Subject 05969-27808 had baseline total bilirubin >2x ULN, ALT >4x ULN, AST >7x ULN
Source: Based on Table 27 of Applicant's Summary of Clinical Safety

The specified hepatic laboratory abnormalities occurred infrequently, particularly among SOF/VEL/VOX subjects. There were no cases with Hy's Law laborartory criteria among SOF/VEL/VOX treated subjects. All 7 subjects who received SOF/VEL/VOX for 12 weeks and met Criterion 2 had elevated ALT at baseline, and in all but one case (Subject 05969-27808, described above), ALT trended down with treatment. Eight subjects (7 with cirrhosis, 1 with Gilbert's syndrome and thalassemia) in the SOF/VEL/VOX 12 Week group had total bilirubin values > 2 x ULN; all subjects had elevated total bilirubin at baseline (Subject 05969-27808, described above, with Grade 3; other subjects had Grade 1 or Grade 2) and had transient fluctuations in total bilirubin over the treatment course and were clinically asymptomatic.

Safety Update Report
In GS-US-367-1171 Deferred Treatment Substudy, two subjects had total bilirubin values > 2 x ULN; both subjects had elevated total bilirubin at baseline; both subjects were clinically asymptomatic. In CO-US-367-2082, one subject with cirrhosis had elevated liver function tests that were assessed as due to hepatocellular carcinoma with complications of portal vein

thrombosis, ascites, brain and spine metastases (see Section 8.4.1); these events were considered unrelated to study medication.

Other Hepatic Analyses of Interest

Although no significant drug-drug interaction was observed when SOF/VEL/VOX was coadministered in with norgestimate/ethinyl estradiol in a Phase 1 trial, a Grade 3 ALT elevation was noted in one subject (ID# 08142-1008, described below). Further analyses were done given the experience with Viekira Pak, which also contains a protease inhibitor.

Approximately 1% of subjects treated with Viekira Pak experienced Grade 3 ALT elevations after starting treatment. However, it was noted that the incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol containing medication. The incidence of clinically relevant ALT elevations among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy was 3% (2/59).

Consequently, similar analyses were conducted to evaluate whether cases of Grade 2 or higher ALT/AST occurred with concomitant SOF/VEL/VOX and estrogen use. These findings are summarized below:

- One subject (ID# 02130-22194, described under the IAC Assessment in this Section) in GS-US-367-1168 had on-treatment Grade 3 ALT and Grade 2 AST.
- One subject in POLARIS-2 (ID# 02760-26043, concomitant etonogestrel/ethinyl estradiol) with baseline Grade 1 AST had on-treatment Grade 2 AST; ALT remained within normal limits throughout.
- One subject in POLARIS-2 (ID# 04238-26007, concomitant depo provera) with baseline Grade 2 AST had on-treatment Grade 3 AST; ALT remained within normal limits throughout.
- One healthy volunteer (ID# 08142-1008) in GS-US-367-1909 (DDI study evaluating SOF/VEL/VOX+VOX and norgestimate/ethinyl estradiol) had these drugs co-administered during study days 36-42. Screening, baseline, and Study Day 35 laboratory values were within normal limits. ALT was Grade 2 on Day 43, Grade 3 on Day 49, Grade 2 on Day 56, and within normal limits on Day 63 (i.e. 7 days after completion of study drug dosing). AST was Grade 1 on Day 49 and returned to normal limits on Day 56.

Overall, two cases of transient Grade 3 ALT elevations were identified in the SOF/VEL/VOX development program. Of 1056 subjects receiving SOF/VEL/VOX in the four phase 3 trials (ISS population), 1 subject (0.1%) experienced Grade 3 ALT elevations after starting treatment. In the ISS population, neither of the 2 women taking a concomitant ethinyl estradiol containing medication experienced Grade 3 ALT elevations after starting treatment. In the ISS population, none of the 11 women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy , had clinically relevant ALT elevations. Based on the available information, no specific product labeling is warranted for ALT abnormalities with concomitant SOF/VEL/VOX and estrogen use. Routine pharmacovigilance will be in place to detect post-marketing signals.

Reviewer Comment: The possibility of drug-related hepatic toxicity has been evaluated independently by the IAC and the clinical review team, and both parties have found no clear evidence of DILI with SOF/VEL/VOX exposure among subjects with compensated liver disease. Based on all available information, no specific product labeling is warranted aside from displaying bilirubin in Section 6 based on prior SOF-containing products and also VOX is an inhibitor of organic anion transporting polypeptide (OATP)1B1 and OATP1B3 and can contribute to bilirubin increases. Routine pharmacovigilance will be in place to detect post-marketing signals.

8.5.2. Cardiac Disorders

Postmarketing cases of serious symptomatic bradycardia have been reported when amiodarone was coadministered with SOF in combination with another HCV DAA. In addition, serious heart failure events occurred in phase 2 development of a structurally different investigational HCV NS5B inhibitor. Therefore, a detailed safety evaluation of cardiac disorders was conducted and the results are summarized in Table 29.

