CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208341Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW ADDENDUM

Date	June 1, 2016
From	Prabha Viswanathan, MD Sarah Connelly, MD
Subject	Clinical Review Addendum
NDA/BLA #	208341
Applicant	Gilead Sciences
Date of Submission	October 28, 2015
PDUFA Goal Date	June 28, 2016
Proprietary Name / Non-Proprietary Name	Epclusa sofosbuvir and velpatasvir (SOF/VEL)
Dosage form(s) / Strength(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with chronic hepatitis C virus infection
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	**SOF/VEL:** Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection without cirrhosis or with compensated cirrhosis **SOF/VEL with ribavirin:** Treatment of adult patients with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 and 6 infection with decompensated cirrhosis

The purpose of this addendum is to address two major review issues that were under consideration at the time the clinical review was finalized: treatment optimization for HCV genotype 3 (GT3) subjects and labeling of HIV antiretroviral drugs. This document will summarize the ultimate conclusions of the clinical review team.

1. Treatment Optimization for GT3 Subjects Without Cirrhosis or with Compensated Cirrhosis

As discussed in the clinical review, GT3 subjects treated with 12 weeks of sofosbuvir/velpatasvir (SOF/VEL) in ASTRAL-3 experienced higher rates of relapse compared to subjects infected with GT 1, 2, 4, 5, or 6 in ASTRAL-1 or ASTRAL-2. A key review issue was whether or not the addition of ribavirin (RBV) would prevent relapse and/or emergence of NS5A RAPs, particularly among subjects with cirrhosis. At the time the clinical review was finalized, the primary clinical team concluded that there are insufficient data to support the addition of RBV for GT3 cirrhotic subjects.

At the Late Cycle Meeting on April 19, 2016, the Division queried the Applicant about their perspective on the addition of RBV for GT3 cirrhotics, (b) (4) The results of this study will be submitted in response to a post-marketing requirement. (b) (4)

Reviewer Comment: Based on the currently available data, the clinical review team and the Applicant agree that SOF/VEL for 12 weeks, without ribavirin, is the most appropriate regimen for all GT3 infected subjects without cirrhosis or with compensated cirrhosis. Once data from the SOF/VEL versus SOF/VEL + RBV trial are available, the optimal regimen for GT3 cirrhotics can be reevaluated.

2. Co-administration of SOF/VEL with HIV Antiretroviral Agents (ARVs)

Phase 1 drug-drug interaction trials form the basis of the information presented in Sections 7 and 12 of the proposed label, supported by preliminary safety results from Trial GS-US-342-1202 (ASTRAL-5), a Phase 3, open-label study evaluating the safety and efficacy of SOF/VEL for 12 weeks in subjects with HIV/HCV co-infection. Interim safety results from ASTRAL-5 were included in the 90 day Safety Update Report, and follow-up summaries through the SVR4 datacut were provided for subjects receiving tenofovir disoproxil fumarate (TDF)-containing ARV regimens as well as subjects on atazanavir-based regimens who developed hepatic laboratory abnormalities.

Summary of ASTRAL-5

A total of 106 subjects with HIV/HCV coinfection and suppressed HIV viral load at study entry were enrolled and treated in ASTRAL-5. At the SVR4 datacut, 102 subjects had completed 12 weeks of SOF/VEL and 4 subjects had prematurely discontinued treatment: two discontinued due to adverse events (AEs) and two were lost to follow-up. Ninety-one subjects (86%) received TDF-containing regimens, of which 56 (53%) received ritonavir or cobicistat ("boosted TDF" regimens). Fifty subjects (47%) were on protease inhibitor (PI) - based regimens, 36 (34%) were on integrase inhibitor (INSTI)-based regimens, and the remaining 20 subjects were on non-nucleoside reverse transcriptase inhibitor (NNRTI) or INSTI+PI-based regimens.

No deaths have occurred in this study. Two subjects (2%) had SAEs that were considered unrelated to study medication: 1 subject had Grade 2 radial nerve palsy, and 1 subject had localized infection, sepsis, and urinary tract infection (all Grade 3). Two subjects (2%) prematurely discontinued SOF/VEL due to AEs: 1 subject who received lamivudine, abacavir, and ritonavir-boosted atazanavir (ATV/r) discontinued on study Day 4 due to Grade 1 vomiting; 1 subject who was receiving emtricitabine (FTC), TDF, and ATV/r discontinued on study Day 41 due to Grade 3 increased hepatic enzymes (see clinical review for additional details). A total of 75 subjects (71%) experienced at least 1 AE; 9 subjects (9%) had Grade 3 AEs and no Grade 4 AEs have been reported. The most commonly reported AEs were fatigue (25%), headache (13%), and arthralgia (9%).

Subjects Receiving Tenofovir-containing ARV Regimens

Phase 1 drug-drug interaction studies demonstrated higher TDF exposures when TDF is coadministered with SOF and VEL. Notable adverse drug reactions associated with TDF exposure include decreased bone mineral density and nephrotoxicity. Given the short duration of therapy for SOF/VEL, bone toxicity is not a great concern; in contrast, renal insufficiency can occur acutely and, if significant, may require modifications to ARV and/or SOF/VEL dosing. Hence, the Division requested the Applicant to assess renal AEs and renal laboratory abnormalities among TDF-treated subjects in ASTRAL-5 to help inform dosing recommendations for TDF with SOF/VEL.

Four subjects (4%) had an AE under the Renal and Urinary Disorders system organ class, including pollakiuria, glycosuria, and proteinuria. Of these, 2 subjects were receiving boosted TDF regimens and 2 subjects were receiving non-boosted TDF-containing regimens. All events were Grade 1 or 2 in severity. A total of 5 subjects experienced a change in serum Cr $\geq$ 0.4 mg/dL, creatinine clearance (CrCl) < 50 ml/min or normoglycemic glycosuria. Of these, 4 were receiving boosted TDF regimens and 1 subject was receiving a non-boosted TDF-containing regimen. These abnormalities were transient and asymptomatic in 4 of the 5 subjects; one subject on a boosted TDF regimen (FTC/TDF/ATV/r) with a history of chronic kidney disease developed 3+ proteinuria, normoglycemic glycosuria, elevated creatinine (3.3 mg/dL at Week 4, up from 1.4 mg/dL at baseline), and decreased CrCl following an episode of acute gastroenteritis with dehydration at Week 4, and his creatinine remained elevated at subsequent visits (2-2.7 mg/dL). No changes were made in ART in any of the five subjects and all completed 12 weeks of SOF/VEL.

Reviewer Comment: Preliminary safety data from ASTRAL-5 are adequate to support labeling for co-administration of SOF/VEL with TDF-containing ARV regimens.

Subjects Receiving ATV/r-Based ARV Regimens

Phase 1 drug-drug interaction studies demonstrated no significant changes in ATV, SOF, or VEL exposure when ATV is coadministered with SOF and VEL, and therefore no unique safety considerations are anticipated. However, review of the Safety Update Report revealed that a significant proportion of subjects on ATV/r-based regimens had elevated bilirubin (in excess of baseline elevations due to ATV/r), and additional information was requested from the Applicant.

A total of 20 subjects received ATV/r-based regimens. By the SVR4 datacut, 13/20 subjects (65%) had symptomatic elevations of total bilirubin > 2 x ULN. Twelve of the 13 subjects had increases of ≥ 0.5 mg/dL and 9/13 had increases of ≥ 1 mg/dL from baseline total bilirubin; the maximum increase was 3.2 mg/dL from baseline. The elevations peaked by Week 6 of SOF/VEL in 12/13 subjects, and the majority of subjects (9/13) had total bilirubin values that were less than or equal to their baseline value at Week 12 of SOF/VEL. All elevations in total bilirubin were attributed to increases in indirect bilirubin only; there were no significant concomitant increases in ALT, AST, alkaline phosphatase, or total bilirubin in any of the 13 subjects. The increased bilirubin values were not associated with clinical AEs and did not lead to treatment interruption or dosage adjustment of SOF/VEL or ARVs for any of the 13 subjects.

Reviewer Comment: Co-administration of SOF/VEL with ATV/r may result in increases in indirect bilirubin that are not associated with clinical adverse events or other hepatic laboratory abnormalities. The mechanism for this observation is unclear. Based on currently available information, no specific laboratory monitoring is required. The clinical review team has proposed inclusion of the following language to Section 6.1 of product labeling to inform prescribers of this observation:

> *Indirect Bilirubin: Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-HCV co-infected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPLCUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.*

In conclusion, the preliminary safety data from ASTRAL-5 are adequate to support labeling for SOF/VEL co-administration with ARVs. Labeling negotiations are ongoing at this time. A PMR will be issued to request formal submission of the final data once with trial has been completed. These data will be used to further characterize the safety and efficacy of SOF/VEL in HIV/HCV co-infected subjects, and to support the clinical pharmacology information contained product labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRABHA VISWANATHAN
06/01/2016

KIMBERLY A STRUBLE
06/01/2016

CLINICAL REVIEW

Application Type	New Drug Application
Application Number(s)	208341
Priority or Standard	Priority
Submit Date(s)	October 28, 2015
Received Date(s)	October 28, 2015
PDUFA Goal Date	June 28, 2016
Division/Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Prabha Viswanathan, MD Sarah Connelly, MD
Review Completion Date	March 29, 2016
Established Name	sofosbuvir and velpatasvir
(Proposed) Trade Name	Epclusa®
Applicant	Gilead Sciences, Inc.
Formulation(s)	Fixed dose combination tablet containing 400 mg sofosbuvir and 100 mg velpatasvir
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

Table of Contents

Table of Tables

Table of Figures

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
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
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ECI	event of clinical interest
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FU	follow up
GT	genotype
HCV	hepatitis C virus
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
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)
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
US	United States

1 Executive Summary

1.1. Product Introduction

Epclusa (SOF/VEL) is a fixed dose combination (FDC) tablet containing two direct acting antiviral (DAA) agents which 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). Velpatasvir (VEL) inhibits activity of the HCV NS5A protein, which is essential for both RNA replication and the assembly of HCV virions. VEL is a new molecular entity (NME) which will be available only in the FDC product currently under review.

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

1.2. Conclusions on the Substantial Evidence of Effectiveness

Data from the four 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 for the treatment of chronic HCV infection in cirrhotic and noncirrhotic (NC) patients infected with HCV GT1, 2, 3, 4, 5, or 6. ASTRAL-1, ASTRAL-2 and ASTRAL-3 evaluated the effectiveness of SOF/VEL in treatment naïve (TN) and treatment experienced (TE) subjects with chronic HCV infection caused by GT 1 ,2, 3, 4, 5, or 6 and compensated liver disease, defined as the absence of cirrhosis or compensated (Child Pugh Turcotte [CPT] A) cirrhosis. ASTRAL-4 evaluated SOF/VEL with or without RBV in TN and TE subjects infected with HCV GT 1-6 with decompensated cirrhosis. The overall sustained virologic response rates at post-treatment week 12 (SVR12), considered a virologic cure, were 95-99% among subjects treated with SOF/VEL for 12 weeks in ASTRAL-1, -2, and -3; and 94% for subjects treated with SOF/VEL + RBV for 12 weeks in ASTRAL-4. All four trials adequately established the effectiveness of SOF/VEL (with or without RBV) across HCV GT 1-6 and across subpopulations.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Sofosbuvir (SOF) is a hepatitis C virus (HCV) NS5B inhibitor and velpatasvir (VEL) is an HCV NS5A inhibitor. SOF/VEL is a fixed-dose combination tablet with a proposed indication for treatment of patients with chronic HCV infection. Intended subpopulations include treatment-naïve (TN) and treatment-experienced (TE) patients and patients with compensated and decompensated cirrhosis.

HCV infection is a serious disease, affecting an estimated 3-5 million people in the US and 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 during this NDA review cycle that confer SVR12 rates greater than 93% for HCV GT 1, 3, 4, 5, or 6-infected patients with compensated liver disease, defined as the absence of cirrhosis or compensated cirrhosis (Child Pugh Turcotte [CPT] A). The first approvals of DAA regimens in HCV GT 1 or 3-infected subjects with decompensated cirrhosis or liver transplant were also granted during this review cycle, with SVR12 rates ranging from 50-92% among GT1 and 83% for GT3 subjects.

While great progress has been made in improving SVR12 rates among patients with all stages of hepatic dysfunction, there is a need for better treatment options for patients with non-GT1 HCV. This need is even greater among subjects with decompensated cirrhosis with any HCV GT. SOF/VEL demonstrated SVR12 rates ranging from 83-100% depending on the Phase 3 trial regimen, HCV GT, cirrhosis stage, and prior treatment history. In addition, SOF/VEL is the first DAA regimen with potent activity across HCV GT 1-6. SOF/VEL is a highly effective, RBV-free, single tablet, once daily treatment option for TN and TE patients with compensated liver disease, regardless of HCV GT. Similarly, treatment with SOF/VEL + RBV confers the highest SVR12 dates observed to date across HCV GT 1-6 in subjects with decompensated cirrhosis.

Consistent with results from other development programs, HCV GT3- infected subjects with cirrhosis and/or prior treatment experience were noted to have lower SVR rates than subjects with any other HCV GT studied. SVR12 rates are 89% for HCV GT3 TE cirrhotic subjects, 91% for GT3 cirrhotics and 90% for GT3 TE subjects. The optimal strategy for improving SVR12 rate in these GT3 subpopulations remains unclear.

No major safety issues unique to SOF/VEL were identified in this review. The most frequent adverse drug reactions were headache, fatigue, and nausea. SOF has been associated with serious bradycardia when co-administered with amiodarone and another DAA; amiodarone treatment was prohibited in the four pivotal trials and no cases of serious bradycardia were observed. RBV is associated with common adverse reactions and serious risks, but these safety issues are well known and are not exacerbated by concomitant administration with SOF/VEL.

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

(1) Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and compensated liver disease: SOF/VEL for 12 weeks
(2) Subjects with HCV GT 1, 2, 3, 4, 5, or 6 infection and decompensated cirrhosis: SOF/VEL + RBV for 12 weeks

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	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	decompensated cirrhosis, or end-stage liver disease. In patients with decompensated cirrhosis, the 5-year survival rate is approximately 50%.	
Current Treatment Options	• The current standard-of-care treatments for CHC are interferon-free, all-oral DAA regimens. Treatment options vary based on HCV GT: ○ GT1: ledipasvir/sofosbuvir; elbasvir/grazoprevir; paritaprevir/ombitasvir/ritonavir + dasabuvir; daclatasvir (in combination with sofosbuvir); and simeprevir (in combination with sofosbuvir) ○ GT2: sofosbuvir + ribavirin ○ GT3: daclatasvir + sofosbuvir; sofosbuvir + ribavirin ○ GT4: ledipasvir/sofosbuvir; elbasvir/grazoprevir; ombitasvir/ paritaprevir/ritonavir with RBV ○ GT5: ledipasvir/sofosbuvir ○ GT6: ledipasvir/sofosbuvir • Treatment with DAAs can result in sustained virologic response determined 12 weeks after the end of treatment (SVR12), considered a virologic cure, in > 93% of CHC patients with compensated liver disease. However, SVR12 rates were lower for certain subpopulations, and some of these regimens require the addition of RBV or longer treatment durations for subjects with cirrhosis and/or prior treatment failure. • During this NDA review cycle, two regimens were approved for treatment of HCV GT 1 or GT 3-infected subjects with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] score B or C) or liver transplant: ○ Treatment with ledipasvir/sofosbuvir + RBV for 12 weeks resulted in	Patients with chronic HCV infection would greatly benefit from new therapeutic options that are well tolerated and equally or more efficacious than current interferon-free DAA options. There is only one approved regimen for subjects with GT2, 5 and 6 HCV. These subjects would benefit from a treatment alternative. 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. There is a specific unmet medical need for highly effective DAA regimens for subjects with decompensated cirrhosis,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	SVR12 rates of 87-88% among GT1-infected pre-transplant subjects with decompensated cirrhosis. ○ Treatment with daclatasvir + sofosbuvir + RBV for 12 weeks resulted in SVR12 rates 92% for CPT B subjects and 50% of CPT C subjects with GT1; 83% of subjects with GT3 achieved SVR12. • At the time of this review, no DAA regimens are approved for patients with decompensated cirrhosis and HCV GT 2, 4, 5, or 6 infection.	particularly for those infected with HCV GT 2, 4, 5, or 6 because no approved regimens are available.
Benefit	• The efficacy of SOF/VEL was established in four Phase 3 clinical trials which cumulatively evaluated 1302 subjects in the SOF/VEL treatment arms. The trial populations varied based on HCV GT and cirrhosis status. ○ ASTRAL-1: TN and TE subjects with compensated liver disease and HCV GT 1, 2, 4, 5, or 6. Subjects received SOF/VEL x 12 weeks or placebo x 12 weeks. ○ ASTRAL-2: TN and TE subjects with compensated liver disease and HCV GT2. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 12 weeks. ○ ASTRAL-3: TN and TE subjects with compensated liver disease and HCV GT3. Subjects received SOF/VEL x 12 weeks or SOF + RBV x 24 weeks. ○ ASTRAL-4: TN and TE subjects with decompensated liver disease (CPT B at screening) with HCV GT 1-6. Subjects received SOF/VEL x 12 weeks, SOF/VEL+RBV x 12 weeks, or SOF/VEL x 24 weeks • The primary efficacy endpoint was SVR12, or virologic cure. As displayed in the tables below, SVR12 results overall ranged from 83-100% depending on the Phase 3 trial regimen, HCV GT, and cirrhosis status.	Four clinical trials provide substantial evidence of effectiveness of SOF/VEL for treatment of CHC GT1-6. • The recommended regimen for subjects with compensated liver disease is SOF/VEL for 12 weeks irrespective of HCV GT or prior treatment experience. • The recommended regimen for subjects with decompensated cirrhosis is SOF/VEL + RBV for 12 weeks, irrespective of HCV GT or prior treatment status. The lower SVR12 rates observed among GT3 subjects, particularly those with cirrhosis, merit consideration of utility of adding RBV to optimize treatment success.

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>
Pooled Analysis of ASTRAL-1, ASTRAL-2, and ASTRAL-3: SVR12 by HCV GT Among Subjects Treated with SOF/VEL Subjects for 12 Weeks n (%)
<table>
<tr><th>GT1</th><th>GT2</th><th>GT3</th><th>GT4</th><th>GT5</th><th>GT6</th><th>Total</th></tr>
<tr><td>323/328 (99%)</td><td>237/238 (99%)</td><td>264/277 (95%)</td><td>116/116 (100%)</td><td>34/35 (97%)</td><td>41/41 (100%)</td><td>1015/1035 (98%)</td></tr>
</table>
ASTRAL-4: SVR12 by Treatment Arm and HCV GT n (%)
<table>
<tr><th></th><th>GT1</th><th>GT2</th><th>GT3</th><th>GT4</th><th>GT6</th><th>Total</th></tr>
<tr><td>SOF/ VEL x 12 wks</td><td>60/68 (88%)</td><td>4/4 (100%)</td><td>7/14 (50%)</td><td>4/4 (100%)</td><td>-</td><td>75/90 (83%)</td></tr>
<tr><td>SOF/ VEL+RBV x 12 wks</td><td>65/68 (96%)</td><td>4/4 (100%)</td><td>11/13 (85%)</td><td>2/2 (100%)</td><td>-</td><td>82/87 (94%)</td></tr>
<tr><td>SOF/ VEL x 24 wks</td><td>65/71 (92%)</td><td>3/4 (75%)</td><td>6/12 (50%)</td><td>2/2 (100%)</td><td>1/1 (100%)</td><td>77/90 (86%)</td></tr>
</table>
No GT5 subjects were enrolled in ASTRAL-4

SVR12 rates were comparable across GT with the exception of GT3; subjects with GT 3 in ASTRAL-3 and ASTRAL-4 had higher rates of virologic failure relative to other GTs. Subgroup analyses demonstrated that cirrhosis, prior treatment failure, and the presence of baseline NS5A polymorphisms were associated with numerically higher rates of treatment failure.
Overall, demographic factors did not impact SVR12 rates.

</td><td>
SOF/VEL fills an important unmet medical need for a 12 week, RBV-free regimen for subjects with GT 1-6 infection and compensated liver disease, irrespective of prior treatment status.

SOF/VEL + RBV fills an important unmet medical need for subjects with decompensated cirrhosis who have few or no treatment options.
</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The safety database for SOF/VEL includes 1302 subjects from the four aforementioned clinical trials and is considered adequate. • ASTRAL-1 included a placebo-controlled comparison for safety with deferred treatment in subjects who were randomized to placebo. • The hepatic safety pool included additional subjects who received SOF/VEL at doses of at least SOF 400 mg and VEL 25 mg in Phase 2 trials. • No major safety issues were encountered during this review. • Headache, fatigue, and nausea were the three most commonly reported adverse drug reactions reported across trials. • Subjects who received RBV with SOF/VEL experienced higher rates of RBV-associated adverse events, at rates consistent with prior HCV DAA trials.	SOF/VEL with or without RBV demonstrated an overall favorable safety profile. The safety issues with RBV are well known and are not exacerbated by SOF/VEL.

Risk Management	• Although no significant safety signals were detected in this review, the SOF/VEL prescribing information will include safety information contained in the current SOF label, even if the events occurred rarely in the SOF/VEL trials:
	  ○ Though no cases were reported in the Phase 3 SOF/VEL trials, Section 5 of the SOF/VEL label will include a warning regarding the risk of serious symptomatic bradycardia related to co-administration of sofosbuvir with amiodarone and another DAA.
	  ○ Rash and depression are being considered for inclusion in Section 6 of the SOF/VEL label.
	• Section 5 will also include a warning regarding risks associated with RBV therapy.
		Safety concerns associated with SOF or RBV are adequately addressed in product labeling.

2 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).

Despite the advances in drug development, many of the approved treatments are limited in their breadth of activity across HCV genotypes and have lower SVR rates in key subpopulations such as prior treatment failures and cirrhotics. Consequently, while subjects with HCV GT 1 or 4 have many treatment options, those with HCV GT 2, 3, 5, and 6 have fewer choices, and in

some cases, only a single option. In addition, there are currently two FDA approved interferon-free treatment options for patients with decompensated cirrhosis, both of which were approved during this NDA review cycle, but are limited to HCV GTs 1 and 3. Other HCV therapeutics are contraindicated or not recommended for use in subjects with advanced liver disease. Hence, there is an unmet need for new therapeutic options that can be used across HCV GTs and for patients with advanced stages of hepatic dysfunction.

In the current NDA, the Applicant seeks approval for SOF/VEL with or without RBV for the treatment of HCV GT 1-6 in subjects with compensated and decompensated liver disease.

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

*Excludes FDC containing sofosbuvir

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The SOF/VEL FDC tablet contains two 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. Both the single entity and the LDV/SOF formulation are commercially available in the US.

This is the first marketing application for any product containing VEL, a new molecular entity.

(b) (4)

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 NDA.

An Investigational New Drug application (IND) for the SOF/VEL FDC was submitted on August 13, 2013 by Gilead Sciences, Inc. After a 30-day safety review, it was determined the Sponsor may proceed with the proposed clinical investigation under IND 118605 on September 12, 2013.

Clinical protocols and the development plan were reviewed by the Division throughout the SOF/VEL 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 June 5, 2014 to discuss the SOF/VEL Phase 3 development program and the proposed registration plan to support a pangenotypic indication. The final Phase 3 ASTRAL-1, -2, -3, and -4 protocol designs later submitted to the Division were determined to be acceptable.

A pre-NDA meeting (teleconference) was held May 26, 2015 to discuss the NDA preparation and submission strategy. One agreement resulting from this meeting was involvement of an Independent Adjudication Committee (IAC) to screen for potential cases of drug-induced liver injury (DILI) in the ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4 Phase 3 trials and three supportive Phase 2 trials.

A request for rolling submission and review of portions of the SOF/VEL NDA was granted July 22, 2015. A subsequent Type B meeting was scheduled September 21, 2015 to discuss topline

data from ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4 trials, and to discuss key review issues that should be addressed in the planned NDA submission. This meeting was cancelled by the Applicant because the Division's preliminary comments addressed the Applicant's concerns.

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 FDC treatment of chronic HCV GT 1 to 6 infection was granted September 30, 2013. Breakthrough Therapy Designation was originally granted April 22, 2014 for SOF/VEL FDC treatment of chronic HCV GT 1, 3, 4, 5, and 6 infection in TN patients. Due to the approval and availability of safe and effective therapies to treat HCV GT 1 infection, the Agency rescinded Breakthrough Therapy Designation April 1, 2015. The Agency and Gilead Sciences, Inc. agreed an unmet medical need for HCV GT 3, 4, 5, and 6 infections still exists. As a result, Gilead submitted a new request for Breakthrough Therapy for the treatment of HCV GT 3, 4, 5, and 6 infection in TN patients. This request was granted May 15, 2015.

3.3. Foreign Regulatory Actions and Marketing History

At the time this review was finalized, neither SOF/VEL nor VEL have been marketed in any country. SOF is approved for use in combination with other agents for the treatment of chronic HCV infection in adults in the US, Canada, the European Union (EU) (tradename Sovaldi®), 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 all 4 pivotal Phase 3 trials, as each contributed significantly to the proposed indication. A total of 8 sites, 2 from each trial, were selected from the large number of sites per study based on enrollment, number of protocol deviations, or results that were dissimilar from the overall trend. Both domestic and foreign sites were selected because this would be the first approval of VEL 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. Product Quality

The commercial SOF/VEL drug product is an immediate-release FDC tablet containing 400 mg SOF and 100 mg VEL. (b) (4) No changes were made to the SOF/VEL 400/100 mg tablet formulation over the entirety of its clinical development, with the exception of the color of the final product, which has no impact on the tablets' physicochemical properties. SOF/VEL tablet clinical supplies and stability lots were manufactured at the two designated commercial manufacturing sites, (b) (4) and 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 its (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. Larry Bai, Dr. George Lunn, 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. The final report from the inspection of the production facilities was not available at the time this review was finalized.

4.3. Clinical Microbiology

This section includes a brief summary of key SOF and VEL 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. Both SOF and VEL 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 variants (RAPs) 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-naive 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 RAPs were at positions 28, 31, and 93.
- SOF/VEL combination therapy: In vitro combination studies demonstrated additive antiviral effect and no antiviral antagonism. Assays assessing cross-resistance between SOF and VEL (SOF against NS5A mutant replicons and VEL against S282T mutant replicons) demonstrated no cross-resistance.

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

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. John Dubinion for full details.

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

VEL: No clear target organs of toxicity were identified in repeat-dose toxicology studies in mice, rats, and dogs administered VEL doses up to 1500, 200, and 100 mg/kg/day for 1, 6 and 9 months, respectively. VEL exposures at these doses were 68, 4, and 9 times the exposure in humans at the recommended SOF/VEL human dose. No significant effects on neurologic or respiratory parameters were observed in rat studies, providing an approximate 4-fold rat to human VEL exposure multiple at the recommended SOF/VEL human dose. No significant cardiovascular effects on hemodynamic or electrocardiographic parameters were noted in telemetry-monitored dog studies, providing an approximate 9-fold dog to human VEL exposure multiple at the recommended SOF/VEL human dose. VEL did not significantly inhibit hERG current in vitro at the maximal feasible concentration (6.5 μM).

VEL was rapidly eliminated from most tissues and mainly excreted in the bile within 24 hours, except from the eye which maintained VEL exposure at 168 hours postdose (the final observation). Studies in rats and rabbits suggest VEL was neither phototoxic nor an ocular irritant. Several minor metabolites were identified; however, unchanged parent drug was the predominant circulating component (in mice, rats, dogs, and human subjects) as well as the primary drug component in feces.

VEL was not genotoxic and had no effects on reproduction or development in mice, rats, and rabbits. Carcinogenicity studies, a 6 month transgenic rasH2 mouse study and a 2 year rat study, are currently ongoing.

Animal SOF and VEL studies did not identify specific overlapping toxicity of potential significant clinical concern.

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. Jenny Zheng and Fang Li for full details.

4.5.1. Mechanism of Action

VEL is an HCV NS5A inhibitor and SOF is a nucleotide HCV NS5B inhibitor.

4.5.2. Pharmacodynamics

The results from Phase 2 studies GS-US-342-0102 and GS-US-342-0109 formed the basis for selecting the 100mg VEL dose for the SOF/VEL FDC as well as the 12 week treatment duration studied in the Phase 3 trials.

- Study 0102 evaluated two doses of VEL (25 and 100 mg) combined with 400 mg SOF, with or without RBV, administered for 8 or 12 weeks, in TN, NC subjects. No difference in dose-response was identified between SOF 400 mg + VEL 25 mg and SOF 400 mg + VEL 100 mg for TN, NC subjects with any HCV GT. Treatment groups 7-14 evaluated 8 week treatment durations among GT 1 and GT2 infected subjects; SVR12 rates in this group ranged from 77% to 89%. In contrast, 12 week regimens resulted in SVR12 rates of 91-96% for GT 1 and GT2, 93% for GT3, 88-100% for GT4, and 100% for GT 5 and 6. Therefore, the 12 week regimen was considered the preferred regimen for all genotypes for the Phase 3 trials.

- Study 0109 evaluated two doses of VEL (25 and 100 mg) combined with 400 mg SOF, with or without RBV, administered for 12 weeks in TE subjects with or without cirrhosis and GT 1 or 3 HCV infection. SVR12 rates were similar for GT1 subjects treated with the 25mg or 100mg VEL dose, with or without RBV (96-100%). For GT 3 subjects, SVR12 rates were higher for the groups treated with 100mg VEL, regardless of RBV; overall for cirrhotics and noncirrhotics combined, SVR12 was 71% for the 25 mg VEL group without RBV (37/52) and 96% for the 100mg VEL group without RBV (50/52). Therefore, the 100 mg VEL dose was selected for the Phase 3 trials. The Division agreed that the 100mg dose is appropriate.

  Overall, the Applicant's dose selection was driven by the desire to have a uniform treatment regimen for all subjects with compensated liver disease (regardless of HCV GT, prior treatment experience or cirrhosis status), particularly in resource-limited settings in which HCV genotyping is not readily available. However, during the End-of-Phase 2 meeting, FDA recommended the Applicant evaluate a longer treatment duration (>12 weeks) in ASTRAL-3 to optimize SVR rates in "harder-to-treat" patient population such as GT3 subjects with cirrhosis. This recommendation was based on the observation that SVR12 rates were 89% (23/25) for GT3 cirrhotic subjects compared to 96% for GT3 noncirrhotic subjects. Rather than including a third ASTRAL-3 treatment group evaluating a longer SOF/VEL treatment duration, the Applicant stated they would increase the size of ASTRAL-4 (which included a SOF/VEL 24 week group and a SOF/VEL+RBV 12 Week group) to enrich the population with HCV GT3 decompensated cirrhotics. The Division concurred with this proposal. The Division also recommended increasing the proportion of ASTRAL-3 subjects with cirrhosis or prior treatment experience, which the Sponsor agreed to.

No exposure-safety relationships were identified for either of the components of SOF/VEL at the approved recommended dosage.

4.5.3. Pharmacokinetics

Absorption, Distribution, Metabolism, and Elimination

The pharmacokinetic properties of SOF, GS-331007 (inactive SOF metabolite) and VEL have been evaluated in healthy adult subjects and in subjects with CHC. Following oral administration of SOF/VEL, SOF was absorbed with a peak median plasma concentration 0.5–1 hour post-dose. Median peak plasma concentration of GS-331007 was observed 3 hours post-dose. VEL median peak concentration was observed 3 hours post-dose.

Food increases the exposure of both SOF and VEL. These changes in exposure are not considered clinically significant for any moiety. Accordingly, SOF/VEL was administered without regards to food in the Phase 3 trials, and Section 2 of the Applicant's proposed product labeling states that SOF/VEL can be taken with or without food.

SOF is approximately 61–65% bound to human plasma proteins but GS-331007 binds minimally in human plasma. VEL is > 99.5% bound to human plasma proteins.

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. Monohydroxylated and demethylated VEL are the metabolites identified in human plasma. Unchanged VEL is the major species present in feces.

Renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of SOF and GS-331007 are 0.5 and 25 hours, respectively. Biliary excretion of parent drug is the major route of elimination for VEL. The median terminal half-life of VEL is approximately 15 hours.

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 approximately 60% and 2072% higher when SOF was dosed 1 hour after hemodialysis.

Based on these results, no SOF dosage adjustment is needed for patients with mild or moderate renal insufficiency (GFR ≥ 30 ml/min/1.73m^2). However, no dosage recommendations can be made for patients with severe or end stage renal disease (GFR < 30 ml/min/1.73 m2) because there are insufficient data regarding the safety of the elevated SOF and GS-331007 exposures.

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. Hence, administration of SOF/VEL in patients with severe or end stage renal disease is limited only by the SOF component.

- 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 (including decompensated cirrhosis) 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 (including decompensated cirrhosis) had no clinically relevant effect on the exposure of VEL.

Based on these results, no SOF/VEL dosage adjustment is required for patients with mild, moderate, or severe hepatic impairment.

- 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 and VEL. No effect has been found for age, race or BMI. Based on population PK analyses, gender was identified as a statistically significant covariate for SOF, GS-331007, and VEL PK. SOF AUC_{tau} and C_{max} in female subjects were approximately 19% and 18% higher, respectively, compared with

male subjects. Female subjects had approximately 27% to 28% higher AUC_{tau} and C_{max} for GS-331007, respectively, compared with male subjects. VEL AUC_{tau}, C_{max}, and C_{tau} were approximately 47%, 43%, and 69% higher in female subjects compared with male subjects. Considering the favorable safety profile of SOF/VEL and high response rates in male and female subjects (SVR12 rates of 97.3% and 99.3%, respectively, in the pooled results from ASTRAL 1, 2, and 3), the relationships between sex and the exposures of SOF, GS-331007 or VEL were not considered clinically relevant.

Extrinsic Factors: Drug Interactions

In vitro studies suggest that both SOF and VEL are substrates for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). In addition, VEL is a substrate of CYP2B6, CYP2C8 and CYP3A 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 and/or VEL leading to reduced therapeutic effect of SOF/VEL. There are no known BCRP inducers at present.

VEL is an inhibitor of drug transporter P-gp, BCRP, and OATP2B1 and may increase intestinal absorption of coadministered substrates for these transporters. In addition, VEL is an inhibitor of OATP1B1 and OATP1B3. Coadministration of SOF/VEL 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 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 (particularly atorvastatin). Please see Section 10 of this review (Labeling) and the clinical pharmacology review for complete details.

Labeling information regarding use of SOF/VEL with HIV antiretrovirals is primarily based on DDI studies, coupled with data from an ongoing Phase 3 study in HIV/HCV co-infected subjects (ASTRAL-5). Preliminary data from ASTRAL-5 were submitted in the Safety Update Report, but are inadequate to adjudicate possible safety concerns. Submission of more complete data was pending at the time this review was finalized. These data will inform ultimate labeling decisions regarding coadministration of SOF/VEL with HIV antiretroviral agents. A summary of the results and the review team's conclusions will be provided in an addendum to the clinical review. In addition, formal submission of the ASTRAL-5 will be requested as a post-marketing requirement.

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 pivotal 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								
ASTRAL-1	3	Randomized, double-blind, placebo-controlled trial with 5:1 randomization	1, 2, 4, 5, 6	SOF/VEL 12 weeks or placebo (PBO) 12 weeks	TN or TE ± cirrhosis (CPT A)	740 in total: 624 SOF/VEL 116 PBO	SVR12	81 sites, 8 countries
ASTRAL-2	3	Randomized, open-label, active controlled trial with 1:1 randomization	2	SOF/VEL 12 weeks or SOF+RBV 12 weeks	TN or TE ± cirrhosis (CPT A)	266 in total: 134 SOF/VEL 132 SOF+RBV	SVR12	51 sites, all in the US and Puerto Rico
ASTRAL-3	3	Randomized, open-label, active controlled trial with 1:1 randomization	3	SOF/VEL 12 weeks or SOF+RBV 24 weeks	TN or TE ± cirrhosis (CPT A)	552 in total: 277 SOF/VEL 275 SOF+ RBV	SVR12	76 sites, 8 countries
ASTRAL-4	3	Randomized, open-label trial with 1:1:1 randomization	1, 2, 3, 4, 5, 6	SOF/VEL 12 weeks or SOF/VEL+RBV 12 weeks or SOF/VEL 24 weeks	TN or TE with CPT B cirrhosis at screening	267 in total: 90 SOF/VEL x 12 weeks 87 SOF/VEL+RBV x 12 weeks 90 SOF/VEL x 24 weeks	SVR12	47 sites, all in the US
Other Studies Pertinent to the Review of Efficacy and Safety*								
GS-US-342-0102	2	Randomized, open-label, dose-ranging trial	1, 2, 3, 4, 5, 6	SOF 400mg + VEL (25 or 100 mg) 12 weeks or SOF 400mg + VEL (25 or 100mg) ± RBV x 8 weeks	TN, NC	377	Safety and SVR12	48 sites, all in the US
GS-US-342-	2	Randomized, open-label,	1 or 3	SOF 400mg + VEL (25	TE ±	323	Safety	58 sites in 3

Trial Identity	Phase	Trial Design	HCV GT	Regimen	Study Population	No. of patients enrolled	Study Endpoint	No. of Centers and Countries
0109		dose-ranging trial		or 100mg) ± RBV 12 weeks	cirrhosis		and SVR12	countries
GS-US-337-0122 (ELECTRON-2, Cohort 4)	2	Randomized, open-label, dose-ranging trial	3	SOF 400mg + VEL (25 or 100mg) ± RBV 8 weeks	TN, NC	103	Safety and SVR12	1 site (ex-US)
Studies Included in the Safety Update Report[§]								
GS-US-342-1202 (ASTRAL-5)	3	Single-arm, open-label trial of subjects with HIV/HCV Co-infection	1, 2, 3, 4, 5, 6	SOF/VEL x 12 weeks with permitted HIV ART regimen	TN or TE ± cirrhosis (CPTA)	106	Safety and SVR12	*Unavailable*
GS-US-342-1446	3	Single-arm, open-label trial of subjects who received placebo in ASTRAL-1	1, 2, 4, 5, 6	SOF/VEL x 12 weeks	TN or TE ± cirrhosis (CPTA)	111	Safety and SVR12	*Unavailable*
GS-US-342-1553	2	Single-arm, open-label trial of prior DAA failures		SOF/VEL + RBV x 24 weeks	TE ± cirrhosis (CPT A)	69	Safety and SVR12	*Unavailable*

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

[§]The Applicant has provided summaries of key safety events for these ongoing studies. Datasets were not provided.

