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APPLICATION NUMBER:

205834Orig1s007, s008, s009

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	February 10, 2016
From	Poonam Mishra, MD, MPH Deputy Director for Safety
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 205834
Supplement#	S007-009
Applicant	Gilead Sciences, Inc.
Date of Submission	August 26, 2015
PDUFA Goal Date	February 26, 2016
Proprietary Name / Established (USAN) names	HARVONI ledipasvir, sofosbuvir
Dosage forms / Strength	Fixed Dose Combination Tablet (FDC) containing: Ledipasvir 90 mg Sofosbuvir 400 mg
Proposed Indication(s)	To expand the use in patients with chronic hepatitis C virus infection with 1. Genotypes 1 & 4, who are post liver transplantation with compensated liver disease 2. Genotype 1, with decompensated liver disease regardless of transplantation status
Recommended:	Approval

1. Introduction

The Applicant (Gilead Sciences, Inc.) has submitted three efficacy supplements to NDA 205834 (7, 8, & 9) seeking to expand the indication in patients with chronic hepatitis C virus (HCV) infection, genotypes 1 & 4 who are posttransplantation with compensated liver disease as well as patients with decompensated liver disease with genotype 1 HCV infection, regardless of transplantation status. Specifically, these efficacy supplements include the following subpopulations:

- S-007: Liver transplant recipients with genotype 1 HCV infection
- S-008: Liver transplant recipients with genotype 4 HCV infection
- S-009: Patients with decompensated cirrhosis with genotype 1 HCV infection

Harvoni, a fixed dose combination (FDC) tablet containing ledipasvir 90 mg/sofosbuvir 400 mg, was approved for the treatment of chronic HCV infection in the United States (US) on October 10, 2014. Ledipasvir (LDV) is an HCV inhibitor targeting the HCV nonstructural protein 5A (NS5A) and sofosbuvir (SOF) is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase. SOF was approved for the treatment of chronic hepatitis C (CHC) infection in combination with other HCV agents on

December 6, 2013. The LDV/SOF FDC was initially approved for the treatment of CHC genotype 1 infection in adults without cirrhosis or with compensated cirrhosis. In 2015, the indication was extended to adults with compensated cirrhosis with genotype 4, 5, or 6; and those with HIV-1/HCV genotype 1 or 4 coinfection.

The submission contains data from two Phase 2 trials GS-US-337-0123 (SOLAR-1) and GS-US-337-0124 (SOLAR-2) to support the safety and efficacy of LDV/SOF plus ribavirin (RBV) for 12 weeks in the proposed patient populations - those with HCV genotype 1 or 4 infection who are liver transplant recipients with compensated liver disease as well as those with HCV genotype 1 infection with decompensated liver disease, regardless of transplantation status.

This CDTL review will provide a brief overview of the clinical safety, efficacy, and virology reviews. For detailed assessments, please refer to respective discipline's primary reviews. In particular, this review will focus on the safety and efficacy data in decompensated population as well as in the post liver transplant population as data in these subpopulations has not been previously submitted and reviewed under this NDA.

2. Background

CHC is a global public health problem with an estimated 185 million people worldwide and 3.2 million persons in the US with HCV infection (Mohd Hanafiah 2013, Armstrong, 2006). The natural history of CHC involves progression to cirrhosis, hepatocellular carcinoma (HCC), end stage liver disease, and death. CHC is the most common reason for liver transplantation in the US. By 2007 there were more yearly deaths in the US related to HCV than HIV-1 and, without effective treatment interventions, significant increases in CHC-associated morbidity, mortality, and healthcare costs were predicted (Ly 2012, Wong 2000).

Evaluating clinical outcomes from prospective, randomized controlled clinical trials in patients infected with HCV is challenging and not feasible because of the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration (many years) to identify late-occurring clinical events such as HCC; therefore, treatment response is defined by virological parameters. The most important virologic parameter has been the sustained virologic response (SVR) which is defined as undetectable HCV RNA in serum after a predefined number of weeks following the completion of therapy.

SVR is an objective endpoint that signifies long-term clearance of hepatitis C and is generally regarded as a "virological cure". Multiple observational cohorts have shown strong correlations between achieving SVR and improved clinical outcomes such as decreased HCC, end-stage liver complications, and mortality. Attainment of SVR in CHC patients has shown to be associated with a decreased progression of fibrosis,

and some studies have even suggested reversal of fibrosis or early cirrhosis (Poynard 2000 & 2002).

With the aging of the infected population, CHC-related complications such as decompensated cirrhosis and HCC are increasing and it is estimated that by 2019-2020 there will be approximately 145,000 annual cases of decompensated cirrhosis and 14,000 cases of HCC (Davis 2010). The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation and HCC. Without effective treatment, the recurrence of HCV after liver transplantation is universal and is associated with accelerated progression of fibrosis and significant morbidity and mortality.

Interferon (IFN)-based regimens have not been recommended for use in patients with decompensated liver disease and liver transplantation had been the only treatment option. Approval of multiple IFN-free regimens since 2013 has paved the way for treatment of these patients who have been awaiting therapy all these years. Currently approved IFN-free regimens for the treatment of HCV infection include SOF plus RBV; fixed-dose LDV/SOF; simeprevir (SMV, a NS3/4A protease inhibitor) in combination with SOF; a co-packaged triple-DAA regimen (Viekira Pak) consisting of ombitasvir, paritaprevir/ritonavir, and dasabuvir (NS5A inhibitor, ritonavir-boosted NS3/4A PI, and nonnucleoside NS5B-palm polymerase inhibitor, respectively); a regimen consisting of ombitasvir, paritaprevir/ritonavir (Technivie); and a regimen of daclatasvir (DCV, NS5A inhibitor) in combination with SOF. Recent approval of a fixed dose combination of elbasvir, a HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor has expanded the available treatment options.