Table 29: Cardiac Events, All Cause, All Grade, POLARIS-1 and POLARIS-4

Dictionary Derived Term	SOF/VEL/VOX 12 Week N=445	SOF/VEL 12 Week N=151	PBO 12 Week N=152
Dyspnoea	4 (1%)	2 (1%)	2 (1%)
Palpitations	1 (<1%)	1 (1%)	0 (0%)
Oedema peripheral	5 (1%)	4 (3%)	5 (3%)
Chest pain	2 (<1%)	1 (1%)	1 (1%)
Syncope	1 (<1%)	2 (1%)	0 (0%)
Blood creatine phosphokinase increased	1 (<1%)	0 (0%)	0 (0%)
Sinus tachycardia	1 (<1%)	0 (0%)	0 (0%)
Blood pressure fluctuation	1 (<1%)	0 (0%)	0 (0%)
Cardiac failure congestive	1 (<1%)	0 (0%)	0 (0%)
Angina unstable	0 (0%)	1 (1%)	0 (0%)
Atrial fibrillation	0 (0%)	1 (1%)	2 (1%)
Ventricular fibrillation	0 (0%)	0 (0%)	1 (1%)
Electrocardiogram QT prolonged	1 (<1%)	0 (0%)	0 (0%)
Total Subjects	12 (3%)	6 (4%)	9 (6%)
Subjects with Related Events	2 (<1%)	3 (2%)	1 (1%)

Source: ISS ADSL and ADAE datasets

Cardiac events occurred infrequently overall, occurring in 3% of subjects in the SOF/VEL/VOX group, 4% of subjects in the SOF/VEL group, and 6% of subjects in the placebo group. Related events among SOF/VEL/VOX subjects occurred at frequencies comparable to placebo. Most events were Grade 1-2 and nonserious.

A focused analysis was performed to identify cases of dizziness or syncope during the first two weeks of treatment among subjects receiving concomitant beta blockers or calcium-channel blockers. Stable beta blocker use was reported for 57 (13%) subjects in the SOF/VEL/VOX group, 9 (6%) of subjects in the SOF/VEL group, and 27 (18%) of subjects in the placebo group. Stable calcium-channel blocker use was reported for 61 (14%) subjects in the SOF/VEL/VOX group, 8 (5%) of subjects in the SOF/VEL group, and 20 (13%) of subjects in the placebo group.

- During the first two weeks of treatment, no clinically relevant changes in heart rate were observed for any subjects receiving chronic beta blockers or calcium channel blockers.
- No AEs suggestive of symptomatic bradycardia were reported across treatment groups.
- No syncopal events were reported across treatment groups.
- Two subjects receiving beta blockers had an AE of dizziness during the first two weeks of SOF/VEL/VOX treatment. Both AEs were Grade 1 and nonserious. These events were assessed as unrelated to study drug; SOF/VEL/VOX dosing was not interrupted or modified, and both subjects completed study treatment.

For comparison, the same analysis was performed among subjects who did not take beta blockers or calcium channel blockers during the first 2 weeks of treatment. A total of 11 SOF/VEL/VOX subjects (3%) experienced at least 1 AE of interest, including palpitations (1 subject, 0.3%), sinus tachycardia (1 subject, 0.3%), and dizziness (9 subjects, 2.3%). The majority of events were Grade 1 severity and no notable changes from baseline heart rate were observed. These AEs of interest were noted among 2% of subjects in the SOF/VEL group and 6% of subjects in the placebo group. No clinically significant changes from baseline heart rate were observed.

Reviewer Comment: Adverse events suggestive of symptomatic bradycardia (syncope, dizziness) were infrequent and occurred at comparable frequencies between subjects with or without exposure to beta blockers or calcium channel blockers. No clinically relevant changes from baseline heart rate were observed across treatment groups, with or without concomitant beta blocker or calcium channel blocker exposure.

Amiodarone was a prohibited concomitant medication in all Phase 3 trials; hence no cases of amiodarone and SOF/VEL/VOX coadministration were available for evaluation.

Overall Cardiac Assessment: No cardiac safety signal was detected from the analyses performed. The overall frequency of cardiac events was low and events of interest occurred primarily among subjects with prior history of cardiac abnormalities (either arrhythmia or coronary disease) or risk factors for cardiac disease. There were no substantial differences in the type or frequency of events between subjects receiving SOF/VEL/VOX with beta blockers or calcium channel blockers and those receiving SOF/VEL/VOX without beta blockers or calcium channel blockers. The reviewer assessments and conclusions are similar for the ISS population and for the Safety Update Report. Based on these findings, no specific product labeling

regarding cardiovascular risk is warranted beyond the Warning and Precaution that is included for all SOF-containing drugs.

8.5.3. Neuropsychiatric Disorders

The current SOF, LDV/SOF and SOF/VEL labels contain language in the *Less Common Adverse Reactions Reported in Clinical Trials* section pertaining to depression and suicidal events. Analyses of depression and/or suicidal events were performed to evaluate a potential causal association with SOF/VEL/VOX using pooled terms from the MedDRA High Level Group Terms (HLGT) "Depressed Mood Disorders and Disturbances" and "Suicidal and Self-Injurious Behaviours NEC."

Depression events were infrequent in POLARIS-1 and POLARIS-4, occurring in 1% of subjects in the SOF/VEL/VOX, SOF/VEL, and placebo groups respectively. All events were Grade 1 or 2 with the exception of one episode of Grade 3 depression in the SOF/VEL group, and one episode of Grade 4 suicide attempt in the SOF/VEL group.