5.2. Review Strategy

Dr. Prabha Viswanathan is the primary clinical reviewer for clinical trials evaluating subjects with compensated liver disease (ASTRAL-1, ASTRAL-2, ASTRAL-3 and Phase 2 trials), and Dr. Sarah Connelly is the primary clinical reviewer for the clinical trial evaluating subjects with decompensated liver disease (ASTRAL-4).

The clinical efficacy review is based on the four pivotal Phase 3 trials ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4. Both clinical reviewers 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 ASTRAL-1, ASTRAL-2, and ASTRAL-3 trials and accompanied by a discussion regarding efficacy outcomes by HCV genotype, baseline CPT and MELD scores, and RBV dosage in the ASTRAL-4 trial. 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 the four aforementioned trials; data from ASTRAL-1, ASTRAL-2, and ASTRAL-3 were pooled to form the integrated safety (ISS) population and data from ASTRAL-4 were analyzed separately. In addition, data from the three Phase 2 trials highlighted in the summary table (Table 2) were 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 regimen, but also included subjects treated with VEL doses < 100 mg and, in some cases, for 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. Drs. Viswanathan and Connelly used JReview, JMP, and MAED software 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 four Phase 3 trials presented below 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. ASTRAL-1

6.1.1. Study Design

Overview and Objectives
ASTRAL-1 (GS-US-342-1138) 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 treatment compared with 12 weeks of placebo treatment in subjects with chronic infection with HCV GT 1, 2, 4, 5, or 6. The primary objectives of the trial are to evaluate the efficacy and safety of treatment with 12 weeks of SOF/VEL in subjects with CHC.

The trial began on July 18, 2014 and is ongoing at this time. The last subject observation included in the NDA submission was made on June 26, 2015, at which point the database was finalized for SVR12 analysis. Subjects were enrolled across 81 study sites in the US, Canada, Great Britain, France, Italy, Germany, Belgium, and China.

Trial Design

Subjects were randomized in a 5:1 ratio in a double-blind manner to receive either SOF/VEL or matching placebo for 12 weeks. Randomization was stratified by HCV genotype (1, 2, 4, 6, and indeterminate) and the presence or absence of cirrhosis at screening. Due to small size of the GT5 population, particularly in the US, all subjects with HCV GT5 infection were enrolled into the SOF/VEL 12 Week group in order to maximize the number of GT5 subjects treated with SOF/VEL.

Men and non-pregnant/non-lactating women ≥ 18 years of age with evidence of chronic HCV GT 1, 2, 4, 5, 6, or indeterminate infection (at least 6 months in duration) and HCV RNA ≥ 10^4 IU/mL at screening were eligible for participation. Both TN and TE subjects were eligible for the trial; TE was defined as prior treatment failure to a regimen containing IFN with or without RBV that was completed at least 8 weeks prior to baseline/Day 1. Subjects with prior exposure to SOF, other nucleotide analogue HCV NS5B inhibitors, or any HCV NS5A inhibitor were excluded. 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 capped at 20% of the target accrual.

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 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. 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.

Protocol Amendments
One protocol amendment has been made since study commencement which did not significantly affect the conduct of the trial.

6.1.2. Study Results

Patient Disposition
Of the 741 enrolled subjects, 740 were randomized to treatment groups and received at least one dose of study medication: 624 in the SOF/VEL group and 116 in the placebo group. Five subjects (0.7%) prematurely discontinued study treatment. Two of the 5 subjects were in the SOF/VEL group, and the reasons for premature discontinuation were AE (1 subject) and lost to follow up (1 subject). Two subjects in the placebo group discontinued due to AEs and one due to investigator discretion.

Protocol Violations/Deviations
A total of 79 important protocol deviations occurred in 75 subjects during the study. Four subjects had 2 deviations and the remainder had a single deviation. Violations of inclusion/exclusion criteria were the most common deviations (n=49), followed by receipt of prohibited concomitant medications (n=11), study medication and improper informed consent (n=7 for each), and management not according to protocol (n=5). 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. ASTRAL-1 Baseline Demographic Characteristics, FAS

Demographic Parameters	**SOF/VEL** (N=624) n (%)	**Placebo** (N=116) n (%)	**Total** (N=740) n (%)
Sex			
Male	374 (60%)	68 (58.6%)	442 (60%)
Female	250 (40%)	48 (41.4%)	298 (40%)
Age			
Mean years (SD)	54 (10.9)	53 (10.4)	54 (10.8)
Median (years)	56	55	56
Min, max (years)	18, 82	25, 74	18, 82
Age Group			
< 65 years	536 (86%)	104 (90%)	640 (87%)
≥ 65 years	88 (14%)	12 (10%)	100 (14%)
Race			
White	493 (79%)	90 (78%)	583 (79%)
Black or African American	52 (8%)	11 (10%)	63 (9%)
Asian	62 (10%)	11 (10%)	73 (10%)
Other[1]	14 (2%)	4 (3%)	18 (2%)
Not disclosed	3 (1%)	0	3 (<1%)
Ethnicity: Hispanic/Latino			
Yes	31 (5%)	5 (4%)	36 (5%)
No	589 (94%)	111 (96%)	700 (95%)
Not disclosed	4 (1%)	0	4 (1%)
Region			
United States	234 (38%)	45 (39%)	279 (38%)
Non-US			
Canada	55 (9%)	7 (6%)	62 (8%)
China	19 (3%)	4 (4%)	23 (3%)
Europe	316 (51%)	60 (52%)	376 (51%)

[1] Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other

Source: ADSL, ASTRAL-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 sites. The impact of the lower representation among older subjects and non-white racial groups will be explored throughout this review.

Table 4. ASTRAL-1 Baseline HCV Disease Characteristics

	Overall (N=740)	Placebo (N=116)	SOF/VEL 12 weeks					
			All (N=624)	GT1 (N=328)	GT2 (N=104)	GT4 (N=116)	GT5 (N=35)	GT6 (N=41)
Cirrhosis								
Yes	142 (19.2%)	21 (18.1%)	121 (19.4%)	73 (22.3%)	10 (9.6%)	27 (23.3%)	5 (14.3%)	6 (14.6%)
No	596 (80.5%)	95 (81.9%)	501 (80.3%)	255 (77.7%)	93 (89.4%)	89 (76.7%)	29 (82.9%)	35 (85.4%)
Missing	2 (0.3%)	0	2 (0.3%)	0	1 (1.0%)	0	1 (2.9%)	0
IL28B								
CC	222 (30.0%)	36 (31.0%)	186 (29.8%)	90 (27.4%)	30 (28.8%)	27 (23.3%)	11 (31.4%)	28 (68.3%)
CT	392 (53.0%)	53 (45.7%)	339 (54.3%)	184 (56.1%)	56 (53.8%)	68 (58.6%)	21 (60.0%)	10 (24.4%)
TT	120 (16.2%)	26 (22.4%)	94 (15.1%)	51 (15.5%)	18 (17.3%)	21 (18.1%)	3 (8.6%)	1 (2.4%)
Missing	6 (0.8%)	1 (0.9%)	5 (0.8%)	3 (0.9%)	0	0	0	2 (4.9%)
Baseline HCV RNA (log_{10}IU/mL)								
Mean (SD)	6.3 (0.65)	6.3 (0.58)	6.3 (0.66)	6.3 (0.59)	6.3 (0.72)	6.1 (0.71)	6.2 (0.68)	6.4 (0.82)
Median	6.4	6.4	6.4	6.4	6.5	6.2	6.4	6.6
Q1, Q3	5.9, 6.7	5.9, 6.8	5.9, 6.7	6.0, 6.7	5.7, 6.8	5.7, 6.5	5.9, 6.7	5.9, 7.0
Min, Max	1.1, 7.8	4.7, 7.5	1.1, 7.8	4.2, 7.5	3.7, 7.4	1.1, 7.1	4.4, 7.4	4.0, 7.8
< 800,000 IU/mL	192 (25.9%)	29 (25.0%)	163 (26.1%)	73 (22.3%)	29 (27.9%)	42 (36.2%)	9 (25.7%)	10 (24.4%)
≥ 800,000 IU/mL	548 (74.1%)	87 (75.0%)	461 (73.9%)	255 (77.7%)	75 (72.1%)	74 (63.8%)	26 (74.3%)	31 (75.6%)
Baseline ALT								
≤ 1.5 x ULN	407 (55.0%)	62 (53.4%)	345 (55.3%)	176 (53.7%)	69 (66.3%)	64 (55.2%)	20 (57.1%)	16 (39.0%)
> 1.5 x ULN	333 (45.0%)	54 (46.6%)	279 (44.7%)	152 (46.3%)	35 (33.7%)	52 (44.8%)	15 (42.9%)	25 (61.0%)
Prior HCV trt history								
TN	506 (68.4%)	83 (71.6%)	423 (67.8%)	218 (66.5%)	79 (76.0%)	64 (55.2%)	24 (68.6%)	38 (92.7%)
TE	234 (31.6%)	33 (28.4%)	201 (32.2%)	110 (33.5%)	25 (24.0%)	52 (44.8%)	11 (31.4%)	3 (7.3%)
Prior HCV treatment (for TE subjects only)	n=234	n=33	n=201	n=110	n=25	n=52	n=11	n=3
DAA+PegIFN+RBV	62 (26.5%)	6 (18.2%)	56 (27.9%)	48 (43.6%)	0	6 (11.5%)	2 (18.2%)	0
DAA	1 (0.4%)	0	1 (0.5%)	1 (0.9%)	0	0	0	0
DAA+RBV	2 (0.9%)	1 (3.0%)	1 (0.5%)	1 (0.9%)	0	0	0	0
PegIFN+RBV	146 (62.4%)	24 (72.7%)	122 (60.7%)	51 (46.4%)	22 (88.0%)	39 (75.0%)	7 (63.6%)	3 (100%)
IFN	8 (3.4%)	0	8 (4.0%)	4 (3.6%)	2 (8.0%)	2 (3.9%)	0	0
IFN+RBV	13 (5.6%)	2 (6.1%)	11 (5.5%)	3 (2.7%)	1 (4.0%)	5 (9.6%)	2 (18.2%)	0
PegIFN	2 (0.9%)	0	2 (1.0%)	2 (1.8%)	0	0	0	0

Source: Table created by Karen Qi, Statistical Review

The determination of cirrhosis status was made by Fibroscan for 62% of subjects (460/740), by Fibrotest + APRI in 21% of subjects (153/740), and by biopsy in 17% of subjects (125/740). A numerically higher proportion of subjects in the SOF/VEL group were diagnosed by biopsy (18% versus 13% for SOF/VEL and placebo, respectively); accordingly, a higher proportion of subjects in the placebo group were diagnosed using Fibrotest + APRI (20% versus 25% for SOF/VEL and placebo, respectively).

Reviewer Comment: Baseline prognostic indicators of treatment success include absence of cirrhosis, lack of prior treatment experience, IL28B CC phenotype, and low baseline HCV viral load. These baseline factors are evenly distributed between the SOF/VEL group and placebo group, but there is some heterogeneity among the HCV GTs. Imbalance between the GTs is reflective of many factors, including the availability of treatment options (e.g. there are more investigational and/or approved regimens for GT1 and 4 than GT2, 4, 5, or 6) which should be kept in mind when interpreting the trial results.

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.

Table 5. ASTRAL-1 Primary Efficacy Results

	SOF/VEL 12 Weeks (N=624)	Placebo (N=116)
SVR12 Achieved		
% (n) (95% CI)	99.0% (618/624) (97.9%, 99.6%)	0% (0/116) n/a
SVR12 Not Achieved		
On-treatment Virologic Failure	0% (0/624)	99.1% (115/116)
Relapse	0.3% (2/623)	n/a (0/0)
Other	0.6% (4/624)	0.9% (1/116)

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

Outcomes of Subjects who did not Achieve SVR12

Missing Data

Four 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 01305-63384 is a 43 year old TN NC man with GT1a HCV infection. He completed the study and achieved SVR4, but was lost to follow-up before the post-treatment Week 12 visit.
- Subject 05283-63398 is a 47 year old TN NC man with GT1a HCV infection. He was lost to follow-up after the Week 6 visit.
- Subject 00472-63493 is a 52 year old TN NC woman with GT1a HCV infection. She withdrew consent and discontinued study treatment on Day 15 due to an AE of anxiety.
- Subject 01386-63561 was a 55 year old TN NC man with GT5a HCV infection. He completed study treatment and died in his sleep of unknown causes on post-treatment Day 8.

Virologic Failure

There were two virologic failures in ASTRAL-1; both were a result of relapse.

- Subject 00529-63184 is a 56 year old TN NC white male with GT1a HCV infection who relapsed at post-treatment Week 4. Sequencing for NS5A resistance associated polymorphisms (RAPs) revealed Q30R at baseline and Y93N at relapse. No NS5B RAPs were detected at either time point.
- Subject 05294-63312 is a 58 year old TE cirrhotic black male with GT1b HCV infection who relapsed at post-treatment Week 4. Baseline sequencing was notable for Q30L, Q30R, and L31M NS5A RAPs; Q30R and Y93H were detected at relapse. No NS5B RAPs were detected at baseline or failure.

Reviewer Comment: The overall SVR12 rate far exceeds the pre-specified rate of 85% and is comparable to the efficacy rates for other recently approved DAA regimens. With only two relapsers among 624 SOF/VEL-treated subjects, these results unequivocally support the efficacy of SOF/VEL 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 treatment experience, cirrhosis status, or HCV GT (for GT 1-6 other than GT3).

Subgroup Analyses

Table 6 describes SVR12 by HCV GT and examines the relationship between GT and baseline prognostic indicators. As previously stated, there were no virologic successes among placebo subjects. Hence, the remainder of this section presents results from the SOF/VEL 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. ASTRAL-1 Subgroup Analysis: SVR12 by HCV GT, SOF/VEL Subjects

% Subjects Achieving SVR 12	Overall (N=624)	GT1 (N=328)	GT2 (N=104)	GT4 (N=116)	GT5 (n=35)	GT6 (N=41)
Overall						
% (n)	99.0% (618/624)	98.5% (323/328)	100% (104/104)	100% (116/116)	97.1% (34/35)	100% (41/41)
95% CI	(97.9%, 99.6%)	(96.5%, 99.5%)	(96.5%, 100%)	(96.9%, 100%)	97.1% (34/35)	(91.4%, 100%)
Prior Treatment						
TN	98.8% (418/423)	98.2% (214/218)	100% (79/79)	100% (64/64)	95.8% (23/24)	100% (38/38)
TE	99.5% (200/201)	99.1% (109/110)	100% (25/25)	100% (52/52)	100% (11/11)	100% (3/3)
Cirrhosis						
Yes	99.2% (120/121)	98.6% (72/73)	100% (10/10)	100% (27/27)	100% (5/5)	100% (6/6)
No	99.0% (496/501)	98.4% (251/255)	100% (93/93%)	100% (89/89)	96.6% (28/29)	100% (35/35)
IL28B Genotype						
CC	99.5% (185/186)	98.9% (89/90)	100% (30/30)	100% (27/27)	100% (11/11)	100% (28/28)
CT	99.1% (336/339)	98.4% (181/184)	100% (56/56)	100% (68/68)	100% (21/21)	100% (10/10)
TT	97.9% (92/94)	98.0% (50/51)	100% (18/18)	100% (21/21)	66.7% (2/3)	100% (1/1)
Baseline HCV RNA						
< 800,000	98.8% (161/163)	98.6% (72/73)	100% (29/29)	100% (42/42)	88.9% (8/9)	100% (10/10)
≥ 800,000	99.1% (457/461)	98.4% (251/255)	100% (75/75)	100% (74/74)	100% (26/26)	100% (31/31)

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

Reviewer Comment: This analysis by GT confirms the activity of SOF/VEL against HCV GT 1, 2, 4, 5, and 6 and supports labeling the labeling of a 12 week treatment duration for each of these genotypes. The high efficacy rate across all subtypes also support uniform dosing recommendations for all subjects with compensated liver disease regardless of prior treatment experience and cirrhosis status.

An additional subgroup analysis was performed to examine the relationship between baseline demographic factors and treatment success. No differences are anticipated given the uniformly high efficacy rate, but the results are presented for completeness in Table 7.

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

	SOF/VEL 12 Weeks (N=624)	95% CI
Age		
< 65 years	98.9% (530/536)	(97.6%, 99.6%)
≥ 65 years	100% (88/88)	(95.9%, 100%)
Gender		
Male	98.7% (369/374)	(96.9%, 99.6%)
Female	99.6% (249/250)	(97.8%, 100%)
Race		
White	99.0% (488/493)	(97.6%, 99.7%)
Black/African American	98.1 % (51/52)	(89.7%, 100%)
Other	100% (76/76)	(95.3%, 100%)
Ethnicity		
Hispanic or Latino	100% (31/31)	(88.8%, 100%)
Not Hispanic or Latino	99.0% (583/589)	(97.8%, 99.6%)
Region		
US	99.6% (233/234)	(97.6%, 100%)
Non-US	98.7% (385/390)	(97.0%, 99.6%)
Baseline BMI		
< 30 kg/m^2	99.0% (484/489)	(97.6%, 99.7%)
≥ 30 kg/m^2	99.3% (134/135)	(95.9%, 100%)

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

Reviewer Comment: The lower bound of the 95% CI exceeds 95% in nearly every subgroup evaluated; among black or Hispanic subjects, the lower bound of the 95% CI was below 90% but had upper bounds of 100%. The wider CI observed in these two populations is likely due to the smaller sample size for these populations. Overall, these results support the efficacy of SOF/VEL for 12 weeks in all demographic subgroups evaluated.

Impact of Baseline NS5A Resistance Associated Polymorphisms
Among the 616 SOF/VEL subjects with baseline NS5A deep sequence data, 49% of subjects (302/616) had baseline NS5A RAPs. A single RAP was identified in 153 subjects, 2 were detected in 87 subjects, and >2 were detected in 62 subjects. SVR12 in each of the three groups was comparable to subjects without baseline NS5A RAPs: 100%, 100%, 98%, and 99%, respectively. Both subjects who failed gained the Y93H RAP that confers high grade resistance to VEL.

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

Reviewer Comment: Treatment with SOF/VEL is highly effective in subjects with and without baseline NS5A RAPs, as evidenced by the fact that only 2 subjects relapsed despite nearly 50% having baseline NS5A RAPs. Hence, screening for baseline RAPs will not be recommended in product labeling because SVR12 rates are already maximized for this population.

6.2. ASTRAL-2

6.2.1. Study Design

Overview and Objectives
ASTRAL-2 (GS-US-342-1139) 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 compared with 12 weeks of SOF + RBV in subjects with chronic HCV GT2 infection. The primary objectives of the trial are to compare the efficacy of 12 weeks of SOF/VEL with 12 weeks of SOF + RBV, which is the current standard of care for GT2, and to evaluate the safety and tolerability of each treatment regimen.

The trial began on September 22, 2014 and is ongoing at this time. The last subject observation included in the NDA submission was made on July 9, 2015. The database was finalized for SVR12 analysis on July 22, 2015. There are 51 clinical trial sites, all of which are in the US including Puerto Rico.

Trial Design
Subjects were randomized in a 1:1 ratio to receive SOF/VEL for 12 weeks or SOF + RBV for 12 weeks. Randomization was stratified by the presence or absence of cirrhosis at screening and prior treatment experience. Subjects were defined as TN or TE and cirrhotic or NC using the same criteria employed in ASTRAL-1 (please refer to Section 6.1.1). Key eligibility criteria were also the largely the same as ASTRAL-1 except that ASTRAL-2 is limited to HCV GT2 and ASTRAL-2 subjects could not have contraindications to RBV therapy.

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

Statistical Analysis Plan
The primary efficacy hypothesis is that the SVR12 rate for subjects treated with 12 weeks of SOF/VEL is noninferior to the SVR12 rate of subjects treated with SOF+RBV 12 weeks by a margin of 10%. The Applicant's justification of the NI margin was discussed during protocol review and was deemed acceptable. Noninferiority is demonstrated if the lower bound of the 2-sided 95% CI for the difference in SVR12 is greater than −10%. If the lower bound of the CI is greater than −10% (i.e., the null hypothesis for noninferiority is rejected), then a 2-sided stratified Cochran-Mantel-Haenszel (CMH) test is used to test for the superiority of SOF/VEL for 12 weeks over SOF+RBV for 12 weeks at a significance level of 0.05. The FAS was used for the primary efficacy analysis with a missing=failure approach to missing data. 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 317 subjects were screened for participation, of which 269 were randomized: 135 subjects in the SOF/VEL group and 134 subjects in the SOF + RBV group. Two-hundred sixty-six of the 269 received at least one dose of study medication and were included in the FAS; all except for 2 of the 266 subjects were evaluable at post-treatment Week 12: one subject in the SOF/VEL group discontinued due to AEs and one subject in the SOF+RBV group was lost to follow-up after the Week 10 study visit.

Protocol Violations/Deviations
A total of 24 important protocol deviations occurred among 22 subjects during the study through post-treatment Week 12. Two subjects had 2 deviations and the remainder had a single deviation. Improper informed consent was the common type of deviation (n=10), followed by violations of inclusion/exclusion criteria (n=8), receipt of prohibited concomitant medications (n=3), management not according to protocol (n=2) and study medication (n=1). There were no major differences in the frequency of these events between the SOF/VEL and SOF+RBV groups. 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. ASTRAL-2 Baseline Demographic Characteristics

Demographic Parameters	**SOF/VEL 12 Weeks** (N=134) n (%)	**SOF + RBV 12 Weeks** (N=116) n (%)	**Total** (N=266) n (%)
Sex			
Male	86 (64%)	72 (55%)	158 (59%)
Female	48 (36%)	60 (46%)	108 (41%)
Age			
Mean years (SD)	57 (10.6)	57 (19.3)	57 (10.0)
Median (years)	58	59	58
Min, max (years)	26, 81	23, 76	23, 81
Age Group			
< 65 years	106 (79%)	110 (83%)	216 (81%)
≥ 65 years	28 (21%)	22 (17%)	50 (19%)
Race			
White	124 (93%)	111 (84%)	235 (88%)
Black or African American	6 (5%)	12 (9%)	18 (7%)
Asian	1 (1%)	5 (4%)	6 (2%)
Other[1]	1 (1%)	3 (2%)	4 (2%)
Not Disclosed	2 (2%)	2 (2%)	2 (2%)
Ethnicity: Hispanic/Latino			
Yes	26 (19%)	23 (17%)	23 (17%)
No	104 (78%)	107 (81%)	107 (81%)
Not disclosed	4 (3%)	2 (2%)	2 (2%)

[1] Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: ADSL, ASTRAL-2 dataset

Reviewer Comment: The two treatment arms are adequately balanced with respect to baseline demographics. All trial sites are in the US, including Puerto Rico, which obviates concerns regarding the applicability of foreign data.

Table 9. ASTRAL-2 Baseline HCV Disease Characteristics

Demographic Parameters	**SOF/VEL 12 Weeks** (N=134) n (%)	**SOF + RBV 12 Weeks** (N=116) n (%)	**Total** (N=266) n (%)
Prior Treatment Experience			
TN	115/134 (86%)	112/132 (85%)	227/266 (85%)
TE*	19/134 (14%)	20/132 (15%)	39/266 (15%)
Cirrhosis Status			
Non-Cirrhotic	19 (14%)	19 (14%)	38 (14%)
Cirrhotic	115 (86%)	112 (85%)	227 (85%)
Missing	0	1 (1%)	1 (<1%)
Baseline HCV RNA Log10 (IU/mL)			
Mean (+/-SD)	6.5 (0.78)	6.4 (0.74)	6.4 (0.76)
Median	6.7	6.6	6.7
Range	3.9, 7.4	3.8, 7.5	3.8, 7.5
IL28B Genotype			
CC	55 (41%)	46 (35%)	101 (38%)
Non-CC	79 (59%)	86 (65%)	165 (62%)

* IFN or peg-IFN ± RBV
Source: ADSL, ASTRAL-2 dataset

The determination of cirrhosis status was made by Fibroscan for 36% of subjects (96/266), by Fibrotest + APRI in 35% of subjects (92/266), and by biopsy in 29% of subjects (77/266). A numerically higher proportion of subjects in the SOF+RBV group were diagnosed by biopsy (36% versus 22% for SOF+RBV and SOF/VEL, respectively).

Reviewer Comment: Other than a slightly higher percentage of subjects with the favorable IL28B CC genotype in the SOF/VEL group, the two trial arms are well matched with respect to baseline prognostic indicators of treatment response.

Efficacy Results - Primary Endpoint
The trial met its primary endpoint of superiority to SOF+RBV with a treatment difference of 5.2% and 95% CI (0.2%, 10.3%). The results are summarized in Table 10.

Table 10. ASTRAL-2 Primary Efficacy Results

	SOF/VEL x 12 Weeks (N=134)	SOF+ RBV x 12 Weeks (N=132)
SVR12 Achieved		
% (n) (95% CI)	99.3% (133/134) (95.9%, 100%)	93.9% (124/132) (88.4%, 97.3%)
SVR12 Not Achieved		
On-treatment Virologic Failure	0% (0/134)	0% (0/132)
Relapse	0% (0/133)	4.5% (6/132)
Other	0.7% (1/134)	1.5% (2/132)

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

Reviewer Comment: Treatment with SOF/VEL conferred 100% efficacy in this cohort of HCV GT2 subjects, regardless of prior treatment experience or cirrhosis. These results demonstrate that SOF/VEL is superior to the current standard of care, and thereby strongly support the efficacy of a 12 week SOF/VEL regimen for all GT2 subjects with compensated liver disease.

Outcomes of Subjects who did not Achieve SVR12

There were no cases of virologic failure in the SOF/VEL group and 6 cases of relapse in the SOF/RBV group. Among the 6 relapsers, 2 were TN NC, 1 was TN with cirrhosis, and 3 were TE NC. Four of the relapses occurred prior to post-treatment Week 4 and the remaining two occurred between post-treatment Week 4 and 12.

One subject in the SOF/VEL group and 2 subjects in the SOF+RBV group had missing data in the post-treatment Week 12 window and were therefore considered failures.

- Subject 05663-65239 in the SOF/VEL group discontinued study medication on Day 1 due to adverse events.
- Subject 01605-65173 in the SOF+RBV group completed study treatment and achieved SVR4, but was lost to follow-up at post-treatment Week 12.
- Subject 05498-65035 in the SOF+RBV group completed the Week 10 visit (71 days of treatment), but did not return for any subsequent study visits and was assumed to be lost to follow-up.

Subgroup Analyses

Similar to the approach used in ASTRAL-1, subgroup analyses were conducted to evaluate differences in treatment response based on baseline disease and demographic characteristics.

The uniformly high rate of treatment success precluded detection of treatment differences between subgroups. Therefore, these analyses are not displayed in this review.

Impact of Baseline NS5A Resistance Associated Polymorphisms
Among the 133 SOF/VEL subjects with baseline NS5A deep sequence data, 56% of subjects (75/133) had baseline NS5A RAPs. A single RAP was identified in 64 subjects and 2 were detected in 11 subjects. SVR12 was 100% in each group.

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

Reviewer Comment: Given the 100% efficacy rate among subjects with and without baseline NS5A polymorphisms, there is no role for NS5A screening because all subjects respond equally favorably to 12 weeks of SOF/VEL.

6.3. ASTRAL-3

6.3.1. Study Design

Overview and Objectives
ASTRAL-3 (GS-US-342-1140) 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 treatment compared with 24 weeks of SOF + RBV in subjects with chronic HCV GT3 infection. The primary objectives of the trial are to compare the efficacy of 12 weeks of SOF/VEL with 24 weeks of SOF + RBV, which is one of two currently-approved regimens in the US for GT3, and to evaluate the safety and tolerability of each treatment regimen.

The trial began on July 14, 2014 and is ongoing at this time. The last subject observation included in the NDA submission was made on September 8, 2015. The database was finalized for SVR12 analysis on September 11, 2015. There are 76 clinical trial sites across 8 countries: US, Canada, Great Britain, France, Germany, Italy, Australia, and New Zealand.

Trial Design
Subjects were randomized 1:1 to receive open-label SOF/VEL for 12 weeks or SOF+RBV for 24 weeks. The eligibility criteria were nearly identical to ASTRAL-1 and ASTRAL-2, with the exception of HCV GT. Please refer to Sections 6.1.1 and 6.2.1.

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

Statistical Analysis Plan
The primary efficacy hypothesis is that the SVR12 rate following treatment with SOF/VEL for 12 weeks is non-inferior to SVR12 following treatment with SOF+RBV for 24 weeks with a noninferiority margin of 10%. The margin was determined based on the difference in SVR12 rates between the 24-week SOF + RBV and 12-week SOF alone regimens in GT3 subjects. Noninferiority and, if appropriate, superiority calculations are the same as those used in ASTRAL-2 (see Section 6.2.1).

Protocol Amendments
Three protocol amendments have been made thus far; the changes do not significantly impact the conduct of the trial.

6.3.2. Study Results

Patient Disposition
A total of 652 subjects were screened, of which 558 subjects were randomized. Five hundred fifty-two subjects received at least one dose of study drug and were included in the FAS: 277 SOF/VEL and 275 SOF+RBV subjects. Twenty-three of the 552 treated subjects prematurely discontinued from the trial: 2 in the SOF/VEL group and 21 in the SOF+RBV group. Reasons for discontinuation in the SOF/VEL group were noncompliance and lack of efficacy. In the SOF+RBV group, 9 subjects discontinued due to AEs, 4 were lost to follow-up, 3 withdrew consent, 2 were noncompliant with study drugs, 2 died, and 1 had lack of efficacy.

Protocol Violations/Deviations
A total of 91 important protocol deviations occurred among 79 subjects during the study through post-treatment Week 12. One subject had 3 deviations, 10 subjects had 2 deviations, and the remainder had a single deviation. Violations of inclusion/exclusion criteria were the most common type of deviation (n=46), followed by receipt of prohibited concomitant medications (n=18), improper informed consent (n=8), and management not according to protocol and study medication (n=6 for each). These events occurred at a slightly numerically higher frequency among SOF+RBV subjects. These protocol violations do not impact the interpretability of the trial results.

Baseline Characteristics
Tables 11 and 12 summarize the baseline demographic and disease characteristics for subjects in the FAS.

Table 11. ASTRAL-3 Baseline Demographic Characteristics

Demographic Parameters	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
Sex			
Male	170 (61%)	174 (63%)	344 (62%)
Female	107 (39%)	101 (37%)	208 (38%)
Age			
Mean years (SD)	49 (10.4)	50 (10.0)	50 (10.2)
Median (years)	52	52	52
Min, max (years)	21, 76	19, 74	19, 76
Age Group			
< 65 years	270 (98%)	261 (95%)	531 (96%)
≥ 65 years	7 (3%)	14 (5%)	21 (4%)
Race			
White	250 (90%)	239 (87%)	489 (89%)
Black or African American	3 (1%)	1 (<1%)	4 (1%)
Asian	23 (8%)	29 (11%)	52 (9%)
Other[1]	1 (0.4%)	5 (2%)	6 (1%)
Not Disclosed	0	1 (<1%)	1 (<1%)
Ethnicity: Hispanic/Latino			
Yes	11 (4%)	11 (4%)	22 (4%)
No	266 (96)	263 (96%)	592 (96%)
Not disclosed	0	1 (<1%)	1 (<1%)
Region (optional)			
United States	60 (22%)	60 (22%)	120 (22%)
Non-US			
Canada	15 (5%)	18 (7%)	33 (6%)
Europe	144 (52%)	145 (53%)	289 (52%)
Australia/New Zealand	58 (21%)	52 (20%)	110 (20%)

[1] Includes American Indian/Alaska Native, Hawaiian or Pacific Islander and other
Source: ADSL, ASTRAL-3 dataset

The determination of cirrhosis status was made by Fibroscan for 67% of subjects (368/552), by Fibrotest + APRI in 18% of subjects (97/552), and by biopsy in 15% of subjects (82/552). All three modalities were used by a comparable number of subjects in each treatment arm.

Reviewer Comment: The two treatment groups are well-matched with respect to demographic characteristics. Nearly 75% of subjects were enrolled in sites in Europe and Australia/New Zealand where HCV GT3 is more prevalent. While international enrollment provides the advantage of a larger patient pool from which to enroll, the disadvantage is the

underrepresentation of African-Americans, a key population in the US. While the low inclusion of African American subjects should be acknowledged, this concern is offset by the fact that the majority of HCV cases (88-92% by some estimates) in African Americans are caused by GT1.[9]

Table 12. ASTRAL-3 Baseline HCV Disease Characteristics

Demographic Parameters	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Total (N=552)
Prior Treatment Experience			
TN	206/277 (74)	204/275 (74%)	410/552 (74%)
TE*	71/277[#] (26%)	71/275 (26%)	142/552 (26%)
Cirrhosis Status			
Non-Cirrhotic	197 (71%)	187 (68%)	384 (70%)
Cirrhotic	80 (29%)	83 (30%)	163 (30%)
Missing	0	5 (2%)	5 (1%)
Baseline HCV RNA Log10 (IU/mL)			
Mean (+/-SD)	6.2 (0.72)	6.3 (0.71)	6.3 (0.72)
Median	6.3	6.4	6.4
Range	3.7, 7.5	3.6, 7.5	3.6, 7.5
IL28B Genotype			
CC	105 (38%)	111 (40%)	216 (39%)
Non-CC	172 (62%)	164 (60%)	336 (61%)

* IFN or peg-IFN ± RBV
[#] Includes one subject previously treated with DAA +PR
Source: ADSL, ASTRAL-3 dataset

Reviewer Comment: The two treatment groups are evenly matched based on baseline prognostic indicators of treatment success.

Efficacy Results - Primary Endpoint

The trial met the primary endpoint of superiority to SOF+RBV with a treatment difference of 15% and 95% CI (10%, 20%). The overall results are summarized in Table 13.

Table 13. ASTRAL-3 Primary Efficacy Results

	SOF/VEL x 12 Weeks (N=277)	SOF+ RBV x 24 Weeks (N=275)
SVR12 Achieved		
% (n) (95% CI)	95% (264/277) (92%, 97%)	80% (221/275) (75%, 85%)
SVR12 Not Achieved		
On-treatment Virologic Failure	0% (0/277)	<% (1/275)
Relapse	4% (11/276)	14% (38/272)
Other	1% (1/277)	5% (15/275)

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

Reviewer Comment: Treatment with SOF/VEL for GT3 provides superior SVR12 rates than the comparator (SOV/RBV for 24 weeks). These outcomes are among the best observed in clinical trials of GT3 patients performed thus far and support labeling of SOF/VEL for 12 weeks for the treatment of GT3 HCV infection.

Outcomes of SOF/VEL Subjects who did not Achieve SVR12

Virologic Failures

There were no on-treatment virologic failures. Eleven SOF/VEL treated subjects were considered relapsers, but in fact one appears to be a reinfection rather than relapse. Subject 01069-62225 had GT3a at baseline and GT1a at relapse.

The baseline demographic and disease characteristics of the 10 relapsers were examined in order to identify factors most likely to predict treatment failure. All subjects were white, non-Hispanic, and less than 65 years of age. One subject was female and the remaining 9 were male. Baseline BMI was in the normal to overweight range (min 21.7, max 30.6 kg/m^2). Table 14 summarizes the baseline disease characteristics for the 10 subjects who relapsed in ASTRAL-3. None of the 10 subjects had detectable NS5B RAPs at baseline or failure.

Table 14. Baseline Disease Characteristics of ASTRAL-3 Relapsers

Subject ID	Baseline HCV RNA ≥ 800,000 IU/mL	Treatment Experienced	Cirrhotic	IL28B non-CC Genotype	BL NS5A RAPs	NS5A RAPs at Relapse
00472-62512	X		X		Y93Y/H	Y93H, A30V
00529-62069	X	X	X			Y93H
00529-62147	X		X	X	Y93H	Y93H
01065-62502		X		X		Y93H
01589-62011	X			X	Y93H	Y93H
02080-62118	X	X	X	X		Y93H
03314-62107	X	X				Y93H
04472-62202	X	X	X	X	A30K	Y93H, A30K
05730-62185	X		X	X		Y93H
05873-62186	X	X	X	X		Y93H

Source: ASTRAL-3 ADEFFOUT and ADSL datasets; Table 5-8 of Applicant's Integrated Virology Study Report

Reviewer Comment: There is no clear pattern among baseline disease characteristics which helps identify subjects who are most likely to fail treatment. The only characteristic shared by nearly all of the 10 subjects is baseline viral load > 800,000 IU/mL, but 70% of ASTRAL-3 subjects overall had baseline viral load > 800,000 IU/mL and 94% went on to achieve SVR12 with SOF/VEL. Hence, baseline viral load itself is not a useful predictor of treatment outcome. The development of the Y93H RAP in each of the 10 relapsers is a significant concern because Y93H confers high level resistance to other NS5A inhibitors, including daclatasvir, which could significantly impact future treatment options.

Missing Data

Two subjects in the SOF/VEL group were counted as failures because they were lost to follow-up and consequently did not have data in the post-treatment Week 12 window. These subjects do not represent true virologic failures.

Subgroup Analyses

Subgroup analyses were performed to evaluate the impact of various demographic and baseline disease characteristics on efficacy. 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. The results are summarized in Tables 15 and 16.

Table 15. ASTRAL-3 Subgroup Analysis of the Primary Endpoint: Baseline Demographic Characteristics.

	SOF/VEL 12 weeks (N=277)	SOF + RBV 24 weeks (N=275)	Diff in SVR12 rate (95% CI)
Age at baseline (years)			
< 65 years	95.2% (257/270)	80.5% (210/261)	14.7% (9.3%, 20.4%)
≥ 65 years	100% (7/7)	78.6% (11/14)	21.4% (-21.3%, 50.8%)
Sex at birth			
Male	93.5% (257/270)	75.9% (132/174)	17.7% (10.1%, 25.4%)
Female	98.1% (105/107)	88.1% (89/101)	10.0% (3.2%, 18.1%)
Race			
Black or African American	100% (3/3)	100% (1/1)	0.0% (-70.8%, 97.5%)
White	95.2% (238/250)	78.2% (187/239)	17.0% (11.1%, 23.1%)
Other	95.8% (23/24)	94.1% (32/34)	1.7% (-15.7%, 16.0%)
Ethnicity			
Hispanic or Latino	100% (11/11)	81.8% (9/11)	18.2% (-12.2%, 51.8%)
Not Hispanic or Latino	95.1% (253/266)	80.2% (211/263)	14.9% (9.4%, 20.6%)
Region			
US	95.0% (57/60)	76.7% (46/60)	18.3% (5.5%, 31.4%)
Non-US	95.4% (207/217)	81.4% (175/215)	14.0% (8.1%, 20.2%)
Body mass index (kg/m^2) at baseline			
< 30 kg/m^2	94.7% (214/226)	81.3% (174/214)	13.4% (7.4%, 19.7%)
≥ 30 kg/m^2	98.0% (50/51)	77.0% (47/61)	21.0% (8.8%, 33.7%)

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

Table 16. ASTRAL-3 Selected Subgroup Analysis of the Primary Endpoint: Baseline Disease Characteristics

	SOF/VEL 12 Weeks % (n)	SOF + RBV 24 Weeks % (n)	Difference in SVR12 Rate (95% CI)
Cirrhosis			
Yes	91% (73/80)	66% (55/83)	25% (11%, 37%)
No	97% (191/197)	87% (163/187)	10% (4%, 16%)
HCV treatment history			
TN	97% (200/206)	86% (176/204)	11% (5%, 17%)
TE	90% (64/71)	63% (45/71)	27% (12%, 40%)
IL28B Genotype			
CC	94% (99/105)	80% (89/111)	14% (4%, 23%)
CT	97% (143/148)	80% (106/133)	17% (9%, 25%)
TT	92% (22/24)	84% (26/31)	8% (-13%, 27%)
Baseline HCV RNA (IU/mL)			
< 800,000	99% (85/86)	89% (72/81)	10% (3%, 19%)
≥ 800,000	94% (179/191)	77% (149/194)	17% (10%, 24%)

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

Reviewer Comment: As shown in Table 16, certain GT3 subgroups are more likely to achieve SVR12 than others. However, no significant trends were observed in the demographic analysis to facilitate identification of groups at highest chance for success or highest risk for failure.