Notably, the majority of the above-mentioned regimens are indicated only in patients with compensated cirrhosis; with limited therapeutic options available to the specific populations such as, those with decompensated cirrhosis or those who are liver transplant recipients. Particularly, HCV protease inhibitor based regimens are either not recommended or contraindicated for use in patients with decompensated liver disease due to risk of liver failure. Specifically, the only approved regimen for decompensated patients is daclatasvir in combination with sofosbuvir taken with or without RBV. For post-transplant patients, available options include the above-mentioned regimen of DCV plus SOF with or without RBV, and Viekira Pak with RBV in patients with normal hepatic function and mild fibrosis (Metavir fibrosis score 2 or lower).

The available data showing the long-term benefits of achieving SVR in HCV patients who have decompensated liver disease and/or post-liver transplantation is limited and needs to be demonstrated in a systematic manner. However, the published data from patients with decompensated cirrhosis due to chronic hepatitis B virus infection suggests that reversal of decompensation is possible with effective therapeutic interventions (Zoulim 2008).

Clinical protocols submitted under IND were reviewed by the review team throughout the course of the product's development, with feedback provided as appropriate. In addition, a pre-NDA meeting was held with the sponsor including the hepatology expert panel convened by the sponsor.

3. CMC/Device

No changes to the chemistry, manufacturing, and controls for the HARVONI tablet are proposed with this application.

4. Nonclinical Pharmacology/Toxicology

No nonclinical safety studies were submitted with these supplements. Refer to original Pharmacology/Toxicology Review for NDA 205834.

Sections 8.1 and 8.2 of the Prescribing Information (PI) were updated to be consistent with the Pregnancy and Lactation Labeling Final Rule. Please refer to Pharmacology/Toxicology Review by Christopher Ellis, Ph.D. for details.

5. Clinical Pharmacology/Biopharmaceutics

No new information for pharmacology; in vitro or nonclinical data; absorption, distribution, metabolism, and elimination (ADME); or pharmacokinetics (PK) profile studies or analyses between healthy and HCV-infected subjects is included with these supplements. New data for population PK analyses was submitted. Please refer to Clinical Pharmacology Review by Dr. Florian for a detailed assessment. In addition, in-depth Clinical Pharmacology/Biopharmaceutics Reviews were conducted during original NDA reviews for sofosbuvir and ledipasvir/sofosbuvir. No new biopharmaceutics information is included within this submission.

As noted in Dr. Florian's review, "The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in this supplement NDA to support a recommendation of approval of LDV/SOF in patients with decompensated cirrhosis and patients who have received a liver transplant."

Key points from Dr. Florian's review are noted below:

- PK for LDV, SOF, and the predominant circulating metabolite of SOF (GS-331007) were evaluated in SOLAR trials. The data from the SOLAR trials was compared with observations from the original LDV/SOF NDA submission.
- No difference in PK was observed based on liver transplantation status, but differences were observed based on degree of hepatic impairment.

- Based on population PK analyses, the observed changes in LDV, SOF, and GS-331007 exposures based on hepatic impairment are not considered clinically relevant and no dose adjustments are recommended.
- No dose adjustments are recommended in posttransplant patients on a cyclosporine containing regimen.
- Decreased SOF, GS-331007, and LDV AUC_T were observed (15-40%) in subjects who relapsed compared to those subjects achieving SVR. However, exposures of SOF, GS-331007, and LDV were not significant predictors of response from multivariate analyses. No dose adjustments are proposed based on this observation.

6. Clinical Microbiology

Please refer to Clinical Virology Review by Dr. Lisa Naeger for a detailed assessment.

Key points from Dr. Naeger's review are noted below:

- In SOLAR-1 and SOLAR-2 trials, the overall prevalence of NS5A resistance-associated polymorphisms (RAPs) in genotype 1 (GT1) subjects was 25%.
- The virologic failure rates in HCV GT1 subjects were comparable for subjects with NS5A RAPs and subjects without NS5A RAPs at 3.4% (5/146) vs. 4.3% (19/443).
- For subjects with baseline NS5A RAPs, virologic failure rates were slightly higher for GT1a subjects compared to GT1b subjects (5.3% vs. 1.4%).
- Relapse rates were 7% (5/71) and 5% (10/217) in GT1 subjects with and without baseline NS5A polymorphisms, respectively, treated with 12 weeks of HARVONI and RBV.
- For subjects with baseline NS5A RAPs, there were no virologic failures in the 24-week duration arms.
- For subjects with genotype 4 (GT4) HCV infection, the presence of baseline NS5A RAPs resulted in higher virologic failure rates for Child-Pugh-Turcotte (CPT) B (33%; 1/3) and CPT C (67%; 2/3) groups in the 12-week duration arm, although the subgroups were very small.

Virologic Failures and Treatment-emergent Substitutions

As noted by Dr. Naeger, "There were 27 virologic failure subjects with GT1 (n=24) and GT4 HCV (n=3): 23 subjects relapsed and 4 subjects discontinued on treatment with a detectable viral load and were included in the FDA virologic failure analysis. Most of the virologic failures were in the 12-week duration arms (n=18) and most had GT1a HCV (n=17). Eight of the virologic failures (30%) had baseline NS5A RAPs. The remaining subjects had no pretreatment RAPs, but most developed treatment-emergent NS5A RAPs at the time of relapse."

Furthermore, “Seventy-eight percent (21/27) of the virologic failures had emergent NS5A resistance substitutions, including one of the virologic failures who discontinued on treatment with detectable viral load. Fourteen virologic failures developed 1 NS5A substitution and 7 developed ≥2 substitutions. Of the virologic failures who relapsed, 91% (21/23) had emergent NS5A resistance substitutions. Emergent NS5A resistance-associated substitutions included K24K/R, M28T, Q30H/R, R30Q, M31V, H58D, and Y93H/C. The most prevalent NS5A substitutions that emerged at failure were Q30H/R or R30Q (33%; n=9) and Y93H (41%; n=11). The majority of treatment-emergent substitutions conferred >1000-fold reduced susceptibility to LDV in cell culture.”