Reviewer Comment: Depression events have been associated with SOF in past trials. There is no clear signal for increased risk of depression events with SOF/VEL/VOX; events occurred in SOF-containing treatment arms at a comparable rate to the placebo group. The reviewer assessments and conclusions are similar for the ISS population. No depression events were identified in the Safety Update Report.

In order to determine whether there is a trend toward tolerability issues caused by anxiety events, an analysis was performed using the High Level Group Term "Anxiety Disorders and symptoms." Anxiety events were infrequent in POLARIS-1 and POLARIS-4, occurring in 2% of subjects in the SOF/VEL/VOX group, 4% of subjects in the SOF/VEL group, and 2% of subjects in the placebo group. All events were Grade 1 or 2.

Reviewer Comment: Anxiety events occurred at similar frequency across the SOF/VEL/VOX, SOF/VEL, and placebo groups. The reviewer assessments and conclusions are similar for the ISS population. No anxiety events were identified in the Safety Update Report.

For completeness of the neuropsychiatric evaluation, additional analyses were performed using the High Level Group Terms "Schizophrenia and other psychotic disorders" and "Sleep Disorders." No significant results were found in these analyses (1 subject in the placebo group with schizophrenia).

Overall Assessment: There is no clear indication for an increased risk of neuropsychiatric events with SOF/VEL/VOX. However, depressive events have been observed in prior trials for Sovaldi and Harvoni, and these respective labels contain language pertaining to depression and suicidal events, as does the Epclusa label. For consistency, similar language could be considered for the SOF/VEL/VOX label as well.

8.5.4. Rash

The current LDV/SOF label includes the following language in the Postmarketing Experience section:

- *Skin and Subcutaneous Tissue Disorders: skin rashes, sometimes with blisters or angioedema-like swellings*

Analyses of rash events were performed to evaluate a potential causal association with SOF/VEL/VOX. Similar to the rash analysis in the original LDV/SOF and SOF/VEL NDA clinical reviews, analyses of rash events pooled the following 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, and rash vesicular.

Rash events were infrequent in POLARIS-1 and POLARIS-4, occurring in 3% of subjects in the SOF/VEL/VOX and SOF/VEL groups, and 1% of subjects in the placebo group. The majority of events were Grade 1 in severity. There were no discontinuations due to rash and no Grade 3 or 4 events were observed. No events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were reported.

The majority of events were assessed by investigators as unrelated to study drug. Rash events that were considered related occurred in 1% of subjects in the SOF/VEL/VOX, SOF/VEL, and placebo groups respectively.

Overall Assessment: The frequency and severity of rash events occurring in SOF/VEL/VOX subjects was low. The reviewer assessments and conclusions are similar for the ISS population. No rash events were identified in the Safety Update Report. Although no specific safety signal was detected for serious rash events with SOF/VEL/VOX, product labeling similar to Sovaldi, Harvoni and Epclusa is recommended for this adverse event of special interest. Any potential signals of serious rash events associated with SOF/VEL/VOX use will be closely monitored in the postmarketing setting.

8.5.5. Rhabdomyolysis

The current SOF, LDV/SOF and SOF/VEL labels contain information pertaining to creatine kinase (CK) elevations. Analyses were performed to assess the frequency of graded increases in creatine kinase among SOF/VEL/VOX recipients and to identify cases of clinical rhabdomyolysis. CK elevations were also evaluated in subjects who received statins, in response to a Tracked Safety Issue for rhabdomyolysis or CK elevations with DAAs.

There were no clinical events of rhabdomyolysis in POLARIS-1 and POLARIS-4. Grade 3/4 CK elevations were infrequent across all groups, occurring in 1% of subjects in the SOF/VEL/VOX, SOF/VEL, and placebo groups respectively (Table 44, Section 8.4.6). None of the subjects with Grade 3/4 CK elevations had concomitant statin use. According to the Applicant, all Grade 3 and 4 elevations were associated with physical exertion.

Overall Assessment: The reviewer assessments and conclusions are also similar for the ISS population and for the Safety Update Report. The Applicant proposed inclusion of creatine kinase in SOF/VEL/VOX product labeling. Although the frequency of Grade 3 and 4 abnormalities was low and there was no apparent clinical significance to the elevations, it is reasonable to include this information in product labeling to be consistent with the Sovaldi, Harvoni, and Epclusa prescribing information. We will continue to monitor closely in the postmarketing setting for any potential signals of rhabdomyolysis associated with SOF/VEL/VOX use.

8.5.6. Pancreatitis

The current SOF, LDV/SOF and SOF/VEL labels contain information pertaining to lipase elevations. Analyses were performed to assess the frequency of graded increases in lipase among SOF/VEL/VOX recipients and to identify cases of clinical pancreatitis. Of note, amylase was not measured.

No clinical cases of pancreatitis were reported in POLARIS-1 and POLARIS-4. Grade 3/4 lipase elevations were infrequent across all groups, occurring in 2% of subjects in the SOF/VEL/VOX group, 1% of subjects in the SOF/VEL group, and 3% of subjects in the placebo group (Table 44, Section 8.4.6).