In order to further characterize the population at highest risk for relapse, an additional subgroup analysis was performed to evaluate the interaction between treatment experience and cirrhosis. These results are summarized in Table 17.

Table 17. ASTRAL-3 Subgroup Analysis of Impact of Cirrhosis and Prior HCV Treatment on SVR12 Rates

Cirrhosis & Prior HCV Treatment	SOF/VEL x 12 Weeks % (n)	SOF + RBV X 24 Weeks % (n)	Difference in SVR12 Rate (95% CI)
Cirrhotic, TE	89% (33/37)	58% (22/38)	31% (11%, 50%)
Non-cirrhotic, TE	91% (31/34)	71% (22/31)	20% (0.5%, 40%)
Cirrhotic, TN	93% (40/43)	73% (33/45)	20% (4%, 36%)
Non-cirrhotic, TN	98% (160/163)	90% (141/156)	8% (3%, 14%)

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

As suggested by the prior analysis, HCV GT 3 TN NC subjects had the highest SVR12 rates, while TE cirrhotic subjects had the lowest SVR12 rates. The difference in SVR12 rates between TN NC and TE cirrhotic subjects is consistent between both treatment groups. The difficulty of treating HCV GT 3 TE cirrhotic subjects is most apparent by the 58% SVR rate among those in the SOF+RBV group.

Impact of Baseline Resistance Associated Polymorphisms

NS5A sequencing data were obtained for 274/275 subjects in the SOF/VEL group. Baseline RAPs were identified in 20% of subjects (56/274). Subjects without baseline RAPs had a 97% SVR 12 rate (211/218) whereas subjects with baseline RAPs had a 93% SVR12 rate (52/56). All four failures among subjects with RAPs occurred in subjects with one RAP at baseline. Ten subjects had 2 or more baseline RAPs and all 10 achieved SVR12.

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

Optimization of SVR12 Rates for GT3

The SVR12 rates observed in ASTRAL-3 represent the highest rates observed to date across all DAA development programs for GT3, particularly for TE and cirrhotic subjects, and approval of the proposed 12 week SOF/VEL regimen would substantially improve the standard of care in this population. However, there is room for improvement.

The review team carefully considered all available data across the SOF/VEL development program to identify the regimen most likely to mitigate the risk of failure among the hardest to treat GT3 subjects. In our review of the data, we sought to answer the following questions:

- Question 1: Does the addition of RBV mitigate the risk of relapse? If so, for which population (i.e. cirrhotics, subjects with BL NS5A RAPs)?

- Question 2: Does extending the treatment duration mitigate the risk of relapse?
- Question 3: What is the role of screening for NS5A polymorphisms? If screening is recommended, what recommendations would be made based on the results?

The remainder of this section will present the data that were evaluated to answer these three questions.

Question 1:
Data from Phase 2 study GS-US-342-0109, ASTRAL-1, and ASTRAL-4 were reviewed, with a focus on GT3 subjects but also careful consideration of trends among GT1 subjects that may inform expectations of treatment response among GT3 subjects.

Study 0109 provides the only available data in the SOF/VEL development program for use of RBV among GT3 cirrhotics. This trial was a randomized, open label, dose-ranging trial evaluating 2 VEL doses (25 mg and 100mg) in combination with 400 mg SOF, ± RBV, in TE subjects with GT 1 or 3 infection, ± cirrhosis. Among GT3 subjects, SVR rates were higher for the 100mg VEL dose compared to the 25mg dose (see Section 4.5). However, the role of RBV was less clear. Table 18 summarizes the results from trial groups 7 and 8, which compared the efficacy of SOF/VEL for 12 weeks with and without RBV in TE GT3 cirrhotics.

Table 18. SVR12 Rates Among TE GT3 Cirrhotics, Trial 342-0109 Groups 7 and 8

	SOF/VEL 12 Weeks	**SOF/VEL + RBV 12 Weeks**	**Diff in SVR12 rate (without RBV– with RBV) [95% CI]**
SVR12 rate [95% CI]	89% (23/26) [70%, 98%]	96% (25/26) [80%, 100%]	-8% [-28%, 10%]
Relapse	11.5% (3/26)	3.8% (1/26)	
BL RAPs	1 (A30K, L31M)	0	
Y93H at failure	2/3	1/1	

Source: Based on analysis performed by Dr. Qi

Reviewer Comment: These results do not definitively demonstrate that the addition of RBV improves SVR12 for GT3 cirrhotics. The study sample size was small, and although the SVR12 rate is numerically higher in the SOF/VEL + RBV group, the difference in SVR12 between the two groups is not statistically significant because the 95% CI included zero. It is also noteworthy that the addition of RBV did not preclude emergence of the Y93H NS5A RAP at the time of failure.

The safety impact of adding ribavirin was also assessed in order to inform the risk/benefit considerations of a SOF/VEL+RBV regimen for GT3 cirrhotics. The RBV label contains a black box warning regarding risk of hemolytic anemia that may lead to worsening of cardiac disease, as well as several items in Warnings and Precautions including risk of hepatic failure and death, severe hypersensitivity reactions, and pulmonary disorders. In study 0109, the proportion of subjects with SAEs and Grade 3 and 4 AEs was nearly equivalent between the SOF/VEL+ RBV group and the SOF/VEL group, but more subjects in the SOF/VEL+RBV group had ADRs and AEs (all cause, all grade) compared to the SOF/VEL group: 69% versus 46% for ADRs, respectively, and 88% versus 77% for overall AEs, respectively. Headache, fatigue, insomnia, and nausea were the both frequently reported ADRs and AEs for both groups.

The safety evaluation also assessed the need for RBV dose reduction. The mean (median) RBV dose in Group 8 was 1116 (1200) mg. The RBV dose was reduced for three subjects (12%) at 43, 45, and 64 days; none of the three subjects discontinued RBV. RBV treatment was temporarily suspended for one subject who experienced the SAE acute myocardial infarction on treatment day 26. Subject 1069-61207 is a 46 year old while man with a history of hypertension, former tobacco use, depression and drug abuse but no family history of CAD or hyperlipidemia. The event was considered unrelated to study drug by the investigator. Overall, the most frequently reported adverse events were headache, fatigue, nausea, insomnia, and diarrhea. Most events were Grade 1 or 2.

ASTRAL-4 (discussed in the next section of this review) evaluated 3 different SOF/VEL regimens in GT1-6 infected subjects with decompensated (CPT B at screening) cirrhosis. Though this trial studied a different population with more advanced hepatic disease, cirrhosis is a spectrum of illness, and results from the decompensated population may help inform efficacy (but not necessarily safety) among compensated cirrhotics. The addition of RBV in ASTRAL-4 resulted in numerically higher SVR12 rates among GT3 subjects compared to 12 or 24 weeks of SOF/VEL alone: 85% for SOF/VEL + RBV 12 weeks (11/13), 50% for SOF/VEL 12 weeks (7/14), and 50% for SOF/RBV for 24 weeks (6/12). Given the small sample size, there was significant overlap in the 95% CI for the three treatment groups (refer to Table 23 in Section 6.4.2). There were no subjects with baseline NS5A RAPs in the SOF/VEL + RBV group, so the impact of RAPs on SVR12 could not be assessed. Both subjects who experienced treatment failure in the SOF/VEL + RBV group had the Y93H NS5A RAP at failure.

Reviewer Comment: Although the difference in SVR12 rates between groups was not statistically significant, the risk/benefit considerations unique to the decompensated population support the use of RBV for GT3 subjects with decompensated cirrhosis (see discussion in Section 6.4.2). However, the risk/benefit assessment is different for subjects with compensated cirrhosis who have much higher SVR12 rates with SOF/VEL x 12 weeks (91% in ASTRAL-3 compared to 50% in ASTRAL-4 for decompensated subjects), in general have better overall health status, and may

have a better chance of successful retreatment in the event that they fail or relapse. Several retreatment strategies are being evaluated in clinical trials of DAA failures and successful retreatment options may be established in the near future. The role of RBV for mitigating failure in subjects with BL NS5A polymorphisms could not be established in ASTRAL-4 due to insufficient data, but it appears that RBV did not prevent the emergence of Y93H among relapsers.

SVR12 rates among cirrhotic GT1 subjects in ASTRAL-1 and ASTRAL-4 were also considered as supportive evidence. Only one cirrhotic GT1 subject relapsed in ASTRAL-1, and this subject had NS5A RAPs at baseline and failure. The results among decompensated GT1 cirrhotics in ASTRAL-4 followed the same trend as GT3, with a numerically higher SVR12 rate in the SOF/VEL + RBV group compared to the SOF/VEL for 12 week or SOF/VEL for 24 week groups: 96% (65/68), 88% (60/68), and 92% (65/71), respectively. Only one of the three non-responders in the SOF/VEL + RBV group was a true failure, and this subject had no detectable NS5A RAPs at baseline or failure.

Reviewer Comment: Results from the GT1 subjects do not provide additional insight into the possible benefit of RBV for GT3 subjects.

Question 2:
As summarized above, SVR12 results from GT 1 and GT3 decompensated subjects in ASTRAL-4 demonstrate SVR12 rates were not improved despite an additional 12 weeks of SOF/VEL treatment. Longer durations of therapy were not evaluated among non-cirrhotics or compensated cirrhotics for any genotype. Therefore, there is no available evidence that extending treatment for compensated GT3 cirrhotics will be effective in reducing relapse.

Question 3:
Resistance testing indicates that the presence of key baseline RAPs, such as Y93H, is associated with higher risk of treatment failure. Hence, identification of subjects with baseline RAPs may help predict their chances for successful treatment. However, such strategies are only helpful if the test result guides a change in management strategy for subjects with RAPs (e.g. treatment with a different DAA regimen, prolonging the course of treatment, or adding another agent such as RBV). At present, the only approved regimens for GT3 are SOF+RBV and DCV+SOF, neither of which would be superior to SOF/VEL: DCV is vulnerable to the same NS5A RAPs as VEL, and SOF/VEL is superior to SOF+RBV in ASTRAL-3. As noted above, the role of RBV is unclear and prolonging treatment is unlikely to be of benefit. Hence, baseline screening would not provide actionable information and is therefore not recommended.

Overall Conclusion: The limited data presented above are insufficient to satisfy the regulatory requirements for recommending the addition of RBV to SOF/VEL for GT3 compensated

cirrhotics, a regimen that was not formally studied in the pivotal trials. Although the SOF/VEL + RBV groups had numerically higher SVR12 rates than the SOF/VEL groups in studies 0109 and ASTRAL-4, the difference was not statistically significant and the risk/benefit considerations that support a more conservative approach to treating decompensated subjects may not apply to all compensated cirrhotics.

The results from ASTRAL-3 demonstrate > 90% efficacy without RBV, and therefore a general recommendation to add RBV to all compensated cirrhotics would introduce RBV-associated toxicity that is likely unneeded for the majority of subjects. In the opinion of the primary clinical review team, the available data do not conclusively show that benefit of adding RBV outweighs the risk for developing these serious toxicities.

Furthermore, the limited data from 3 subjects suggests that RBV does not prevent emergence of the Y93H NS5A polymorphism. In addition, neither a prolonged treatment course nor screening for baseline NS5A polymorphism are likely to reduce the risk of relapse or the emergence of NS5A resistance among GT3 cirrhotics.

The need for treatment optimization among GT3 subjects, particularly cirrhotics, is acknowledged. During the Mid-Cycle communication teleconference, DAVP queried the Applicant regarding their perspective on strategies to minimize failure for GT3 cirrhotics. (b) (4)

(b) (4)

. Hence, a PMR will be issued to conduct a clinical trial to demonstrate a clinically meaningful difference in treatment response between subjects treated with SOF/VEL and SOF/VEL + RBV in GT3 cirrhotics. (b) (4)

This topic will be discussed once again with the Applicant during the Late Cycle meeting. If the opinion of the review team changes as discussions with the Applicant ensue, the justification will be summarized in an addendum to the clinical review.

6.4. ASTRAL-4

6.4.1. Study Design

Overview and Objective
ASTRAL-4 is an ongoing Phase 3, open-label, multicenter trial to investigate the efficacy and safety of SOF/VEL FDC in subjects with chronic HCV infection and CPT B cirrhosis at screening. The primary objectives of this trial as noted by the Applicant were the following:

- To evaluate the efficacy of treatment with SOF/VEL FDC with and without RBV for 12 weeks and SOF/VEL FDC for 24 weeks in subjects with chronic HCV infection and CPT class B cirrhosis as measured by the proportion of subjects with SVR12
- To evaluate the safety and tolerability of each treatment regimen

Secondary objectives included: SVR4, SVR24, proportion of subjects with virologic failure, change of CPT score and Model for End-Stage Liver Disease (MELD) score, HCV RNA kinetics during treatment and after treatment cessation, emergence of viral resistance to SOF and VEL during treatment and after treatment cessation, steady-state PK of study drugs.

Trial Design
This Phase 3, randomized, open label, multicenter trial assessed the antiviral efficacy, safety and tolerability of SOF/VEL±RBV for 12 weeks and SOF/VEL for 24 weeks in subjects with chronic HCV GT 1-6 infection and CPT B cirrhosis at screening who have not had a liver transplant. Eligible subjects were randomized 1:1:1 to one of the following treatment groups:

- Group 1 (SOF/VEL 12 Week group): SOF/VEL for 12 weeks
- Group 2 (SOF/VEL+RBV 12 Week group): SOF/VEL+RBV for 12 weeks
- Group 3 (SOF/VEL 24 Week group): SOF/VEL for 24 weeks

Weight-based RBV dosing was selected in accordance with the prescribing information (total daily dose of RBV was 1000 mg for subjects weighing < 75 kg or 1200 mg for subjects weighing ≥ 75 kg; administered in a divided twice daily dose). RBV dose adjustments were permitted for hemoglobin decreases as outlined in the protocol, reflecting labeled RBV dose modification guidelines.

All subjects were to complete the posttreatment Week 4 and 12 visits regardless of treatment duration. Subjects who had HCV RNA less than the lower limit of quantitation (< LLOQ) at the posttreatment Week 12 visit were also to complete the posttreatment Week 24 visit unless a confirmed viral relapse occurred. Subjects with prior exposure to SOF or any other nucleotide analogue HCV NS5B inhibitor or any HCV NS5A inhibitor were excluded.

Randomization was stratified by HCV GT (1, 2, 3, 4, 5, 6 and indeterminate). Subjects who did not achieve SVR were eligible for enrollment in the Sequence Registry Study (GS-US-248-0123),

which is monitoring the persistence of resistance mutations for up to 3 years. Subjects who achieved SVR were eligible for enrollment in the Cirrhosis SVR Registry Study (GS-US-337-1431) to evaluate durability of SVR and clinical progression or regression of liver disease (including the incidence of HCC) for up to 5 years. An external multidisciplinary data monitoring committee (DMC) reviewed the progress of the trial and performed interim review of safety data after the first 75 subjects enrolled completed through Week 4. No change to trial conduct was recommended by the DMC.

The ASTRAL-4 trial began on July 31, 2014 and is ongoing at this time. The last subject observation included in the NDA submission was made on September 8, 2015. Randomized and treated subjects were enrolled at one of 47 US sites.

Study Endpoints
The primary efficacy endpoint was SVR12, the same endpoint as for ASTRAL-1, -2 and -3 trials. HCV RNA was analyzed using COBAS AmpliPrep/COBAS TaqMan HCV Quantitative Test v2.0. The primary efficacy endpoint analysis (for SVR12) in this interim CSR was conducted after all subjects completed the posttreatment Week 12 visit or prematurely discontinued.

Secondary endpoints included: SVR4, SVR24, percentage of subjects with HCV RNA < LLOQ while on treatment, HCV RNA (log10 IU/mL) and change from baseline in HCV RNA (log10 IU/mL) through end of treatment (EOT), change of CPT score and MELD score, proportion of subjects with virologic failure, HCV RNA kinetics during treatment and after treatment cessation, characterization of HCV drug resistance substitutions at baseline, during, and after therapy with SOF/VEL±RBV.

Statistical Analysis Plan
The primary ASTRAL-4 efficacy hypothesis was that the SVR12 rate in each SOF/VEL-containing treatment group was superior to the assumed spontaneous rate of 1%. At the time of ASTRAL-4 trial initiation there were no approved treatment options for this population, thus an active-control design was not feasible. The 1% spontaneous rate selected by the Applicant was deemed acceptable because non-treatment rarely results in spontaneous cure.

A sample size of 75 subjects in each treatment group was expected to provide over 99% power to detect at least 40% improvement in SVR12 rate from the assumed spontaneous rate of 1% or less using a two-sided exact one-sample binomial test at significance level of 0.0167.

Reviewer Comment: The comparison to a historical control was reasonable to the review team as there was no standard treatment in this HCV CPT B cirrhosis population at the time of ASTRAL-4 trial initiation.

Planned subgroup analyses of SVR12 rates included: HCV genotype randomization stratification,

age (< 65 years, ≥ 65 years), sex, race, ethnicity, baseline BMI, IL28B, baseline HCV RNA, baseline CPT score, baseline MELD score, prior HCV treatment response, completed treatment/discontinued treatment, adherence (study regimen, SOF/VEL, RBV).

The ASTRAL-4 primary efficacy analysis population used for FDA analyses was the FAS, which included all subjects who were randomized and received at least one dose of study drug. Please refer to the NDA 208341 Statistical Review for detailed evaluation of the Applicant's planned statistical analysis.

Protocol Amendments
The original ASTRAL-4 protocol was amended three times during the trial. These amendments are not considered to have had an impact on trial integrity or FDA efficacy result interpretation.

6.4.2. Study Results

Patient Disposition
Subject disposition is shown in Table 19. A total of 268 subjects were randomized and 267 subjects received at least one SOF/VEL study drug dose: Subject 00522-64212 was randomized to the SOF/VEL+RBV 12 Week group though was not treated due to AE.

Overall, 96% subjects completed study treatment. The most common reason for SOF/VEL-containing treatment discontinuation was for AE (9 subjects), followed by lack of efficacy (2 subjects) and non-compliance (1 subject).

Table 19. Subject Disposition in ASTRAL-4

Subject Disposition	SOF/VEL 12 Week	SOF/VEL+RBV 12 Week	SOF/VEL 24 Week	Total
Subjects Randomized	90	88	90	268
Subjects Randomized and Treated (Safety Analysis Set)	90	87	90	267
Subjects Randomized and Treated with At Least One Dose of Active Study Drug (Full Analysis Set)	90	87	90	267
Study Treatment Status				
Completed Study Treatment	89 (99%)	82 (94%)	84 (93%)	255 (96%)
Discontinued Study Treatment	1 (1%)	5 (6%)	6 (7%)	12 (4%)
Reason for Premature Discontinuation of Study Treatment				
Adverse Event	1 (1%)	4 (5%)	4 (4%)	9 (3%)
Lack of Efficacy	0	1 (1%)	1 (1%)	2 (1%)
Non-compliance with study drug	0	0	1 (1%)	1 (<1%)

Source: ADSL (ASTRAL-4)

Protocol Violations/Deviations

The review team's assessment of ASTRAL-4 protocol deviations does not raise significant concern that these deviations affected ASTRAL-4 data quality or data interpretation. Important protocol deviations occurred in 44 subjects during the trial and were evenly distributed between treatment groups. Thirty-eight subjects had a single important deviation, five subjects had two important deviations and one subject had three important deviations. The majority of important protocol deviations were for subjects who were enrolled in violation of inclusion/exclusion criteria (e.g., on prohibited medication), subjects not managed according to protocol (e.g., SAEs not reported within 24 hours, CPT assessments not performed on treatment) or deviations in study medications (e.g., RBV dose less than specified per protocol).

Reviewer Comment: These protocol violations had no bearing on the interpretability of the trial results. As discussed in Section 4.1, two ASTRAL-4 trial sites were inspected. The final reports from the clinical site inspections were pending at the time this review was finalized.

Table of Demographic Characteristics

Overall the median age was 59 years (range 40 to 73 years). The majority of subjects were white (90%) and male (70%). Demographics and baseline characteristics listed in Table 20 were generally balanced among the ASTRAL-4 treatment groups.

Table 20. Demographics and Baseline Characteristics, ASTRAL-4

Characteristics	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90	Total N=267
Age at Baseline (Years)				
Median	58.5	59	58	59
Min, Max	42, 73	40, 71	46, 72	40, 73
Sex				
Male	57 (63%)	66 (76%)	63 (70%)	186 (70%)
Female	33 (37%)	21 (24%)	27 (30%)	81 (30%)
Race				
Black or African American	6 (7%)	5 (6%)	6 (7%)	17 (6%)
White	79 (88%)	79 (91%)	81 (90%)	239 (90%)
Asian	3 (3%)	0	2 (2%)	5 (2%)
Other*	2 (2%)	3 (3%)	1 (1%)	6 (2%)
Ethnicity				
Hispanic or Latino	13 (14%)	13 (15%)	13 (14%)	39 (15%)
Not Hispanic or Latino	77 (86%)	74 (85%)	77 (86%)	228 (85%)
Baseline Body Mass Index (kg/m^2)				
Median	29.7	28.8	29.0	29.2
Min, Max	16.7, 55.6	19.5, 54.9	18.4, 49.8	16.7, 55.6
Baseline Body Mass Index Category				
≥30 mg/m^2	42 (47%)	33 (38%)	38 (42%)	113 (42%)

*Other: 1 subject American Indian or Alaska Native, 1 subject Native Hawaiian or Other Pacific Islander, 1 not permitted, 3 other.
Source: ADSL (ASTRAL-4)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Table 21 shows ASTRAL-4 baseline disease characteristics. The majority of subjects had HCV GT 1 infection (78%) with other HCV GTs comprised of GT 2 (4%), GT 3 (15%), GT 4 (3%) and GT 6 (<1%). No subjects with HCV GT 5 infection were enrolled. The methods of cirrhosis determination were liver biopsy (11%, 29 subjects), Fibroscan (24%, 65 subjects) and FibroTest (65%, 173 subjects): cirrhosis determination methods reflect recent trend toward use of noninvasive methods. The majority of subjects were previously HCV treatment-experienced (55%), including 19% subjects who failed prior DAA+PEG/RBV treatment.

Approximately 10% subjects who were CPT B at screening were subsequently CPT A or C at baseline, reflecting the dynamic changes in CPT parameters over time. Most subjects had baseline MELD score ≤15 (95%).

Table 21. Selected Baseline Disease Characteristics, ASTRAL-4

Disease Characteristics	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90	Total N=267
HCV Genotype				
1	68 (76%)	68 (78%)	71 (79%)	207 (78%)
1a	50 (56%)	54 (62%)	55 (61%)	159 (60%)
1b	18 (20%)	14 (16%)	16 (18%)	48 (18%)
2	4 (4%)	4 (5%)	4 (4%)	12 (4%)
3	14 (16%)	13 (15%)	12 (13%)	39 (15%)
4	4 (4%)	2 (2%)	2 (2%)	8 (3%)
6	0	0	1 (1%)	1 (<1%)
CPT Score Category				
A [5-6]	3 (3%)	6 (7%)	7 (8%)	16 (6%)
B [7-9]	86 (96%)	77 (89%)	77 (86%)	240 (90%)
C [10-12]	1 (1%)	4 (5%)	6 (7%)	11 (4%)
MELD Score Category				
<10	36 (40%)	29 (33%)	26 (29%)	91 (34%)
≤15	86 (96%)	83 (95%)	85 (94%)	254 (95%)
>15	4 (4%)	4 (5%)	5 (6%)	13 (5%)
Baseline Ascites				
None	16 (18%)	22 (25%)	15 (17%)	53 (20%)
Mild/Moderate	72 (80%)	61 (70%)	74 (82%)	207 (78%)
Severe	2 (2%)	4 (5%)	1 (1%)	7 (3%)
Baseline Encephalopathy				
None	38 (42%)	33 (38%)	31 (34%)	102 (38%)
Grade 1-2	52 (58%)	54 (62%)	59 (66%)	165 (62%)
Grade 3-4	0	0	0	0
Baseline Platelet Count (x 10^3/µL)				
Median	74.5	86	80	82
Min, Max	35, 233	32, 268	37, 379	32, 379
Baseline Platelet Count Category				
<75 x 10^3/µL	45 (50%)	32 (37%)	38 (42%)	115 (43%)
IL28B Genotype				
CC	20 (22%)	22 (25%)	20 (22%)	62 (23%)
CT	51 (57%)	46 (53%)	49 (54%)	146 (55%)
TT	19 (21%)	19 (22%)	19 (21%)	57 (21%)
Missing	0	0	2 (2%)	2 (1%)
Baseline HCV RNA (log10 IU/mL)				
Median	6.0	5.9	5.9	6.0
Min, Max	3.7, 7.2	3.9, 7.1	3.5, 7.2	3.5, 7.2
Baseline HCV RNA Category				

Disease Characteristics	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90	Total N=267
≥800,000 IU/mL	59 (66%)	45 (52%)	45 (50%)	149 (56%)
Estimated Glomerular Filtration Rate Using the Cockcroft-Gault Equation (mL/min)				
Median	83.9	86.3	86.1	84.7
Min, Max	15.4, 169.1	49.9, 166.8	43.2, 197.9	15.4, 197.9
Prior HCV Therapy Treatment Response				
Treatment-Naive	32 (36%)	40 (46%)	48 (53%)	120 (45%)
Treatment-Experienced	58 (64%)	47 (54%)	42 (47%)	147 (55%)
Prior HCV Treatment				
DAA+PEG/RBV	9 (16%)	12 (26%)	7 (17%)	28 (19%)
PEG/RBV	30 (52%)	27 (57%)	28 (67%)	85 (58%)
IFN/RBV	15 (26%)	5 (11%)	5 (12%)	25 (17%)
Other	3 (5%)	3 (6%)	2 (5%)	8 (5%)
Missing	1 (2%)	0	0	1 (1%)
Prior Response				
Relapse/Breakthrough	15 (26%)	10 (21%)	12 (29%)	37 (25%)
Non-Responder	38 (66%)	33 (70%)	27 (64%)	98 (67%)
Not Applicable	4 (7%)	4 (9%)	3 (7%)	11 (7%)
Missing	1 (2%)	0	0	1 (1%)

Source: ADSL (ASTRAL-4)

Treatment Compliance, Concomitant Medications, and Rescue Medication Use
SOF/VEL-containing treatment adherence, assessed by tablet counts, was high. The percentage of ASTRAL-4 subjects with at least 80% SOF/VEL adherence ranged 92-95% and was similar across the three groups.

Efficacy Results - Primary Endpoint
The primary efficacy endpoint analysis in these trials was conducted when all subjects completed the post-treatment Week 12 visits or prematurely discontinued from the trial.

This section also includes discussion of on-treatment virologic failure and relapse rates, along with discussion of efficacy data by HCV genotype.

All three ASTRAL-4 treatment groups met the primary endpoint, with SVR12 rates superior to 1% spontaneous rate (p-value <0.001 for each group) as displayed in Table 22. The overall ASTRAL-4 SVR12 rate was highest in the SOF/VEL+RBV 12 Week group (94%) compared with the SOF/VEL 12 Week (83%) and SOF/VEL 24 Week (86%) groups. The 95% confidence intervals (CI) for SVR12 rates did overlap across the three treatment groups. In most cases, failure to achieve SVR12 was due to relapse across all treatment groups. Overall relapse rate at post-treatment Week 12 for SOF/VEL+RBV 12 Week group was 2%, compared with 4% and 6% in the SOF/VEL

12 Week and SOF/VEL 24 Week groups, respectively. On-treatment virologic failure (breakthrough) occurred in two ASTRAL-4 subjects: Subject 03060-64249 (HCV GT 3, SOF/VEL+RBV 12 Week) with undetectable plasma drug levels suggesting non-adherence, and Subject 04421-64013 (HCV GT 3, SOF/VEL 24 Week).

The contribution of RBV to the SOF/VEL 12 Week regimen is supported by:

- +11% treatment difference in SVR12 rates and -10% treatment difference in relapse rates between SOF/VEL+RBV 12 Week and SOF/VEL 12 Week groups which the review team considers clinically relevant.
- Exploratory statistical analyses demonstrating the SOF/VEL+RBV 12 Week group had a nominally significantly higher SVR12 rate than the SOF/VEL 12 Week (p=0.031 based on Fisher's exact test).
- Lack of obvious differences in SVR12 and relapse rates between SOF/VEL 12 Week and 24 Week groups.

Table 22. ASTRAL-4 Primary Efficacy Results

	SOF/VEL 12 Weeks (N=90)	SOF/VEL + RBV 12 Weeks (N=87)	SOF/VEL 24 Weeks (N=90)
SVR12 rate [95% CI][1]	83.3% (75/90) [74.0%, 90.4%]	94.3% (82/87) [87.1%, 98.1%]	85.6% (77/90) [76.6%, 92.1%]
Not achieving SVR12			
On-treatment virologic failure	0% (0/90)	1.1% (1/87)	1.1% (1/90)
Relapse	12.2% (11/90)	2.4% (2/85)	8.0% (7/88)
Other	4.4% (4/90)	2.3% (2/87)	5.6% (5/90)

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

HCV Genotype

Table 23 displays ASTRAL-4 efficacy results by HCV genotype. A limitation of ASTRAL-4 was the small overall numbers of enrolled subjects with HCV genotypes other than HCV GT 1. Despite this limitation, the review team recommends the SOF/VEL+RBV 12 Week regimen for all HCV genotypes in the decompensated population as outlined below by specific HCV genotype.

An overarching consideration for the SOF/VEL+RBV 12 Week recommendation across HCV genotypes pertains to optimizing HCV treatment success in patients with decompensated cirrhosis. Achieving SVR in patients with CHC is associated with improvements in clinical outcomes such as decreased development of HCC, hepatic events and all-cause mortality. Clinical outcome data in decompensated cirrhotic patients who achieve SVR is not well-documented, in part because approved HCV treatment options were previously limited in this population. Patients with decompensated cirrhosis awaiting liver transplant may benefit by

delaying or eliminating the need for liver transplant. Although certain patients may still undergo transplantation due to their advanced disease or deteriorating liver function, effective HCV therapy pre-transplantation prevents HCV recurrence post-transplantation, with associated clinical benefits of improved graft survival and overall mortality.[10]

Table 23. ASTRAL-4 Efficacy Results, By HCV Genotype

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

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

HCV Genotype 1

The SOF/VEL+RBV 12 Week regimen is recommended for the HCV GT 1 decompensated population, representing 78% of enrolled ASTRAL-4 subjects, acknowledging overlapping SVR12

rate 95% CIs across all groups. The review team considered the following data to support this recommendation:

- SOF/VEL+RBV 12 Week group had the highest SVR12 rate (96%) and lowest relapse rate (1%) compared with the SOF/VEL 12 Week (88% and 7%, respectively) and SOF/VEL 24 Week (92% and 4%, respectively) groups. A similar trend was observed with the HCV GT 1a and 1b subtypes.
- +7% treatment difference in SVR12 rates and -6% treatment difference in relapse rates between SOF/VEL+RBV 12 Week and SOF/VEL 12 Week groups which the review team considers clinically relevant to support the contribution of RBV to the SOF/VEL regimen.
- Few SOF/VEL+RBV 12 Week regimen discontinuations in HCV GT 1 subjects due to AEs (2%).

Thus, the totality of the data support the recommendation of the SOF/VEL+RBV 12 Week regimen for HCV GT 1 decompensated patients in the label to optimize treatment success with the SOF/VEL-containing regimen and minimize relapse.

HCV Genotype 3

The SOF/VEL+RBV 12 Week regimen is recommended for the HCV GT 3 decompensated population, representing 15% of enrolled ASTRAL-4 subjects, acknowledging overlapping SVR12 rate 95% CIs across all groups. The review team considered the following data to support this recommendation:

- SOF/VEL+RBV 12 Week group had the highest SVR12 rate (85%) and lowest relapse rate (8%) compared with the SOF/VEL 12 Week (50% and 43%, respectively) and SOF/VEL 24 Week (50% and 40%, respectively) groups.
- +35% treatment difference in SVR12 rates and -35% treatment difference in relapse rates between SOF/VEL+RBV 12 Week and SOF/VEL 12 Week groups which the review team considers clinically relevant to support the contribution of RBV to the SOF/VEL regimen.
- Extending SOF/VEL treatment from 12 to 24 weeks did not improve SVR12 rates or reduce relapse rates.
- Few SOF/VEL+RBV 12 Week regimen discontinuations in HCV GT 3 subjects due to AEs (15%).

Thus, the totality of the data support the recommendation of the SOF/VEL+RBV 12 Week regimen for HCV GT 3 decompensated patients in the label to optimize treatment success with the SOF/VEL-containing regimen and minimize relapse.

HCV Genotype 2, 4, 5, 6

All HCV GT 2, 4 and 6 subjects achieved SVR12 across treatment groups, with the exception of Subject 02760-64102 (HCV GT 2, SOF/VEL 24 Week) who discontinued due to an AE. No HCV GT 5 subjects were enrolled in ASTRAL-4. A single HCV GT 6 subject received SOF/VEL 24 Week

regimen. Due to small sample sizes, the 95% CIs for SVR12 rates were wide.

The SOF/VEL+RBV 12 Week regimen is recommended for HCV GT 2, 4, 5, and 6 decompensated population, recognizing the limited number of enrolled subjects in these HCV genotype subgroups. The review team considered the following data to support this recommendation:

- ASTRAL-1 and ASTRAL-2 data demonstrate efficacy of the SOF/VEL regimen in HCV GT 5 and 6 subjects with compensated liver disease.
- No currently approved treatment options in HCV GT 2, 4, 5 or 6 decompensated population making these populations ones with an unmet medical need.
- Wide SVR12 rate 95% CIs due to small sample sizes with less precision around the point estimate.
- No SOF/VEL+RBV 12 Week regimen discontinuations in HCV GT 2 or 4 subjects due to AEs.

It is acknowledged that high SVR12 rates based on point estimates were observed HCV GT 2, 4, and 6 subjects in the SOF/VEL 12-24 Week groups and it is possible a RBV-containing regimen is not needed in some patients. However, the small sample sizes and wide SVR 12 95% CIs with lower bounds less than 40% in these HCV genotypes do not provide precision around these SVR12 point estimates. Thus, the review team considered the totality of the data and took a conservative approach in supporting the SOF/VEL+RBV 12 Week regimen in the HCV GT 2, 4, 5, 6 decompensated population to optimize treatment success with the SOF/VEL-containing regimen and minimize relapse for the reasons mentioned above. The Applicant could conduct a larger SOF/VEL-containing trial in the HCV GT 2, 4, 5, 6 decompensated cirrhosis subgroups to determine definitively if RBV is needed; however, feasibility issues of enrolling sufficient numbers in these subgroups are recognized.

Efficacy Results - Secondary and other relevant endpoints

Selected secondary endpoints and other relevant endpoints are discussed in this section: please refer to Dr. Qi's statistical review for further details.

Change in CPT and MELD Score

Pre-specified ASTRAL-4 secondary efficacy endpoints included changes in CPT and MELD scores from baseline to 12 weeks and 24 weeks post-treatment. As noted in the protocol, the objective was determining therapeutic efficacy as measured by the change of CPT score and MELD score.

CPT and MELD scores stage disease severity in patients with end-stage liver disease. The CPT score is a composite score based on laboratory parameters (total bilirubin, albumin, INR) and physical examination findings (presence or absence of encephalopathy and ascites) and is used worldwide to stage the clinical severity of a patient with cirrhosis. Higher CPT scores correlate with increased mortality. The use of CPT score has limitations due to inclusion of the subjective

variables ascites and encephalopathy, which are influenced by medical therapy.[11] The MELD score is calculated from three objective laboratory parameters: creatinine, bilirubin, INR. The lower the MELD score, the higher the 3-month survival rate in patients with cirrhosis. In the US, MELD is used to prioritize liver transplant recipients. A MELD score ≥ 15 is generally the threshold at which liver transplantation is recommended.

Changes in CPT and MELD scores from baseline to post-treatment Week 12 in ASTRAL-4 were analyzed by Dr. Qi to determine longer-term clinical impact of achieving SVR12: summaries from these analyses are presented below. No definitive conclusions to support overall efficacy of ASTRAL-4 SOF/VEL-containing treatment could be determined based on these CPT and MELD score analyses, particularly as the majority of subjects' scores improved or stayed unchanged regardless of SVR12 status. (b) (4) To assess the durability of SVR and the impact of achieving SVR12 on clinical outcomes in patients with cirrhosis, including decompensated cirrhosis (e.g., progression or regression of liver disease, occurrence of HCC, need for liver transplantation), a PMC to submit 5 year follow-up data from their long-term registry trial will be requested.

CPT Score
Among subjects who achieved SVR12 in the SOF/VEL+RBV 12 Week group, 40% (33/82) and 49% (40/82) had an improvement or no change of CPT scores from baseline to post-treatment Week 12, respectively. Improvement in CPT score was due to improvements in albumin and bilirubin. A higher percentage of CPT score improvement occurred in the SOF/VEL 24 Week group (53%, 41/77) which may be attributed to longer total follow-up compared to the SOF/VEL±RBV 12 Week groups.

Among the five subjects who did not achieve SVR12 in the SOF/VEL+RBV Week 12 group, one subject had no change in CPT score and one subject had +1 point worsening of CPT score from baseline to post-treatment Week 12. The remaining three subjects did not have post-treatment CPT values.