7. Clinical/Statistical- Efficacy

Please refer to the Statistical Review by Wen Zeng, PhD, Clinical Review by Charu Mullick, MD and Virology Review by Lisa Naeger, PhD for a complete review of efficacy.

The Applicant conducted two Phase 2 trials which were randomized, open-label, multicenter studies and were identical in study design (Table 1). The only difference between the trials was the location of the clinical sites (US versus ex-US sites). SOLAR-2 trial was not conducted under an IND. The Applicant provided adequate justification for the applicability of the data generated from SOLAR-2 trial to the US HCV-infected population.

Table 1: Clinical Trials included in the sNDA

Trial	Treatment	N^a	Region	Trial Population
GS-US-337-0123 (SOLAR-1)	LDV/SOF+RBV for 12 or 24 weeks	337	US	Treatment-naive and treatment-experienced adult subjects with chronic genotype 1 or 4 HCV infection, who were posttransplantation with compensated liver disease or with decompensated liver disease regardless of transplantation status
GS-US-337-0124 (SOLAR-2)	LDV/SOF+RBV for 12 or 24 weeks	333	Europe, Canada, Australia, New Zealand	Same as above

^a Subjects who received at least 1 dose of LDV/SOF
 Source: Adapted from Applicant’s Clinical Overview (Table 1)

Subjects were enrolled into Cohort A or B based on liver transplantation status and into 1 of the following 7 groups based on severity of hepatic impairment.

In Cohort A, subjects with cirrhosis who had not undergone transplantation were enrolled into one of the following two groups based on severity of hepatic impairment at their screening visit:

- Group 1: subjects with cirrhosis and moderate hepatic impairment (CPT B; score of 7 to 9 [decompensated])
- Group 2: subjects with cirrhosis and severe hepatic impairment (CPT C; score of 10 to 12 [decompensated])

In Cohort B, posttransplantation subjects with or without cirrhosis were enrolled into one of the following five groups based on severity of hepatic impairment at their screening visit.

- Group 3: posttransplantation subjects without cirrhosis (fibrosis stage F0-F3) and with no evidence of hepatic decompensation
- Group 4: posttransplantation subjects with cirrhosis and mild hepatic impairment (CPT A; score of 5 to 6 [compensated])
- Group 5: posttransplantation subjects with cirrhosis and moderate hepatic impairment (CPT B; score of 7 to 9 [decompensated])
- Group 6: posttransplantation subjects with cirrhosis and severe hepatic impairment (CPT C; score of 10 to 12 [decompensated])
- Group 7: posttransplantation subjects with fibrosing cholestatic hepatitis

Within each of the 7 treatment groups, subjects were randomized in a 1:1 ratio to receive LDV/SOF+RBV for 12 or 24 weeks.

The primary efficacy endpoint in both clinical trials was the proportion of subjects achieving SVR12 (HCV RNA < lower limit of quantitation [LLOQ] 12 weeks after last dose of study drug).

Overall, the clinical and statistical reviewer's independent analyses confirmed the Applicant's primary efficacy findings and relevant secondary endpoint analyses for the two clinical trials. The following sections summarize the key findings of the FDA's clinical and statistical reviewers.

The intent-to-treat population (ITT) included 670 subjects; out of which 455 subjects were post-liver transplant. A total of 329 subjects with decompensated cirrhosis were enrolled including 78 subjects with baseline MELD scores greater than 15. The majority of subjects had genotype 1 infection (94%); and 6% of subjects had genotype 4 infection. Across all groups, the majority of subjects were male (77%) and white (91.5%). The median age was 59 years (range: 21 to 81). Majority of subjects (78%) had failed a prior HCV therapy.

The trial demographics and baseline disease characteristics were comparable between the treatment arms. Of the 670 subjects, 628 subjects (94%) completed the trial and 42 subjects (6%) discontinued LDV/SOF treatment prematurely. The common reasons for treatment discontinuations were due to an adverse event (n=19, 3%), death (n=8, 1%), liver transplantation (n=7, 1%), and investigator’s discretion (n=3, <1%).

Efficacy in Genotype 1 Subjects

This section will discuss the demonstrated efficacy results in genotype 1 subjects evaluated in SOLAR-1 and SOLAR-2 trials. The section is further divided based on the baseline disease stage.

Post-transplant Subjects without Cirrhosis or with Compensated Cirrhosis

The SVR12 rates in post-transplant groups without cirrhosis (F0-F3 Fibrosis) and in those with compensated cirrhosis (CPT A) were 95% and 98% respectively with 12 weeks of LDV/SOF in combination with RBV. The observed SVR12 rates are consistent with those demonstrated in previous clinical trials of LDV/SOF conducted in patients without cirrhosis or with compensated cirrhosis.

Table 2: SVR12 for Genotype 1 Post-transplant Subjects without Cirrhosis or with Compensated Cirrhosis – SOLAR-1 and SOLAR-2 (pooled data)

Cohort	Group/Stage	LDV/SOF + RBV 12 weeks	LDV/SOF + RBV 24 weeks
		SVR12 n/N (%) [95% CI]	SVR12 n/N (%) [95% CI]
Posttransplantation	3: F0-F3 Fibrosis	94.9% (94/99) [88.6%, 98.3%]	99.0% (99/100) [94.6%, 100.0%]
	4: CPT A	98.2% (55/56) [90.5%, 100%]	96.2% (51/53) [87.0%, 99.5%]

Source: Adapted from Efficacy Analyses by Dr. Zeng and Clinical Review by Dr. Mullick

Similar SVR12 rates were observed with 12 and 24 weeks durations hence extending the treatment duration was not indicated in this subpopulation based on these trial results.