Reviewer Comment: The reviewer assessments and conclusions are also similar for the ISS population and for the Safety Update Report. Although the lipase elevations are not associated with clinical pancreatitis, the Applicant proposed labeling consistent with the approach used in the Sovaldi, Harvoni, and Epclusa labels. We will continue to monitor closely in the postmarketing setting for any potential signals of pancreatitis associated with SOF/VEL/VOX use.

8.5.7. Pancytopenia

The current SOF label includes the following language in the *Less Common Adverse Reactions Reported in the Clinical Trials* section:

- *Hematologic Effects: pancytopenia (particularly in subjects receiving concomitant pegylated interferon)*

No pancytopenia cases occurred for SOF/VEL/VOX.

Reviewer Comment: Although SOF is labeled for pancytopenia, particularly occurring in subjects receiving concomitant interferon which carries a Warning and Precaution regarding bone marrow suppression, no pancytopenia signal is identified with SOF/VEL/VOX use and thus no relevant labeling is recommended. We will continue to monitor closely in the postmarketing setting for any potential signals of pancytopenia events associated with SOF/VEL/VOX use.

8.5.8. Safety Profile Among Subjects with Baseline CPT A Cirrhosis

Safety analyses were performed to identify unique SOF/VEL/VOX safety signals in subjects with cirrhosis (n=205) compared to subjects without cirrhosis (n=240).

There was one death (61 year old non-cirrhotic subject, see Section 8.4.1). The percentage of subjects with SAEs was equal between the two groups at 2%. The percentage of subjects with Grade 3/4 AEs was 2% and 1% respectively. All-cause AEs of any severity occurred in 82% and 75% respectively; headache was the only AE with a ≥2% risk difference between the two groups (24% versus 20%). Graded laboratory abnormalities occurred in 73% and 65% respectively; this observation is driven primarily by differences in the percentages of cirrhotic and non-cirrhotic subjects with total bilirubin elevations (14% versus 6%), glucose elevations (39% versus 33%), lipase elevations (17% versus 13%), and decreased platelets (19% versus 5%). Grade 3/4 laboratory abnormalities occurred in 8% and 5% respectively.

Reviewer Comment: Other than bilirubin elevations (see Section 4.5.3 and Section 8.4.6), no exposure or unique safety issues are identified in the CPT A population. We will continue to monitor closely in the postmarketing setting for any potential serious safety signals associated with SOF/VEL/VOX use in the CPT A population because patients can fluctuate between CPT A and CPT B, and can also fluctuate between MELD scores.

8.6. Safety Analyses by Demographic Subgroups

Consistent with our approach for the overall safety review, the impact of age, sex, and race on the frequencies of adverse events were assessed for POLARIS-1 and POLARIS-4, as well as for the ISS population. Overall, we did not find any demographic subgroups at substantially higher risk for serious or severe AEs. This section contains a brief summary of our findings, organized by demographic variable. The discussion is limited to POLARIS-1 and POLARIS-4 subjects treated with SOF/VEL/VOX. Any notable findings from the ISS population (i.e. safety issues from POLARIS-2 and POLARIS-3 that were not observed in, or differed from, POLARIS-1 and POLARIS-4) are presented where applicable.

As noted in Section 4.5 (Clinical Pharmacology), several demographic factors including age, sex, BMI, and race were evaluated to determine whether these factors have an effect on SOF and VEL and VOX PK. Exposure-safety analyses performed by the FDA pharmacometrics team did not reveal any significant safety concerns associated with the higher exposures in any demographic subgroup.

Age
Subjects <65 years of age (n=371) were compared to subjects ≥65 years old (n=74). The older cohort comprised 16% of the SOF/VEL/VOX 12 Week population. There was one death (61 year old, see Section 8.4.1). The percentage of subjects with SAEs was 2% and 4% respectively. The percentage of subjects with Grade 3/4 AEs was 1% and 4% respectively. All-cause AEs of any severity occurred in 77% and 82% respectively. Headache, fatigue, diarrhea, and nausea were the most frequent AEs in both groups. The percentage of subjects with graded laboratory abnormalities was equal between the two groups at 69%.

Reviewer Comment: No overall safety differences were observed between subjects aged ≥65 years and younger subjects.

Gender
Women comprised 23% of the SOF/VEL/VOX 12 Week population (102/445). There was one death (61 year old male, see Section 8.4.1). SAEs occurred in 3% of women and 2% of men; Grade 3/4 events occurred in 4% of women and 1% of men. All-cause AEs of any severity occurred in 87% of women and 75% of men; this observation is driven primarily by differences in the percentages of women and men with headache (29% versus 25%), fatigue (25% versus 22%), nausea (21% versus 11%), and asthenia (8% versus 6%). Graded laboratory abnormalities occurred in 68% of women and 69% of men.

As noted in the SOF/VEL review, women have higher drug exposures to SOF and VEL compared to men. However, given the similarities in the types of AEs reported between men and women and the predominance of Grade 1 and 2 events, neither the differences in drug exposure nor the relatively higher rate of AEs among women appear clinically significant in SOF/VEL/VOX.