Most subjects remained in the same CPT class as baseline. Of the 209 subjects with baseline CPT B who achieved SVR12, 167 subjects (80%) remained class B, 34 (16%) improved to class A, and 4 (2%) worsened to class C (4 subjects had missing data). Among the 31 subjects with baseline CPT B who did not achieve SVR12, 15 (48%) remained class B, 3 (10%) improved to class A, and 3 (10%) worsened to class C (10 subjects had missing data). The few numbers of subjects with baseline CPT A or C limits meaningful conclusions. CPT class shifts were generally similar regardless of treatment group.

MELD Score

Among subjects who achieved SVR12 in the SOF/VEL+RBV 12 Week group, 50% (41/82) and 15% (12/82) had an improvement or no change in MELD score from baseline to post-treatment Week 12, respectively. No clinically significant MELD score improvement occurred in the SOF/VEL 24 Week group compared to the SOF/VEL±RBV 12 Week groups. Of the 10 subjects with baseline MELD score ≥15, 40% (4/10) had MELD score <15 at post-treatment Week 12. Improvement in MELD score was due to improvement in bilirubin.

Among the five subjects who did not achieve SVR12 in the SOF/VEL+RBV Week 12 group, one subject had no change in MELD score and one subject had +2 point worsening of MELD score from baseline to post-treatment Week 12. The remaining three subjects did not have post-treatment MELD values.

Most subjects remained in the same MELD category of <15 or ≥15 as baseline. Of the 208 subjects with baseline MELD category <15 who achieved SVR12, 197 subjects (95%) remained <15 and 6 (3%) worsened to ≥15 (5 subjects had missing data). Among the 32 subjects with baseline MELD category <15 who did not achieve SVR12, 20 (63%) remained <15 and the remaining 12 subjects had missing data. Of the 26 subjects with baseline MELD category ≥15 who achieved SVR12, 10 subjects (38%) remained ≥15 and 16 (62%) improved to <15. The single subject with baseline MELD category ≥15 who did not achieve SVR12 remained ≥15. These MELD shifts were generally similar regardless of treatment group.

Subgroup Analyses

Subgroup analyses were performed for SVR12 rates by baseline demographics and selected disease characteristics in ASTRAL-4 subjects, overall and by selected HCV genotypes. Please see the Statistical Review by Dr. Qi for further details. These subgroup analyses should be interpreted with caution because they had no multiple comparison adjustments, had small sample size in some of the subgroups, and lacked an active control group.

Overall the SOF/VEL+RBV 12 Week group consistently had higher SVR12 rates across most subgroups by patient demographics and selected baseline disease characteristics compared with the SOF/VEL 12 and 24 Week groups as presented in Tables 24 and 25. These analyses performed in the HCV GT 1 and 3 subgroups had similar trends as detailed in Dr. Qi's review.

Table 24. SVR12 Rates by Baseline Demographics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	95% CI	SVR12 rate	95% CI	SVR12 rate	95% CI
Age at baseline (years)						
< 65 years	81.5% (66/81)	(71.3%, 89.2%)	95.9% (71/74)	(88.6%, 99.2%)	84.8% (67/79)	(75.0%, 91.9%)
≥ 65 years	100% (9/9)	(66.4%, 100%)	84.6% (11/13)	(54.6%, 98.1%)	90.9% (10/11)	(58.7%, 99.8%)
Sex at birth						
Male	78.9% (45/57)	(66.1%, 88.6%)	92.4% (61/66)	(83.2%, 97.5%)	82.5% (52/63)	(70.9%, 90.9%)
Female	90.9% (30/33)	(75.7%, 98.1%)	100% (21/21)	(83.9%, 100%)	92.6% (25/27)	(75.7%, 99.1%)
Race						
Black or African American	66.7% (4/6)	(22.3%, 95.7%)	100% (5/5)	(47.8%, 100%)	83.3% (5/6)	(35.9%, 99.6%)
White	83.5% (66/79)	(73.5%, 90.9%)	93.7% (74/79)	(85.8%, 97.9%)	85.2% (69/81)	(75.6%, 92.1%)
Other	100% (5/5)	(47.8%, 100%)	100% (3/3)	(29.2%, 100%)	100% (2/2)	(15.8%, 100%)
Ethnicity						
Hispanic or Latino	84.6% (11/13)	(54.6%, 98.1%)	100% (13/13)	(75.3%, 100%)	100% (13/13)	(75.3%, 100%)
Not Hispanic or Latino	83.1% (64/77)	(72.9%, 90.7%)	93.2% (69/74)	(84.9%, 97.8%)	83.1% (64/73)	(72.9%, 90.7%)
BMI at baseline						
< 30 kg/m^2	81.3% (39/48)	(67.4%, 91.1%)	92.6% (50/54)	(82.1%, 97.9%)	90.4% (47/52)	(79.0%, 96.8%)
≥ 30 kg/m^2	85.7% (36/42)	(71.5%, 94.6%)	97.0% (32/33)	(84.2%, 99.9%)	78.9% (30/38)	(62.7%, 90.4%)

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

Table 25. SVR12 Rates by Selected Baseline Disease Characteristics in ASTRAL-4 (All Treated)

	SOF/VEL 12 Weeks		SOF/VEL + RBV 12 Weeks		SOF/VEL 24 Weeks	
	SVR12 rate	95% CI	SVR12 rate	95% CI	SVR12 rate	95% CI
IL28B						
CC	80.0% (16/20)	(56.3%, 94.3%)	100% (22/22)	(84.6%, 100%)	85.0% (17/20)	(62.1%, 96.8%)
CT	82.4% (42/51)	(69.1%, 91.6%)	93.5% (43/46)	(82.1%, 98.6%)	85.7% (42/49)	(72.8%, 94.1%)
TT	89.5% (17/19)	(66.9%, 98.7%)	89.5% (17/19)	(66.9%, 98.7%)	89.5% (17/19)	(66.9%, 98.7%)
Baseline HCV RNA (IU/mL)						
< 800,000	87.1% (27/31)	(70.2%, 96.4%)	95.2% (40/42)	(83.8%, 99.4%)	91.1% (41/45)	(78.8%, 97.5%)
≥ 800,000	81.4% (48/59)	(69.1%, 90.3%)	93.3% (42/45)	(81.7%, 98.6%)	80.0% (36/45)	(65.4%, 90.4%)
Baseline MELD score						
< 10	77.8% (28/36)	(60.8%, 89.9%)	100% (29/29)	(88.1%, 100%)	92.3% (24/26)	(74.9%, 99.1%)
10 – 15	86.0% (43/50)	(73.3%, 94.2%)	90.7% (49/54)	(79.7%, 96.9%)	81.4% (48/59)	(69.1%, 90.3%)
16 – 20	100% (3/3)	(29.2%, 100%)	100% (4/4)	(39.8%, 100%)	100% (5/5)	(47.8%, 100%)
21 – 25	100% (1/1)	(2.5%, 100%)	0/0	n/a	0/0	n/a
Prior HCV treatment history						
TN	84.4% (27/32)	(67.2%, 94.7%)	90.0% (36/40)	(76.3%, 97.2%)	85.4% (41/48)	(72.2%, 93.9%)
TE	82.8% (48/58)	(70.6%, 91.4%)	97.9% (46/47)	(88.7%, 99.9%)	85.7% (36/42)	(71.5%, 94.6%)

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

CPT Class

The ASTRAL-4 trial was designed to enroll subjects with CPT B cirrhosis. Approximately 10%

subjects who were CPT B at screening were subsequently CPT A or C at baseline, reflecting the dynamic changes in CPT parameters over time. As presented in Table 26, all CPT A subjects achieved SVR12 across the three treatment groups with the exception of one subject in the SOF/VEL 24 Week group who achieved SVR4 and had missing SVR12 data. Of the 11 CPT C subjects, one HCV GT 4 subject achieved SVR12 in the SOF/VEL 12 Week group, four subjects (HCV GT 1, 3, 4) achieved SVR12 in the SOF/VEL+RBV 12 Week group, and five subjects (HCV GT 1) achieved SVR12 in the SOF/VEL 24 Week group. A single CPT C subject in the SOF/VEL 24 Week group discontinued due to an AE.

Table 26. SVR12 Rates by Baseline CPT Class in ASTRAL-4 (All Treated)

CPT class	SOF/VEL 12 Weeks	SOF/VEL + RBV 12 Weeks	SOF/VEL 24 Weeks
CPT A (n=16)	**100% (3/3)** [29%, 100%]	**100% (6/6)** [54%, 100%]	**86% (6/7)** [42%, 100%]
	3 GT 1a	3 GT 1a; 1 GT 1b; 2 GT 3	5 GT 1a*; 2 GT 1b
CPT B (n=240)	**83% (71/86)** [73%, 90%]	**94% (72/77)** [86%, 98%]	**85.7% (66/77)** [76%, 93%]
CPT C (n=11)	**100% (1/1)** [3%, 100%]	**100% (4/4)** [40%, 100%]	**83.3% (5/6)** [36%, 100%]
	GT 4	2 GT 1a; 1 GT 3; 1 GT 4	5 GT 1a; 1 GT 2** (d/c 2° AE)

*Subject 01516-64077 achieved SVR4 and had missing SVR12 data
**Subject 02760-64102 discontinued due to adverse event
Source: Adapted from Dr. Qi's Statistical Analysis; ADSL and ADEFFOUT datasets, ASTRAL-4

Despite the small overall number of subjects with baseline CPT C cirrhosis, the review team supports extending the SOF/VEL+RBV 12 Week dosing recommendation to both the CPT B and C populations. This recommendation is based upon consideration of decompensated cirrhosis as a single population rather than two discreet decompensated cirrhosis sub-populations of CPT B and CPT C. No exposure or unique safety issues have been identified precluding SOF/VEL+RBV use in the CPT C population. In addition, use of a broader decompensated cirrhosis definition in dosage and administration labeling allows for shifts in CPT class, which was observed in ASTRAL-4 along with SOLAR-1/-2 (LDV/SOF+RBV regimens in decompensated cirrhosis and post-transplant populations) and ALLY-1 (DCV+SOF+RBV in cirrhosis and post-transplant populations) trials.

Impact of Baseline Resistance Associated Polymorphisms

Of the 254 SOF/VEL subjects with baseline NS5A deep sequence data in ASTRAL-4, 25% of subjects (64/254) had baseline NS5A RAPs. Relapse rates were 0% for subjects with HCV GT 2, GT 4 or GT 6; therefore, assessment of the impact of baseline RAPs on virologic response is limited to HCV GT 1 and 3.

HCV Genotype 1

The overall HCV GT 1 relapse rates were lower in the SOF/VEL+RBV 12 Week group (2%; 1/66) compared the SOF/VEL 12 Week and 24 Week groups (4%-8%). Among HCV GT 1 subjects with baseline NS5A RAPs, no subject in the SOF/VEL+RBV 12 Week group relapsed (0/17) compared with 17% (2/12) and 11% (2/19) of subjects in the SOF/VEL 12 and 24 Week groups, respectively. Lower relapse rates were also observed in the SOF/VEL+RBV 12 Week group in subjects without baseline NS5A RAPs (2%, 1/49) compared to the SOF/VEL 12 Week group (6%, 3/49). Relapse rates were similar (2%) between the SOF/VEL+RBV 12 Week and SOF/VEL 24 Week groups in subjects without baseline NS5A RAPs.

HCV Genotype 3

The overall HCV GT 3 relapse rates were lower in the SOF/VEL+RBV 12 Week group (8%; 1/12) compared to SOF/VEL 12 Week and 24 Week groups (approximately 46%). The impact of baseline NS5A RAPs in the ASTRAL-4 HCV GT 3 population is limited by small subgroups: no subjects with baseline NS5A RAPs in the SOF/VEL+RBV 12 Week group, three subjects in the SOF/VEL 12 Week group, one subject in the SOF/VEL 24 Week group. Among HCV GT 3 subjects with baseline NS5A RAPs, relapse occurred in one subject in each of the SOF/VEL 12 Week (33%, 1/3) and 24 Week (100%, 1/1) groups.

Three subjects in the SOF/VEL+RBV 12 Week group had baseline NS5B nucleoside analog inhibitor polymorphisms and all three subjects achieved SVR12.

Please refer to Dr. Lisa Naeger's virology review for additional details regarding censoring and NS5A/NS5B RAP identification methodologies, the types and frequencies of NS5A/NS5B RAPs observed in the trial, and the implications of these RAPs for treatment success.

Reviewer Comment: SOF/VEL+RBV 12 Week treatment is effective in HCV GT 1 decompensated subjects with and without baseline NS5A RAPs. The impact of baseline NS5A RAPs in other HCV GTs is less clear due to small sample sizes, particularly in the HCV GT 3 population where no subject in the SOF/VEL+RBV 12 Week group had a baseline NS5A RAP. Language in the Microbiology Section 12.4 of the label is proposed stating there are insufficient data to determine the impact of baseline NS5A RAPs in the HCV GT 3 decompensated cirrhosis population.

Development of NS5A/NS5B Resistance Substitutions

This section primarily focuses on development of NS5A and/or NS5B resistance substitutions occurring in ASTRAL-4 SOF/VEL+RBV 12 Week-treated subjects, the recommended regimen in the HCV decompensated cirrhosis population. No HCV GT 2 or 4 subject treated with this regimen experienced virologic failure. The single HCV GT 1 virologic failure subject had no NS5A or NS5B resistance substitutions at failure. The two HCV GT 3 virologic failure subjects had

NS5A resistance substitutions M28V+Y93H and S38P+Y93H emerge at failure. One of these subjects also developed low levels (<5%) of NS5B nucleoside analog inhibitor resistance substitutions N142T and E237G at failure: PK data from this subject suggested non-adherence.

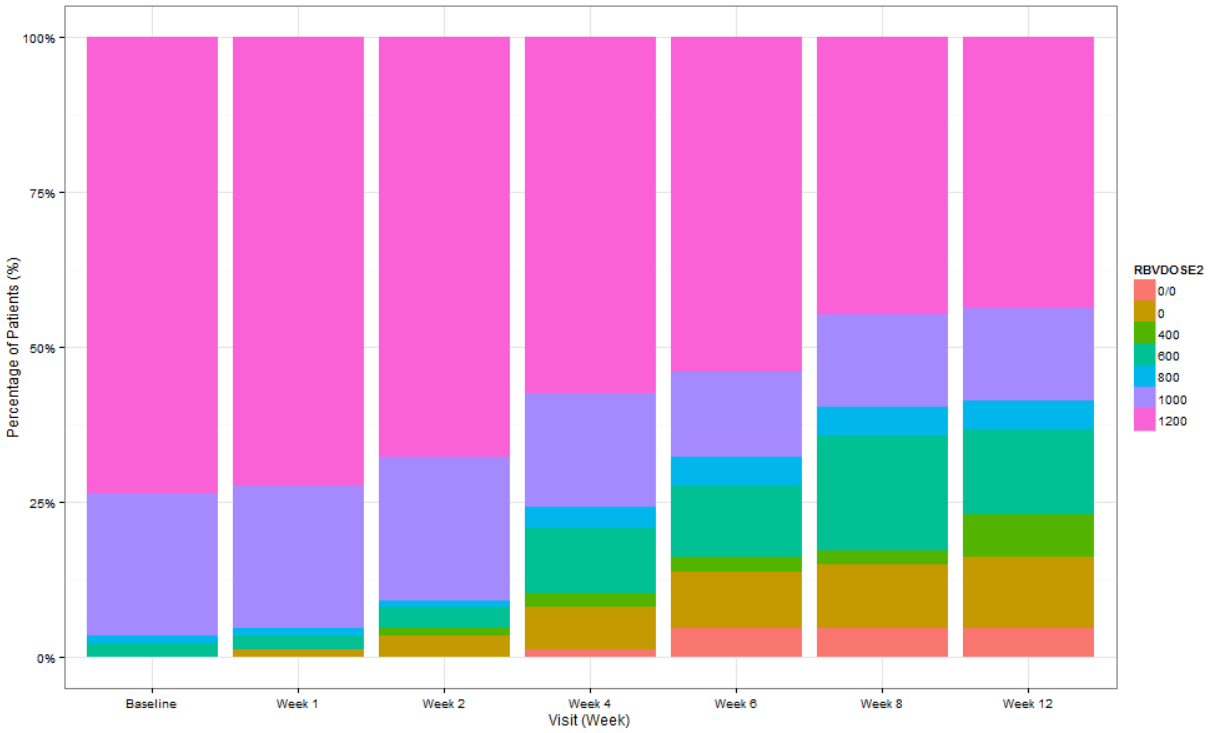
Reviewer Comment: Y93H is a known emergent NS5A resistance substitution, particularly in HCV GT 3. Language in the Microbiology Section 12.4 of the label is proposed to describe these emergent NS5A and NS5B resistance substitutions.

Impact of Ribavirin Dosing

ASTRAL-4 RBV dosing, dose reduction and time on therapy were evaluated to determine the impact on SVR12 rates. The protocol specified RBV weight-based dosing 1000-1200 mg daily, with RBV dosage modification based on hemoglobin decreases or investigator discretion. Once RBV was withheld due to a laboratory abnormality or clinical manifestation, the protocol stated an attempt may be made to restart RBV at 600 mg daily and further increase the dose to 800 mg daily. However, the protocol did not recommend increasing RBV to the original assigned dose. All but two ASTRAL-4 subjects initiated weight-based RBV dosing in the SOF/VEL+RBV 12 Week group: (1) Subject 06991-64164 started at 800 mg daily RBV dose and achieved SVR12, (2) Subject 06991-64042 started at 600 mg daily RBV dose and subsequently experienced post-treatment fatal respiratory failure (Section 8.4.1). Both subjects had HCV GT 1a infection.

The following figure displays ASTRAL-4 RBV dosing by on-treatment week (Figure 1). Median RBV dose in ASTRAL-4 was 1000 mg/day and the majority of subjects (63%, 55/87) maintained an average RBV dose ≥1000 mg/day. Few SOF/VEL+RBV-treated subjects had baseline CPT A (N=6) or C (N=4) limiting further analysis of RBV dosing by on-treatment week based on baseline CPT class. Among the four subjects with baseline CPT C cirrhosis, one subject maintained an average RBV dose ≥1000 mg/day.

Figure 1. Ribavirin Dosing by On-Treatment Week for ASTRAL-4



Source: Analysis by Dr. Jeffry Florian, Pharmacometrics Team Leader

SVR12 rates were ≥95% among ASTRAL-4 subjects with average RBV dose >600 mg daily as displayed in Table 27. SVR12 rates were generally lower among subjects with average RBV dose ≤600 mg daily.

RBV discontinuation in ASTRAL-4 was associated with lower SVR12 rates; however, RBV dose reduction did not impact SVR12 rates. A total of 16% ASTRAL-4 subjects discontinued RBV with median time to discontinuation of 28 days (range 4 to 71 days): SVR12 rates were 79%. Among subjects who remained on RBV, 26% reduced RBV dose with median time to dose reduction of 36 days (range 6 to 75 days): SVR12 rates were 100%.

Table 27. Ribavirin Dosing and SVR12 Rates in ASTRAL-4

Category		% of Subjects (n/N)	SVR12 Rate, % (n/N)
RBV dose	≥1000 mg	63% (55/87)	95% (52/55)
	>600 mg	87% (76/87)	96% (73/76)
	400-600 mg	3% (3/87)	67% (2/3)
	200-400 mg	5% (4/87)	75% (3/4)
	≤ 200 mg	5% (4/87)	100% (4/4)
RBV dose reduced		26% (23/87)	100% (23/23)
RBV discontinued		16% (14/87)	79% (11/14)

Source: Analysis by Dr. Jeffry Florian, Pharmacometrics Team Leader

Reviewer Comment: Most ASTRAL-4 subjects maintained RBV weight-based dosing throughout the 12 week treatment duration, with some subjects reducing or discontinuing RBV as expected due to known RBV-associated toxicities. Despite the need to dose reduce RBV, SVR12 rates were ≥95% among subjects who received an average RBV dose >600 mg daily. The limited number of ASTRAL-4 CPT C subjects prevents reaching conclusions regarding association between initiating SOF/VEL+RBV weight based dosing, ability to maintain RBV dose and SVR12 rates; however, all four SOF/VEL+RBV-treated CPT C subjects achieved SVR12. Because decompensated cirrhosis, particularly CPT C cirrhosis, is associated with comorbidities including renal impairment which may warrant lower RBV dose, language is recommended in Section 2 of the SOF/VEL label stating the RBV starting dose and on-treatment dose can be decreased based on hemoglobin and creatinine clearance, and to refer to the RBV prescribing information for RBV dose modifications.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Results from ASTRAL-1, -2, and -3 were pooled to compile a summary table describing SVR12

rates by HCV genotype (Table 28). A 12 week course of SOF/VEL is clearly effective across all 6 evaluated HCV GTs.

Table 28: Percentage of Subjects Achieving SVR12, Pooled Analysis of ASTRAL 1-3 Subjects Treated with SOF/VEL 12 Weeks

GT1	GT2	GT3	GT4	GT5	GT6	Total
323/328 (99%)	237/238 (99%)	264/277 (95%)	116/116 (100%)	34/35 (97%)	41/41 (100%)	1015/1035 (98%)

Source: ISE ADEFF dataset

7.1.2. Subpopulations

SVR12 results in ASTRAL-1, -2, -3, 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. Two different VEL doses were studied in Phase 2 (25 mg and 100 mg), both in combination with the 400 mg SOF dose. No clear dose-response relationship was identified for any GT other than GT3. It appeared that the higher VEL dose of 100mg was significantly associated with higher SVR12 rates for GT3, particularly among cirrhotics. Hence, the 100mg dose was selected for the SOF/VEL FDC currently under review.

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. 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 any of the four pivotal 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

SOF/VEL would be the first DAA HCV treatment regimen that yields high SVR rates across HCV GT 1-6, including difficult to treat populations such as prior treatment failures and cirrhotics, both compensated and decompensated. The simplicity of uniform dosing recommendations for

all genotypes regardless of prior treatment failure and cirrhosis status (for subjects with compensated disease) could improve the provision of care in settings both within the US and abroad, particularly those with limited capabilities for genotyping and limited access to non-invasive modalities for cirrhosis assessments.

7.2.2. Other Relevant Benefits

SOF/VEL is a fixed dose combination tablet that is administered once daily without respect 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 with or without RBV for the treatment of CHC infection in subjects with compensated or decompensated liver disease has been established by the results from the four pivotal Phase 3 trials discussed in Section 6. Data from ASTRAL-1, -2, and -3 demonstrate that 12 weeks of SOF/VEL yields high SVR rates for nearly all subpopulations across the 6 HCV GTs studied. This finding is supported by the results of ASTRAL-4, which demonstrates high rates of success with 12 weeks of SOF/VEL + RBV in a population that is traditionally difficult to treat.

Overall SVR12 rates in the four Phase 3 trials were 95 to 99% for subjects with compensated liver disease who received 12 weeks of SOF/VEL and 94% for subjects with decompensated liver disease who received 12 weeks of SOF/VEL + RBV. SVR12 rates were numerically higher than the overall rates for some GTs (e.g. GT2, 4, and 6) and lower for others (e.g. GT3). There was also variability in SVR rates is some subpopulations (e.g. cirrhosis, prior treatment failure). Overall, HCV GT3 was associated with the lowest SVR rates among subjects with compensated or decompensated liver disease; however, the SVR12 rates observed in ASTRAL-3 and -4 suggest that SOF/VEL treatment confers a better chance of SVR than other currently available therapies (which are limited in choice), particularly for subjects with decompensated disease. This would also be the first approved RBV-free regimen for HCV GT2 subjects with compensated cirrhosis, and the first approved regimen of any kind for subjects with HCV GT 2, 4, 5, or 6 infection and decompensated cirrhosis.

8 Review of Safety

8.1. Safety Review Approach

The safety review was focused on the four pivotal Phase 3 trials discussed in Section 6. Data from ASTRAL-1, ASTRAL-2, and ASTRAL-3 were pooled to form the integrated safety (ISS) population. Pooling of these studies was appropriate because the trial design and conduct of these three studies were similar and the trial populations were comparable in terms of underlying disease severity. Data from ASTRAL-4 were analyzed separately because we anticipated that the frequency and severity of AEs may differ in this population of

decompensated cirrhotics compared to the ISS population, and that pooling of the data may confound interpretation of the safety results.

Dr. Prabha Viswanathan performed the ISS safety analyses and Dr. Sarah Connelly performed the ASTRAL-4 safety analyses. Though the study populations were sufficiently distinct to merit separate analyses, the results from the ISS and ASTRAL-4 are presented together in each section of the review in order to convey a complete picture of the range of safety events across the spectrum of liver disease. Unless otherwise specified, the analyses presented in this section were performed by Dr. Viswanathan or Dr. Connelly using the analysis datasets for ASTRAL-1, ASTRAL-2, ASTRAL-3, and ASTRAL-4 as well as the ISS datasets. Data were analyzed with JReview and 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 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. 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 ASTRAL trials and three additional ongoing trials that were not included previously:

- GS-US-342-1202 (ASTRAL-5) is evaluating the safety and efficacy of SOF/VEL for 12 weeks in subjects with HCV infection and HIV-1 coinfection
- GS-US-342-1446 is evaluating the safety and efficacy of SOF/VEL for 12 weeks in subjects who received placebo in the ASTRAL-1 study
- GS-US-342-1553 is evaluating the safety and efficacy of SOF/VEL + RBV for 24 weeks in a retreatment study of subjects who failed prior DAA therapy

Deaths, SAEs, discontinuations due to AEs, and hepatic ECIs reported in the SUR are included in the relevant safety sections. October 30, 2015 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 29 describes the overall exposure to SOF+VEL in the 12 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 was 24 weeks.

Table 29: Safety Population, Size and Denominators

Primary Safety Database for SOF/VEL Individuals exposed to SOF+VEL for the indication under review, either as two single agents or in the fixed dose formulation N= 3126			
Clinical Trial Groups	New Drug[a] (SOF+VEL) (n=2603)	Active Control[b] (SOF+RBV) (n=407)	Placebo (n=116)
Phase 1: Healthy Volunteers	499	N/A	N/A
Phase 2: HCV-infected[c]	802	N/A	N/A
Phase 3: HCV-infected	1302	407	116

[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 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 with or without RBV

8.2.2. Relevant characteristics of the safety population:

Demographic characteristics of subjects in the ISS are summarized in Table 30 and baseline HCV disease characteristics are summarized in Table 31. Baseline characteristics for each of the four pivotal trials are described individually in Section 6, including the ASTRAL-4 trial in the decompensated cirrhosis population.

Table 30. Summary of Demographic Characteristics, ISS Population

Demographics	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Age				
Mean (SD)	53 (11.0)	53 (10.4)	57 (9.3)	50 (10.0)
≥ 64 years N (%)	123 (12%)	12 (10%)	22 (17%)	14 (5%)
Sex N (%)				
Male	630 (61%)	68 (59%)	72 (55%)	174 (63%)
Female	405 (39%)	48 (41%)	60 (46%)	101 (37%)
Race N (%)				
White	867 (84%)	90 (78%)	111 (84%)	239 (87%)
Black	61 (6%)	11 (10%)	12 (9%)	1 (<1%)
Asian	86 (8%)	11 (10%)	5 (4%)	29 (11%)
Other/ No info	21 (2%)	4 (3%)	4 (3%)	6 (2%)
Location N (%)				
US	428 (41%)	45 (39%)	132 (100%)	60 (22%)

Source: ISS ADSL dataset

Table 31. Summary of Baseline HCV Disease Characteristics, ISS Population

	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
HCV Genotype N(%)				
Genotype 1a	210 (20%)	46 (40%)	-	-
Genotype 1b	118 (11%)	19 (16%)	-	-
Genotype 2	238 (23%)	21 (18%)	132 (100%)	-
Genotype 3	277 (27%)	-	-	275 (100%)
Genotype 4	116 (11%)	22 (19%)	-	-
Genotype 5	35 (3%)	-	-	-
Genotype 6	41 (4%)	8 (7%)	-	-
Prior Treatment Experience N (%)				
Experienced	291 (28%)	33 (28%)	20 (15%)	71 (26%)
Naive	744 (72%)	83 (72%)	112 (85%)	204 (74%)
Cirrhosis N (%)				
No	813 (79%)	95 (82%)	112 (85%)	187 (68%)
Yes	220 (21%)	21 (18%)	19 (14%)	83 (30%)
Missing	2 (<1%)	0	1 (1%)	5 (2%)
Baseline HCV RNA N (%)				
< 800,000 IU/mL	272 (26%)	29 (25%)	31 (23%)	81 (29%)
>= 800,000 IU/mL	763 (74%)	87 (75%)	101 (77%)	194 (71%)

Source: ISS ADSL dataset

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 or VEL. 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 comprehensive and adequate to assess the safety of SOF/VEL for the proposed indication, dosage regimen, duration of treatment, and patient population. The Phase 3 trials evaluated over 1300 subjects treated at the proposed dose and duration of SOF/VEL, which meets FDA's recommendation for a 1000-1500 subject safety database for treatment of patients with compensated liver disease and an approximately 300 subject safety database for treatment of patients with decompensated liver disease.[12]

The safety database for SOF/VEL 100 mg + RBV 12 week regimen consists of 167 subjects (ASTRAL-4, -0109 trials) with additional 189 subjects receiving a lower VEL dose or shorter 8 Week regimen (-0102, -0109, -0122 trials). There is extensive clinical experience with RBV use in

patients with chronic HCV infection, including decompensated cirrhosis, and RBV is currently approved with other SOF/NS5A combination regimens in the decompensated population. Thus, the review team considers the totality of the safety data sufficient to assess the safety of SOF/VEL+RBV 12 Week regimen in the HCV decompensated population.

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 reviewers verified the Applicant's translation of verbatim terms to preferred terms for events reported in ASTRAL-1, -2, -3, and -4.

8.3.3. Routine Clinical Tests

In ASTRAL 1-4, routine clinical evaluation and laboratory testing occurred at pre-specified intervals: Treatment Weeks (TW) 1, 2, 4, 6, 8, 10, and 12 (all treatment groups) and TW 16, 20 and 24 (SOF/VEL 24 Week group); 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 will present the results from the ISS population, followed by results from ASTRAL-4. 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. Events included in the SUR from ASTRAL 1-4 and the 3 additional studies will also be discussed briefly in each section, as appropriate. 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 the ISS population and ASTRAL-4 are presented in Tables 32 and 33, respectively.

Table 32. Overview of Adverse Events, ISS Population

Subjects Experiencing Event n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Any AE	822 (79%)	89 (77%)	101 (76%)	260 (95%)
Grade 2, 3, or 4 AE	297 (29%)	28 (24%)	42 (32%)	135 (49%)
Grade 3 or 4 AE	33 (3%)	1 (1%)	3 (2%)	23 (8%)
Related AE	520 (50%)	52 (45%)	75 (57%)	215 (78%)
Related Grade 3 or 4 AE	7 (1%)	0	1 (1%)	6 (2%)
SAE	23 (2%)	0	2 (2%)	15 (6%)
Related SAE	0	0	0	1 (<1%)
Discontinuation of any/all study drugs due to AE	2 (<1%)	2 (2%)	0	9 (3%)
Dose modification or interruption due to AE	1 (< 1%)	0	13 (10%)	30 (11%)
Death	3 (<1%)	0	0	3 (1%)

Source: ISS ADSL and ADAE datasets

Table 33. Overview of Adverse Events, ASTRAL-4

Subjects Experiencing Event n (%)	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90
Any AE	73 (81%)	79 (91%)	73 (81%)
Grade 2, 3, or 4 AE	37 (41%)	46 (53%)	46 (51%)
Grade 3 or 4 AE	16 (18%)	11 (13%)	17 (19%)
Related AE	45 (50%)	60 (69%)	34 (38%)
Related Grade 3 or 4 AE	0	2 (2%)	2 (2%)
SAE	17 (19%)	14 (16%)	16 (18%)
Related SAE	0	1 (1%)	1 (1%)
AE Leading to Permanent D/C of Any Study Drug	1 (1%)	13 (15%)	4 (4%)
AE Leading to Permanent D/C of SOF/VEL*	1 (1%)	4 (5%)	4 (4%)
AE Leading to Permanent D/C of RBV	-	13 (15%)	-
AE Leading to Interruption/Modification of Any Study Drug	0	27 (31%)	2 (2%)
AE Leading to Interruption/Modification of SOF/VEL	0	0	2 (2%)
AE Leading to Interruption/Modification of RBV	-	27 (31%)	-
Death (treatment-emergent and post-treatment)	3 (3%)	3 (3%)	3 (3%)

*All subjects in SOF/VEL+RBV 12 Week group also discontinued RBV
Source: ADAE, ADSL ASTRAL-4 datasets

Reviewer Comment: Adverse events occurred at similar frequency between the combined SOF/VEL groups, the placebo group, and the SOF + RBV 12 week group. Subjects in the SOF + RBV 24 week group experienced the highest rate of adverse events, particularly Grade 3 and 4 events, which are likely attributable to longer RBV duration; differences between treatment groups will be assessed more critically in the sections to follow.

The ASTRAL-4 overall AE summary is favorable with few subjects discontinuing SOF/VEL due to AEs (3% overall). Compared to the ISS population, the higher percentages of Grade 3 or 4 AEs and SAEs in ASTRAL-4 reflect events occurring in this population with advanced underlying liver disease. Related Grade 3 or 4 AEs and SAEs were infrequent (<2% and <1% overall, respectively).

8.4.1. Deaths

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

A total of 6 deaths occurred through the time of NDA submission, 3 of which were treatment-emergent and 3 of which occurred more than 3 months after completing treatment. Three of the events occurred in SOF/VEL subjects, and 3 in SOF+RBV subjects. Each case is discussed briefly below.

Events in the SOF/VEL treatment groups:

1. Subject 01386-63561 was a 55 year old TN, NC white man with GT5 HCV who participated in ASTRAL-1. He completed 12 weeks of treatment with SOF/VEL and had no AEs or laboratory abnormalities during his treatment course. His vital signs and ECGs were normal. Eight days following the last dose, the subject died in his sleep of unknown causes. His past medical history was notable for dyslipidemia, for which he was treated with ezetimibe and simvastatin. No other medications were reported and he was a nonsmoker. Family history was noncontributory. The event was unconsidered 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, as well as the company's assessment. The Applicant confirmed the details above but no additional information was available and the autopsy report could not be obtained due to legal issues. The Applicant concludes that the death was not treatment-related, but rather was likely related to the subject's cardiovascular risk factors. Given the available information, most notably the lack of adverse events, vital sign/ECG abnormalities or laboratory abnormalities, I concur with this assessment.

2. Subject 03054-65012 was a 58 year old TN, cirrhotic white man with GT2 HCV who was randomized to receive SOF/VEL in ASTRAL-2. He completed 12 weeks of treatment and was later diagnosed with metastatic lung cancer on post-treatment day 69. He subsequently died on post-treatment day 112. The event was unconsidered unrelated to study drug or procedures.

   Reviewer Comment: I agree with the investigator's assessment that this death was a result of the subject's malignancy and unrelated to study medication.

3. Subject 02111-65015 was a 56 year old TN, NC white woman with GT2 HCV who was randomized to receive SOF/VEL in ASTRAL-2 and completed the full 12 weeks of treatment. On post-treatment day 131, she was found unconscious at home. Resuscitation was attempted at her home and at the hospital but was unsuccessful. Supportive care was ultimately withdrawn and she died of cardiac arrest. The subject's past medical history was notable for depression and substance abuse; her concomitant medications included Seroquel, Tramadol, oxycodone, and lorazepam. No acute psychiatric AEs were reported during the study; the only AEs were influenza-like illness and pruritus and her safety monitoring labs were unremarkable.

   No autopsy was performed and the death was attributed to cardiac arrest. Toxicology screen performed in the hospital was positive for opiates, benzodiazepines and alcohol.

The investigator's assessment is that the event was unrelated to study medication and may have been precipitated by a drug overdose.

Reviewer Comment: While drug overdose is the most evident cause of death in this subject, additional details were requested. The Applicant confirmed the information in the initial narrative, including the fact that an autopsy was not performed; additional information was not available. The Applicant concludes that the death was caused by a drug and alcohol overdose. I agree that this is the most likely explanation for her death.

Events in the SOF+RBV treatment groups

4. Subject 04262-62067 was a 52 year old TN, cirrhotic Hispanic man with GT3 HCV who was randomized to receive SOF+RBV in ASTRAL-3. The subject was abducted and assaulted and died of multiple gunshot wounds on Day 74. The event was considered unrelated to study drug or procedures.

   Reviewer Comment: I agree with the investigator's assessment that this death was a result of violent crime and unrelated to study medication.

5. Subject 01154-62556 was a 58 year old TE, NC white woman with GT3 HCV who was randomized to receive SOF+RBV in ASTRAL 3. She was found dead in her bed on Day 141 of treatment and the death was attributed to "natural causes." She had been tolerating treatment well up to that point; the only AEs reported were pruritus and gastritis which were treated with topical ointments and ranitidine. She had a history of depression but was not receiving antidepressants during the study period. An autopsy was not performed and no further details are available. The event was considered unrelated to study drug or procedures.

   Reviewer Comment: The cause of death is entirely unclear in this case, and additional details were requested. The Applicant states that the subject was noted to be distressed about her social situation including a family estrangement, and confirmed that an autopsy was not performed. The Applicant concluded that the cause of death is unknown and that the role of the subjects' depression and social stressors cannot be determined. I concur that the cause of death is unknown and that the contribution of her comorbid conditions cannot be assessed with certainty.

6. Subject 3902-62126 was a 66 year old TN, cirrhotic white man with GT3 HCV who was randomized to receive SOF+RBV in ASTRAL 3 and completed 24 weeks of treatment. The subject was found dead at home on post-treatment day 118; his death was unwitnessed, but an autopsy concluded that the cause of death was coronary artery disease and epilepsy. The subject has a history of myocardial infarction and congestive heart failure, COPD,

epilepsy and deep venous thromboembolism. He was hospitalized two weeks prior to the fatal event for an exacerbation of congestive heart failure and pneumonia, at which time he was started on furosemide, ramipril, bisoprolol, and antibiotics. The event was considered unrelated to study drug or procedures.

Reviewer Comment: The subject's death was likely due to his underlying chronic disease conditions, which had flared in the weeks immediately preceding his death. Additional information was requested from the Applicant, including a copy of the autopsy report. The Applicant confirmed the details from the original narrative and submitted the autopsy report, which listed only the cause of death and did not provide additional information. The Applicant concluded that the subject's death was related to his underlying medical conditions, and I agree with this assessment.