Subjects with Decompensated Cirrhosis irrespective of Transplantation status

The SVR12 rates in those with decompensated cirrhosis (CPT B & C) were lower compared to subjects without cirrhosis or compensated cirrhosis and ranged from 89% to 57% with 12 weeks of LDV/SOF in combination with RBV.

Table 3: SVR12 for Genotype 1 Subjects with Decompensated Cirrhosis – SOLAR-1 and SOLAR-2 (pooled data)

Cohort	Group/Stage	LDV/SOF + RBV 12 weeks	LDV/SOF + RBV 24 weeks
		SVR12 n/N (%) [95% CI]	SVR12 n/N (%) [95% CI]
Pretransplantation	1: CPT B	86.5% (45/52) [74.2%, 94.4%]	92.0% (46/50) [80.8%, 97.8%]
	2: CPT C	87.5% (35/40) [73.2%, 95.8%]	82.6% (38/46) [68.6%, 92.2%]
Posttransplantation	5: CPT B	89.1% (41/46) [76.4%, 96.4%]	95.6% (43/45) [84.9%, 99.5%]
	6: CPT C	57.1% (4/7) [18.4%, 90.1%]	77.8% (7/9) [40.0%, 97.2%]

Source: Adapted from Efficacy Analyses by Dr. Zeng and Clinical Review by Dr. Mullick

I agree with Dr. Mullick’s dosing recommendations for post-transplant CPT C patients in spite of limited data in this subgroup. The dosing recommendation for this subgroup is supported by available SVR12 data in CPT B patients irrespective of transplant status as well as data in CPT C patients who did not undergo liver transplant. There was no consistent trend in SVR12 rates to suggest the need for longer treatment duration of 24 weeks for patients with decompensated cirrhosis; for example, SVR12 rates for pretransplant CPT C group were 87.5% with a 12 week regimen compared to 82.6% with 24 weeks duration. The number of subjects enrolled in the post-transplant CPT C group was very limited to draw any conclusions about the treatment duration based on these data. In summary, although the trial data in post-transplant CPT C subjects was limited, the totality of data in the CPT B and C subgroups was considered. The demonstrated efficacy in the pretransplant CPT B and C subgroups was leveraged to derive the dosing recommendation for post-transplant CPT C patients.

As noted earlier, the clinical impact of achieving SVR12 in patients with advanced liver disease is not well documented. Patients with decompensated liver disease who are awaiting liver transplant may benefit by delaying the need for liver transplant or eliminating the need for the liver transplant at all. Certain patients may still need a transplant due to their advanced disease or deteriorating liver function and having an undetectable HCV RNA at the time of transplant may prevent HCV recurrence in the new graft. Historically, liver transplant recipients with chronic HCV have a significantly lower 5-year survival compared to other recipients due to a higher rate of graft failure from recurrent disease.

Efficacy in Genotype 4 Subjects

Table 4 below shows SVR12 rates for genotype 4 subjects including post-transplant subjects without cirrhosis or with compensated cirrhosis and those with decompensated Cirrhosis irrespective of transplantation status in SOLAR-1 and SOLAR-2 trials.

Table 4: SVR12 for Genotype 4 Subjects– SOLAR-1 and SOLAR-2 (pooled data)

Cohort	Group/stage	LDV/SOF + RBV 12 weeks	LDV/SOF + RBV 24 weeks
		SVR12 n/N (%) [95% CI]	SVR12 n/N (%) [95% CI]
Pretransplantation (decompensated)	G1: CPT B	75% (3/4) [19.4%, 99.4%]	100% (2/2) [15.8%, 100.0%]
	G2: CPT C	33% (1/3) [0.8%, 90.6%]	50% (1/2) [1.3%, 98.7%]
Posttransplantation	G3: F0-F3 Fibrosis	100% (8/8) [63.1%, 100.0%]	100% (5/5) [47.8%, 100.0%]
	G4: CPT A	75% (3/4) [19.4%, 99.4%]	100% (5/5) [47.8%, 100.0%]
	G5: CPT B	100% (2/2) [15.8%, 100.0%]	75% (3/4) [19.4%, 99.4%]
	G6: CPT C	0 (0/1) [0.0%, 97.5%]	0

Source: Adapted from Efficacy Analyses by Dr. Zeng and Clinical Review by Dr. Mullick

The efficacy was demonstrated in post-transplant genotype 4 subjects without cirrhosis or with compensated cirrhosis (Groups 3 & 4). LDV/SOF + RBV for 12 weeks resulted in high efficacy rates of 100% and 75%. The subject who did not achieve SVR12 in Group 4 did not experience virologic relapse. I concur with Dr. Mullick’s conclusion to recommend a 12 week LDV/SOF + RBV treatment regimen for post-transplant CPT A patients based on findings in Group 4, and supporting data from Group 3. This recommendation also takes into consideration the approved 12-week duration of LDV/SOF treatment in genotype 4 patients with compensated cirrhosis.

Although genotype 4 subjects with decompensated disease were enrolled in the trial, the available data in each subgroup is limited to make a determination about an optimal duration to support an indication in the HCV GT4 infected population with decompensated cirrhosis. The Applicant has not requested to expand the indication in this subpopulation of genotype 4 patients.

Efficacy in Subjects with Fibrosing Cholestatic Cirrhosis (FCH)

There were a total of eleven subjects with FCH enrolled in the SOLAR trials, 7 subjects in the 12 week treatment arm and 4 subjects in the 24 week treatment arm. All subjects achieved SVR12.

Relapse Rates

Overall, 20 of 589 subjects (3.4%) with genotype 1 HCV infection relapsed and 3 of 36 subjects (8.3%) with genotype 4 HCV infection relapsed. A pooled analysis was done to assess the role of treatment duration in decompensated subjects (Groups 1, 2, 5, and 6) with genotype 1 HCV infection, irrespective of transplantation status. Relapse rates were 8.1% and 4.3% in subjects who received LDV/SOF+RBV for 12 or 24 weeks, respectively, and the difference in relapse rates was 3.8% with 95% CI of [-2.1%, 10.2%].