Race
Differences between racial groups were more difficult to assess due to the predominance of white subjects in the study population. Analyses of black (12%) and non-black (88%) subjects are summarized. There was one death (subject of African descent, see Section 8.4.1). SAEs occurred in 4% of black subjects and 2% of non-black subjects. Grade 3/4 AEs occurred in 4% of black subjects and 1% of non-black subjects. All-cause AEs of any severity occurred in 63% of black subjects and 80% of non-black subjects; this observation is driven primarily by differences in the percentages of black subjects and non-black subjects with headache (24% versus 26%), fatigue (19% versus 23%), diarrhea (13% versus 20%), nausea (11% versus 14%), and asthenia (4% versus 7%). Graded laboratory abnormalities occurred in 80% of black subjects and 67% of non-black subjects; this observation is driven primarily by differences in the percentages of black subjects and non-black subjects with hypokalemia (15% versus 3%) and hyponatremia (13% versus 7%); the laboratory differences may also be suggestive of the small proportion of black subjects. Grade 3/4 laboratory abnormalities occurred in 4% of black subjects and 6% of non-black subjects.

One unexpected finding was that, of 43 subjects with total bilirubin elevations, 42 were non-black. However, rates of Grade 1 elevations were comparable for black subjects (4%) versus non-black subjects (6%) in POLARIS-2 and -3; the reasons for these differences are unclear.

Reviewer Comment: It is possible that the differences may be less notable had there been more equal representation between racial groups.

Overall Demographic Safety Analysis Conclusion: Adverse events occurred with similar frequency and severity across all demographic groups. No patterns were identified to suggest a higher risk for specific events in any population.

8.7. Specific Safety Studies/Clinical Trials

No additional trials have been conducted to evaluate specific safety concerns.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

The relatively short duration of SOF/VEL/VOX treatment (12 weeks) and follow-up (generally 24 weeks) in clinical trials limits the assessment for oncologic events. Treatment-emergent oncologic events were infrequent in POLARIS-1 and POLARIS-4, occurring in 4 subjects (1%) in the SOF/VEL/VOX group, zero subjects in the SOF/VEL group, and 2 subjects (1%) in the placebo group. PTs included basal cell carcinoma, adrenal neoplasm, ovarian cancer, invasive ductal breast carcinoma, and laryngeal papilloma.

Reviewer Comment: Based on the available data from the Phase 3 trials, there is no clinical evidence of carcinogenicity for SOF/VEL /VOX.

In POLARIS-1 and POLARIS-4, a total of 5 hepatocellular carcinoma (HCC) cases were identified, all occurred post-treatment, all subjects were cirrhotic, and all were assessed by investigators as unrelated to study drug:

- SOF/VEL/VOX (n=4): HCC was identified on Day 120 (GS-US-367-1170-04021-27742), Day 152 (GS-US-367-1171-00472-24387), Day 171 (GS-US-367-1171-01386-24385), and Day 207 (GS-US-367-1171-04021-24246).
- SOF/VEL (n=1): HCC was identified on Day 151 (GS-US-367-1170-02689-27517).

In the ISS analyses, two additional HCC cases were identified, both in SOF/VEL subjects who were cirrhotic, both occurred post-treatment (on Day 117 and Day 158 respectively) and both were assessed by investigators as unrelated to study drug.

In the Safety Update Report, two additional HCC cases were identified, both in SOF/VEL/VOX subjects who were cirrhotic, and both were assessed by investigators as unrelated to study drug (see Section 8.4.1 and Section 8.4.2).

Reviewer Comment: A strong association between chronic HCV infection and HCC has been observed, with a reported annual HCC incidence of 3%-5% in the chronic HCV cirrhotic population.[22,23] The narratives were reviewed and I agree with the investigators' assessments that these HCC cases are unlikely to be related to study drug. The reports of HCC identified do not demonstrate a definitive causal relationship between SOF/VEL/VOX and development or acceleration of HCC, rather these HCC cases are more likely explained by underlying cirrhosis. The Applicant is conducting long term registrational trials which include monitoring for development of HCC. In addition, surveillance for malignancies will occur postmarketing in collaboration with DPV II.

In an IND Safety Report (submitted on May 3, 2017), HCC was identified on Day 258 post-

treatment in a SOF/VEL/VOX subject who was non-cirrhotic (GS-US-367-1170-04021-27742). Although the investigator assessed that diagnosis 258 days post-treatment made a possible drug contribution less likely, and noted that "several factors are involved in the carcinogenesis and development of HCC", the investigator could not definitively exclude a possible drug contribution in this female patient with no cirrhosis, no nonalcoholic fatty liver disease (NALFD) and no diabetes.

Reviewer Comment: While I agree with the investigator's assessment, the association between chronic HCV infection and HCC is a confounder in this case. Based on the totality of the available data discussed above and in Section 8.4.1 (regarding FDA's review of the available data and conclusion that no HCV DAA class labeling regarding HCC occurrence/recurrence was warranted at this time) , continued postmarketing pharmacovigilance in collaboration with DPV II is recommended.

8.8.2. Human Reproduction and Pregnancy

Pregnant and lactating women were excluded from participation for all Phase 2 and Phase 3 trials. However, a total of two pregnancies have been reported during the SOF/VEL/VOX development program, both in female subjects in the SOF/VEL/VOX 8 Week group in GS-US-367-1172 (POLARIS-2). Both cases are briefly summarized below.

1) A female subject prematurely discontinued study drug on Day 28 following confirmation of pregnancy. The pregnancy ended in an elective abortion.
2) A female subject who received SOF/VEL/VOX for 8 weeks had a confirmed pregnancy on posttreatment Day 55. The pregnancy ended in a miscarriage, and was reported as a non-treatment emergent SAE.