ASTRAL-4

Ten total deaths were reported in ASTRAL-4, nine in the original application and one in the SUR (Table 34). Two treatment-emergent deaths occurred: sepsis following duodenal ulcer perforation (SOF/VEL+RBV 12 Week), myocardial infarction in a subject with ongoing tobacco use (SOF/VEL 24 Week). None of the 10 deaths were considered treatment-related by the investigator, and I concur with the investigators' assessments. Causes of death were associated with underlying decompensated liver disease, risk factors for fatal event or precipitating event not considered related to study treatment. The two treatment-emergent deaths were reviewed by the IAC and assessed as unlikely related to DILI.

Table 34. Treatment-Emergent and Nontreatment-Emergent Deaths, ASTRAL-4

Subject Number	Study Day of Death	Study Treatment Duration	Cause of Death	Comment
Treatment-Emergent Deaths				
SOF/VEL+RBV 12 Weeks				
03060-64241	PT Day 15	22 days	Sepsis	69 yo man with history of diverticulosis, alcohol use, portal gastropathy, CPT B, MELD 12 hospitalized for duodenal ulcer perforation Day 23. Study drug d/c Day 22. Underwent surgical management with complicated postoperative course including bacterial and fungal peritonitis, ischemic colitis, renal failure, pneumoperitoneum, atrial fibrillation, possible alcohol withdrawal/delirium tremens, hepatic encephalopathy, pneumonia, and subsequently died of sepsis PT Day 15.
SOF/VEL 24 Weeks				
03060-64200	PT Day 3	9 days	Acute myocardial infarction	52 yo man with ongoing tobacco use, CPT B, MELD 10 experienced myocardial infarction Day 10 leading to death two days later. Last study drug dose Day 9.
Nontreatment-Emergent Deaths				
SOF/VEL 12 Weeks				
01249-64047	PT Day 86	84 days	Liver failure	55 yo woman with history femoral hernia, CPT B, MELD 9, esophageal varices, portal hypertensive gastropathy who experienced small bowel incarceration within femoral hernia Day 42 and underwent exploratory laparotomy, hernia repair. Completed HCV regimen and PT Day 13 experienced upper GI bleed, resolved with medical management. PT Day 62 hospitalized with hip fracture s/p fall associated with intoxication and subsequently developed DIC, atrial fibrillation, liver failure leading to death PT Day 86.
04421-64014	PT Day 35	87 days	Sepsis, MOF	58 yo woman CPT B, MELD 12 completed HCV treatment. Hospitalized PT Day 33 for SBP, pneumonia, chronic renal failure and died from sepsis, MOF PT Day 35.

Subject Number	Study Day of Death	Study Treatment Duration	Cause of Death	Comment
07275-64103	PT Day 65	84 days	Septic shock	59 yo man with history of back pain, DM, CPT B, MELD 12 completed HCV treatment. Developed spinal osteomyelitis/epidural abscess PT Day 26 associated with paralysis from the waist down. Underwent laminectomy, incision/drainage, treated with antibiotics; however, subject later declined further medical treatment and subsequently developed septic shock resulting in death on PT Day 65.
SOF/VEL+RBV 12 Weeks				
04371-64235	PT Day 147	85 days	Cardiopulmonary arrest secondary to end stage liver disease	51 yo man CPT B, MELD 8, alcoholic cirrhosis, esophageal varices, portal HTN, hepatic encephalopathy completed HCV treatment. ~PT Day 143 hospitalized due to alcoholic liver disease with ascites, hypercoaguable state, acute kidney disease, hyponatremia. Subsequently developed cardiopulmonary arrest and died PT Day 147.
06991-64042	PT Day 33	84 days	Respiratory failure	65 yo man CPT B, MELD 10 completed HCV treatment. Following day hospitalized for ~6 days with ascites and SBP. PT Day 14 hospitalized for hyponatremia, subsequently experienced worsening ascites, aspiration pneumonia, atrial fibrillation leading to fatal respiratory failure PT Day 33.
SOF/VEL 24 Weeks				
02760-64102	PT Day 39	28 days	Liver failure	67 yo man CPT C, MELD 12, ascites, esophageal varices, hepatic encephalopathy, experienced incarcerated umbilical hernia Day 28 associated with worsening hepatic encephalopathy, acute kidney injury leading to study drug d/c. Subsequently experienced liver failure and died PT Day 39.
09891-64195	PT Day 102	168 days	Cardiopulmonary arrest	53 yo woman CPT B, MELD 15 completed HCV treatment. Hospitalized PT Day 96 for SBP, E coli bacteremia and died from sepsis, MOF with cardiopulmonary arrest PT Day 102.
0331-64096 (SUR)	PT Day 169	170 days	Decompensated cirrhosis, HCC	53 yo man CPT B, MELD 11 completed HCV treatment. PT Day 34 diagnosed with HCC, portal vein thrombosis, decompensated cirrhosis which subsequently led to death PT Day 169.

PT-posttreatment, yo-year old, d/c-discontinued, DIC- disseminated intravascular coagulation, MOF-multiorgan failure, HTN-hypertension, SUR-Safety Update Report, HCC-hepatocellular carcinoma
Source: ADSL, ADAE datasets; Subject Narratives, ASTRAL-4

Safety Update Report

No additional deaths were reported in the ISS population, and no deaths were reported in Studies 342-1553, 342-1446, or 342-1202.

8.4.2. Serious Adverse Events

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

SAEs were infrequent across all 3 studies, occurring in 2% of subjects in the SOF/VEL and SOF+RBV 12 week treatment groups and 5% of subjects in the SOF+RBV 24 week treatment group. There were no SAEs in the placebo group. Table 35 provides a summary of the events by system organ class (SOC).

Table 35: Treatment-emergent SAEs by SOC, ISS Population

Primary System Organ Class	SOF/VEL 12 Week N=1035	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Infections and infestations	7 (1%)	0 (0%)	2 (1%)
Gastrointestinal disorders	4 (<1%)	0 (0%)	0 (0%)
Cardiac disorders	3 (<1%)	0 (0%)	0 (0%)
Nervous system disorders	2 (<1%)	0 (0%)	2 (1%)
Injury, poisoning and procedural complications	2 (<1%)	0 (0%)	3 (1%)
Respiratory, thoracic and mediastinal disorders	1 (<1%)	0 (0%)	1 (<1%)
Reproductive system and breast disorders	1 (<1%)	0 (0%)	0 (0%)
Vascular disorders	1 (<1%)	0 (0%)	1 (<1%)
Psychiatric disorders	1 (<1%)	1 (1%)	2 (1%)
Musculoskeletal and connective tissue disorders	1 (<1%)	1 (1%)	2 (1%)
General disorders and administration site conditions	1 (<1%)	0 (0%)	1 (<1%)
Hepatobiliary disorders	1 (<1%)	0 (0%)	0 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (<1%)	0 (0%)	0 (0%)
Skin and subcutaneous tissue disorders	0 (0%)	0 (0%)	1 (<1%)
TOTAL SUBJECTS	23 (2%)	2 (2%)	15 (5%)

Source: ISS ADSL and ADAE datasets

Reviewer comment: Acute infections comprise a large proportion of the SAEs observed, which are unlikely to be related to either the underlying disease condition (in this population with compensated liver disease) or study medication.

The only event that occurred in more than one SOF/VEL subject was acute myocardial infarction; all other events occurred in a single subject (see Table 60 in Section 13.3 for a complete list). Both cases of acute MI occurred in subjects with cardiovascular risk factors and occurred in the post-treatment period. Brief narratives are provided below.

- Subject 00542-63063 is a 63 year old TN, NC white female with GT2 HCV infection and a history of hypertension, depression, drug/alcohol/tobacco use and limb paresthesias. She was randomized to the SOF/VEL group in ASTRAL-1 and completed 12 weeks of treatment. On post-treatment day 10 she experienced an acute ST elevation myocardial infarction. She underwent cardiac catheterization and stent placement and the event was considered resolved on posttreatment Day 13. The investigator assessed the event as not related to blinded study treatment.

- Subject 4472-62133 is a 62 year old TE, cirrhotic Asian female with GT3 HCV and a history of hypertension, diabetes mellitus, and hyperlipidemia. She was randomized to the SOF/VEL group in ASTRAL-3 and completed 12 weeks of treatment. On post-treatment day 24 she experienced a non-ST elevation myocardial infarction. She underwent angioplasty and the event was considered resolved on post-treatment Day 38. The investigator assessed the event as not related to blinded study treatment.

Reviewer Comment: Both events occurred in subjects with underlying risk factors for coronary artery disease. I agree with the investigators that the events were unrelated to study medication.

Only one SAE was considered treatment related and occurred in the SOF +RBV group.

- Subject 00475-62417 is a 53 year old TN, NC white female who was randomized to receive SOF +RBV 24 weeks in ASTRAL-3. She developed a Grade 2 generalized maculo-papular rash on study Day 6 for which she was hospitalized. A skin biopsy revealed nonspecific eczematiform changes. Treatment with SOF+RBV was not interrupted and the subject was successfully managed with antihistamines and topical corticosteroids. The rash was considered resolved on study Day 18. The investigator assessed the event as related to study drug.

Reviewer Comment: I agree that the temporal association between onset of study medication and onset of rash are suspicious for an adverse drug reaction. Several types of rashes have been reported in SOF clinical trials, and RBV is also associated with rash.

Overall assessment of SAEs in the ISS Population - Reviewer Comment: No specific drug-related safety concern has been identified from the broad range of SAEs reported with rare frequency in ASTRAL-1, - 2, and -3. There was no clustering of events to suggest a pattern. All narratives were reviewed which did not uncover new concerns.

<u>ASTRAL-4</u>

Overall 16%-19% SOF/VEL-treated ASTRAL-4 subjects experienced a treatment-emergent SAE

across treatment groups. Treatment-emergent SAEs are summarized by SOC in Table 36. SAEs occurring in the infections and infestations and gastrointestinal disorders SOCs were the most commonly reported, though these SOCs occurred ≤8% in any SOF/VEL-containing treatment group and no infestation or gastrointestinal disorder SOC was considered related to study drug by the investigator.

Table 36. Treatment Emergent SAEs by SOC, ASTRAL-4

System Organ Class Dictionary-Derived Term	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90
Number of Subjects with SAE (%)	17 (19%)	14 (16%)	16 (18%)
Blood and lymphatic system disorders	1 (1%)	1 (1%)	0
Cardiac disorders	1 (1%)	0	2 (2%)
Endocrine disorders	0	0	1 (1%)
Gastrointestinal disorders	7 (8%)	4 (5%)	4 (4%)
General disorders and administration site conditions	1 (1%)	0	0
Hepatobiliary disorders	1 (1%)	0	2 (2%)
Infections and infestations	4 (4%)	7 (8%)	2 (2%)
Injury, poisoning and procedural complications	1 (1%)	1 (1%)	3 (3%)
Metabolism and nutrition disorders	1 (1%)	2 (2%)	0
Musculoskeletal and connective tissue disorders	0	1 (1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1%)	0	3 (3%)
Nervous system disorders	3 (3%)	2 (2%)	1 (1%)
Psychiatric disorders	1 (1%)	0	0
Respiratory, thoracic and mediastinal disorders	0	2 (2%)	2 (2%)
Skin and subcutaneous tissue disorders	0	1 (1%)	0
Vascular disorders	0	0	1 (1%)

Source: ADAE ASTRAL-4 dataset

SAEs considered related to study treatment by the investigator occurred in 2 subjects (0.7%): dyspnea related to RBV (01657-64124) and hepatorenal syndrome (HRS)/hypertension (HTN)/peritonitis/ sepsis related to SOF/VEL (03055-64017).

Reviewer Comment: Dyspnea is a known RBV-associated adverse reaction and I agree with the investigator's assessment. Please see Section 8.5.1 Hepatotoxicity for further discussion of Subject 03055-64017. This latter case was reviewed by the IAC and assessed as unlikely related to SOF/VEL-containing treatment.

There was no consistent pattern to the types of SAEs reported across treatment arms. SAEs occurring in more than one subject were hepatic encephalopathy (5 subjects), sepsis (5 subjects), upper gastrointestinal hemorrhage/ gastrointestinal hemorrhage (5 subjects), HCC (3

subjects), hyponatremia (3 subjects), anemia (2 subjects), cellulitis (2 subjects), Escherichia infection (2 subjects), gastric varices hemorrhage (2 subjects), hip fracture (2 subjects), nausea (2 subjects), seizure (2 subjects) and urinary tract infection (2 subjects).

SAEs reported in the SOF/VEL+RBV 12 Week group, the recommended HCV regimen in the decompensated population, are listed in Table 37. Most SAEs (71%, 10/14 subjects) were due to infectious etiology, RBV use and/or events associated with decompensated cirrhosis (e.g., hematemesis, hepatic encephalopathy, SBP).

Table 37. Treatment Emergent SAEs in SOF/VEL+RBV 12 Week Group, ASTRAL-4

Treatment Arm	Dictionary-Derived Term	Study Day, Start of AE	Study Day, End of AE	Grade	Outcome	Related
SOF/VEL+RBV 12 Week						
00585-64188	Infectious colitis	10	13	3	Resolved	No
01657-64108	Hematemesis, Anemia	80	86	2	Resolved	No
01657-64124	Dyspnea	.	93	2	Resolved	Yes, RBV
01657-64126	Cellulitis	60	101	3	Resolved	No
	Skin ulcer	79	81	2	Resolved	No
01668-64205	Escherichia infection	105	.	3	Recovering	No
	Sepsis	105	109	3	Resolved	No
02689-64231	UTI	4	7	1	Resolved	No
	Bacteremia	53	63	2	Resolved	No
02760-64074	UTI	37	44	3	Resolved	No
03060-64241	Duodenal ulcer perforation	23	.	4	Fatal	No
	Sepsis	36	.	4	Fatal	No
04421-64166	Pleural effusion	90		3	Ongoing	No
06919-64223	Device related infection, Hyponatremia, Sepsis, Syncope	13	17	3	Resolved	No
	Seizure	13	17	2	Resolved	No
	Hepatic encephalopathy	43	48	3	Resolved	No
	Hyperkalemia	43	48	1	Resolved	No
06991-64042	Ascites associated with SBP	85	.	3	Recovering	No
	Hyponatremia	98	.	3	Fatal	No
07585-64119	Hepatic encephalopathy	22	27	2	Resolved	No
	Ileus	31	37	2	Resolved	No
08230-64058	Hip fracture	113	117	2	Resolved	No
08430-64136	Rhabdomyolysis	78	81	2	Resolved	No

Source: ADAE ASTRAL-4

Safety Update Report

Five new SAEs were reported among subjects in the ISS population; four events occurred in

subjects treated with SOF/VEL in ASTRAL-1 and one in a subject treated with SOF+RBV 12 weeks in ASTRAL-2. All events occurred after more than 12 weeks off-treatment and were considered non-treatment emergent. Events in the SOF/VEL group were: 1) acute coronary syndrome, 2) basosquamous carcinoma of the tongue, 3) bladder neoplasm, and 4) renal colic. The SOF+RBV subject had cervical spinal stenosis. All events were considered unrelated to study medication. No new SAEs were reported in ASTRAL-4.

Two SAEs were reported in ASTRAL 5: localized infection of the toe and radial nerve palsy. The subject with localized toe infection (05751-67242) also prematurely discontinued study medication due to elevated transaminases and will be discussed in Section 8.5.1. Both events were considered unrelated to study medication.

Five SAEs were reported in Study 342-1446. All events occurred in single subjects, and two subjects had 2 events: 1) gallbladder adenocarcinoma (resulted in premature discontinuation), 2) hepatocellular carcinoma in a subject with cirrhosis, 3) cellulitis and lymphangitis of the right arm secondary to a foreign body, 4) corrective surgery for a meniscus tear, and 5) lower limb fracture following a fall. All events were deemed unrelated to study medication and dosing of SOF/VEL was not interrupted for cases 2-5.

One SAE was reported in Study 342-1553: a case of nephrolithiasis requiring stone removal and antibiotics in a subject with a past medical history of nephrolithiasis. The event was considered unrelated to study medication and SOF/VEL dosing was not interrupted.

Reviewer Comment: I agree with the investigator's assessment that the reported events are not related to study medication.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

Discontinuations due to AEs were infrequent across the three studies. A total of 2 subjects discontinued in the SOF/VEL group, 9 in the SOF+RBV 24 week group, and 2 in the placebo group. The subjects' narratives were reviewed and the events are briefly summarized below.

SOF/VEL: Two subjects discontinued within the first treatment week. One subject experienced difficulty concentrating, headache and anxiety after the first dose, all of which were deemed drug-related. The other subject had Grade 3 anxiety on treatment day 4 which was considered unrelated to study drug.

SOF+RBV 24 weeks: Nine subjects discontinued prematurely, primarily due to RBV-associated AEs. Insomnia was the only event occurred in more than one subject (n=3). Other preferred terms reported in single subjects included anger, anxiety, arthritis, cerebrovascular accident, decreased appetite, dysphagia, gastrointestinal disorder, hemiplegia, intentional overdose,

lethargy, nausea, peripheral artery stenosis, psychotic disorder, and weight decreased.

Placebo: Two subjects met pre-specified stopping criteria for elevated ALT or AST ≥ 5x nadir. Both subjects discontinued from the trial and were offered active treatment.

Reviewer Comment: Headache is a commonly reported event which will be reflected in product labeling. It is possible that difficulty concentrating and anxiety were also drug related. Neuropsychiatric AEs will be discussed in greater detail in subsequent sections.

ASTRAL-4

Subjects meeting any of the following criteria were required to stop all study drug(s):

- Total bilirubin (TB) >3x Day 1 (baseline)/nadir and ALT and/or AST >3x baseline/nadir
    - If TB >5 mg/dL, TB should have been repeated on a weekly basis
- Direct bilirubin >3 mg/dL
- Confirmed ALT and/or AST >10x baseline value or nadir
- Confirmed ALT >15x ULN
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 AE assessed as related to SOF/VEL

All discontinuation due to AE narratives were reviewed.

Overall 3% ASTRAL-4 subjects permanently discontinued SOF/VEL-containing treatment due to an AE (Table 38). No AE leading to SOF/VEL discontinuation occurred in more than one subject. One subject (03055-64017) discontinued SOF/VEL due to AEs considered related to HCV treatment by the investigator (discussed Section 8.5.1). The majority of AEs leading to SOF/VEL discontinuation were also considered SAEs: one subject (04421-64166, SOF/VEL+RBV 12 Week) discontinued SOF/VEL+RBV due to non-serious AEs of Grade 2 nausea and vomiting Day 79 considered not related to study drug. In the SOF/VEL+RBV 12 Week group, four subjects (5%) discontinuing SOF/VEL also discontinued RBV. In the SOF/VEL+RBV 12 Week group, nine subjects permanently discontinued RBV due to AEs while SOF/VEL continued. These discontinuations occurred based on AEs associated with RBV use including anemia, fatigue, dyspnea, pruritus and rash.

Table 38. Adverse Events Leading to Discontinuation from Study Drug, ASTRAL-4

Treatment Arm	Dictionary-Derived Term	Day, Start/End of AE	Last Day SOF/VEL	SAE	Grade	Outcome	Related
SOF/VEL 12 Week							
07275-64023	Diffuse large B-cell lymphoma	9/-	27	Yes	3	Ongoing	No
SOF/VEL+RBV 12 Week							
02760-64074	UTI	37/44	36	Yes	3	Resolved	No
03060-64241	Duodenal ulcer perforation	23/-	22	Yes	4	Fatal	No
04421-64166	Nausea/ Vomiting	79/-	80	No	2	Ongoing	No
07585-64119	Ileus	31/37	31	Yes	2	Resolved	No
SOF/VEL 24 Week							
02760-64102	Incarcerated umbilical hernia	29/35	28	Yes	3	Resolved	No
03055-64017	Escherichia infection	39/50	35	Yes	1	Resolved	No
	Hepatorenal syndrome	35/43	35	Yes	4	Resolved	Yes
	Hypotension	35/52	35	Yes	4	Resolved	Yes
	Peritonitis	35/39	35	Yes	3	Resolved	Yes
	Sepsis	35/39	35	Yes	4	Resolved	Yes
03060-64200	Acute MI	10/-	9	Yes	4	Fatal	No
	Acute Kidney Injury	10/12	9	No	3	Fatal	No
	Acute Respiratory Failure	10/12	9	No	3	Fatal	No
05275-64229	Hyperbilirubinemia	92/176	91	Yes	3	Resolved	No

Source: ADAE, ADSL ASTRAL-4 datasets

Reviewer Comment: A single discontinuation due to vomiting does not support specific labeling for SOF/VEL: nausea is already proposed for inclusion in Section 6 of the label. The related AEs in Subject 03055-64017 may reflect progression of underlying decompensated liver disease as discussed in Section 8.5.1. The remaining assessments that discontinuations due to AE were not related to HCV treatment are reasonable.

Safety Update Report

Two subjects in ASTRAL-5 prematurely discontinued study medication due to the following AEs: 1) grade 1 vomiting on study Day 4, considered related to study medication; and 2) localized infection of the toe, considered unrelated to study medication. The second case was also noted as a serious adverse event and will be discussed in greater detail in Section 8.5.1 (hepatotoxicity).

One subject prematurely discontinued from Study 342-1446 due to diagnosis of gallbladder adenocarcinoma, which was also an SAE. One subject discontinued from Study 342-1553 due to Grade 2 irritability. SOF/VEL + RBV was initially suspended on Day 16 and the subject was restarted on SOF/VEL without RBV on Day 28. After seven days of persistent irritability, the subject permanently discontinued treatment; the event was ongoing through post-treatment day 165. Events in both subjects were considered unrelated to study medication.

Overall Assessment: The types of AEs prompting discontinuation are quite different between the ISS population and the ASTRAL-4 decompensated population, which is reflective of the differences in baseline health status between these populations. The overall safety profile is acceptable for each population. There is a suggestion that CNS events (e.g. headache, anxiety, irritability) are resulting in tolerability issues among subjects with compensated liver disease. Though many of the events are considered unrelated by the investigators, the trend merits further and will be discussed in the analysis of neuropsychiatric events (Section 8.5.3).

8.4.4. Significant Adverse Events

This section describes Grade 3 and 4 events that occurred in the treatment-emergent period. Some of these events were also considered SAEs; hence, there is some overlap between events reported in this section and 8.4.2.

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

Grade 3 and 4 AEs occurred infrequently in the ISS population; among the 4 treatment groups, subjects in the SOF+RBV x 24 week arm of ASTRAL-3 had the highest rate of events, presumably due to the longer duration of RBV (Table 39). The majority of events occurred in a single subject and no clustering of similar events was observed. Events occurring in more than 2 subjects in the SOF/VEL group included headache (n=5), anxiety (n=3) and acute myocardial infarction (n=2). All 5 cases of headache and one case of anxiety were considered treatment-related. Both cases of myocardial infarction were deemed unrelated and the narratives for these events were described in Section 8.4.2. Both Grade 4 events in the SOF/VEL arm were also considered unrelated: malignant neoplasm and death during sleep. Though death is not truly a Grade 4 event, it was assigned as such by the investigator and therefore included in this analysis.

Table 39. Grade 3 and 4 AEs Reported in 2 or More Subjects, ISS Population

Subjects Experiencing Event n (%)	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Number of Subjects with Grade 3/4 event	33 (3%)	1 (1%)	3 (2%)	23 (8%)
Highest Grade 3	31 (3%)	1 (1%)	2 (2%)	20 (7%)
Highest Grade 4	2 (<1%)	0 (0%)	0 (0%)	3 (1%)
Dictionary Derived Term				
Headache	5 (<1%)	0 (0%)	0 (0%)	2 (1%)
Anxiety	3 (<1%)	0 (0%)	0 (0%)	2 (1%)
Abdominal pain	1 (<1%)	0 (0%)	0 (0%)	2 (1%)
Acute myocardial infarction	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Cellulitis	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Back pain	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Hypertension	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Vomiting	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)

Source: ISS ADSL and ADAE datasets

ASTRAL-4

ASTRAL-4 AEs ≥Grade 3 in severity ranged 13%-19% across the SOF/VEL-containing groups. Six subjects experienced Grade 4 AEs which were also SAEs: gastrointestinal hemorrhage/Mallory-Weiss syndrome with subsequent sepsis which resulted in death (Subject 05969-64191, SOF/VEL 12 Week), duodenal ulcer perforation with subsequent sepsis (Subject 03060-64241, SOF/VEL+RBV 12 Week), HCC (Subject 00619-64062, SOF/VEL 24 Week), traumatic hydrothorax (Subject 01657-64105, SOF/VEL 24 Week), myocardial infarction which resulted in death (Subject 03060-64200, SOF/VEL 24 Week) and HRS/hypotension/sepsis (Subject 03055-64017, SOF/VEL 24 Week).

Overall, ≥Grade 3 AEs considered related to study drug by the investigator were 1.5%: no treatment-related ≥Grade 3 AEs were reported in the SOF/VEL 12 Week group. Treatment-related ≥Grade 3 AEs included:

- SOF/VEL 12 Week group: none
- SOF/VEL+RBV 12 Week group: dyspnea/fatigue resulting in RBV discontinuation, asthenia/tremor associated with hepatic encephalopathy resulting in RBV dose reduction
- SOF/VEL 24 Week group: HRS/hypotension/sepsis/peritonitis, weight decreased

Reviewer Comment: As noted, several of these events have been discussed in prior sections. No clear safety signal emerges from these ISS and ASTRAL-4 results. In ASTRAL-4, reported Grade 4

AEs and related ≥ Grade 3 AEs events were due to infectious etiology, RBV use and/or associated with decompensated cirrhosis (e.g., hematemesis, hepatic encephalopathy, SBP).

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

The most common AEs reported across the 3 pivotal trials were headache, fatigue, nausea, insomnia, nasopharyngitis, and diarrhea. The frequency of events was relatively consistent across treatment arms, including placebo. The majority of events were Grade 1 in severity. Table 40 summarizes common AEs irrespective of severity and causality and Table 41 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 40. Treatment-emergent AEs Reported in ≥ 5% of SOF/VEL Subjects, All Grade and All Causality, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Headache	296 (29%)	33 (28%)	29 (22%)	89 (32%)
Fatigue	217 (21%)	23 (20%)	47 (36%)	105 (38%)
Nausea	135 (13%)	13 (11%)	19 (14%)	58 (21%)
Nasopharyngitis	121 (12%)	12 (10%)	2 (2%)	33 (12%)
Insomnia	87 (8%)	11 (9%)	18 (14%)	74 (27%)
Diarrhoea	73 (7%)	8 (7%)	6 (5%)	21 (8%)
Asthenia	58 (6%)	9 (8%)	0 (0%)	26 (9%)
Cough	57 (6%)	4 (3%)	6 (5%)	35 (13%)
Arthralgia	56 (5%)	9 (8%)	8 (6%)	22 (8%)
Back pain	56 (5%)	11 (9%)	7 (5%)	20 (7%)
Upper respiratory tract infection	50 (5%)	3 (3%)	5 (4%)	12 (4%)
Irritability	49 (5%)	4 (3%)	9 (7%)	40 (15%)
Constipation	47 (5%)	3 (3%)	5 (4%)	21 (8%)
Total Subjects with AE	822 (79%)	89 (77%)	101 (77%)	260 (95%)

Source: ISS ADSL and ADAE datasets

Table 41. Treatment-emergent ADRs Reported in ≥ 2% of SOF/VEL Subjects, All Grade, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Headache	218 (21%)	25 (22%)	26 (20%)	76 (28%)
Fatigue	163 (16%)	18 (16%)	38 (29%)	89 (32%)
Nausea	98 (9%)	10 (9%)	14 (11%)	48 (17%)
Insomnia	56 (5%)	7 (6%)	15 (11%)	61 (22%)
Asthenia	41 (4%)	4 (3%)	0 (0%)	18 (7%)
Irritability	36 (3%)	3 (3%)	8 (6%)	34 (12%)
Diarrhoea	35 (3%)	5 (4%)	4 (3%)	9 (3%)
Dizziness	31 (3%)	2 (2%)	8 (6%)	15 (5%)
Constipation	24 (2%)	0 (0%)	1 (1%)	12 (4%)
Pruritus	23 (2%)	3 (3%)	2 (2%)	31 (11%)
Arthralgia	22 (2%)	4 (3%)	1 (1%)	12 (4%)
Rash	21 (2%)	1 (1%)	4 (3%)	12 (4%)
Myalgia	20 (2%)	4 (3%)	4 (3%)	8 (3%)
Abdominal pain	20 (2%)	1 (1%)	3 (2%)	7 (3%)
Dyspepsia	18 (2%)	2 (2%)	1 (1%)	15 (5%)
Muscle spasms	18 (2%)	3 (3%)	0 (0%)	7 (3%)
Decreased appetite	17 (2%)	5 (4%)	1 (1%)	11 (4%)
Total subjects with ADR	520 (50%)	52 (45%)	75 (57%)	215 (78%)

Source: ISS ADSL and ADAE datasets

Reviewer Comment: Both analyses (all AEs and ADRs) yield similar results, affirming that headache, fatigue, nausea, and insomnia are the most frequently reported AEs with SOF/VEL. However, the occurrence of these events was similar among SOF/VEL and placebo subjects, which suggests that the underlying HCV disease state may be contributing to the findings as well. Fatigue, nausea, and insomnia were reported more commonly in the RBV-containing groups; this is an expected finding, as these events have been consistently observed with RBV exposure.

While cross-study AE comparisons have limitations, the clinical review team believes that presenting data from at least one of the RBV-containing control arms (SOF + RBV x 12 weeks in ASTRAL-2 or SOF + RBV x 24 weeks in ASTRAL-3) provides valuable insight into the relative safety profile of SOF/VEL versus SOF+RBV, which can essentially be considered a comparison of VEL versus RBV toxicity since the same SOF dose is used in each arm. Given that the majority of events in the SOF+RBV arm occurred during the first 12 weeks of treatment, inclusion of the 12 week arm only , which mirrors the proposed 12 week SOF/VEL treatment duration, is adequate. Inclusion of (b) (4) *would be consistent*

with the approach taken with other DAA products for HCV infection. (b) (4) .

ASTRAL-4

The AE tables in this section display ASTRAL-4 treatment-emergent AEs as defined in Section 8.1. An overall presentation of AEs without regard to causality is included, with subsequent AE analyses focusing on ADRs. ASTRAL-4 was neither placebo- nor active-controlled; therefore, use of investigator-causality assessment is used to define adverse drug reactions, acknowledging the bias that is introduced by excluding events from the rate calculation based on the judgment of individual investigators.

A summary of all grade, treatment-emergent AEs reported in ≥5% subjects in any group is provided in Table 42. All groups had >80% subjects reporting AEs. The three most commonly reported AEs in each group were:

- SOF/VEL 12 week: fatigue (26%), headache (26%), nausea (24%)
- SOF/VEL+RBV 12 Week: fatigue (39%), anemia (31%), nausea (25%)
- SOF/VEL 24 Week: fatigue (23%), nausea (20%), headache (19%)

The most common AEs in subjects receiving SOF/VEL+RBV 12 Week treatment with ≥5% greater frequency compared with SOF/VEL 12 or 24 Week groups are highlighted in Table 42.

Table 42. Treatment-Emergent AEs Reported in ≥5% of Subjects in Any Treatment Group, All Grade and All Cause by Preferred Term, ASTRAL-4

Dictionary-Derived Term	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90
Total Subjects with AE	73 (81%)	79 (91%)	73 (81%)
Fatigue	23 (26%)	34 (39%)	21 (23%)
Anemia	4 (4%)	27 (31%)	3 (3%)
Nausea	22 (24%)	22 (25%)	18 (20%)
Diarrhea	6 (7%)	18 (21%)	7 (8%)
Headache	23 (26%)	18 (21%)	17 (19%)
Insomnia	9 (10%)	12 (14%)	9 (10%)
Muscle spasms	3 (3%)	10 (11%)	4 (4%)
Cough	2 (2%)	9 (10%)	0
Dyspnea	4 (4%)	9 (10%)	2 (2%)
Abdominal pain	7 (8%)	6 (7%)	4 (4%)
Peripheral edema	7 (8%)	6 (7%)	7 (8%)
Abdominal discomfort	1 (1%)	5 (6%)	3 (3%)
Ascites	5 (6%)	5 (6%)	0
Hepatic encephalopathy	4 (4%)	5 (6%)	1 (1%)
Hypertension	2 (2%)	5 (6%)	0
Rash	6 (7%)	5 (6%)	7 (8%)
Vomiting	8 (9%)	5 (6%)	5 (6%)
Pruritus	10 (11%)	4 (5%)	4 (4%)
Arthralgia	7 (8%)	3 (3%)	2 (2%)
Pyrexia	6 (7%)	4 (5%)	3 (3%)
Constipation	6 (7%)	3 (3%)	6 (7%)
Back pain	6 (7%)	1 (1%)	4 (4%)
Upper respiratory tract infection	3 (3%)	2 (2%)	8 (9%)
Nasopharyngitis	2 (2%)	3 (3%)	8 (9%)
Gastroesophageal reflux disease	2 (2%)	2 (2%)	8 (9%)
Decreased appetite	4 (4%)	2 (2%)	5 (6%)

Source: ADAE ASTRAL-4 dataset

A summary of all grade, treatment-emergent, ADRs reported in ≥5% subjects in any groups is provided in Table 43. Most ADRs were mild or moderate severity. The SOF/VEL+RBV 12 Week group had a higher percentage of subjects with ADRs (69%) compared with the other treatment groups (38%-50%). The three most commonly reported ADRs in each group were:

- SOF/VEL 12 Week: headache (20%), fatigue (17%), nausea (14%)
- SOF/VEL+RBV 12 Week: fatigue (32%), anemia (26%), nausea (15%)
- SOF/VEL 24 Week: fatigue (16%), nausea (8%), headache (7%)

Adverse reactions in subjects receiving SOF/VEL+RBV 12 Week treatment with ≥5% greater frequency compared with SOF/VEL 12 or 24 Week groups include anemia, fatigue, diarrhea, dyspnea, nausea and insomnia.

Table 43. Treatment-Emergent ADRs Reported in ≥5% of Subjects in Any Treatment Group, All Grade by Preferred Term, ASTRAL-4

Dictionary-Derived Term	SOF/VEL 12 Week N=90	SOF/VEL+RBV 12 Week N=87	SOF/VEL 24 Week N=90
Total Subjects with AE	45 (50%)	60 (69%)	34 (38%)
Fatigue	15 (17%)	28 (32%)	14 (16%)
Grade 1	13 (14%)	21 (24%)	11 (12%)
Grade 2	2 (2%)	6 (7%)	3 (3%)
Grade 3	0	1 (1%)	0
Anemia	0	23 (26%)	0
Grade 1	-	11 (13%)	-
Grade 2	-	12 (14%)	-
Nausea	13 (14%)	13 (15%)	7 (8%)
Grade 1	11 (12%)	11 (13%)	5 (6%)
Grade 2	2 (2%)	2 (2%)	2 (2%)
Headache	18 (20%)	10 (11%)	6 (7%)
Grade 1	12 (13%)	9 (10%)	5 (6%)
Grade 2	6 (7%)	1 (1%)	1 (1%)
Insomnia	6 (7%)	10 (11%)	5 (6%)
Grade 1	6 (7%)	8 (9%)	4 (4%)
Grade 2	0	2 (2%)	1 (1%)
Diarrhea	2 (2%)	9 (10%)	1 (1%)
Grade 1	2 (2%)	7 (8%)	1 (1%)
Grade 2	0	2 (2%)	0
Dyspnea	0	5 (6%)	0
Grade 1	-	2 (2%)	-
Grade 2	-	2 (2%)	-
Grade 3	-	1 (1%)	-

Source: ADAE ASTRAL-4 dataset

Exploratory analyses comparing the safety profile of SOF/VEL 12 Week versus 24 Week durations did not identify a negative safety consequence for extending SOF/VEL treatment from 12 to 24 weeks in the HCV decompensated cirrhosis population. The majority of treatment-emergent ADRs occurred within the first 12 weeks of treatment: the only event identified occurring beyond 12 weeks in ≥2% subjects was fatigue (2%).

Reviewer Comment: All ASTRAL-4 ADRs with more than a 5% difference between the SOF/VEL+RBV 12 Week group and SOF/VEL 12 or 24 Week groups are known toxicities

associated with RBV use. Language in Section 6.1 Clinical Trials Experience, Adverse Reactions in Subjects with Decompensated Cirrhosis of the label is proposed recommending inclusion of ADRs ≥ 10% in the SOF/VEL+RBV 12 Week group: fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%).

8.4.6. Laboratory Findings

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

ASTRAL-1, ASTRAL-2 and ASTRAL-3 (ISS Population)

For most parameters, Grade 3 and 4 abnormalities occurred infrequently and at a similar rate in subjects treated with SOF/VEL relative to the comparator arms. Laboratory analyses did not reveal any new significant safety concerns. Graded chemistry results are summarized in Table 44, and hematology results in Table 45.