Analysis of Changes in CPT and MELD Scores

Pre-specified secondary efficacy endpoints in both trials include changes in CPT and Model for End-Stage Liver Disease (MELD) scores from Day 1 of study treatment to 12 weeks and 24 weeks posttreatment. As noted in the protocol, the objective was to determine the therapeutic efficacy as measured by the change of CPT score and MELD score. MELD and the CPT scores are used to assess chronic liver disease severity.

The CPT score is widely used. It was originally developed for the assessment of the outcome of patients with cirrhosis and portal hypertension. The CPT score is derived using following 5 variables: albumin, total bilirubin, international normalized ratio for prothrombin time (INR), presence and degree of ascites, and presence and degree of encephalopathy. Higher CPT scores correlate with increased mortality. The use of CPT score has limitations due to inclusion of variables such as ascites and encephalopathy, which are subjective and influenced by medical therapy (Gotthardt 2009).

MELD is a scoring system for the severity of liver disease initially developed as a model in predicting poor survival in patients after transjugular intrahepatic porto-systemic shunt (TIPS). A modification of this score was developed to predict mortality in patients with cirrhosis of different etiologies and severities of liver disease. The MELD score is calculated using 3 objective parameters: serum creatinine, serum total bilirubin, and INR. This MELD score was found to be superior to the CPT score in predicting 3-month mortality and therefore the MELD score was implemented in 2002 in the US for the prioritization of liver transplant recipients (Gotthardt 2009).

Although a substantial proportion of subjects who attained SVR12 showed an improvement in MELD and CPT scores at 12 weeks posttreatment, few subjects remained stable and a small percentage of subjects worsened. Improvement in CPT

score was driven by improvement in albumin and bilirubin. Improvement in MELD score was driven primarily by improvement in bilirubin. For detailed analyses, please refer to Dr. Wen's review.

 (b) (4)
Recognizing the importance of clinical outcome findings in patients with cirrhosis, including decompensated cirrhosis, who are sustained responders, the Division has reached an agreement with the Applicant on a postmarketing commitment to submit 5 year follow-up data.

8. Safety

Please refer to Clinical Review by Dr. Mullick for a detailed assessment of safety.

This section will provide a focused summary of the safety data from the two SOLAR trials. The safety profile of LDV/SOF has been well-characterized in multiple previous clinical trials and has generally been safe and well-tolerated. Please refer to clinical reviews by Dr. Sarah Connelly dated July 10, 2014 for original NDA and dated October 20, 2015 for efficacy supplements (S 2-6). The two clinical trials being evaluated under the current efficacy supplements were conducted to demonstrate safety and efficacy in patient populations not previously studied.

The safety evaluation in the patient population specifically enrolled in two SOLAR trials is challenging for numerous reasons related to baseline disease characteristics of the enrolled subjects. Subjects with advanced liver disease (Child-Pugh B and C cirrhosis) represent a highly vulnerable patient population with other coexisting factors such as portal hypertension leading to esophageal varices/bleeding, immune dysfunction predisposing to increased risk of infections, hemodynamic derangements leading to renal dysfunction including hepatorenal syndrome (HRS), and synthetic liver dysfunction leading to complications. Spontaneous bacterial peritonitis (SBP), sepsis, hyponatremia and hepatic encephalopathy are common clinical presentations in patients with decompensated cirrhosis. Other systemic complications of chronic liver disease include hepatopulmonary syndrome and portopulmonary syndrome. The 1-year mortality for patients with decompensated cirrhosis ranges from approximately 20% for patients with CPT B cirrhosis to greater than 50% for patients with CPT C cirrhosis (D'Amico 2006).

In addition, SOLAR trials included subjects who were post liver transplantation. Liver transplant recipients are on chronic immunosuppressive therapy to prevent graft rejection and are prone to side effects related to immunosuppressants drugs. Nephrotoxicity is a well-recognized side effect of calcineurin inhibitors (CNIs). It has been reported that approximately 20% of liver transplant recipients experience chronic renal failure within 5 years (Ojo 2003).

In such populations, careful evaluation is needed to distinguish adverse drug reactions due to the treatment regimen being evaluated versus the expected events secondary to the natural progression of disease, and/or worsening of other comorbid conditions, and/or the effects secondary to toxicity of concomitant medications. The comprehensive safety assessment also took into consideration the established safety profile based on data in other LDV/SOF trials reviewed under the LDV/SOF NDA, the ongoing and completed postmarketing assessments, published literature reports and any relevant available data provided by the Applicant from real-world observational cohort study (HCV-TARGET database).

The integrated clinical safety review provided by Dr. Mullick describes pooled data from the two trials. Overall, 336 subjects received LDV/SOF+RBV for 12 weeks and 334 subjects received LDV/SOF+RBV for 24 weeks. A total of 329 subjects (49%) had decompensated cirrhosis (either pre- or posttransplantation), of whom 78 subjects (24%) had a MELD score >15 (a threshold used for listing a patient for liver transplantation in US). It should be noted that subjects with CPT scores up to 12 were included in the trials. The safety database is considered to be adequate as the data from SOLAR trials is supported by additional data in other populations approved at the time of initial NDA approval as well as NDA efficacy supplements 2-6.

Major Safety Results

The following sections summarize the findings from Dr. Mullick's review.

A total of 20 treatment-emergent deaths were reported, most of which (n=16), occurred in subjects with decompensated cirrhosis (CPT B or CPT C). Eleven subjects (2%) underwent treatment-emergent liver transplants, 10 of these 11 subjects achieved posttransplantation virologic response at 12 weeks posttransplantation (pTVR12). The 1 subject who did not achieve pTVR died 15 days after undergoing a liver transplantation. None of the deaths or the transplants were attributed to study treatment by the investigators or the Independent Adjudication Committee (IAC) consisting of four external hepatology experts. These events will be adequately conveyed in the label to facilitate an informed decision while weighing the risks and benefit of the therapeutic options.