8.8.3. Pediatrics and Assessment of Effects on Growth

Pediatric studies have not been initiated and, as such, no pediatric data are available for review with this application. However, the Applicant has discussed the size and scope of future pediatric trials with DAVP. In conformance with current regulatory requirements, the Applicant submitted an initial Pediatric Study Plan (iPSP) for SOF/VEL/VOX on November 25, 2015. The document was reviewed and found to be generally satisfactory by both the review division as well as the Pediatric Review Committee (PeRC). The Applicant incorporated the Agency's recommendations and the revised PSP was approved by the Division and the PeRC. The Division issued a notice of Agreed PSP on April 29, 2016. The Agreed iPSP included the 8 week regimen in DAA-naïve subjects and the 12 week regimen in DAA-experienced subjects. The Applicant submitted an amendment to the Agreed iPSP on December 6, 2016. Based on the results and indication sought in adults, the modified plan included only the 12 week regimen in DAA-experienced subjects. The document was reviewed and found to be generally satisfactory by both the review division as well as the Pediatric Review Committee (PeRC). The proposed pediatric studies reflect the PREA PMR that will be issued.

In brief, the proposed pediatric development plan includes three studies to evaluate the safety and efficacy of SOF/VEL/VOX in children ages 12 to < 18 years of age who have failed prior DAA therapies:

(b) (4)

- Study GS-US-367-2094 will be an observational study of safety and efficacy of SOF/VEL/VOX in pediatric subjects ages 12 to < 18 years of age with HCV GT 1-6 infection and who are DAA-experienced. Study GS-US-367-2094 will be conducted after approval of the use of SOF/VEL/VOX in adolescent patients. A total of 20 subjects are proposed for enrollment.

(b) (4)

The Applicant has requested a deferral of pediatric studies of children 12-17 years of age until data from Phase 3 studies and the preliminary PK data from the lead-in portion of the SOF/VEL adolescent Study GS-US-342-1143 are available and have been reviewed by the Agency. The Division is in agreement with this proposal. The Applicant has also requested a partial waiver of pediatric studies in children < 12 years of age. The Division agrees with this proposal as well for the following reasons: (1) there is a high rate of spontaneous viral clearance and lack of significant disease progression in children < 3 years of age; (2) DAAs are anticipated to be approved first for adolescents, therefore few children < 12 years of age will have been treated with a DAA; (3) 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. The deferral and waiver requests were presented to the PeRC, and the PeRC agreed with the Applicant's proposal and the Division's recommendations.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The potential for drug abuse, withdrawal, or rebound with SOF/VEL/VOX was not evaluated but is not anticipated. In the event of an overdose, hemodialysis can remove the active SOF metabolite, GS-331007 but is unlikely to remove a significant amount of VEL or VOX, both of

which are highly plasma protein bound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Current SOF-containing labels include a Warning and Precaution for serious symptomatic bradycardia when SOF is coadministered with amiodarone and another HCV DAA. This labeling change in March 2015 resulted from postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention reported when amiodarone was coadministered with SOF in combination with another DAA. Bradycardia generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. Section 5.2 and Section 7.1 were revised to state coadministration of amiodarone with a SOF-containing regimen may result in serious symptomatic bradycardia. Originally the label stated coadministration of amiodarone with Sovaldi in combination with another DAA may result in serious symptomatic bradycardia. In response to PMR 2993-1 (see below) Gilead conducted several in vitro studies. Please refer to reviews by Wendy Wu (entered into DAARTs by Renmeet Grewal), Jenny Zheng and Sarah Connelly for details. Collectively the results from the in vitro studies show a pharmacodynamic interaction can occur with SOF and amiodarone alone without additional DAAs; hence the the SOF label was revised as noted above to remove reference to “in combination with another DAA”.

Postmarketing Requirement 2993-1:
Using appropriate in vitro approaches (including, but not limited to, patch clamp studies of L-type and T-type calcium channels and transporter phenotyping),evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between sofosbuvir and amiodarone, with and without other hepatitis C virus (HCV) direct acting antiviral drugs (DAA).

Reviewer Comment: Although no cases were reported in the Phase 3 SOF/VEL/VOX trials, similar Warnings and Precautions language is proposed for the SOF/VEL/VOX label regarding the risk for serious symptomatic bradycardia when SOF/VEL/VOX is coadministered with amiodarone.

Effective February 2017, current SOF-containing labels include a Boxed 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 DAA drugs for chronic HCV infection. This safety information was identified from adverse event reports from the FDA Adverse Event Reporting System (FAERS) and medical literature.

Reviewer Comment: Although no cases were reported in the Phase 3 SOF/VEL/VOX trials, similar Boxed Warning and Warnings and Precautions language is proposed for the

SOF/VEL/VOX label regarding the risk for HBV reactivation in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy.

Effective April 2017, LDV/SOF is labeled for angioedema as a postmarketing ADR based on one published case report (Hynicka LM and Khambaty, 2016), one FAERS report, and the Applicant's analysis of 200 potential angioedema events, 11 of which can be plausibly linked to LDV/SOF. The majority of cases resolved without treatment after LDV/SOF discontinuation and did not require emergency intervention. Please refer to the Pharmacovigilance Review prepared by Dr. Mihaela Jason on March 2, 2017. Dr. Jason's review summarizes the FAERS report and the literature report regarding angioedema with the use of LDV/SOF.