Table 44. Liver Function Tests and Other Chemistry Lab Results, All Grade, ISS Population

Parameter and max Analysis Toxicity Grade	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
LIVER FUNCTION TESTS				
Increased Alanine Aminotransferase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	30 (3%)	33 (28%)	2 (2%)	2 (1%)
Grade 2 (2.5 to 5 × ULN)	6 (1%)	25 (22%)	3 (2%)	3 (1%)
Grade 3 (> 5 to 10 × ULN)	2 (<1%)	9 (8%)	0 (0%)	2 (1%)
Grade 4 (> 10 × ULN)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Increased Aspartate Aminotransferase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	22 (2%)	37 (32%)	4 (3%)	7 (3%)
Grade 2 (> 2.5 to 5 × ULN)	10 (1%)	22 (19%)	2 (2%)	2 (1%)
Grade 3 (>5 to 10 x ULN)	3 (<1%)	3 (3%)	1 (1%)	0 (0%)
Grade 4 (> 10 × ULN)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Increased Bilirubin (mg/dL)				
Grade 1 (> 1 to 1.5 × ULN)	38 (4%)	10 (9%)	26 (20%)	68 (25%)
Grade 2 (> 1.5 to 2.5 × ULN)	12 (1%)	0 (0%)	8 (6%)	24 (9%)
Grade 3 (>2.5 to 5 x ULN)	0 (0%)	0 (0%)	3 (2%)	2 (1%)
Grade 4 (>5 x ULN)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Increased Alkaline Phosphatase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	12 (1%)	6 (5%)	2 (2%)	4 (1%)
Grade 2 (> 2.5 to 5 × ULN)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Increased Prothrombin Intl. Normalized Ratio				
Grade 1 (1.1 to 1.5 x ULN)	8 (1%)	1 (1%)	1 (1%)	2 (1%)

Grade 2 (>1.5 to 2 x ULN)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Grade 3 (>2 to 3x ULN)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Increased Gamma Glutamyl Transferase (U/L)				
Grade 1 (1.25 to 2.5 × ULN)	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
OTHER CHEMISTRY LABS				
Increased Creatinine (mg/dL)				
Grade 1 (> 1.5 to 2 mg/dL)	7 (1%)	0 (0%)	2 (2%)	0 (0%)
Grade 2 (> 2 to 3 mg/dL)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Grade 3 (>3 to 6 mg/dL)	0	0	1 (1%)	1 (<1%)
Increased Creatine Kinase (U/L)				
Grade 1 (3 to <6x ULN)	47 (5%)	4 (3%)	7 (5%)	10 (4%)
Grade 2 (6 to <10x ULN)	8 (1%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (10 to <20x ULN)	5 (<1%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (≥20 x ULN)	4 (<1%)	0 (0%)	0 (0%)	4 (1%)
Increased Glucose (mg/dL)				
Grade 1 (116 to 160 mg/dL)	329 (32%)	39 (34%)	37 (28%)	103 (37%)
Grade 2 (> 160 to 250 mg/dL)	110 (11%)	9 (8%)	25 (19%)	28 (10%)
Grade 3 (> 250 to 500 mg/dL)	23 (2%)	6 (5%)	5 (4%)	6 (2%)
Increased Triacylglycerol Lipase (U/L)				
Grade 1 (>1 to 1.5 x ULN)	61 (6%)	6 (5%)	11 (8%)	12 (4%)
Grade 2 (>1.5 to 3 x ULN)	51 (5%)	4 (3%)	3 (2%)	15 (5%)
Grade 3 (>3 to 5 x ULN)	29 (3%)	1 (1%)	2 (2%)	2 (1%)
Grade 4 (>5 x ULN)	5 (< 1%)	0 (0%)	1 (1%)	3 (1%)

Source: ISS ADSL and ADLB datasets

Reviewer Comment: Grade 3 and 4 laboratory abnormalities were uncommon across study 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 and alkaline phosphatase were observed most frequently among subjects in the placebo group, who had ongoing HCV replication. The lower rate of elevated bilirubin in the SOF/VEL group relative to the two SOF+RBV groups is largely attributable to RBV-associated hemolytic anemia. Elevated CK was observed in all three active treatment groups and may be related to SOF exposure; VEL does not seem to contribute. Elevated CK was typically associated with exercise and there were no cases of rhabdomyolysis. Grade 3 elevated lipase was observed more frequently in the SOF/VEL groups, though the differences between cohorts are small. 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, lipase is the only chemistry laboratory parameter that merits inclusion in product labeling based solely on the results observed in the SOF/VEL development

program. The Applicant has proposed inclusion of CK as well; although Grade 3 and 4 elevations were uncommon and unrelated to rhabdomyolysis, it is reasonable to include information in the label in order to remain consistent with the labeling for Sovaldi and Harvoni.

Table 45. Hematology Laboratory Results, All Grade, ISS Population

Parameter/ max Analysis Toxicity Grade	**SOF/VEL 12 Week N=1035**	**Placebo 12 Week N=116**	**SOF + RBV 12 Week N=132**	**SOF + RBV 24 Week N=275**
Decreased Hemoglobin (g/dL)				
Grade 1 (10 to < 10.9 g/dL OR any decrease 2.5 to < 3.5 g/dL from baseline)	17 (2%)	1 (1%)	45 (34%)	95 (35%)
Grade 2 (9 to < 10 g/dL OR any decrease 3.5 to < 4.5 g/dL from baseline)	6 (1%)	0 (0%)	22 (17%)	57 (21%)
Grade 3 (7 to < 9 g/dL OR any decrease ≥ 4.5 g/dL from baseline)	0 (0%)	0 (0%)	7 (5%)	25 (9%)
Decreased Neutrophils, Segmented (cells/mm^3)				
Grade 1 (1000 to 1300/mm^3)	44 (4%)	8 (7%)	3 (2%)	12 (4%)
Grade 2 (750 to < 1000/mm^3)	8 (1%)	3 (3%)	2 (2%)	2 (1%)
Grade 3 (500 to < 750/mm^3)	4 (<1%)	1 (1%)	0 (0%)	1 (<1%)
Decreased Lymphocytes (cells/mm^3)				
Grade 1 (600 to 650/mm^3)	5 (<1%)	1 (1%)	2 (2%)	10 (4%)
Grade 2 (500 to < 600/mm^3)	11 (1%)	1 (1%)	5 (4%)	8 (3%)
Grade 3 (350 to < 500/mm^3)	7 (1%)	1 (1%)	1 (1%)	3 (1%)
Grade 4 (< 350/mm^3)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Decreased Platelets (cells/mm^3)				
Grade 1 （100,000 to < 125,000/mm^3)	75 (7%)	9 (8%)	14 (11%)	22 (8%)
Grade 2 (50,000 to < 100,000/mm^3)	87 (8%)	8 (7%)	3 (2%)	28 (10%)
Grade 3 (25,000 to < 50,000/mm^3)	4 (<1%)	0 (0%)	0 (0%)	1 (<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 subjects. As expected, anemia was common in the RBV-treated arms, and is consistent with the hyperbilirubinemia reported in these treatment groups. Lymphopenia and neutropenia were uncommon in all cohorts. Given the low frequency of hematologic abnormalities and the similarities in laboratory profile between the SOF/VEL and placebo, hematologic laboratory parameters are not recommended for inclusion in product labeling.

ASTRAL-4

Analyses of ASTRAL-4 laboratory findings did not reveal clinically relevant trends for most laboratory parameters. On-treatment ≥Grade 3 laboratory abnormalities were reported in 55%

SOF/VEL-treated subjects as listed in Table 46. Please refer to Sections 8.5.5 and 8.5.6 for discussion regarding CK and lipase assessments, respectively. The remainder of this section will focus on hematologic, hepatic and other ≥Grade 3 laboratories.

Table 46. Grade 3 or 4 Laboratory Data, ASTRAL-4

Laboratory Parameter Maximum Toxicity Grade	SOF/VEL 12 Week	SOF/VEL+RBV 12 Week	SOF/VEL 24 Week	Total
Total Number of Subjects in Analysis	90	87	90	267
Total Subjects with ≥Grade 3 Laboratory	43 (48%)	54 (62%)	50 (56%)	147 (55%)
Aspartate Aminotransferase (U/L)				
Grade 3 (>5 to 10x ULN)	1 (1%)	1 (1%)	0	2 (1%)
Total Bilirubin (mg/dL)				
Grade 3 (>2.5 to 5x ULN)	3 (3%)	20 (23%)	4 (4%)	27 (10%)
Grade 4 (>5x ULN)	1 (1%)	2 (2%)	1 (1%)	4 (1%)
Albumin (g/dL)				
Grade 3 (<2.0 g/dL)	0	2 (2%)	0	2 (1%)
International Normalized Ratio of Prothrombin Time				
Grade 3 (>2 to 3x ULN)	1 (1%)	0	0	1 (<1%)
Creatine Kinase (U/L)				
Grade 3 (10 to <20x ULN)	0	0	0	0
Grade 4 (≥20x ULN)	0	1 (1%)	0	1 (<1%)
Amylase (U/L)				
Grade 3 (>2 to 5x ULN)	1 (1%)	1 (1%)	3 (3%)	5 (2%)
Grade 4 (>5x ULN)	1 (1%)	0	1 (1%)	2 (1%)
Lipase (U/L)				
Grade 3 (>3 to 5x ULN)	0	2 (2%)	1 (1%)	3 (1%)
Grade 4 (>5x ULN)	2 (2%)	0	1 (1%)	3 (1%)
Glucose-Hyperglycemia (mg/dL)				
Grade 3 (>250 to 500 mg/dL)	13 (14%)	13 (15%)	18 (20%)	44 (16%)
Grade 4 (>500 mg/dL)	1 (1%)	1 (1%)	0	2 (1%)
Creatinine (mg/dL)				
Grade 3 (>3 to 6 mg/dL)	0	0	1 (1%)	1 (<1%)
Sodium-Hyponatremia (mEq/L)				
Grade 3 (121 to <125 mEq/L)	1 (1%)	0	1 (1%)	2 (1%)
Grade 4 (<121 mEq/L)	0	0	1 (1%)	1 (<1%)
Hemoglobin (g/dL)				
Grade 3 (7.0 to <9.0 g/dL OR any decrease from Baseline ≥4.5 g/dL)	4 (4%)	10 (11%)	5 (6%)	19 (7%)
Leukocytes (x10^3/uL)				
Grade 3 (1 to <1.5 x10^3/uL)	1 (1%)	1 (1%)	4 (4%)	6 (2%)
Grade 4 (<1 x10^3/uL)	1 (1%)	1 (1%)	0	2 (1%)
Lymphocytes (x10^3/uL)				

Laboratory Parameter Maximum Toxicity Grade	SOF/VEL 12 Week	SOF/VEL+RBV 12 Week	SOF/VEL 24 Week	Total
Grade 3 (0.35 to <0.5 x10^3/uL)	10 (11%)	12 (14%)	8 (9%)	30 (11%)
Grade 4 (<0.35 x10^3/uL)	3 (3%)	12 (14%)	6 (7%)	21 (8%)
Neutrophils (x10^3/uL)				
Grade 3 (0.5 to <0.75 x10^3/uL)	2 (2%)	1 (1%)	2 (2%)	5 (2%)
Grade 4 (<0.5 10^3/uL	0	1 (1%)	1 (1%)	2 (1%)
Platelets (x10^3/uL)				
Grade 3 (25 to <50 x10^3/uL)	15 (17%)	10 (11%)	18 (20%)	43 (16%)
Grade 4 (<25 x 10^3/uL)	1 (1%)	0	0	1 (<1%)

Source: ADLB, ASTRAL-4

Hematologic Laboratories

The most commonly observed ≥Grade 3 hematology laboratory abnormalities were decreased hemoglobin, lymphocytes and platelet counts, known effects of RBV therapy or expected in the decompensated cirrhosis population.

Hemoglobin

Erythropoiesis-stimulating agents (ESA) such as epoetin alfa used to treat anemia were permitted in ASTRAL-4. A single SOF/VEL+RBV-treated subject (06919-64223) received epoetin during the trial. No subject in the SOF/VEL+RBV 12 Week group received a blood transfusion. Two subjects in the SOF/VEL 12 Week group (05969-64191, 06214-64264) received blood transfusions following a gastrointestinal bleed.

Anemia is the most common cause of RBV dose reduction. Hemoglobin (hgb) values of <10 g/dL and <8.5 g/dL are the values recommended in the approved RBV package inserts and used in ASTRAL-4 for RBV dose-reduction and discontinuation, respectively. More subjects in the SOF/VEL+RBV 12 Week group had hgb values <10 g/dL (23%) and 8.5 g/dL (7%) compared with the SOF/VEL 12-24 Week groups (8%-9% and 1%, respectively). The six subjects receiving SOF/VEL+RBV 12 Week with post-baseline hgb <8.5 g/dL all modified RBV dose, including five subjects who permanently discontinued RBV while SOF/VEL continued, with resulting ≤65% adherence to RBV (range 13%-65%).

Reviewer Comment: Anemia is a known toxicity associated with RBV use. As discussed in Section 6.4.2 the majority of ASTRAL-4 SOF/VEL+RBV-treated subjects (63%, 55/87) maintained an average RBV dose ≥1000 mg/day.

In the SOF/VEL 12 and 24 Week groups, two subjects had hgb <8.5 g/dL. One subject (03055-64017) in the SOF/VEL 24 Week group with baseline hgb 9.8 g/dL experienced decreased hgb to 7.4 g/dL associated with Grade 4 AEs of HRS, sepsis and hypotension which led to liver transplantation (See Section 8.5.1). One subject (07585-64027) in the SOF/VEL 12 Week group

had baseline hgb of 11.1 g/dL with decrease to 10.6 g/dL Week 4 and nadir of 8.1 g/dL Week 6. No associated AEs were reported at the time of hgb decline. While SOF/VEL treatment continued, hgb increased to baseline by Week 10.

Lymphocytes

Lymphopenia is associated with decompensated liver disease.[13] All treatment groups experienced more than 10% ≥Grade 3 lymphopenia, with higher percentage occurring in the SOF/VEL+RBV 12 Week group (28%) as expected because RBV is known to further contribute to lymphopenia.[14]

Platelets

Low platelet counts are associated with decompensated liver disease, and ASTRAL-4 permitted enrollment of subjects with Grade 3 platelet counts at screening. The SOF/VEL+RBV 12 Week group had the lowest percentage of ≥Grade 3 decreased platelet counts (11%) compared with the SOF/VEL 12 and 24 Week groups (18%-20%). RBV has been demonstrated to elevate endogenous erythropoietin secretion which may stimulate platelet production.[15] Across SOF/VEL-containing treatment groups ≥Grade 3 decreased platelet counts were isolated, associated with lymphoma (07275-64023) or were fluctuations within a generally stable range.

Leukocytes, Neutrophils

Few subjects experienced ≥Grade 3 decreased leukocytes or neutrophils and no relevant trends were observed across treatment groups. Transient Grade 4 decreased neutrophils occurred in two subjects, including one subject with baseline Grade 3 decreased neutrophils: both subjects continued SOF/VEL-containing treatment and no infection AEs were reported.

Reviewer Comment: No unique SOF/VEL hematologic safety signal is observed in ASTRAL-4: ≥Grade 3 hematologic laboratory abnormalities reflect known RBV effects or expected findings in the decompensated cirrhosis population. Because the SOF/VEL+RBV 12 Week regimen is recommended in the HCV decompensated cirrhosis population, language regarding hemoglobin decreases is proposed for the label Section 6.1, guided by currently labeled RBV dose adjustments:

> *Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% subjects treated with [TRADENAME] (b) (4) RBV for 12 weeks, respectively.*

Hepatic Laboratories

Liver Enzyme Elevations

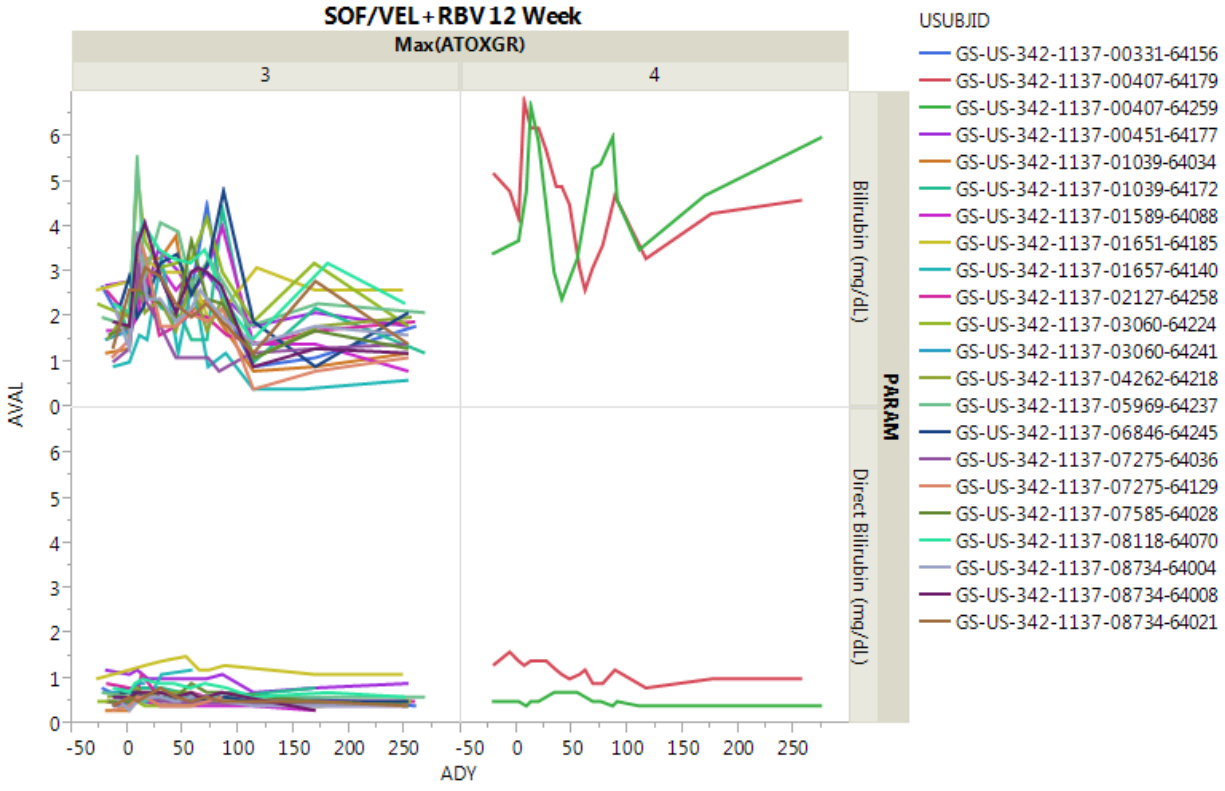
Two subjects (2%) experienced isolated treatment-emergent Grade 3 AST elevations. These two subjects (07275-64023, 08430-64136) are discussed in Section 8.5.1 and had alternative etiologies for AST elevations: lymphoma, rhabdomyolysis occurring in the setting of recent surgery. No ASTRAL-4 subject had treatment-emergent ≥Grade 3 ALT elevations.

Bilirubin Elevations

Screening total bilirubin >5 mg/dL was an ASTRAL-4 exclusion criterion. Bilirubin elevations ≥Grade 3 (>2.5x ULN) were reported in 12% SOF/VEL-treated subjects (31 subjects): 4% in the SOF/VEL 12 Week group, 25% in the SOF/VEL+RBV 12 Week group and 6% in the SOF/VEL 24 Week group. Four SOF/VEL-treated ASTRAL-4 subjects experienced Grade 4 increased bilirubin. Two subjects (00407-64179, 00407-64259) received SOF/VEL+RBV 12 Week regimen and Grade 4 hyperbilirubinemia likely reflects RBV-toxicity, supported by associated stable direct bilirubin, alkaline phosphatase, ALT and ALT values. The two additional subjects with Grade 4 hyperbilirubinemia were reviewed by the IAC (Section 8.5.1), and have alternative etiologies for these elevations: Subject 07275-64023 (SOF/VEL 12 Week) had AST and bilirubin elevations associated with diagnosis of lymphoma, and Subject 04421-64003 (SOF/VEL 24 Week) had transient bilirubin elevations s/p hip fracture associated with hematoma resorption.

Specific to the SOF/VEL+RBV 12 Week regimen, ≥Grade 3 bilirubin elevations were associated with stable direct bilirubin values as shown in Figure 2.

Figure 2. Grade 3 and 4 Bilirubin Elevations: SOF/VEL+RBV 12 Week Regimen, ASTRAL-4



Source: ADLB dataset, ASTRAL-4

Reviewer Comment: The higher percentage of subjects with ≥Grade 3 bilirubin elevations in the SOF/VEL+RBV 12 Week group is consistent with the known side effect profile of RBV-associated hemolysis.

Other ≥Grade 3 Laboratories
Other Grade 3 or 4 laboratory abnormalities were generally transient, asymptomatic, occurred in subjects with risk factors (e.g., hyperglycemia in subjects with diabetes, hyperglycemia, increased baseline/screening glucose and/or increased hemoglobin A1C) and/or represented a single grade shift from baseline/screening value.

Reviewer Comment: Review of additional ASTRAL-4 ≥Grade 3 laboratory data does not support relevant SOF/VEL labeling.

Safety Update Report
The frequency and severity of laboratory abnormalities described in studies ASTRAL-5, 342-1553, and 342-1446 are consistent with the safety profile observed in the ISS population. Reported cases in more than one subject include Grade 3 lipase without pancreatitis, Grade 3 CK associated with exercise and without rhabdomyolysis, and Grade 3 hyperglycemia in subjects with diabetes mellitus.

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 ASTRAL -1, -2, -3, and -4. Please refer to Section 8.5.2 for a more specific discussion regarding changes in heart rate in subjects receiving SOF/VEL±RBV 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, with an additional assessment at Week 24 for the SOF + RBV 24 week group in ASTRAL-3 and the SOF/VEL 24 Week group in ASTRAL-4. The Applicant reports four subjects with treatment-emergent abnormal ECGs deemed clinically significant by the investigator:

- Subject 00731-63339 is a 50 year old male subject treated with SOF/VEL x 12 weeks in ASTRAL-1. He had QT prolongation on his Week 12 ECG with a 56ms increase was noted relative to his baseline ECG (QTc 419msec and 475msec, respectively). The subject was asymptomatic throughout. His QTc trended back down on follow-up ECGs at post-treatment Weeks 4 and 12, 451 and 450msec, respectively. The investigator considered the event to be drug-related, but noted that the subject was receiving concomitant medications that could also prolong the QT interval (perazine and paroxetine).

- Subject 00380-62020 is a 53 year old female with a prior history of unconfirmed atrial fibrillation, treated with SOF/VEL x 12 weeks in ASTRAL-3. She had a normal ECG at screening but had atrial fibrillation with rapid ventricular response at Week 12. She was asymptomatic but was started on metoprolol for rate control and was stable at the 6 month follow-up visit. The investigator considered the event unrelated to study drug.

- Subject 00619-64112 (SOF/VEL 12 Week, ASTRAL-4)
  49 year old woman with HTN, obesity, heart murmur on concomitant propranolol, furosemide with screening ECG assessed as abnormal with septal infarct but not clinically significant. At baseline and Week 1, ECGs assessed as abnormal but not clinically significant with sinus bradycardia, low voltage QRS with inferior infarct. At Week 12 (EOT visit), ECG was deemed clinically significant: sinus bradycardia with sinus arrhythmia, septal and inferior infarct with new ST changes concerning for myocardial ischemia. The subject was asymptomatic. Subsequent cardiology assessment diagnosed CAD with normal EF 66%. The subject was managed with aggressive risk reduction and noted to be stable approximately 3 months later. The investigator considered this event unrelated to study drug.

- Subject 06919-64202 (SOF/VEL 24 Week, ASTRAL-4)
  58 year old man with HTN on concomitant propranolol, spironolactone, furosemide with baseline ECG assessed as abnormal but not clinically significant with a right bundle branch block and left anterior fascicular block leading to beta blocker discontinuation. At the next visit (Week 1), the subject had a change in his ECG deemed to be clinically significant: premature atrial complexes with right bundle branch block and left anterior fascicular block. A week later the subject complained of sharp pain in his left arm lasting 10 seconds with no associated shortness of breath which resolved without intervention. There was no recurrence of symptoms and no further evaluation was performed by the investigator. A Week 12 ECG showed similar findings with prior ECGs and this was deemed not clinically significant by the investigator. At the most recent visit, more than 6 months after the initial event, the subject was noted to be stable.

Reviewer Comment: All four subjects with ECGs deemed clinically significant by the investigator were generally asymptomatic at the time of abnormal ECGs and had either cardiac risk factors, abnormal screening/baseline ECGs or concomitant medications that confounded assessment. 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 VEL to prolong the QT interval. Study GS-US-281-1054 was a randomized, partial-blinded placebo- and positive-controlled, 4-period, 8-treatment sequence, single-dose crossover study of 48 healthy subjects

who received VEL 100 mg, VEL 500 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 VEL (100 mg and 500 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between VEL (100 mg and 500 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 VEL (100 mg and 500 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Time	ΔΔQTcF	90% CI (ms)
VEL 100 mg	0.5	1.8	(-0.4, 4.1)
VEL 500 mg	5	1.5	(-0.8, 3.8)
Moxifloxacin 400 mg*	6	11.5	(9.2, 13.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 7.3 ms at 3 hours after dosing.

> The supratherapeutic dose (500 mg) produces mean Cmax values of 3.1-fold the mean Cmax for the therapeutic dose (100 mg) when administered in combination with sofosbuvir (SOF) 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, VEL does not prolong QTc to any clinically relevant extent. Please refer to the QT-IRT review by Moh Jee Ng for additional details (IND 115670, April 15, 2015)

8.4.10. Immunogenicity

Because SOF and VEL 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. For the ISS population, analyses were performed using the relevant SOC or High Level Group Term (HLGT)

and by Standardized MedDRA Queries (SMQ) generated using MAED software. MAED was not used for ASTRAL-4 because all 3 trial groups included SOF/VEL.

8.5.1. Hepatotoxicity

Detailed analyses of hepatic events were performed as SOF/VEL is being administered to subjects with underlying liver disease, including decompensated cirrhosis. Based on review of the available data, we do not believe a definitive causal relationship between SOF/VEL 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 ISS compensated liver disease population:
  - Of the 55 cases screened for DILI evaluation by the IAC, there was only one case in which DILI could not be definitively excluded; causality was confounded by concomitant medications and concurrent illness in this subject.
  - 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 1% of subjects treated with SOF/VEL and generally improved, rather than worsened, with treatment.

- In ASTRAL-4 decompensated cirrhosis population:
  - Two cases identified as potential DILI cases by the IAC were confounded by concomitant medications, cholelithiasis and/or viral illness. The remaining nine cases meeting IAC screening criteria for potential DILI were unlikely related to SOF/VEL use due confounding events, alternative explanations and/or isolated liver laboratory elevations which improved while HCV treatment was continued.
  - Reported hepatic events were low (2%) and do not raise concern for direct SOF/VEL toxicity as these events are seen in the decompensated cirrhosis population or are associated with confounding factors.
  - No ALT increases>5x ULN were reported and AST increases >5x ULN were infrequent (1%), with alternative explanations for these increases (Section 8.4.6).
  - Bilirubin increases >2.5x ULN were infrequent (12%) with most cases occurring in the SOF/VEL+RBV 12 Week group, attributed to RBV toxicity (Section 8.4.6).

Language in the *Hepatic Impairment* Section 8.7 of the label is proposed recommending clinical and hepatic monitoring (including direct bilirubin) as clinically indicated in the decompensated population, similar to language in the currently approved LDV/SOF label. Any potential signals of hepatotoxicity associated with SOF/VEL use will be closely monitored in the postmarketing setting.

Independent Adjudication Committee

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
   — Total bilirubin (TB) >3x baseline/Day 1 or nadir and ALT and/or AST >3x baseline or nadir
   — Direct bilirubin (DB) > 3mg/dL
   — AST > 10 × Day 1 or nadir, confirmed by immediate repeat testing
   — ALT > 10 × Day 1 or nadir, confirmed by immediate repeat testing
   — ALT > 15 × ULN, confirmed by immediate repeat testing

Phase 2 and ISS Compensated Liver Disease Trials

6. Conventional biochemical screening criteria for possible DILI (any subject with on-treatment [i.e., post-baseline] and up to 3 days after the last dose of any study drug)

- ALT or AST > 5 x ULN or > 5 x baseline abnormal value
- Alk Phos > 2x ULN or 2 x baseline abnormal value
- Otherwise unexplained TB > 2.5 mg/dL or INR > 1.5

ASTRAL-4 Decompensated Cirrhosis Trial

7. Revised biochemical screening criteria for possible DILI (any subject with on-treatment [i.e., post-baseline] and up to 3 days after the last dose of any study drug)
   - ALT or AST > 3 × nadir post-baseline
   - ALT or AST > 2 × baseline
   - Increase from baseline in DB > 1 mg/dL

The last criterion was specific to ASTRAL-4, based on the following principles to develop the ALT and AST criteria for evaluating and identifying potential cases of DILI in subjects with advanced liver disease treated with SOF/VEL±RBV:

Relative versus absolute cutoffs: A relative cutoff (fold change >ULN or change from baseline/nadir) was preferred over an absolute cutoff (given value over a pre-specified threshold) because the relative cutoff minimizes differences between laboratories, accounts for differences in subject populations, and is more adaptable across a wider range of disease severity.

Change relative to ULN versus change from baseline/nadir: Change from baseline or nadir was preferred to fold change >ULN because ULN quantifies the severity of disease relative to a normal population, not the change in the severity of disease in a given patient relative to their pre-exposure status.

Nadir versus baseline: AST and ALT values are expected to decline in response to HCV treatment. Therefore, a change from baseline is a less sensitive marker of potential liver injury compared with a change from nadir. For this reason, for ALT and AST, it was proposed that a change from nadir would be preferred.

A change from baseline was preferred for bilirubin since these levels do not rapidly decline with decline in HCV RNA. Because ASTRAL-4 included a RBV-containing group and RBV is known to cause indirect hyperbilirubinemia, DB was preferred over TB and was considered more reflective of liver function and injury. The IAC also recommended using the criterion of increase from baseline in DB >1 mg/dL to identify potential cases of DILI for review.

Additionally, the IAC believed the current drug-induced liver injury network (DILIN) causality scoring system (definite, very likely, probable, possible, and unlikely) was not applicable to this subject population with advanced liver disease comorbidities who are often receiving numerous concomitant medications. Rather, the IAC determined a more meaningful approach would be to categorize subjects as those for whom DILI could be excluded, those for whom DILI could not be excluded and those with insufficient data to make a determination.

Reviewer Comment: The IAC criteria were reviewed by the Division prior to NDA submission and determined to be acceptable. The IAC criteria used for ASTRAL-4 are similar to criteria used in NDA 205834 LDV/SOF SOLAR-1 and SOLAR-2 trials.

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. The compensated liver disease population (Phase 3 ISS and supportive Phase 2) and ASTRAL-4 decompensated cirrhosis populations are presented separately because of different IAC criteria used in each population.

Compensated Liver Disease

This section presents data in the following format:

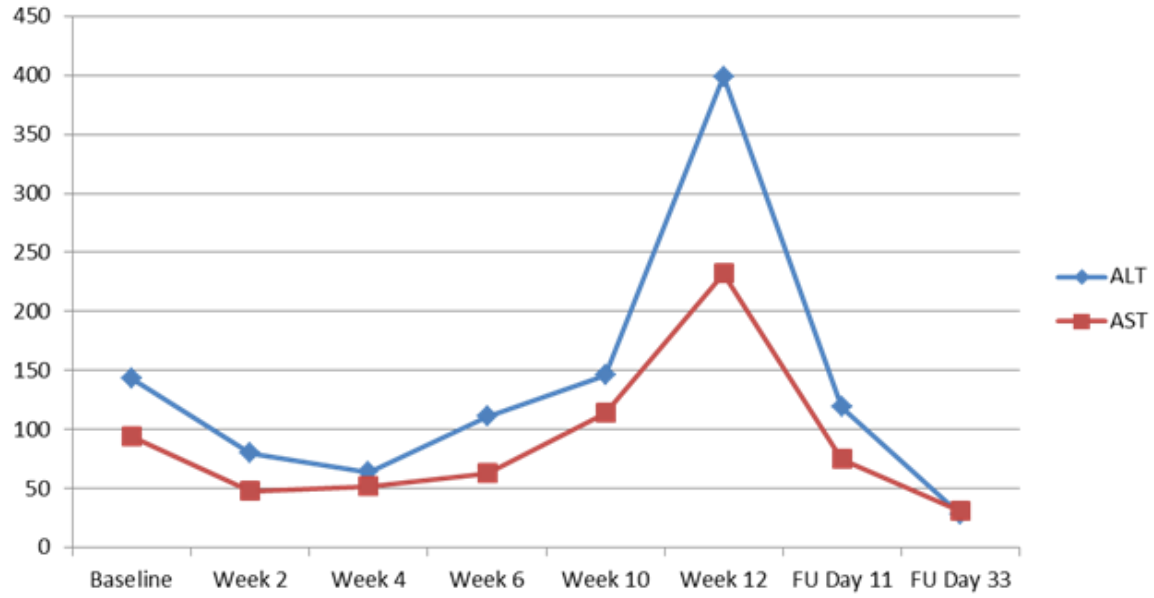
- IAC Assessment
- Hepatic and Hepatobiliary AEs
- Notable hepatic laboratory abnormalities

IAC Assessment

Fifty-six cases met at least 1 of the 6 criteria for IAC review: 27 cases in ASTRAL-1; 8 cases in ASTRAL-2; 12 cases in ASTRAL-3; and 9 cases in Phase 2 studies. DILI was excluded in 39 cases and the remaining 17 were discussed. The committee members reviewed the criteria and determined that they were effective for adjudicating cases in the decompensated population enrolled in ASTRAL-4, but were not optimal for the other studies because many cases were isolated and asymptomatic ALT/AST elevations. Hence, the IAC decided to use conventional DILI criteria in their review of cases from ASTRAL-1, -2, and-3 and Phase 2 studies (described above in IAC methods).

Using these criteria, one case was identified in which DILI could not be excluded. Subject 5730-61176 is a 58 year old NC white female with GT3 HCV who received open-label SOF + VEL 25 mg + RBV 12 weeks in Phase 2 Study 0109. The subject had an unexplained increase in ALT and AST that was temporally associated with starting new antihypertensive medications (Day 11) and receiving antibiotics and steroids for an asthma exacerbation (Day 22). Study medications and her antihypertensives were discontinued on Day 81 and her ALT and AST subsequently normalized (Figure 3). Bilirubin and alkaline phosphatase levels remained normal throughout her treatment course.

Figure 3. Trend in ALT and AST for Subject 5730-61176, Trial 0109



Reviewer Comment: I agree with the IAC that DILI cannot be excluded in this case, as assessment is confounded by the initiation of several medications, many of which were discontinued at the same time.

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 5 subjects reporting events. In the SOF/VEL group, 1 subject reported hepatic pain and 2 subjects reported jaundice. In the SOF +RBV x 24 week group, 2 subjects reported jaundice. All events were Grade 1 and all jaundice events were considered drug related, but there were no discontinuations or treatment interruptions due to the events. The two jaundice events in the SOF/VEL group occurred in the two subjects with elevated bilirubin, described below.

Hepatic Laboratory Abnormalities

Subjects meeting any one of the following three laboratory criteria were identified for further review (Table 47):

- 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 47. 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=1558)	1 (<1%)	21 (1%)	20 (1%)
SOF/VEL 12 Weeks (N=1035)	0 (0%)	8 (1%)	2 (<1%)
Placebo 12 Weeks (N = 116)	0 (0%)	10 (9%)	1 (1%)
SOF+RBV 12 Weeks (N = 132)	1 (1%)	0 (0%)	5 (4%)
SOF+RBV 24 Weeks (N = 275)	0 (0%)	3 (1%)	12 (4%)
Phase 2 Studies[2] (N=802)	0 (0%)	11 (1%)	12 (1%)

[1] ASTRAL-1, ASTRAL-2, ASTRAL-3:
[2]342-0102, 342-0109, 337-0122 (cohort 4)
Source: Based on Table 27 of Applicant's Summary of Clinical Safety

The specified hepatic laboratory abnormalities occurred infrequently, particularly among SOF/VEL subjects. There were no Hy's Law cases among SOF/VEL treated subjects. All 8 subjects who received SOF/VEL for 12 weeks and meet Criterion 2 had elevated ALT at baseline, and in all but one case, ALT trended down with treatment. Subject 00595-62086 is a 50 year old TE NC white male with GT3 HCV and a history of heavy alcohol use. His ALT trended down from Grade 3 at baseline to Grade 1-2 through Week 8, but rose again to Grade 3 at Week 10 and 12. The subject achieved SVR12 but his ALT remained elevated (Grade 2) 7 months post-treatment. The investigator and Applicant suspect "a comorbid illness in the setting of viral suppression." The FDA review team concurred that the prolonged duration of elevated ALT was likely due to an etiology other than study medication or HCV itself.

Two subjects with cirrhosis in the SOF/VEL 12 Week group had total bilirubin values > 2 x ULN. Both subjects had elevated total bilirubin at baseline (Grade 1 and Grade 2) and had transient fluctuations in total bilirubin over the treatment course.

Events in the comparator groups were frequently attributable to either untreated HCV in the placebo group or RBV exposure in the SOF+RBV groups. The same trends were observed among the Phase 2 subjects.

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 exposure among subjects with compensated liver disease. Based

on all available information, no specific product labeling is warranted, and routine pharmacovigilance will be in place to detect post-marketing signals.

ASTRAL-4 Decompensated Cirrhosis Population

This section presents data in the following format to provide a comprehensive ASTRAL-4 hepatotoxicity assessment.

- IAC Assessment
- Hepatic and Hepatobiliary AEs
- Liver Transplantation
- Notable hepatic laboratory abnormalities

IAC Assessment

A total of 10 cases were originally assessed by the IAC using the above mentioned screening criteria. The cases are listed in Table 48. The primary clinical review team requested IAC assessment of an additional case of hyperbilirubinemia resulting in SOF/VEL discontinuation (05275-64229). There were no hepatic failure SAEs or other SOF/VEL discontinuations due to hepatic AEs. Two cases (02130-64039, 05275-64229) were categorized as DILI could not be excluded and will be discussed in more detail. The remaining nine cases were assessed as unlikely related to SOF/VEL treatment by the IAC.

Reviewer Comment: Based on narrative review, IAC assessment that the remaining nine cases are unlikely related to SOF/VEL-containing treatment is reasonable due to factors such as confounding events and/or isolated laboratory elevations which improved while HCV treatment continued.