Overall, nonfatal serious adverse events (SAEs) were reported in 22% of subjects. The majority of SAEs were observed in patients with decompensated cirrhosis, and were assessed unrelated to study treatment by the investigators, and were attributed to the underlying advanced liver disease. Among treatment-related SAEs, ribavirin-induced anemia events were most frequently observed. Excluding anemia-related SAEs, treatment-related SAEs were observed in seven subjects (1%) in the trial.

A total of 20 subjects (3%) discontinued LDV/SOF due to an AE; the majority of discontinuations were in decompensated cirrhosis groups (15/20). No obvious trend was noted in the AEs reported.

The commonly occurring adverse drug reactions (ADRs) in the trial population were similar to those previously reported with LDV/SOF and/or RBV use and are currently labeled for these agents. ADRs reported in at least 20% of subjects were fatigue, headache, nausea, anemia, and pruritus.

Notable Safety Evaluations

Hepatic Safety Assessment in SOLAR Trials

Evaluation of drug-induced liver injury (DILI) in patients with underlying liver disease such as CHC is challenging. Even though patients with preexisting liver disease may not be at increased risk of DILI, the drug-related hepatic insult may result in serious liver injury due to compromised hepatic reserve in patients with advanced liver disease including decompensated disease.

A thorough assessment of DILI was done in these trials as patients with advanced liver disease were enrolled in these trials, the subpopulation which has never been systematically evaluated. The IAC reviewed data from subjects who met pre-specified criteria which were agreed upon during previous discussions with the Applicant prior to the sNDA submission. For a full description of the selection of these criteria, please refer to Dr. Mullick's review. A total of 61 subjects were adjudicated by IAC, out of which an alternative causality other than DILI was agreed upon by the IAC in 56 subjects.

Detailed analysis and comprehensive review of case narratives was conducted by Dr. Mullick. As noted in her review, "Four possible cases of DILI were confounded by the underlying hepatic disease and/or concurrent use of potentially hepatotoxic medication, and not attributed to study treatment by the IAC. In 11 separate cases, mild increases in alanine transaminase (ALT) or aspartate aminotransferase (AST) from baseline or nadir were observed, without an associated rise in direct bilirubin. These ALT or AST increases were in posttransplant patients with compensated cirrhosis or without cirrhosis; the observed increases were transient, resolved without intervention, and were assessed by the IAC to be of trivial clinical significance. While an etiology was not identified, the findings may represent the effect of another variable such as concomitant immunosuppressive medication, concurrent mild viral infection, or exercise."

In summary, based on Dr. Mullick's assessment, which I am in agreement with, no new safety concern for DILI was identified based on SOLAR trial findings. This conclusion is also supported by previously reviewed clinical trial data in populations with less advanced cirrhosis and postmarketing assessments. Routine ongoing postmarketing surveillance will continue in collaboration with Office of Surveillance and Epidemiology (OSE) to identify any emerging hepatic safety signals.

The review team is recommending clinical and hepatic laboratory monitoring during the treatment period, as clinically indicated.

Evaluation of Adverse Events in Liver Transplant Recipients

Posttransplant patients may have baseline renal dysfunction due to long-term immunosuppressants use. This may impact ribavirin use as well as Harvoni use. The greatest median hemoglobin decreases from baseline were observed for posttransplantation subjects. These were attributed to higher initial doses of RBV and relatively lower eGFR_{CG} values at baseline in posttransplant subjects.

Cardiac Safety Evaluation

Since LDV/SOF was approved on October 10, 2014, cases of symptomatic bradycardia, including one fatal cardiac arrest and one case requiring pacemaker intervention, have been reported in patients receiving LDV/SOF or SOF with another HCV direct-acting antiviral in combination with amiodarone. Postmarketing assessment in collaboration with the drug sponsor, OSE as well as consult review from the Division of Cardiovascular and Renal Products (DCRP) resulted in the updates to the product PI in March, 2015. FDA Drug Safety Communication was also issued and a Letter to Health Care Providers was issued by Gilead.

A post approval PMR was issued to further evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between sofosbuvir and amiodarone, with and without other HCV direct acting antiviral drugs (DAA). The requested studies are ongoing and the final results are awaited.

In addition, an assessment of postmarketing cases of cardiac failure and/or cardiomyopathy done in collaboration with DCRP did not identify an obvious causal association: most cases occurred in patients with underlying cardiac comorbidities and/or advanced liver disease. No labeling recommendations were made based on these assessments. Please refer to consult reviews by Dr. Shari Targum archived on 4/21/2015, 9/2/2015 and 1/19/2016 for detailed assessments related to the reported postmarketing cardiac events noted above.

No additional cardiac –related labeling recommendations have been made by Dr. Mullick at this time based on her assessment of the data from the two SOLAR trials.

Evaluation of Renal Adverse Events

Nephrotoxicity is not a known safety issue described with use of LDV/SOF in previous clinical trials in patients without cirrhosis or with compensated cirrhosis. The safety and efficacy of LDV/SOF have not been established in patients with severe renal impairment with GFR less than 30 mL/min/1.73m² or end stage renal disease requiring hemodialysis.

A detailed analysis done by Dr. Mullick to evaluate treatment-emergent AEs of renal failure or acute renal failure identified 22 unique cases, the majority of whom (n=15) had CPT B or C cirrhosis Only 2 events resulted in treatment discontinuation, and 2

other events were assessed by the investigator as related to study treatment. No labeling recommendations have been made based on these findings. There is an ongoing assessment of postmarketing renal events in SOF-containing regimens. Other safety evaluations of interest included pancreatitis, pancytopenia, skin reactions, and rhabdomyolysis. No labeling recommendations have been made for these events based on SOLAR data.