Reviewer Comment: Although no clear signal is identified for angioedema with SOF/VEL/VOX use, product labeling similar to LDV/SOF is recommended.

8.9.2. Expectations on Safety in the Postmarket Setting

Safety analyses and conclusions in this review are primarily based upon data from the submitted Phase 2 and 3 trial populations. The eligibility criteria for the four phase 3 trials may mitigate potential safety concerns that may be observed with wider usage in the postmarket setting. Emergence of new events can be managed by routine pharmacovigilance activities.

8.10. Additional Safety Issues From Other Disciplines

All additional safety issues from other disciplines are included in this review.

8.11. Integrated Assessment of Safety

No major safety issues or concerns specifically related to SOF or VEL or VOX were identified in this review. In the POLARIS-1 and POLARIS-4 population, as well as the ISS population, headache, fatigue, and nausea were the most common AEs reported and all occurred at rates similar to the active comparator or placebo. In ISS analyses, no notable differences appeared when comparing SOF/VEL/VOX 8 Week versus 12 Week durations.

Sections 5 and 6 of the SOF/VEL/VOX label will include information from the Sovaldi label. No new safety issues unique to SOF/VEL/VOX have been identified that merit inclusion in labeling.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting will not be convened for this application.

10 Labeling Recommendations

10.1. Prescribing Information

Labeling negotiations are ongoing. Below are general clinical recommendations for proposed

labeling. Major labeling recommendations or changes will be further summarized in a clinical review addendum as warranted. Outstanding labeling issues include whether to describe the POLARIS-4 indication by class (i.e. nucleotide analog NS5B polymerase inhibitor treatment-experienced who are NS5A inhibitor treatment-naïve) or by specific drug name (i.e. sofosbuvir).

1 INDICATIONS AND USAGE

The review team concludes the contribution of VOX is demonstrated for all genotypes in NS5A inhibitor treatment-experienced adults without cirrhosis or with compensated cirrhosis.

The review team also concludes the contribution of VOX is demonstrated for HCV genotypes 1a or 3 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who areNS5A inhibitor treatment-naïve.

To further explain why an indication is granted for all HCV genotypes in NS5A inhibitor treatment-experienced patients; whereas, only HCV genotypes 1a and 3 are indicated for NS5A inhibitor treatment-naïve patients, the following statement is included in section 1 and similar explanation is provided in section 14 to accompany the trial results.

- No additional benefit of VOSEVI has been established over sofosbuvir/velpatasvir for the treatment of HCV genotypes 1b, 2, 4, 5 and 6 in nucleotide analog NS5B polymerase inhibitor treatment-experienced adults who are NS5A inhibitor treatment-naïve [see Dosage and Administration (2.2) and Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

The review team recommends describing the following adult populations for whom SOF/VEL/VOX is indicated:

- Genotype 1, 2, 3, 4, 5, or 6 in NS5A inhibitor treatment-experienced
- Genotype 1a or 3 in nucleotide analog NS5B polymerase inhibitor treatment-experienced who are NS5A inhibitor treatment-naïve

4 CONTRAINDICATIONS

The review team recommends that coadministration of SOF/VEL/VOX with rifampin is contraindicated.

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience

- POLARIS-1 and POLARIS-4 will be displayed separately so that both placebo and SOF/VEL arms are described. Adverse reactions from both of these comparator groups comprise the best available data to display the safety information and to help inform the safety profile of SOF/VEL/VOX. In addition, the 10% cut-off should be revised to 5% to allow the display of more ADRs. *(See Section 8.4.5)*
- In consultation with the Labeling Development Team, the decision was made to add a section entitled “Less Common Adverse Reactions Reported in Clinical Trials.” The

purpose of this section is to include information about ADRs observed in clinical trials evaluating SOF (and included in current SOF, LDV/SOF, and SOF/VEL labels), even if events occurred rarely in the SOF/VEL/VOX trials. This section will likely include depression and rash. *(See Sections 8.5.3 and 8.5.4)*

- Laboratory data from POLARIS-1 and POLARIS-4 will be displayed separately in the Laboratory Abnormalities so that both placebo and SOF/VEL arms are described. *(See Section 8.4.6)*

7 DRUG INTERACTIONS

7.3 Established and Potentially Significant Drug Interactions

The following changes are proposed to Table 3: Potentially Significant Drug Interactions

- Co-administration with BCRP substrates is not recommended.
- Revise antimycobacterials to state that rifampin decreases exposure of sofosvuvir, velpatasvir, and voxilaprevir from multiple doses and increases the exposure of voxilaprevir from single dose significantly, and coadministration is contraindicated.
- Revise PPI section to state that omeprazole 20 mg or lower can be coadministered and use with other PPIs has not been studied.
- The observed higher degree of interaction with rosuvastatin from SOF/VEL/VOX (as compared to cyclosporine) demonstrates the unpredictability of a potentially significant DDI with most of the unstudied statins. The statins recommendations in Section 7 should be revised to state that for pitavastatin, coadministration is not recommended due to an increased risk for severe myopathy at >4 mg, as shown in pitavastatin premarketing clinical studies. For other unstudied statins, including atorvastatin, fluvastatin, lovastatin, and simvastatin, the lowest necessary dose should be used when coadministered with VOSEVI.
- Revise ARVs to state that tipranavir/ritonavir coadministration is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