Table 48. ASTRAL-4 Subjects Meeting IAC DILI Screening Criteria

Subject #	DILI Screening Criteria Met	IAC Assessment	Comments
SOF/VEL 12 Week			
07275-64023	ALT or AST > 2 × BL DB >3 mg/dL; ΔDB >1 mg/dL	Unlikely	Infiltrating B cell lymphoma
07275-64103	ALT or AST >3x nadir; ALT or AST >2x BL	Unlikely	Isolated event Week 6
SOF/VEL+RBV 12 Week			
03060-64241	Death	Unlikely	Perforated duodenal ulcer
08430-64136	ALT or AST >3 × nadir ALT or AST >2 × BL	Unlikely	Rhabdomyolysis (s/p surgery/anesthetic agents)
SOF/VEL 24 Week			
02130-64039	ΔDB >1 mg/dL	Possibly	Temporal association without a clear etiology
03055-64017	Transplant; Δ DB > 1 mg/dL	Unlikely	SBP, progression of liver disease
03060-64200	Death	Unlikely	Coronary artery disease
04371-64234	ALT or AST > 3 × nadir	Unlikely	Isolated event s/p fracture
04421-64003	ΔDB > 1 mg/dL	Unlikely	Transient; Hematoma resorption s/p hip fracture
07275-64131	TB >3× baseline or nadir ALT or AST >3x nadir; ALT or AST >2x BL	Unlikely	Isolated event Week 8
05275-64229	TB >3× BL or nadir; ΔDB >1 mg/dL	Possibly	Temporal association, positive dechallenge

Source: Adapted from ASTRAL-4 Clinical Summary of Safety, Table 48: Subjects who met IAC Criteria for Evaluation for DILI (Safety Analysis Set)

Details regarding the two cases (02130-64039, 05275-64229) categorized as DILI could not be excluded are presented below:

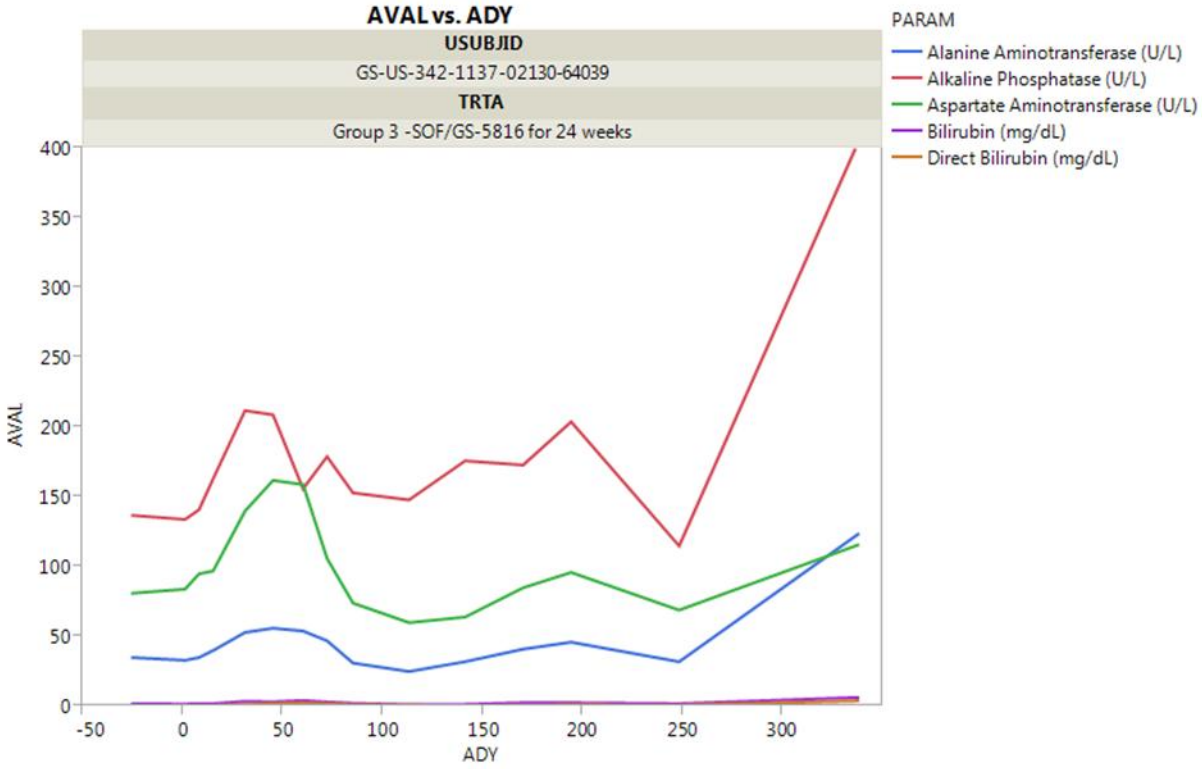
Subject 02130-64039 (SOF/VEL 24 Week) Week 6 Change in DB >1 mg/dL

47 year old, white man with baseline CPT B-8, MELD 12, ascites, varices experienced Week 6 DB increase to 2.1 mg/dL (baseline 0.8 mg/dL). DB improved at subsequent visits and was 0.6 mg/dL at Week 20. TB was also elevated at 3.2 mg/dL (range 1.6 mg/dl to 4.2 mg/dL on treatment). AST levels fluctuated 60 U/L to 162 U/L. Baseline CK was approximately 1.8x ULN with on-treatment fluctuations from within normal limits (Week 14) to 7.1x ULN (Week 8). No signs or symptoms of muscle injury, rhabdomyolysis or worsening liver disease, including jaundice, were reported. The only associated AE at the time of bilirubin elevation was Grade 1 fatigue. Historical records dating back to May 2014 showed fluctuations in lab

values including TB (1.3 mg/dL–2.3 mg/dL) and AST (43 U/L–114 U/L). No new concomitant medications were reported ongoing at the time of the laboratory abnormalities; however, at baseline amiloride was changed to eplerenone. This subject completed HCV treatment and achieved SVR12.

IAC Assessment: Temporal association without clear etiology. The IAC agreed with the investigator's decision to continue SOF/VEL.

Figure 4. Trend in Liver Enzymes and Bilirubin for Subject 02130-64039, ASTRAL-4



Source: ADLB dataset, ASTRAL-4

Reviewer Comment: The IAC evaluation of this case is considered thorough. While the contribution of SOF/VEL to this case of DB elevation cannot be fully excluded, improvement in DB and other liver laboratory parameters while SOF/VEL continued do not raise concern for significant SOF/VEL hepatotoxicity. In addition, this case may be confounded by concomitant eplerenone use. In eplerenone label (aldosterone antagonist), increases of ALT greater than 120 U/L and bilirubin greater than 1.2 mg/dL were reported 1/2259 patients administered eplerenone tablets and 0/351 placebo-treated patients.

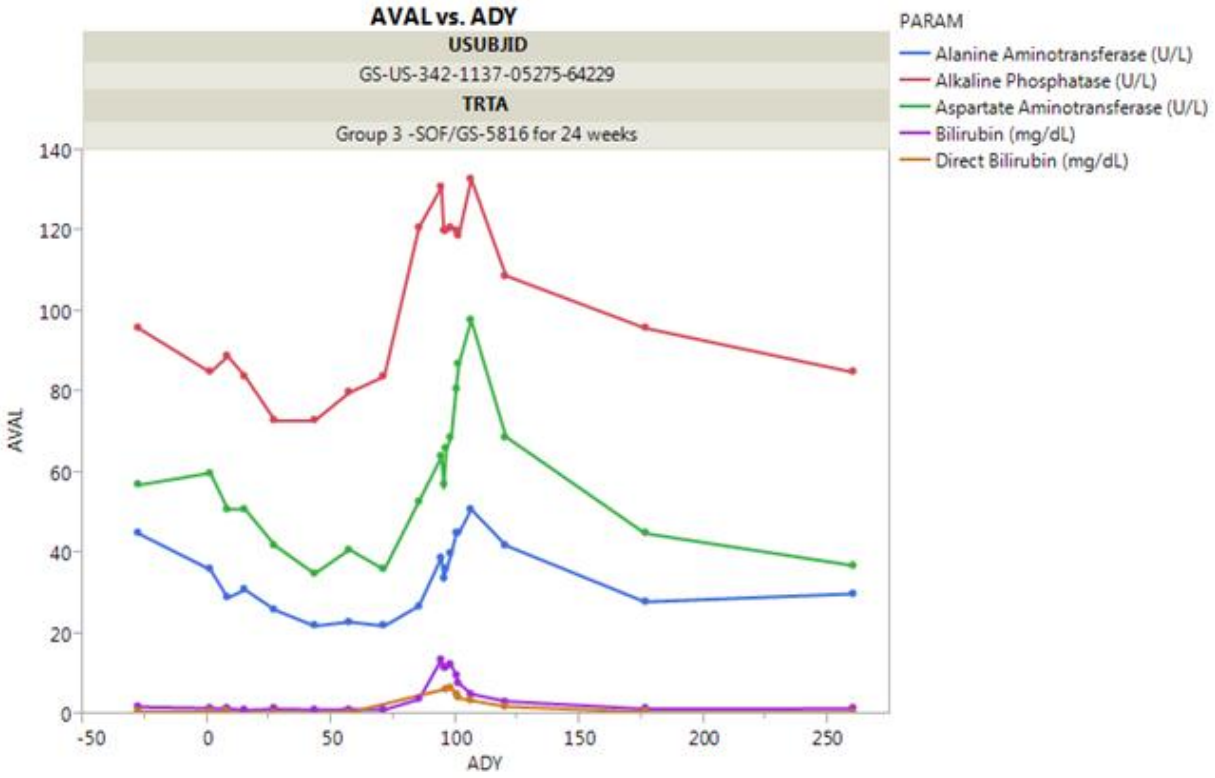
Subject 05275-64229 (SOF/VEL 24 Week) Week 12 TB >3x baseline, Change in DB >1 mg/dL

65 year old man with BL CPT B-8, MELD 11, portal HTN, ascites, esophageal varices, hepatic

encephalopathy, cholelithiasis experienced increase TB to 3.8 mg/dL Day 85 associated with ongoing Grade 2 colitis. The subject developed subsequent increase TB to ~14 mg/dL Day 91 associated with nausea, vomiting, back pain, clay colored stools, dark urine, weight loss, jaundice and pruritus leading to HCV therapy discontinuation. Also associated with transient alkaline phosphatase and AST >ALT elevations. The subject reported a sick contact at home with upper respiratory symptoms; no recent travel, alcohol use or new concomitant medications except Zofran. Metronidazole had been prescribed Day 1-13 for colitis along with concomitant ciprofloxacin which continued for SBP prophylaxis. Liver U/S demonstrated mildly prominent common bile duct, multifocal gallbladder polyps, coarse liver with portal HTN (splenomegaly and ascites). MRCP/MRI liver evaluation ruled out ductal dilatation. No serologic evidence of hepatitis A/B/E infection. Stool studies were negative for ova/parasites, clostridium difficile, fecal leukocytes. A liver biopsy demonstrated cirrhosis, lobular hepatitis and moderate cholestasis (Gr 1-2 of 4). The subject recovered and positive dechallenge is noted as displayed in Figure 5. The subject achieved SVR12. The event of hyperbilirubinemia was assessed as unrelated to study drug by the investigator.

IAC Assessment: DILI could not be excluded due to the temporal association with SOF/VEL therapy and the improvement in bilirubin values off therapy. However, alternative etiologies including mechanical obstruction (clinical presentation of nausea, vomiting and abdominal pain in a setting of known cholelithiasis), viral illness (initial consideration of the transplant hepatologist) as well as the contributions of other agents such as ciprofloxacin could not be excluded.

Figure 5. Trend in Liver Enzymes and Bilirubin for Subject 05275-64229, ASTRAL-4



Source: ADLB dataset, ASTRAL-4; Response to FDA Information Request February 3, 2016

Reviewer Comment: This case was not captured for initial IAC review as no DB value was reported. The subsequent IAC evaluation of this case is considered thorough. It is challenging to determine any contribution of SOF/VEL to this event occurring in a subject with baseline decompensated liver disease. Positive dechallenge supports a potential causal association with SOF/VEL; however, I agree with the IAC assessment that alternative etiologies including mechanical obstruction supported by cholelithiasis history and transient alkaline phosphatase elevation, associated viral illness and/or other agents such as ciprofloxacin cannot be excluded and it is possible the subject would have recovered while SOF/VEL continued. Based on the totality of available data and confounding factors in this single case, no specific hepatotoxicity Warnings and Precautions product labeling is recommended.

Hepatic and Hepatobiliary AEs

In ASTRAL-4, overall hepatic events defined by the MedDRA High Level Group Term *Hepatic and Hepatobiliary Disorders* were low (2%, 6/267 subjects). Two cases of Grade 1 portal vein thrombosis were reported, including one SAE (06991-64025). Two additional subjects experienced hepatic SAEs: hyperbilirubinemia/jaundice (05275-64229) discussed under IAC Assessment, HRS (03055-64017) discussed in Section 8.4.2 associated with SBP leading to liver

transplantation. The remaining two cases were Grade 1 events of jaundice and liver disorder ('liver tingling') in the SOF/VEL+RBV 12 Week group.

Reviewer Comment: Reported hepatic events in ASTRAL-4 do not raise concern for direct SOF/VEL toxicity as these events are seen in the decompensated cirrhosis population or are associated with confounding factors as in Subject 05275-64299.

Liver Transplantation
Two subjects were admitted for liver transplantation (OLT). One subject received a liver transplant and a second subject was taken for transplant however the procedure was cancelled.

Subject 03055-64017 (SOF/VEL 24 Week)

59 year old man with decompensated liver disease (CPT B/C 9−10, MELD 15-19), esophageal varices, ascites, encephalopathy, and portal vein thrombosis who received OLT posttreatment Day 8. During screening, acute kidney injury associated with hepatic encephalopathy occurred leading to screen failure and subsequent rescreening. On Day 35, the subject experienced SAEs of Grade 3 SBP, Grade 4 sepsis, HRS, and hypotension leading to study drug discontinuation. These events were assessed as related to study drugs by the investigator. The subject was listed for liver transplantation (MELD score 38) and underwent OLT post-treatment Day 8. The subject subsequently achieved SVR12.

Reviewer Comment: This subject's baseline decompensated liver disease is a known risk factor for SBP with subsequent HRS, sepsis, hepatic decompensation and therefore provides a plausible alternative etiology for these events. This case was reviewed by the IAC who assessed this case unlikely related to SOF/VEL-containing treatment (Table 48).

Subject 02127-64161 (SOF/VEL 24 Week)

47 year old man baseline CPT C decompensated cirrhosis, MELD 14, portal HTN (esophageal varices, portal hypertensive gastropathy, ascites, splenomegaly), long term prior smoker, prior alcohol use who was admitted for OLT Day 41. The subject was listed for OLT prior to enrollment; however, OLT was anticipated >12 weeks after Day 1 per eligibility criteria. On Day 41 the subject was admitted for OLT following a successful match. In the OR, hemodynamic data demonstrated severe portal HTN and pulmonary HTN leading to OLT cancellation. The investigator assessed this event as unrelated to study drug. In the investigator's opinion, this event was due to longstanding cirrhosis and high output heart failure. The subject completed SOF/VEL 24 week regimen and subsequently achieved SVR12.

Reviewer Comment: The Applicant was queried for additional information regarding events leading to the scheduled OLT procedure, including addressing if this procedure was planned prior to SOF/VEL initiation and the contribution of SOF/VEL to the events. Their response received February 3, 2016 states:

The event of pulmonary arterial hypertension was an incidental finding in a largely asymptomatic subject on the transplant list who had pre-existing evidence of mild right ventricular enlargement and significant portal hypertension (ascites, encephalopathy, varices, and portal hypertensive gastropathy). Prior to the subject's hospitalization for a planned liver transplantation, he developed symptoms consistent with pulmonary hypertension and right heart disease which is consistent with the diagnosis of portopulmonary hypertension. Portopulmonary hypertension is considered present when pulmonary arterial hypertension (PAH) exists in a patient who has coexisting portal hypertension, and no alternative cause of the PAH exists, which was the case in this subject.[16-18] The liver transplant was a planned procedure prior to enrollment and there is no evidence that SOF/VEL played a role in unmasking or worsening of pulmonary hypertension, or in the timing and eligibility of liver transplantation in this subject.

I agree with the investigator's and Applicant's assessments that the planned OLT and diagnosis of portopulmonary HTN are more likely reflective of progression of underlying decompensated liver disease rather than manifestation of SOF/VEL toxicity in this case.

Hepatic laboratory abnormalities

Please refer to Section 8.4.6 for discussion regarding ASTRAL-4 ≥Grade 3 liver enzyme and bilirubin elevations. No ALT increases>5x ULN were reported and AST increases >5x ULN were infrequent (1%), with alternative explanations for these increases. Bilirubin increases >2.5x ULN were infrequent (12%) with most cases occurring in the SOF/VEL+RBV 12 Week group, attributed to RBV toxicity.

<u>AST or ALT >3x ULN and Bilirubin >2x ULN</u>

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e., aminotransferase elevation) accompanied by jaundice has a poor prognosis. The modified Hy's Law definition used by FDA as indicator of clinical concern for DILI includes: ALT or AST >3x ULN, total bilirubin >2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury). Note, the appropriate application and interpretation of use of this definition in HCV clinical trials in subjects with decompensated liver disease due to HCV is unknown.

Three cases of treatment-emergent AST >3x ULN and total bilirubin >2x ULN were identified within ASTRAL-4 SOF/VEL-treated subjects. One case was considered possible DILI by the IAC (2130-64039) and is discussed above. The two other cases do not satisfy Hy's Law due to other explanations for increases in liver enzymes: Subject 05275-64152 (SOF/VEL 12 Week) had AST values that were appropriately decreasing in response to HCV treatment with bilirubin values that were lower than baseline, Subject 07275-64023 (SOF/VEL 12 Week) had AST and bilirubin elevations associated with diagnosis of lymphoma.

Safety Update Report

Preliminary safety data from ASTRAL-5 regarding SOF/VEL coadministration with ATV/r merit special consideration. ASTRAL-5 is an ongoing open-label study evaluating the efficacy and safety of SOF/VEL 12 weeks in TN and TE subjects with GT 1 to 6 HCV infection, ± cirrhosis, who are coinfected with HIV-1. Eligible subjects are HIV virally suppressed on protocol-permitted ART regimens with CD4 counts ≥ 100 cells/mm^3. At the time of the SUR datacut, the mean duration of exposure to SOF/VEL was 8.4 weeks, with 30% of subjects having completed 12 weeks of treatment.

Among the 21 subjects receiving ATV/r in combination with FTC/TDF or ABC/3TC, 13 subjects had elevated bilirubin > 2 x ULN (6 Grade 2 and 7 Grade 3). Baseline bilirubin was elevated In nearly every case, which is commonly observed with ATV/r, but increased further within 1-2 weeks of starting SOF/VEL. Due to limited data beyond 4 weeks of SOF/VEL treatment, it is unclear when the bilirubin will peak and when or whether it will trend down to baseline without intervention. No clinical adverse events were reported in conjunction with these laboratory findings.

The mechanism for increased bilirubin is unclear in these subjects and assessment is complicated by the fact that the report provides only total bilirubin rather than the direct and indirect values. DDI studies between SOF/VEL and ATV/r demonstrate only modest increases in ATV/r when the drugs are coadministered. VEL exposures are also increased but exposures of SOF and active metabolite are relatively constant.

An information request was sent on March 16, 2016 seeking longitudinal laboratory data and the Applicant's posited explanation for the mechanism causing elevations in bilirubin. The response was not received at the time this review was finalized. Determinations regarding need for labeling in Section 7.3 will be made pending review of the submission.

Aside from the ATV/r bilirubin issue, available hepatic laboratory data from ASTRAL-5 and Studies 342-1446 and 342-1553 follow the same pattern observed in the integrated Phase 2 and Phase 3 population. Six subjects treated with RBV had elevated bilirubin values and one subject had elevated ALT at Week 1 that was trending down from baseline and continued to trend down. One subject in ASTRAL-5 (05751-67242) with HIV/HCV coinfection and cirrhosis was receiving SOF/VEL with his HIV ART regimen of FTC/TDF + ATV/r. His medical history is also notable for hypertension, diabetes, and gout. On study Day 27 he was hospitalized for gout flare and infection of the left great toe and was started on multiple medications including antibiotics and analgesics. Over the course of the week he developed renal insufficiency which required modification of his ART regimen from TDF/FTC to ABC/3TC; he continued on ATV/r as previously prescribed. In addition, his ALT began to trend upward, rising from the normal range on Day 15 (23 U/L) to 3.2 x ULN on day 41 (136 U/L). He ultimately met protocol-defined

criteria for SOF/VEL discontinuation (elevated ALT or AST > 5x baseline or nadir) on Day 48. His AST also increased from a nadir or 18 U/L on Day 15 to a peak of 93 U/L (2.6 x ULN) on Day 44. His alkaline phosphate and total bilirubin were stable. The Applicant states that the subject's ALT and AST began to normalize following discontinuation of SOF/VEL, but antibiotics were also discontinued on week prior.

Reviewer Comment: Causality assessment for this event is confounded by acute illness and numerous concomitant medications, some of which have nephrotoxic or hepatotoxic potential. The contribution of SOF/VEL remains unclear. Of note, this subject was mentioned in the SAE section and Discontinuation due to AE section.

8.5.2. Cardiac Disorders

As mentioned in Section 2.2, 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 with this SOF/VEL review.

ASTRAL-1, ASTRAL-2, and ASTRAL-3 (ISS Population)
Two sets of analyses were conducted in order to maximize capture of all relevant events, the first using the Cardiac Disorders SOC and the second using a combination of the following cardiac related SMQs: Arrhythmia related investigations, signs and symptoms; Cardiac arrhythmia terms; Cardiac arrhythmias; Cardiac failure; Cardiomyopathy; Conduction Defects; Myocardial Infarction; Torsade de pointes/QT prolongation. The SMQ analysis is presented in this review, as it more accurately identifies events of interest. The results are summarized in Table 49.

Table 49. Cardiac Events by Pooled Cardiac SMQs, All Cause, All Grade, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Dyspnoea	20 (2%)	2 (2%)	3 (2%)	22 (8%)
Palpitations	12 (1%)	2 (2%)	6 (5%)	11 (4%)
Oedema peripheral	12 (1%)	0 (0%)	1 (1%)	1 (<1%)
Chest pain	9 (1%)	1 (1%)	3 (2%)	3 (1%)
Syncope	5 (<1%)	0 (0%)	3 (2%)	6 (2%)
Peripheral swelling	3 (<1%)	0 (0%)	0 (0%)	2 (1%)
Blood creatine phosphokinase increased	2 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Tachycardia	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Acute myocardial infarction	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Blood pressure fluctuation	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Nocturia	1 (<1%)	0 (0%)	0 (0%)	(<1%)
Pulmonary congestion	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Orthostatic hypotension	1 (<1%)	0 (0%)	1 (1%)	0 (0%)
Lower respiratory tract congestion	1 (<1%)	0 (0%)	2 (2%)	0 (0%)
Atrial fibrillation	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Sudden death	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Electrocardiogram QT prolonged	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Extrasystoles	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Ischaemic cardiomyopathy	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Supraventricular tachycardia	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Sinus arrhythmia	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Nocturnal dyspnoea	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Total Subjects	69 (7%)	4 (3%)	15 (11%)	41 (15%)
Subjects with Related Events	12 (1%)	1 (1%)	9 (7%)	25 (9%)

Source: ISS ADSL and ADAE datasets were used to create an SMQ_MAED dataset

Cardiac events occurred infrequently overall but were in general numerically higher in the two RBV-containing groups. Related events among SOF/VEL subjects occurred at frequencies comparable to placebo. Most events were Grade 1-2 and nonserious. Four of the events were SAEs, all of which occurred in the SOF/VEL group: 2 cases of acute myocardial infarction (AMI), one case of sudden death, and one case of palpitations. The AMI cases were reviewed in Section 8.4.2 and the sudden death case was reviewed in Section 8.4.1.

The subject with palpitations (02803-63392) is a 55 year old white male with a history of depression and opiate abuse, managed with escitalopram and methadone, who was

randomized to receive SOF/VEL in ASTRAL-1. He experienced AEs of myalgia and influenza-like illness during the first two weeks of treatment and subsequently reported palpitations at study Week 4. One week later he was hospitalized for asthenia, at which time the palpitations were still present and ECG showed ventricular extrasystole. Escitalopram was discontinued, his methadone dose was decreased, and the palpitations were reported as resolving. The investigator assessed the event as unrelated to study medication and treatment with SOF/VEL was not interrupted.

Three additional cases of dysrhythmia events occurred in the SOF/VEL group, none of which were SAEs. Two of the three events were described in Section 8.4.8 (ECGs). In brief, one case described prolonged QT interval at Week 12 that improved after SOF/VEL treatment was completed. The event was considered treatment-related. The second case described a patient with history of atrial fibrillation who developed atrial fibrillation with rapid ventricular response. This case was considered unrelated. The third case was Subject 02803-63510, a 49 year old female who reported palpitations on Day 42 (Grade 1) which were ongoing throughout the study period. Baseline ECG was notable for sinus tachycardia and she had a high-normal heart rate throughout the study (80-100 beats per minute). She completed study treatment without interruption and her Week 12 ECG was normal. The event was considered treatment-related by the investigator.

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 149 subjects overall (10%) of which 96 subjects were in the SOF/VEL group (9%). Stable calcium-channel blocker use was reported for 7 subjects (0.4%) overall, of which 5 subjects were in the SOF/VEL group (0.4%).

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 among subjects in the three comparator groups, but 5 events of interest were noted among SOF/VEL subjects. One subject receiving diltiazem had Grade 1 dizziness from Day 1 throughout treatment and Grade 1 palpitations from Day 12 throughout treatment. Her heart rate and blood pressure remained consistent over time with no significant changes relative to baseline. Four subjects receiving beta blockers (4%) had an AE of dizziness during the first two weeks of SOF/VEL treatment. All AEs were Grade 1 and nonserious. Three events were assessed as related to study drug but SOF/VEL dosing was not interrupted or modified, and all subjects completed study treatment. No significant changes from baseline heart rate were observed for these 5 subjects and none had additional cardiac AE at the time.

For the purposes of 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. In total, 22/938 SOF/VEL subjects (2%), experienced at least 1 AE of interest, including palpitations (4 subjects, 0.4%), tachycardia (1 subject, 0.1%), dizziness (16 subjects, 1.7%), and syncope (1 subject, 0.1%). The majority of events were Grade 1 severity and no notable changes from baseline heart rate were observed. Similar rates of AEs of interest were noted among subjects in the three comparator groups: 4% in the placebo group, 6% in the SOF+RBV 12 week group, and 3% in the SOF + RBV 24 week group. Once again, 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 in the SOF/VEL or comparator 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 coadministration were available for evaluation.

ASTRAL-4

Approximately 6% (15 subjects) of SOF/VEL-treated subjects experienced a Cardiac Disorder treatment-emergent AE. No clinical AEs of bradycardia were reported. Most cardiac events were non-serious and ≤ Grade 2 in severity and none led to SOF/VEL discontinuation or interruption. A single cardiac event of Grade 2 palpitations on Day 14 was considered related to SOF/VEL+RBV 12 Week treatment by the investigator. Cardiac SMQ analysis conducted in a similar manner to ASTRAL-1, -2 and -3 pooled analysis identified the same SOF/VEL+RBV 12 Week group subject with treatment-related palpitations and six additional subjects with treatment-related events: one subject with Grade 1 worsening ascites in the SOF/VEL 12 Week group and five subjects (6%) with dyspnea in the SOF/VEL+RBV 12 Week group. These related cardiac SMQ events are considered expected in the decompensated cirrhosis population (ascites) or associated with known RBV adverse events (dyspnea).

Three subjects experienced cardiac SAEs (03060-64200, 01651-64254, 05505-64141). Two SAEs of MIs, including one fatal case discussed in Section 8.4.1, occurred in subjects with cardiac risk factors or extensive cardiac history providing reasonable alternative causal etiology for these events. One SAE of transient atrial fibrillation occurred in a female subject with history of palpitations on Day 122 with echocardiogram demonstrating severe left atrial enlargement, mild mitral regurgitation: this subject completed SOF/VEL 24 Week treatment.

Three subjects had reported cardiac failure/pulmonary edema events, considered nonserious by the investigator (01516-64092, 01651-64254, 03060-64241). These events occurred in subjects with associated ongoing comorbidities providing reasonable alternative causal etiology for these events (hypertrophic cardiomyopathy in subject with positive family history, MI, perforated duodenal ulcer with complication postoperative course leading to fatal sepsis).

Two subjects had additional cardiac arrhythmia events (05275-64174, 06991-64042): posttreatment atrial fibrillation associated with GI bleed and anemia, posttreatment supraventricular tachycardia/atrial fibrillation associated with complicated hospitalization/aspiration pneumonia leading to fatal respiratory failure.

Similar analyses to those in the ISS population were performed (1) to identify any subjects receiving concomitant beta blockers or calcium-channel blockers who experienced AEs suggesting symptomatic bradycardia or other cardiac AEs during the first two weeks of study treatment and (2) to assess changes in heart rate during study treatment for subjects who were or were not receiving a stable regimen of a beta blocker or calcium-channel blocker.

Stable beta blocker use at baseline was reported for 156 subjects overall (58%), with similar frequency across all SOF/VEL-containing arms. Stable calcium channel use at baseline was reported for three subjects overall (1%), including one subject on concomitant beta blocker.

No subject on concomitant beta blockers or calcium channel blockers experienced clinically significant symptomatic bradycardia during the first 2 weeks of SOF/VEL treatment. No clinically relevant changes in heart rate were observed during SOF/VEL±RBV treatment with or without concomitant beta blocker or calcium channel blocker (diltiazem, verapamil).

No ASTRAL-4 subject received amiodarone during the trial.

Overall Cardiac Assessment: No cardiac safety signal was detected from the analyses performed for ASTRAL 1-3 and ASTRAL-4. 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 with beta blockers or calcium channel blockers and those receiving SOF/VEL without beta blockers or calcium channel blockers. 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 and LDV/SOF 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 in the ISS population and ASTRAL-4 to evaluate a potential causal association with SOF/VEL-containing treatment using pooled terms from the MedDRA High Level Group Terms (HLGT) "Depressed Mood Disorders and Disturbances" and "Suicidal and Self-Injurious Behaviours NEC."

ASTRAL-1, ASTRAL-2, and ASTRAL -3 (ISS Population)

As described in Table 50, depression events were more common in the SOF/VEL group versus the placebo group (in which no events were reported), but lower than the SOF + RBV groups. All events were Grade 1 or 2 with the exception of one episode of Grade 3 depression in the SOF + RBV 24 week group, which occurred in a subject with suicidal ideation. The event occurred in a male subject with a history of psychiatric illness. On post-treatment Day 4, he reported suicidal ideation, depression, mood swings, and increased anxiety. He was started on an antidepressant and the AEs resolved.

Table 50. Depression Events, All Cause, All Grade, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Depressed mood	19 (2%)	0 (0%)	3 (2%)	7 (3%)
Depression	13 (1%)	0 (0%)	4 (3%)	11 (4%)
Dysthymic disorder	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Suicidal ideation	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Anhedonia	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Tearfulness	0 (0%)	0 (0%)	2 (2%)	3 (1%)
Total Subjects	33 (3%)	0 (0%)	8 (6%)	22 (8%)
Subjects with Related Events	15 (1%)	0 (0%)	1 (1%)	15 (5)

Source: ISS ADSL and ADAE datasets

Reviewer Comment: Depression events have been associated with SOF in past trials. While there is no clear signal for increased risk of depression events with SOF/VEL, it is notable that events occurred in all three SOF-containing treatment arms but no events occurred in the placebo group.

In Section 8.4.3, three SOF/VEL subjects were identified who prematurely discontinued study medication due to treatment-emergent anxiety/agitation AEs: one subject reported headache and anxiety (Grade 2), one reported anxiety (Grade 3), and one reported irritability (Grade 2). 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." The results are shown in Table 51.

Table 51. Anxiety AEs, All Cause, All Grade, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Anxiety	23 (2%)	1 (1%)	8 (6%)	21 (8%)
Agitation	3 (<1%)	1 (1%)	1 (1%)	1 (<1%)
Nervousness	2 (<1%)	2 (2%)	1 (1%)	1 (<1%)
Stress	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Panic attack	1 (<1%)	0 (0%)	1 (1%)	2 (1%)
Total	29 (3%)	4 (3%)	9 (7%)	24 (9%)
Related Events	10 (1%)	1 (1%)	5 (4%)	12 (4%)

Source: ISS ADSL and ADAE datasets

The majority of events were Grade 1 or 2, but there were 3 cases of Grade 3 anxiety in the SOF/VEL group and two cases of Grade 3 anxiety in the SOF+RBV 24 week group.

Reviewer Comment: Anxiety events occurred at similar frequency between the SOF/VEL group and placebo group. However, there was a trend toward higher severity of events among SOF/VEL subjects relative to placebo and a possible impact on tolerability, with three subjects discontinuing treatment prematurely (2 in the ISS population and one reported in the Safety Update Report). The higher rates observed in the RBV-containing groups are likely attributable to RBV. However, as was discussed with depressive events, the possible contribution of SOF is acknowledged. While specific labeling regarding anxiety events are not warranted based on these few events, general acknowledgement of neuropsychiatric ADRs, consistent with Sovaldi and Harvoni labeling, is appropriate.

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.

ASTRAL-4

No ASTRAL-4 subjects reported treatment-emergent events within the Suicidal and Self-Injurious Behaviours NEC HLGT.

The overall incidence of depression events (all cause) and treatment-related depression events in SOF/VEL-treated subjects was 4% (10 subjects) and <1% (1 subject), respectively. Most depression events were ≤ Grade 2 and no subject discontinued or interrupted SOF/VEL due to a depression event. All subjects with on-treatment depression events had an underlying psychiatric history. One subject with history of schizoaffective disorder and bipolar disorder experienced SAEs of Grade 3 worsened depression Day 67-80 and approximately 2 weeks

posttreatment which were not considered related to study drug (01039-64143, SOF/VEL 12 Week).

In the SOF/VEL+RBV 12 Week group, no subject experienced a treatment-related depression event. In the SOF/VEL 12-24 Week groups, the overall incidence of treatment-related depression events was 0.6%. A single subject with history of ongoing depression and anxiety experienced treatment-related Grade 2 depression Day 11 that was ongoing at the time of data lock (00585-64263, SOF/VEL 12 Week).

The overall incidence of anxiety and agitation events was 3% (8 subjects) for all cause events and 1% (3 subjects) for related events. Most anxiety events were ≤ Grade 2 and no subject discontinued or interrupted SOF/VEL due to an anxiety event. One subject experienced Grade 3 agitation that began and resolved during treatment week 4. The event occurred during a period of illness due to acute bacterial infections and the event was considered unrelated to study medication (03060-64247, SOF/VEL + RBV 12 week).

Overall Assessment: There is no clear indication for an increased risk of neuropsychiatric events with SOF/VEL-containing treatment. 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. For consistency, similar language is recommended for the SOF/VEL 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-containing treatment. Similar to the rash analysis in the original LDV/SOF NDA clinical review, 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.

<u>ASTRAL-1, ASTRAL-2, and ASTRAL -3 (ISS Population)</u>
The number of subjects reporting rash was numerically higher in the SOF/VEL group compared to placebo (4% versus 2%, respectively); all events were mild to moderate in severity. RBV is known to be associated with rash, and therefore it is not surprising that subjects in the RBV-containing arms had more rash AEs. There were no discontinuations based on rash and no Grade 3 or 4 events were observed in any of the four treatment groups.

Table 52. Summary of Rash Events, ISS Population

max Standard Toxicity Grade	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Grade 1	39 (4%)	2 (2%)	7 (5%)	18 (7%)
Grade 2	6 (<1%)	0 (0%)	4 (3%)	3 (1%)
Overall	45 (4%)	2 (2%)	11 (8%)	21 (8%)
Related	30 (3%)	1 (1%)	7 (5%)	17 (6%)

Source: ISS ADSL and ADAE datasets

ASTRAL-4

No events of Stevens Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme were reported in ASTRAL-4. Within the MedDRA Skin and Soft Tissue Body SOC, one SAE was reported that was not concerning for SOF/VEL toxicity: Subject 01657-64126 (SOF/VEL+RBV 12 Week) with diabetes mellitus, diabetic neuropathy, obesity (baseline BMI 39.9 kg/m^2) experienced lower extremity cellulitis and group B streptococcal bacteremia with subsequent development of a lower extremity ulcer. The remainder of AEs reported within the Skin and Soft Tissue SOC were not SAEs and were ≤ Grade 2.

As shown in Table 53, the overall incidence of rash events (all cause) and treatment-related rash events in SOF/VEL-treated subjects was 8% (22 subjects) and 4% (10 subjects), respectively. All rash events were ≤ Grade 2, no SAEs occurred and no subjects discontinued or interrupted SOF/VEL due to a rash event. Three subjects in the SOF/VEL+RBV 12 Week group discontinued or reduced RBV due to treatment-related rash events. Median time to onset was variable across the SOF/VEL-containing groups (18 to 42 days). Approximately 68% of SOF/VEL-treated subjects had rash onset within the first six weeks: 73% SOF/VEL-alone group (11/15 subjects in SOF/VEL 12-24 Week groups), 57% SOF/VEL+RBV 12 Week group (4/7 subjects).

Treatment-related rash events occurred in 5% of SOF/VEL+RBV-treated subjects and 1%-6% SOF/VEL-treated subjects without RBV. In the SOF/VEL 12-24 Week groups all treatment-related rash events occurred within the first 12 weeks of treatment, resulting in an overall incidence of 3%.

Table 53. Summary of Rash Events, ASTRAL-4

Dictionary-Derived Term	SOF/VEL 12 Week	SOF/VEL+RBV 12 Week	SOF/VEL 24 Week
Total Number of Subjects in Analysis	90	87	90
Total Subjects with Rash Event (%)	7 (8%)	7 (8%)	8 (9%)
Maximum Grade			
Grade 1, n (%)	6 (7%)	4 (5%)	7 (8%)
Grade 2, n (%)	1 (1%)	3 (3%)	1 (1%)
Related Events, n (%)	5 (6%)	4 (5%)	1 (1%)
Time to onset of first event, days – median (range)	*18 (9-62)*	*42 (3-85)*	*31 (6-157)*

Source: ADAE, ASTRAL-4

Overall Assessment: The frequency and severity of rash events occurring in SOF/VEL-treated subjects was low across all four trials: no subjects experienced ≥Grade 3 or SAE rash events. Although rash events in SOF/VEL-treated subjects occur below the 2% ADR cutoff for the ISS population and below the 10% ADR cutoff for the ASTRAL-4 population proposed in Section 6 of the label, the review team considers the totality of the data supportive to recommend inclusion of rash events in the Less Common Adverse Reactions Reported in Clinical Trials section. These data include: (1) treatment-related rash reported in a numerically higher percentage of SOF/VEL subjects (3%) compared to placebo subjects (1%) in the ISS population supporting a causal association between rash and SOF/VEL treatment, (2) treatment-related rash reported in 3% SOF/VEL-treated subjects in the absence of RBV and in 5% SOF/VEL+RBV-treated subjects in ASTRAL-4, (3) rash events reported in the current Sovaldi and Harvoni labels. Hence, although no specific safety signal was detected for serious rash events with SOF/VEL, product labeling similar to Sovaldi and Harvoni is recommended. RBV is labeled for serious rash events, and language in the Clinical Trials Experience Section 6.1 of the label is also proposed referring to the RBV prescribing information for description of RBV-associated adverse reactions when administered with SOF/VEL. Any potential signals of serious rash events associated with SOF/VEL use will be closely monitored in the postmarketing setting.

8.5.5. Rhabdomyolysis

The current SOF and LDV/SOF labels contain information pertaining to creatine kinase elevations. Analyses were performed to assess the frequency of graded increases in creatine kinase among SOF/VEL recipients and to identify cases of clinical rhabdomyolysis.

ASTRAL-1, ASTRAL-2, and ASTRAL -3 (ISS Population)
Graded elevations occurred at comparable frequencies among the four treatment groups (Table 54). According to the Applicant, all Grade 3 and 4 elevations were associated with physical exertion. There were no clinical events of rhabdomyolysis.