Laboratory abnormalities

The decrease in hemoglobin values which were observed is consistent with the known hematological toxicity of RBV. Hemolytic anemia can be appropriately managed in clinical setting by RBV dosage adjustments or blood transfusions if clinically indicated. In most subjects hemoglobin values return to baseline after discontinuation of RBV.

The observed Grade 3 and 4 increased total bilirubin values were generally consistent with RBV-induced hemolysis. Increases in indirect bilirubin from RBV-induced hemolysis, and the understanding that patients with advanced liver disease often have elevated total bilirubin at baseline were taken into consideration during safety assessments.

Postmarketing Safety Data

FDA Pharmacovigilance Review/OSE Consult Review

A consult from the Division of Pharmacovigilance II (DPV II) in the OSE was requested to review and analyze reports in the FDA's Adverse Event Reporting System (FAERS) for the postmarketing use of LDV/SOF to identify any new and emerging safety signals.

For detailed assessment, refer to Post-market Safety Review archived by Dr. Mihaela Jason on 12/4/2015. The review concluded, "No new safety signals were identified in this review of FAERS post-marketing reports of LDV/SOF use." In addition, DPV II will assess the cases reporting the unlabeled events of anemia, renal failure, and hepatic decompensation and failure in a separate review. We will await DPV's review and recommendations. Any labeling changes, if indicated, will be incorporated at a later time.

In a previous review by DPV II, two cases of rhabdomyolysis had been reported following LDV+SOF initiation in a previously stable atorvastatin-treated patients with abatement of the adverse events after LDV+SOF was discontinued, suggesting a possible drug-drug interaction between LDV+SOF and atorvastatin. At this time, this safety issue is being further evaluated in consultation with the Office of Clinical Pharmacology.

I am in agreement with the review team's assessment of safety and labeling recommendations. The demonstrated safety and tolerability profile is acceptable in this patient population with advanced liver disease and/or post-liver transplant.

9. Advisory Committee Meeting

No advisory committee meeting was held.

10. Pediatrics

As required by the Pediatric Research Equity Act, the pediatric study was waived from birth to less than 3 years at the time of the original approval of LDV/SOF because necessary studies are impossible or highly impracticable. This is because spontaneous clearance is possible and very few patients in this age group require treatment.

The pediatric studies for ages 3 to 17 years were deferred at the time of initial approval of NDA as well as at the time of subsequent efficacy supplements because product was ready for approval for use in adults and the pediatric studies have not been completed. The required studies are noted in the approval letters dated October 10, 2014 and November 12, 2015. The Applicant is required to conduct the following studies listed below.

- Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ledipasvir/sofosbuvir in pediatric subjects 3 to 17 years of age with chronic hepatitis C.
- Collect and analyze long-term safety data for subjects enrolled in the pediatric ledipasvir/sofosbuvir safety, pharmacokinetic and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of ledipasvir/sofosbuvir including growth assessment, sexual maturation and characterization of ledipasvir/sofosbuvir resistance associated substitutions in viral isolates from subjects failing therapy.

It was determined that the proposed subpopulations/regimen is covered under the current approved indication and thus would not trigger PREA. The Applicant is required to conduct the postmarketing pediatric studies as per the schedule outlined in the initial NDA approval letter.

11. Other Relevant Regulatory Issues

No substantive regulatory issues remain to be resolved at the time of writing this CDTL Review.

Office of Scientific Investigation Inspections

Two domestic and two international clinical sites were inspected. Overall, the data generated and submitted by the Applicant from these four sites are considered acceptable to support the approval of this application. Please refer to the OSI Consult Review archived on 01/04/2016 for further details.

Good Clinical Practice

The applicant noted that the clinical trials were conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Financial Disclosures

A detailed review was done by Dr. Mullick. As noted in Dr. Mullick's review, "In one of the two trials, SOLAR-1, multiple investigators had significant financial arrangements with the Applicant. The implications of this finding, chiefly, the potential for investigator bias for key study endpoints were carefully considered by the review team. The statistical and clinical reviewers performed additional analyses to assess an impact on key endpoints. Based on the findings in additional analyses, the review team concluded a low likelihood of substantial investigator bias as a result of financial arrangements."

In addition, The Applicant was also asked to provide the sensitivity analyses for the primary efficacy endpoint SVR 12 excluding subjects enrolled from sites where the principal investigator and/or sub-investigators received significant payments or held significant equity interest as defined in 21 CFR 54.2. A similar analysis for treatment-emergent adverse events, and drug-related adverse events was also requested. Based on the review of the available information, Dr. Mullick concluded a lack of substantial bias on part of the investigators as a result of significant financial arrangements.

Postmarketing Requirement (PMR) 2780-7

The Applicant notes that the submission of SOLAR-1 study report (Interim SVR12 Clinical Study Report) fully addresses the PMR 2780-7 which requires submission of the final report and datasets from the trial GS-US-337-0123, in order to provide safety data and dosing recommendations for subjects with decompensated cirrhosis and/or in subjects receiving concomitant immunosuppressive agents post-liver transplant (e.g. cyclosporine).

12. Labeling

The proposed package insert (PI or label) was reviewed by all disciplines involved in the sNDA review. In addition, a focused review by the Division's Associate Director of labeling (ADL), Dr. Stacey Min, was also done and the recommendations were incorporated. Important elements of labeling discussions and revisions are noted below:

- **Section 1: INDICATIONS AND USAGE**

The indication statement was revised to include Harvoni is indicated “with or without ribavirin” for the treatment..... as Harvoni will be dosed with ribavirin in substantial subpopulations including posttransplant and those with decompensated cirrhosis.

- **Section 2: DOSAGE AND ADMINISTRATION**

Table 1 was updated to include the additional patient populations and the recommended treatment regimens and durations for the expanded indication.