- Revise to state that no dosage recommendation can be given for patients with severe renal impairment or ESRD due to higher exposures (up to 20-fold) of the predominant sofosbuvir metabolite in these patients. *(See Section 4.5.3)*

8.7 Hepatic Impairment

- Revise to state that VOSEVI is not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C) due to higher exposures of voxilaprevir in these patients. *(See Section 4.5.3)*

12 CLINICAL PHARMACOLOGY

12.4 Microbiology

- Revise for clarity and consistency with other recently approved HCV DAA labels

14 CLINICAL STUDIES

14.2 Clinical Trials in DAA-Experienced Subjects with Decompensated Cirrhosis

- Provide additional details of the treatment experience for POLARIS-1: Of the 263 subjects treated with VOSEVI in POLARIS-1, the most common prior NS5A inhibitors were ledipasvir (LDV) (51%), daclatasvir (27%), ombitasvir (11%), velpatasvir (7%), and elbasvir (3%).
- Revise the POLARIS-4 table to provide more detailed descriptions to explain why only GT1a and GT3 are indicated. (*See Section 6.2.2)*
- Provide additional details of the treatment experience for POLARIS-4: Of the 85% of subjects who previously failed a regimen containing sofosbuvir, 69% had prior exposure to sofosbuvir with or without peginterferon alfa/ribavirin or ribavirin, 15% had prior exposure to sofosbuvir + HCV protease inhibitor (boceprevir, telaprevir or simeprevir) with or without peginterferon alfa/ribavirin, and <1% had prior exposure to sofosbuvir + investigational agent. Of the 15% of subjects without prior sofosbuvir exposure, these subjects received investigational DAAs or an approved HCV protease inhibitor, with or without peginterferon alfa/ribavirin.
- Our rationale for defining the POLARIS-4 patient population in the proposed labeling is based on the findings that the majority of subjects had failed a SOF-containing regimen and that the treatment difference tended to be numerically large among the subjects with previous exposure to SOF (Table 30). The contribution of VOX was not evident in those receiving non SOF-containing regimens, including GT1a

(b) (4)

[redacted]

10.2. Patient Labeling

Patient labeling will be updated in accordance with the final agreed upon prescribing information in the Package Insert. Because negotiations pertaining to prescribing information were ongoing at the time of completion of this review, patient labeling was not yet updated.

11 Risk Evaluation and Mitigation Strategies (REMS)

No issues were identified to necessitate REMS.

12 Postmarketing Requirements and Commitments

Post-marketing requirements and commitments were still under discussion at the time this review was completed. This section includes PMRs and PMCs that will be proposed by the clinical review team.

- A PMR will be issued for pediatric trials to assess safety and efficacy of SOF/VEL/VOX for 12 weeks in pediatric subjects ages 12 to < 18 years of age with chronic HCV GT 1-6 infection and who are DAA-experienced, as required under the Pediatric Research Equity Act (PREA).

Additional postmarketing requirements or commitments may be proposed at a later time based on ongoing labeling and review discussions.

13 Appendices

13.1. References

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13.2. Financial Disclosure

There were no financial disclosures of significant concern, individually or collectively. The financial disclosures described below do not affect approvability of SOF/VEL/VOX.

Covered Clinical Study (Name and/or Number):
GS-US-367-1171 (POLARIS-1), GS-US-367-1172 (POLARIS-2), GS-US-367-1173 (POLARIS-3), GS-US-367-1170 (POLARIS-4), GS-US-367-1168, GS-US-367-1169, GS-US-367-1871, GS-US-337-1468, Cohorts 4 and 5 (LEPTON)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 765 Overall: 137 Principal Investigators, 628 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 41		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 40 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1 1. Dr. Trevor Hawkins was a PI on studies GS-US-367-1168 and GS-US-367-1169 from 12		

January 2015 to 28 August 2015. Dr. Hawkins became a full-time employee of Gilead on September 14, 2015 and is no longer an investigator for these studies, or any other Gilead-sponsored clinical study.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant adequately examined financial disclosure information from all clinical investigators for the covered clinical trials, as recommended in the *Guidance for Industry: Financial Disclosure by Clinical Investigators*. The Applicant certified in Form FDA 3454 that, as the sponsor of the submitted studies, the Applicant has not entered into any financial arrangement with the listed clinical investigators (list was included in the submission) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant also certified that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. The Applicant further certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Those investigators who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3) are noted in the above template. The Form FDA 3455 for each investigator was provided.

Overall, the number of investigators with a financial interest is low, approximately 5%. Due to the multicenter nature of these trials, the potential bias by any one investigator is minimized. Moreover, the efficacy endpoints are determined using objective measurements of HCV-RNA PCR by central laboratories and hence should not be vulnerable to bias on the part of the investigator.

In conclusion, the likelihood that trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

13.3. Supplemental Tables

None

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/s/

KIRK M CHAN-TACK
05/05/2017

KIMBERLY A STRUBLE
05/05/2017