Table 54. Summary of Graded Increases in Creatinine Kinase, ISS Population

Creatine Kinase max Analysis Toxicity Grade	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Grade 1 (3 to <6x ULN)	47 (5%)	4 (3%)	7 (5%)	10 (4%)
Grade 2 (6 to <10x ULN)	8 (1%)	0 (0%)	0 (0%)	0 (0%)
Grade 3 (10 to <20x ULN)	5 (<1%)	0 (0%)	0 (0%)	0 (0%)
Grade 4 (≥20x ULN)	4 (<1%)	0 (0%)	0 (0%)	4 (1%)

Source: ISS ADLB and ADSL datasets

ASTRAL-4

A single treatment-emergent case of rhabdomyolysis was reported in ASTRAL-4 occurring post-surgery and associated with anesthetic agents which are labeled for rhabdomyolysis (succinylcholine, propofol).

- 08430-64136 (SOF/VEL+RBV 12 Week) Rhabdomyolysis
  57 year old woman underwent cochlear implant surgery requiring use of succinylcholine, propofol, and droperidol and two days later (Day 77) was diagnosed with rhabdomyolysis associated with myalgia, thigh muscle weakness, Grade 3 AST and Grade 4 CK. SOF/VEL continued, RBV was discontinued due to anemia and the subject recovered. This event was considered unrelated to study drug by the investigator and likely due to anesthetic agents.

CK elevations ≥ Grade 1 occurred in 6% subjects overall (Table 55), with only the single subject (<1%) discussed above experiencing ≥ Grade 3 CK elevations.

Table 55. Summary of Graded Increases in Creatinine Kinase, ASTRAL-4

Creatine Kinase Maximum Toxicity Grade	SOF/VEL 12 Weeks	SOF/VEL+RBV 12 Weeks	SOF/VEL 24 Weeks
Total Number of Subjects in Analysis	90	87	90
Total Subjects with ≥Grade 1 Elevations (%)	6 (7%)	3 (3%)	6 (7%)
Grade 1 (3 to <6x ULN)	2 (2%)	1 (1%)	3 (3%)
Grade 2 (6 to <10x ULN)	4 (4%)	1 (1%)	3 (3%)
Grade 3 (10 to <20x ULN)	0	0	0
Grade 4 (≥20x ULN)	0	1 (1%)	0

Source: ADLB, ASTRAL-4

Overall Assessment: The Applicant has proposed inclusion of creatine kinase in SOF/VEL 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 and Harvoni prescribing information. We will

continue to monitor closely in the postmarketing setting for any potential signals of rhabdomyolysis associated with SOF/VEL use.

8.5.6. Pancreatitis

The current SOF and LDV/SOF labels contain information pertaining to lipase elevations. Analyses were performed to assess the frequency of graded increases in lipase among SOF/VEL recipients and to identify cases of clinical pancreatitis.

ASTRAL-1, ASTRAL-2, and ASTRAL -3 (ISS Population)

Graded lipase elevations were observed in all four treatment groups, including placebo, but the frequency of Grade 3 and 4 events is numerically higher among SOF/VEL subjects (Table 56). Amylase was not measured in ASTRAL-1, -2, or -3. Several cases of Grade 3 lipase were also identified in the Safety Update Report. None of the cases in the ISS population or the SUR were associated with clinical pancreatitis.

Table 56. Summary of Graded Increases in Serum Lipase, ISS Population

Lipase (U/L) max Analysis Toxicity Grade	SOF/VEL 12 Week N=1035	Placebo 12 Week N=116	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Grade 1 (>1 to 1.5x ULN)	61 (6%)	6 (5%)	11 (8%)	12 (4%)
Grade 2 (>1.5 to 3x ULN)	51 (5%)	4 (3%)	3 (2%)	15 (5%)
Grade 3 (>3 to 5x ULN)	29 (3%)	1 (1%)	2 (2%)	2 (1%)
Grade 4 (>5x ULN)	5 (< 1%)	0 (0%)	1 (1%)	3 (1%)

Source: ISS ADLB and ADSL datasets

ASTRAL-4

No clinical cases of pancreatitis were reported in ASTRAL-4. Table 57 displays graded amylase and lipase laboratory data from ASTRAL-4. Amylase was assessed at all study visits and lipase was performed as a reflex test when amylase values were ≥ 1.5x ULN. Overall, transient, asymptomatic amylase and lipase elevations > 3x ULN were observed in 2.6% and 2.2% SOF/VEL-treated subjects, respectively. In the SOF/VEL+RBV 12 Week group, amylase and lipase elevations > 3x ULN were observed in 1.1% and 2.3% SOF/VEL-treated subjects, respectively. In the SOF/VEL 12-24 Week groups, amylase and lipase elevations > 3x ULN were observed in 3.3% and 2.2% SOF/VEL-treated subjects, respectively.

Table 57. Summary of Graded Increases in Serum Amylase and Lipase, ASTRAL-4

Maximum Toxicity Grade	SOF/VEL 12 Week	SOF/VEL + RBV 12 Week	SOF/VEL 24 Week	Total
Total Number of Subjects in Analysis	90	87	90	267
Amylase				
Total Subjects with ≥Grade 1 Elevations (%)	19 (21%)	12 (14%)	21 (23%)	52 (19%)
Grade 1 (>1 to 1.5x ULN)	15 (17%)	7 (8%)	12 (13%)	34 (13%)
Grade 2 (>1.5 to 3x ULN)	2 (2%)	4 (5%)	5 (6%)	11 (4%)
Grade 3 (>3 to 5x ULN)	1 (1%)	1 (1%)	3 (3%)	5 (2%)
Grade 4 (>5x ULN)	1 (1%)	0	1 (1%)	2 (1%)
Lipase				
Total Subjects with ≥Grade 1 Elevations (%)	3 (3%)	2 (2%)	6 (7%)	11 (4%)
Grade 1 (>1 to 1.5x ULN)	1 (1%)	0	3 (3%)	4 (1%)
Grade 2 (>1.5 to 3x ULN)	0	0	1 (1%)	1 (<1%)
Grade 3 (>3 to 5x ULN)	0	2 (2%)	1 (1%)	3 (1%)
Grade 4 (>5x ULN)	2 (2%)	0	1 (1%)	3 (1%)

Source: ADLB ASTRAL-4

Reviewer Comment: Though the lipase elevations are not associated with clinical pancreatitis, labeling is warranted to alert health care providers of the potential risk. Amylase and lipase data in ASTRAL-4 are similar to data from ASTRAL-1, -2 and -3 and it is recommended to add ASTRAL-4 SOF/VEL+RBV 12 Week lipase data to the SOF/VEL label. This approach is consistent with the approach used in the LDV/SOF label which includes lipase data from LDV/SOF regimens in the ION-1, -2 and -3 trials along with data from LDV/SOF+RBV regimen in the SIRIUS trial. We will continue to monitor closely in the postmarketing setting for any potential signals of pancreatitis associated with SOF/VEL 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)*

The LDV/SOF label does not contain language related to pancytopenia because no cases of pancytopenia were identified during review of the pivotal Phase 3 data supporting the original LDV/SOF NDA approval or during review of the s002-006 data.

No pancytopenia cases occurred in the ISS population. The one subject with treatment-emergent pancytopenia in ASTRAL-4 was not concerning for SOF/VEL toxicity: Subject 07275-64023 (SOF/VEL 12 Week) was diagnosed with lymphoma and experienced pancytopenia associated with chemotherapy treatment.

Reviewer Comment: Though 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 use and thus no relevant labeling is recommended. This recommendation is supported by lack of pancytopenia signal identified in NDA/sNDA reviews of the interferon-free LDV/SOF regimen. We will continue to monitor closely in the postmarketing setting for any potential signals of pancytopenia events associated with SOF/VEL use.

8.5.8. Safety Profile Among Subjects with Baseline CPT A, B or C Cirrhosis

Safety analyses were performed to identify unique SOF/VEL-containing treatment safety signals in subjects with different baseline CPT cirrhosis classes. As stated previously, ASTRAL-4 enrolled subjects with CPT B cirrhosis at screening; however, a proportion of subjects switched to class A or C at baseline.

Subjects with baseline CPT C cirrhosis (N=11) had higher percentages of SAEs in the SOF/VEL+RBV 12 Week (50%, 2/4 subjects) and SOF/VEL 24 Week (50%, 3/6 subjects) groups compared to subjects with baseline CPT A or B (approximately 15%) cirrhosis, reflecting more advanced underlying liver disease. SAEs in CPT C subjects included infectious colitis, cellulitis/skin ulcer in the SOF/VEL+RBV 12 Week group and incarcerated umbilical hernia (fatal), pulmonary HTN, HRS/hypotension/peritonitis/sepsis/adrenal insufficiency associated with OLT in the SOF/VEL 24 Week group. One CPT C subject died from liver failure posttreatment Day 39 following development of incarcerated umbilical hernia and subsequent complications (02760-64102; SOF/VEL 24 Week).

Anemia was the only AE occurring in more than one CPT C subject (3 subjects, SOF/VEL+RBV 12 Week group). Two CPT C subjects discontinued RBV and one subject dose reduced RBV due to AEs of anemia and asthenia.

Reviewer Comment: No exposure or unique safety issues are identified precluding SOF/VEL+RBV use in the CPT C population: the reported safety events are seen in this population with advanced liver disease. Despite small overall subject numbers subjects with baseline CPT C cirrhosis, the review team supports extending the SOF/VEL+RBV 12 Week dosing recommendation to both the CPT B and C populations. This recommendation is based upon consideration of decompensated cirrhosis as a single population rather than two discreet decompensated cirrhosis sub-populations of CPT B and CPT C. Additional safety data of SOF/VEL-containing therapy in the CPT C population is recommended as a PMR to further evaluate unique safety signals that may impact future labeling. We will continue to monitor closely in the postmarketing setting for any potential serious safety signals associated with SOF/VEL use in the CPT C population.

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 the ASTRAL-1, 2, and 3 in aggregate (ISS population), and ASTRAL-4 separately. 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 subjects treated with SOF/VEL.

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 PK. Female sex was the only statistically significant covariate, with higher exposures relative to males for SOF, GS-331007, and VEL. Exposure-safety analyses performed by the FDA pharmacometrics team did not reveal any significant safety concerns associated with the higher exposures in females or in any other demographic subgroup.

Age

ISS Population

Subjects < 65 years of age (n=912) were compared to subjects ≥65 years old (n=123). The older cohort comprised 12% of the ISS population. Five of the 6 deaths occurred in subjects < 65 years of age; though deaths were numerically higher among the younger cohort, all 6 subjects were 52 to 66 years of age which cluster around the threshold for comparison (65 years). In addition, all deaths were deemed unrelated to study medication. The percentage of subjects with SAEs and Grade 3 and 4 AEs was equal between the two groups at 2% and 4% respectively. Related events (ADRs) were numerically higher among subjects < 65 years of age (56% for < 65 years versus 50% for greater than 65 years) but the percentage of subjects with all-cause adverse events of any severity grade were nearly equal at 81-82%. Headache, fatigue, and nausea were the most frequent ADRs and AEs in both groups. A higher percentage of subjects ≥65 years had graded laboratory abnormalities (70% versus 64%). This difference was largely driven by a higher proportion of subjects ≥65 years with hyperglycemia, the majority of whom were diabetic. Because the risk of diabetes itself increases with advancing age, the observed relationship between hyperglycemia and age is unlikely related to SOF/VEL exposure.

ASTRAL-4

There was no upper age limit entry criterion in ASTRAL-4. An age cutoff of 65 years was selected to evaluate safety events in elderly subjects. Approximately 12% subjects in ASTRAL-4 were ≥65 years old (33 subjects, range 65-76 years): 9 subjects SOF/VEL 12 Week, 13 subjects SOF/VEL+RBV 12 Week and 11 subjects SOF/VEL 24 Week groups.

Higher percentages of SOF/VEL-treated subjects aged ≥65 years experienced SAEs (22%-36%) compared with subjects aged <65 years (14%-19%). There was no pattern to the types of SAEs

reported in these SOF/VEL-treated subjects aged ≥65 years. Sepsis (N=2) was the only SAE preferred term reported in more than one SOF/VEL-treated subject aged ≥65 years. In the SOF/VEL+RBV 12 Week group, more subjects aged ≥65 years had ADRs (85%) compared with subjects <65 years (66%). This difference was driven by higher percentages of treatment-related fatigue (54%), insomnia (31%) and diarrhea (31%) in subjects ≥65 years compared with subjects <65 years (range 7%-28% for fatigue, insomnia or diarrhea). Overall ADRs were similar between subjects aged ≥65 years versus <65 years in the SOF/VEL 12 (44% versus 51%) and 24 Week (36% versus 38%) groups. The most common ADRs occurring in SOF/VEL alone-treated subjects aged ≥65 years from ASTRAL-4 were fatigue (18%, 3 subjects) and nausea (18%, 3 subjects).

Reviewer Comment: No overall SOF/VEL-containing treatment safety differences were observed between subjects aged ≥65 years and younger subjects: other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Gender

ISS Population

Women comprised 39% of the ISS SOF/VEL population (405/1035). Among the 6 deaths, 4 occurred in men and 2 occurred in women. SAEs and Grade 3 or 4 AEs occurred at numerically higher rates in women versus men: SAEs occurred in 4% of women and 2% of men; Grade 3 and 4 events occurred in 4% of women and 3% of men. There was no pattern to these events. ADRs occurred in a comparable percentage of women and men (68% and 67%, respectively), but the overall incidence of AEs was higher in women compared to men: 85% versus 79%, respectively. This observation is driven primarily by differences in the percentages of women and men with headache (33% versus 26%), fatigue (28% versus 24%), nausea (21% versus 10%), insomnia (14% versus 11%), and nasopharyngitis (13% versus 10%). In contrast, Grade 3 and 4 laboratory abnormalities were slightly more common in men (9%) than women (5%). As noted in Section 4.5, 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.

ASTRAL-4

In ASTRAL-4, women comprised 30% (81 subjects) of enrolled subjects. Similar percentages of female and male subjects experienced SAEs in the SOF/VEL 12 and 24 Week groups. SOF/VEL+RBV-treated female subjects had higher percentage of SAEs (7 subjects, 33%) compared with male subjects (7 subjects, 11%); however, there was no identified pattern to the types of SAEs in this group and no SAE occurred in more than one subject. Women had higher percentage of treatment-related AEs across all SOF/VEL-containing groups (44%-71%)

compared with men (35%-68%). The most common ADRs occurring in SOF/VEL alone-treated female subjects were headache (13 subjects, 22%), fatigue (11 subjects, 18%) and nausea (8 subjects, 13%). The most common ADRs occurring in SOF/VEL+RBV-treated female subjects from ASTRAL-4 were anemia (9 subjects, 43%), fatigue (8 subjects, 38%) and nausea (6 subjects, 29%). ADRs occurring ≥5% more in SOF/VEL-treated women than in men were:

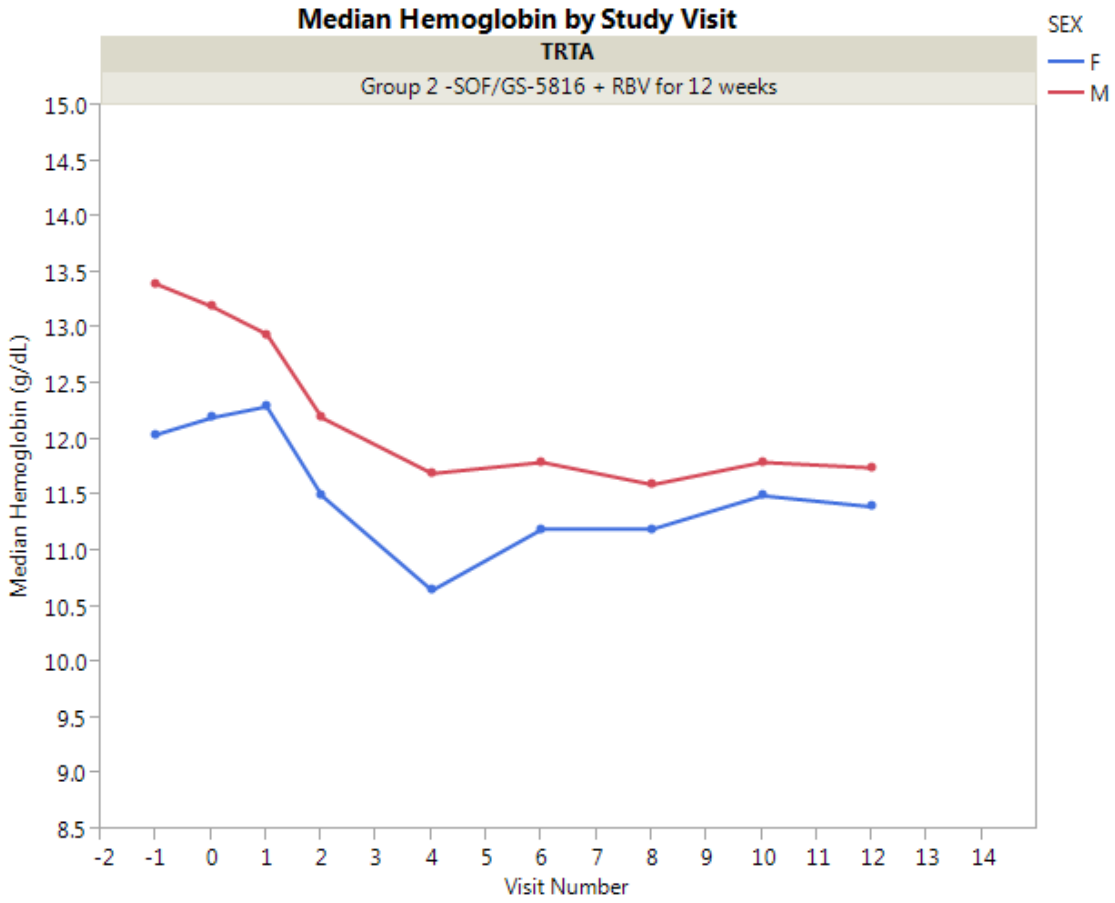
- SOF/VEL 12 or 24 Week Groups: headache (22% versus 9%)
- SOF/VEL+RBV 12 Week Group: anemia (43% versus 21%), fatigue (38% versus 30%), nausea (29% versus 11%)

ADRs occurring ≥5% more in SOF/VEL-treated men than in women were:

- SOF/VEL 12 or 24 Week Groups: insomnia (8% versus 2%)
- SOF/VEL+RBV 12 Week Group: insomnia (15% versus 0%)

Female subjects in the SOF/VEL+RBV 12 Week group had higher percentages of AEs leading to RBV discontinuation (5 subjects, 24%) or interruption/modification (10 subjects, 48%) compared with male subjects (12% and 25%, respectively). This finding is supported by data presented in Figure 6 demonstrating female subjects in the SOF/VEL+RBV 12 Week group had greater median on-treatment hemoglobin decrease versus male subjects.

Figure 6. Median Hemoglobin by Study Visit in SOF/VEL+RBV 12 Week Arm, By Gender, ASTRAL-4



Source: ADLB, ASTRAL-4

Review Comment: This numerical trend of greater anemia and RBV discontinuation/modification in women receiving RBV-containing treatment does not raise concern for a unique RBV toxicity in SOF/VEL-treated female subjects. Compared with men, women in ASTRAL-4 had lower pretreatment hemoglobin levels (median 12.2 g/dL versus 13.2 g/dL, respectively) and by lower median BMIs (27.8 kg/m2 versus 28.8 kg/m2, respectively) which may account for higher overall RBV exposures from the weight-based RBV dosing.

Race

ISS Population

Differences between racial groups were more difficult to assess due to the predominance of white subjects in the study population. In the SOF/VEL group, 84% of subjects are white, 6% are black, 8% are Asian, and 2% are other (Pacific Islander, Alaska native, mixed race). For this

analysis, Asians were grouped with "other" to form three comparison groups: white, black, and non-white/non-black.

SAEs occurred in a similar percentage of subjects in each racial group (3% white, 1% black, 3% non-white/non-black), as did Grade 3 and 4 AEs (4% white, 2% black, 3% non-white/non-black). ADRs occurred among a numerically higher percentage of white subjects compared to the other two groups (57% white, 47% black, 49% non-white/non-black) but there was no clear pattern in the types of ADRs that led to this imbalance. Overall AEs (all grade, all cause) were reported in 81% of whites, 74% of blacks, and 66% of non-white/non-blacks. Safety analyses were conducted by SOC and PT to identify specific organ systems or disease processes driving the imbalance. Tables 58 and 59 summarize SOC or PT with a > 5% difference in occurrence between any two of the three groups.

Table 58. SOCs with >5% Increased Frequency in One Racial Group, All Cause, All Grade, ISS SOF/VEL Population

Body System Organ Class	White n=867	Black n=61	Non-white/non-black n=102
Total AEs	706 (81%)	45 (74%)	67 (66%)
Gastrointestinal disorders	319 (37%)	16 (26%)	32 (31%)
Nervous system disorders	318 (37%)	27 (44%)	23 (23%)
General disorders and administration site conditions	292 (34%)	14 (23%)	28 (27%)
Infections and infestations	289 (33%)	17 (28%)	29 (28%)
Psychiatric disorders	194 (22%)	5 (8%)	15 (15%)
Respiratory, thoracic and mediastinal disorders	123 (14%)	9 (15%)	8 (8%)

Source: ISS ADAE and ADSL datasets

Table 59. PTs with >5% Increased Frequency in One Racial Group, All Cause, All Grade, ISS SOF/VEL Population

Dictionary Derived Term	White n=867	Black n=61	Non-white/non-black n=102
Total AEs	706 (81%)	45 (74%)	67 (66%)
Headache	254 (29%)	22 (36%)	17 (17%)
Nausea	126 (15%)	3 (5%)	6 (6%)
Diarrhoea	63 (7%)	2 (3%)	8 (8%)
Irritability	48 (6%)	0 (0%)	1 (1%)
Cough	47 (5%)	6 (10%)	4 (4%)
Pruritus	24 (3%)	5 (8%)	3 (3%)
Myalgia	32 (4%)	0 (0%)	6 (6%)

Source: ISS ADAE and ADSL datasets

Reviewer Comment: There is no clear pattern to the differences in AE reporting between racial groups, and it is possible that the differences may be less notable had there been more equal representation between racial groups.

ASTRAL-4
No differences in overall AE profile were identified in ASTRAL-4 based on assessment of race. No deaths occurred in Black/African American or Asian subjects. A single SAE occurred in a Black/African American subject of radius/tibia fracture. The only related AE occurring in more than one Black/African American subject receiving SOF/VEL+RBV 12 Week was fatigue (N=2, 40%). Related AEs occurring in more than one Black/African American subject receiving SOF/VEL 12 or 24 Week were fatigue (N=2, 17%) and nausea (N=2, 17%).

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 treatment (generally 12 weeks) and follow-up (generally 24 weeks) in clinical trials limits the assessment for oncologic events. Seven subjects in the ISS SOF/VEL population had an event in the Neoplasms Benign, Malignant, and Unspecified SOC, none of which were treatment emergent. PTs included skin papilloma, lymphoproliferative disorder, melanocytic naevus, metastasis to the central nervous system, pituitary tumor, lung neoplasm malignant, and lung cancer neoplastic. There were no cases of HCC.

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

ASTRAL-4
In ASTRAL-4, 10 subjects (3.7%) experienced an event within the SOC of Neoplasms Benign, Malignant and Unspecified: 7 subjects with treatment emergent AEs (HCC (4), prostate cancer, sweat gland tumor, lymphoma) and 3 subjects with post-treatment AEs (HCC (2), lymphoma). None of these events was considered related to study drug by the investigator. One additional 'hepatic lesion case' (08230-64033, SOF/VEL 24 Week) was further categorized by the Applicant as possible or probable HCC and one HCC case was confirmed in the SUR (00331-64096, SOF/VEL 24 Week).

The eight cases of HCC or possible/probable HCC reported in ASTRAL-4 (2.6%) occurred in subjects with decompensated cirrhosis with most cases occurring more than six months after SOF/VEL treatment initiation (88%, range of onset Day 77 to >3.5 months post SOF/VEL 24 Week treatment). All but one case occurred in the SOF/VEL 24 Week group which had the longest treatment and posttreatment follow up period (approximately 48 weeks): no HCC cases occurred in the SOF/VEL+RBV 12 Week group. One subject died posttreatment Day 169 as a result of HCC (00331-64096, SOF/VEL 24 Week, SUR report).

Reviewer Comment: A strong association between chronic HCV infection and HCC has been observed, and HCC occurs almost exclusively in patients with advanced hepatic fibrosis or cirrhosis. Bruix J and Sherman M report an annual HCC incidence of 3%-5% in the chronic HCV cirrhotic population.[19] CPT B and C cirrhosis are independent risk factors for developing HCC in the cirrhotic population.[20] The reports of HCC identified in ASTRAL-4 do not demonstrate a definitive causal relationship between SOF/VEL and development or acceleration of HCC, rather these HCC cases are more likely explained by the underlying decompensated cirrhosis status.

The remaining ASTRAL-4 reported neoplasms do not support relevant SOF/VEL labeling because they either occurred in a single subject or are associated with chronic HCV infection which confounds causality assessment (lymphoma in two subjects, one Day 9 (07275-64023, SOF/VEL 12 Week) and one >3 months posttreatment (01039-64171, SOF/VEL 24 Week, lost to follow up/noncompliance Day 100).

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.

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 five pregnancies have been reported during the SOF/VEL development program, 2 in female subjects and 3 in the female partners of male subjects. The 5 cases are briefly summarized below.

1) A female subject in Study 0102 who received SOF + VEL 100 mg for 12 weeks had a confirmed pregnancy confirmed on post-treatment Day 97. She went on to deliver a full-term, healthy baby girl.
2) A female subject in Study 0122 who received SOF + VEL 100 mg for 8 weeks had a confirmed pregnancy > 7 weeks post treatment completion. She subsequently underwent an uncomplicated elective induced abortion.
3) The female partner of a male subject treated with SOF/VEL for 12 weeks in ASTRAL-1 was pregnant at the start of the study. She delivered a full-term, healthy baby boy.
4) The female partner of a male subject treated with SOF + VEL 25 mg + RBV for 8 weeks had a confirmed pregnancy on her partner's post-treatment Day 146. No additional information is

available.

5) The female partner of a male subject treated with SOF + VEL 25mg in Study 0109 had a confirmed pregnancy during the study. The subject discontinued study treatment on Day 11 and subsequently withdrew consent. No additional information is available.

No additional pregnancies were reported in the SUR.

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 on August 1, 2014. 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 February 18, 2015.

In brief, the proposed pediatric development plan includes two studies to evaluate the safety and efficacy of SOF/VEL in children ages 3 to < 18 years of age. (b) (4)

The Applicant has requested a deferral of pediatric studies until data from Phase 3 studies are complete 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 < 3 years of age. The Division agrees with this proposal as well, given the high rate of spontaneous viral clearance and lack of significant disease progression in this age group. The deferral and waiver requests will be presented to the PeRC, and final actions regarding these requests will be made pursuant to the PeRC's recommendations.

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

The potential for drug abuse, withdrawal, or rebound with SOF/VEL 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, which is 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. The mechanism for this effect is unknown: a PMR (NDA 204671 PMR 2993-1) was issued to evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between SOF and amiodarone, with and without other HCV DAAs using appropriate in vitro approaches (including, but not limited to, patch clamp studies of L-type and T-type calcium channels and transporter phenotyping). These mechanistic studies are ongoing.

Reviewer Comment: Similar Warnings and Precautions language regarding the risk for serious symptomatic bradycardia when SOF/VEL is coadministered with amiodarone is proposed for the SOF/VEL label.

(b) (4)

(b) (4)

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 pivotal 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

There are no additional safety issues from other disciplines that are not presented elsewhere in this review.

8.11. Integrated Assessment of Safety

No major safety issues or concerns specifically related to SOF or VEL were identified in this review. In the ISS population as well as the decompensated population, headache, fatigue, and nausea were the most common AEs reported across major clinical trials in which subjects received SOF/VEL without RBV for 12 weeks, and all occurred at rates similar to the active comparator or placebo. No notable differences appeared with increased duration of SOF/VEL without RBV from 12 to 24 weeks in ASTRAL-4. Decompensated subjects treated with SOF/VEL with RBV had notably higher rates of most AEs compared to SOF/VEL without RBV, as well as events commonly reported with RBV exposure such as anemia, dyspnea, rash, and pruritus. In addition to these common adverse reactions, RBV is associated with serious risks, but these safety issues are well known. There was no suggestion that coadministration of SOF/VEL with RBV exacerbated the toxicity potential of either SOF/VEL or RBV.

Sections 5 and 6 of the SOF/VEL label will include information from the Sovaldi label as well as reference to RBV labeling. No new safety issues unique to SOF/VEL 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.

1 INDICATIONS AND USAGE

For consistency with labeling of other DAAs, add the phrase “with or without ribavirin” to the indication sentence

2 DOSAGE AND ADMINISTRATION

In the title of Table 1, replace [redacted] (b) (4) with "GT 1, 2, 3, 4, 5, 6 HCV." [redacted] (b) (4) .

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience

- In accordance with current best practices for labeling, [redacted] (b) (4) In addition, the 5% cut-off should be revised to 2% to allow the display of more ADRs. The clinical team also recommends the inclusion of the SOF+ RBV 12 week group as an additional comparator, which helps characterize the safety profile of SOF/VEL. *(See Section 8.4.5)*
- For the same reasons listed above, the section describing ASTRAL-4 events should be revised to include all grade ADRs in the SOF/VEL+RBV 12 Week group occurring ≥10%. *(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 label), even if events occurred rarely in the SOF/VEL trials. This section will likely include depression and rash. *(See Sections 8.5.3-8.5.7)*
- Laboratory data from ASTRAL-4 will be included in the Laboratory Abnormalities section for completeness. *(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

- Revise PPI section to state that coadministration is not recommended. This recommendation is based on reduced solubility of VEL with higher gastric pH, which results in significantly lower VEL exposures.
- Revise anticonvulsants and antimycobacterials to state that coadministration is not recommended
- Add topotecan to the list of agents that are not recommended
- [redacted] (b) (4) regarding TDF-containing products if ASTRAL-5 safety data are favorable. The Applicant has agreed to submit updated ASTRAL-5 safety data during this review cycle, and the final determination regarding labeling of SOF/VEL with TDF-containing products will be made pending review of the data. *(See Section 4.5)*
- Add atorvastatin to the table based on post-marketing reports of rhabdomyolysis with other SOF-containing DAA regimens. *(See Section 8.9.1)*

7.4 Drugs without Clinically Significant Interactions with [TRADENAME]

- Add TAF-containing products and rilpivirine containing products
- Revise language regarding methadone

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Revise pregnancy and lactation language to conform to the most recent PLLR guidance
- Add a warning about RBV to 8.3 (Females and Males of Reproductive Potential) for consistency with other DAA regimens administered with RBV

8.6 Renal Impairment

- Add reference to the RBV package insert for dosing recommendations for patients with renal insufficiency

8.7 Hepatic Impairment

- Add language about laboratory monitoring for patients with decompensated cirrhosis *(See Section 8.5.1)*

12 CLINICAL PHARMACOLOGY

12.4 Microbiology

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

14 CLINICAL STUDIES

14.1 Description of Clinical Trials

- Edit the description of trials in 14.1 to enable inclusion of all trial arms (including unapproved regimens) in the overview of trial design

14.3 Clinical Trials in Subjects with Decompensated Cirrhosis

- Remove information about (b) (4) . (*See Section 6.4.2)*

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 for the treatment of chronic hepatitis C in children, as required under the Pediatric Research Equity Act (PREA).
- Formal submission of data from ASTRAL-5 will be requested as a PMR to assess the safety of treatment with SOF/VEL in subjects with HIV/HCV coinfection who are receiving antiretroviral therapy for HIV.
- A PMR to evaluate the safety and efficacy of SOF/VEL + RBV in GT3 cirrhotics will be recommended.
- A PMR regarding submission of trial data in the HCV population with decompensated CPT C cirrhosis is recommended to obtain SOF/VEL safety data in a broader decompensated cirrhosis population. Please see Section 8.5.8 for additional details supporting this recommendation.
- To assess the durability of SVR and impact of achieving SVR12 on clinical outcomes in patients with cirrhosis, including decompensated cirrhosis (e.g., progression or regression of liver disease, occurrence of HCC, need for liver transplantation), a PMC to submit 5 year follow-up data from the ongoing long-term registry trial (GS-US-337-1431), will be requested.

The clinical pharmacology team has proposed issuing a PMR for a DDI study between SOF/VEL and atorvastatin. (b) (4) .

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

13 Appendices

13.1. References

1. Gower E, Estes C, Blach, S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of hepatitis C infection. Journal of Hepatology, 2014; 61:S45-S57.
2. Dibonaventura MD, Yuan Y, Lescrauwaet B, et al. Multicountry burden of chronic hepatitis C viral infection among those aware of their diagnosis: a patient survey. PLoS One. 2014;9(1):e86070.

3. Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology. 2014;59(1):318–327.
4. Fattovich G, Giustina G, Degos F, Tremolada F, Diodati G, Almasio P, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997;112 (2):463-72.
5. Planas R, Ballesté B, Alvarez MA, Rivera M, Montoliu S, Galeras JA, Santos J, Coll S, Morillas RM, Solà R. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. J Hepatol. 2004 May;40(5):823-30.
6. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308(24):2584-93.
7. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol. 2011;9(6):509-516.
8. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol. 2010;8(3):280-8, 288.
9. Pearlman BL. Hepatitis C Infection in African Americans. Clin Infect Dis. (2006) 42 (1): 82-91.
10. Everson GT. Treatment of patients with hepatitis C virus on the waiting list. Liver Transpl. 2003;9(11):S90-S94.
11. Gotthardt D, Weiss KH, Baumgärtner M, Zahn A, Stremmel W, Schmidt J, Bruckner T, Sauer P. Limitations of the MELD score in predicting mortality or need for removal from waiting list in patients awaiting liver transplantation. BMC Gastroenterol. 2009 Sep 25;9:72.
12. Guidance for Industry Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment (Draft Guidance October 2013) http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm225333.pdf
13. Romo EM, Munoz-Robles JA, Castillo-Rama M, Meneu JC, Moreno-Elola A, Perez-Saborido B, et al. Peripheral blood lymphocyte populations in end-stage liver diseases. J Clin Gastroenterol 2007;41 (7):713-21.
14. Harrington PR, Fleischer R, Connelly SM, Lewis LL, Murray J. Ribavirin Reduces Absolute Lymphocyte Counts in Hepatitis C Virus-Infected Patients Treated With Interferon-Free, Direct-Acting Antiviral Regimens. Clin Infect Dis. 2015 Sep 15;61(6):974-7.
15. Kobayashi T, Hige S et al. Anemia and thrombocytosis induced by ribavirin monotherapy in patients with chronic hepatitis C. J Gastroenterol 2012 (47):1228–1237.

16. Castro M, Krowka MJ, Schroeder DR, Beck KC, Plevak DJ, Rettke SR, et al. Frequency and clinical implications of increased pulmonary artery pressures in liver transplant patients. Mayo Clin Proc 1996;71 (6):543-51.
17. Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991;100 (2):520-8.
18. Ramsay MA, Simpson BR, Nguyen AT, Ramsay KJ, East C, Klintmalm GB. Severe pulmonary hypertension in liver transplant candidates. Liver Transpl Surg 1997;3 (5):494-500.
19. Bruix J, Sherman M. Management of Hepatocellular Carcinoma: An Update. Hepatology 2010 as referenced in Table 2 of UpToDate Epidemiology and etiologic associations of hepatocellular carcinoma. Schwartz JM, Carithers RL. January 6, 2016.
20. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut. 2001 Feb;48(2):251-9.

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.

Covered Clinical Study (Name and/or Number):
GS-US-342-1138 (ASTRAL-1), GS-US-342-1139 (ASTRAL-2), GS-US-342-1140 (ASTRAL-3), GS-US-342-1137 (ASTRAL-4), GS-US-342-0102, GS-US-342-0109, GS-US-337-0122, Cohort 4 (ELECTRON-2)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 909 Overall: 150 Principal Investigators, 759 Sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 44		
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: 42 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 2 1. [redacted] was a PI on studies [redacted] until study completion; and a PI on Studies [redacted] until August 28, 2015. [redacted] became a full-time employee of Gilead on [redacted] and is no longer an investigator for these four studies, or any other Gilead-sponsored clinical study. 2. [redacted] was a sub-investigator at [redacted] site for studies [redacted] until 01 February 2015. [redacted] became a full-time employee of Gilead on [redacted] is no longer an investigator for Studies [redacted], 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 3%. 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

Table 60. Treatment-emergent SAEs Reported in at Least 1 SOF/VEL Subject, Preferred Terms, ISS Population

Dictionary Derived Term	SOF/VEL 12 Week N=1035	SOF + RBV 12 Week N=132	SOF + RBV 24 Week N=275
Acute myocardial infarction	2 (<1%)	0 (0%)	0 (0%)
Upper limb fracture	1 (<1%)	0 (0%)	0 (0%)
Sudden death	1 (<1%)	0 (0%)	0 (0%)
Cellulitis	1 (<1%)	0 (0%)	1 (<1%)
Small intestinal obstruction	1 (<1%)	0 (0%)	0 (0%)
COPD	1 (<1%)	0 (0%)	1 (<1%)
Rotator cuff syndrome	1 (<1%)	0 (0%)	0 (0%)
Pneumonia	1 (<1%)	0 (0%)	0 (0%)
Palpitations	1 (<1%)	0 (0%)	0 (0%)
Ovarian cyst ruptured	1 (<1%)	0 (0%)	0 (0%)
Mania	1 (<1%)	0 (0%)	0 (0%)
Lung neoplasm malignant	1 (<1%)	0 (0%)	0 (0%)
Ligament sprain	1 (<1%)	0 (0%)	0 (0%)
Intracranial aneurysm	1 (<1%)	0 (0%)	0 (0%)

Influenza	1 (<1%)	0 (0%)	0 (0%)
Haematochezia	1 (<1%)	0 (0%)	0 (0%)
Gastroenteritis	1 (<1%)	0 (0%)	0 (0%)
Abdominal pain	1 (<1%)	0 (0%)	0 (0%)
Abscess limb	1 (<1%)	0 (0%)	0 (0%)
Bronchitis	1 (<1%)	0 (0%)	0 (0%)
Appendicitis	1 (<1%)	0 (0%)	0 (0%)
Vestibular neuronitis	1 (<1%)	0 (0%)	0 (0%)
Cholecystitis acute	1 (<1%)	0 (0%)	0 (0%)
Enteritis	1 (<1%)	0 (0%)	0 (0%)
Epilepsy	1 (<1%)	0 (0%)	0 (0%)
Extremity necrosis	1 (<1%)	0 (0%)	0 (0%)
Food poisoning	1 (<1%)	0 (0%)	0 (0%)

Source: ISS ADAE and ADSL datasets

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRABHA VISWANATHAN
03/29/2016

SARAH M CONNELLY
03/29/2016

KIMBERLY A STRUBLE
03/29/2016