	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks*
	Treatment-experienced** without cirrhosis	HARVONI 12 weeks
	Treatment-experienced** with compensated cirrhosis (Child-Pugh A)	HARVONI 24 weeks†
	Treatment-naïve and treatment-experienced** with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + ribavirin‡ 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced** liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + ribavirin§ 12 weeks
Genotype 4, 5 or 6	Treatment-naïve and treatment-experienced**, without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks

* HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL [see *Clinical Studies (14.2)*].

**Treatment-experienced patients include those who have failed a peginterferon alfa + ribavirin based regimen with or without an HCV protease inhibitor.

† HARVONI+ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin [see *Clinical Studies (14.2)*]. See footnote § for ribavirin dosage recommendations.

‡ In patients with decompensated cirrhosis, the starting dosage of ribavirin is 600 mg and can be titrated up to 1000 mg for patients <75 kg and 1200 mg for those ≥75 kg in two divided doses with food. If the starting dosage of ribavirin is not well tolerated, the dosage should be reduced as clinically indicated based on hemoglobin levels.

§ The daily dosage of ribavirin is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in two divided doses with food.

An additional footnote was added to the table to clarify the lower starting dose of RBV in patients with decompensated cirrhosis.

- **Section 6: ADVERSE REACTIONS**

This section was updated with a subsection to describe adverse reactions observed in liver transplant recipients and/or subjects with decompensated cirrhosis.

- **Section 8: USE IN SPECIFIC POPULATIONS**

Sections 8.1 Pregnancy and 8.2 Lactation were updated to comply with the PLLR. In addition Section 8.3 Females and Males of Reproductive Potential was added to due to use of ribavirin in treatment regimens.

Section 8.7 was updated to include recommendations for clinical and hepatic laboratory monitoring, as clinically indicated, in patients with decompensated cirrhosis receiving treatment with HARVONI and ribavirin.

- **Section 12.4: Microbiology**

This section was updated to include data from SOLAR-1 and SOLAR-2 trials.

- **Section 14: CLINICAL STUDIES**

This section was updated to include the description and results from SOLAR-1 and SOLAR-2 trials. The Applicant was asked to include relapse rates in addition to SVR12 rates in the efficacy table (Table 16) and the table has been revised accordingly.

The Applicant proposed

(b) (4)

- **Section 17: PATIENT COUNSELING INFORMATION**

As per recommendations by ADL, Dr. Min, this section was revised to be consistent with other HCV labels.

In addition, the proposed Patient Information was reviewed by the Patient Labeling Team and their recommendations are being incorporated. Please refer to Consult Review for details.

Please refer to the Labeling Review completed by Christian Yoder, Regulatory Project Manager, for the final version of the agreed upon labeling.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I am in agreement with multi-disciplinary review team's assessment/conclusions and recommend approval of this application to expand the indication in patients with hepatitis C virus (HCV) infection, genotypes 1 & 4 who are posttransplantation with compensated liver disease as well as patients with decompensated liver disease with genotype 1 HCV infection, regardless of transplantation status.

- **Risk Benefit Assessment**

The efficacy of Harvoni in intended patient populations was demonstrated in two clinical trials. Results from these two trials show high SVR rates. Subgroup analyses documented similar response rates in subjects based on demographic and baseline disease characteristics (e.g. age, sex, race, baseline HCV-RNA level).

The safety and tolerability profile of Harvoni have been well-characterized across multiple patient populations including those with compensated cirrhosis and in patients co-infected with HIV-1 infection. No new safety concerns were observed in these two trials evaluating patients with advanced liver diseases (decompensated cirrhosis) and/or post liver transplantation.

The review team recognizes that the patient with advanced liver disease is at increased risk of disease progression and clinical complications inherent to the baseline disease stage. However, we anticipate that these patients with advanced liver disease will receive treatment under close supervision of a specialist who can timely identify and manage the changing clinical status of this patient population. Any potential risk of therapy can be mitigated in the clinical setting by clinical and hepatic monitoring, as indicated.

Overall, the risk benefit assessment favors approval of Harvoni for treatment of chronic hepatitis C in the patient populations studied in the clinical trials. The noted safety signals should be continued to be monitored in the post-marketing period as part of routine pharmacovigilance surveillance. The long-term clinical outcomes need to be assessed in the ongoing Cirrhosis registry.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

Based on the known safety profile of LDV/SOF FDC at this time, the Review Team does not recommend a Risk Evaluation and Management Strategy (REMS).

- **Recommendation for other Postmarketing Requirements and Commitments**

The long-term benefits of achieving SVR such as halting disease progression, alleviating need for liver transplant, and improving overall prognosis of patients with decompensated liver disease, needs to be evaluated and documented in a systematic manner. The Applicant is conducting a long-term follow-up registry (GS-US-337-1431), to document improvements in clinical outcomes such as progression of liver disease, liver-related mortality, occurrence of HCC, or liver failure requiring liver transplantation. The purpose of this registry is to determine if achieving SVR translates into a morbidity and mortality benefit for this particular population of patients. A second aim of this study is to characterize predictors of disease regression, or conversely, to identify risk factors associated with further hepatic decompensation, despite viral eradication.

The Division has requested that results from this long-term follow-up registry be submitted as PMC. The following PMC has been agreed by Gilead with final report submission due in October, 2022.

Collect, analyze and submit data on subjects with cirrhosis including decompensated cirrhosis who achieve sustained virologic response following treatment with a sofosbuvir-based regimen to evaluate durability of virologic response and to characterize clinical outcomes such as progression or regression of liver disease, liver-related mortality, occurrence of hepatocellular carcinoma, or liver failure requiring liver transplantation. Data collected should include 5 years of follow-up.

- Recommended Comments to Applicant

No additional comments need to be conveyed to the Applicant at this time.

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/s/

POONAM MISHRA
02/10/2016