FDA ANTIVIRAL DRUGS ADVISORY COMMITTEE MEETING

OCTOBER 25, 2013

BACKGROUND PACKAGE FOR NDA 204671

SOFOSBUVIR (GS-7977)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION RESEARCH

OFFICE OF ANTIMICROBIAL PRODUCTS

DIVISION OF ANTIVIRAL PRODUCTS

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Background Package
NDA 204671
Sofosbuvir (GS-7977)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought sofosbuvir to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

I. REGULATORY BACKGROUND AND INTRODUCTION

This document provides the Antiviral Drugs Advisory Committee a summary of FDA analyses of the data submitted by Gilead Sciences, Inc. to support an indication for sofosbuvir use in combination with other agents in adult patients with genotypes 1 to 6 and/or adult patients awaiting liver transplantation. During the scheduled October 25, 2013 Advisory Committee meeting, the Committee will be asked to consider the safety and efficacy data submitted in support of the sofosbuvir application The background materials provided represent the preliminary findings and opinions of the multidisciplinary review team and are based on their reviews of the Applicant's submissions. Please note that the FDA analyses presented herein may differ somewhat from those presented by the Applicant. This document represents the review team's preliminary findings to date.

Sofosbuvir is a prodrug of a nucleotide analog inhibitor of the HCV NS5B RNA-dependent RNA polymerase and represents the first drug in this class submitted for review in the United States.

The Applicant requests approval for sofosbuvir 400 mg once daily in combination with ribavirin in HCV genotype 2 and 3 infected patients, and for sofosbuvir in combination with ribavirin and pegylated interferon alfa (PEG) in HCV genotype 1, 4, 5 and 6 infected patients. The specific wording proposed by the Applicant remains under review and has not been finalized.

II. SUMMARY OF EFFICACY

Data from four Phase 3 trials form the principal basis for characterizing the safety and efficacy of sofosbuvir in patients with chronic HCV infection.

- Three trials were conducted in subjects with HCV genotype 2 or 3:
  - P7977-1231 (FISSION) evaluated sofosbuvir + ribavirin (SOF+RBV) treatment for 12 weeks in treatment-naïve subjects
  - GS-US-334-0107 (POSITRON) evaluated SOF+RBV for 12 weeks in subjects who were interferon intolerant, ineligible, or unwilling to take interferon
  - GS-US-334-0108 (FUSION) evaluated SOF+RBV for 12 or 16 weeks in treatment-experienced subjects
- An additional trial, GS-US-334-0110 (NEUTRINO), evaluated SOF+PEG+RBV for 12 weeks in HCV GT 1, 4, 5 or 6 treatment-naïve subjects.

The primary endpoint in all four Phase 3 trials is sustained virologic response defined as HCV RNA < lower limit of quantification (LLOQ) 12 weeks after the discontinuation of active treatment (SVR12).

All sofosbuvir-containing arms used sofosbuvir 400 mg once daily and weight-based ribavirin (1000 or 1200 mg daily doses). These trials included a subset of subjects with compensated cirrhosis which represents a harder to treat subgroup. The details of the trial designs are provided by the Applicant in their background document.

A. HCV Genotype 2 and 3 Population

1. Efficacy in HCV Genotype 2 and 3 treatment-naïve population (FISSION)

This Phase 3, randomized, multicenter, open-label active-controlled trial enrolled treatment-naïve subjects with HCV genotype (GT) 2 or 3 in approximately a 1:3 ratio. Eligible subjects were randomized equally to one of the following treatment groups:

- SOF+RBV for 12 weeks
- PEG+RBV: PEG 180 μg weekly + RBV 800 mg daily for 24 weeks

Subjects were stratified by HCV genotype (2 or 3), screening HCV RNA levels (< 6 $\log_{10}$ IU/mL or ≥ 6 $\log_{10}$ IU/mL), and cirrhosis (present or absent). It should be noted higher ribavirin doses (1000 or 1200 mg) were used in the sofosbuvir-containing arm compared with the control arm (800 mg).

A total of 499 randomized subjects received treatment (256 subjects in the SOF+RBV group; 243 subjects in the PEG+RBV group), including 20% with compensated cirrhosis. The overall SVR12 rate was 67% in both groups (Table 1). The difference in proportions (95% confidence interval, CI) was 0.1% (-8% to 8%). The lower bound of the 2-sided 95% CI for the difference between groups (i.e., [SOF+RBV] − [PEG+RBV]) was within the prespecified noninferiority margin of -15%. One subject experienced virologic breakthrough at Week 8. This subject was infected with HCV GT3a genotype/subtype, had IL28B CT genotype and a baseline viral load of 7 $\log_{10}$ IU/mL. This subject had evidence of poor compliance with low plasma concentrations of

GS-331007, the predominant circulating metabolite. There was only population sequence available from the Week 8 sample. The substitutions T84S, A150T and E202D emerged in NS5B on treatment and were not associated with detectable reduced susceptibility to sofosbuvir.

In the SOF+RBV group, HCV GT2 subjects had higher SVR12 rates compared with HCV GT3 subjects, 95% versus 56%, respectively. Within each genotype, relapse accounted for most treatment failures with HCV GT3 having a relapse rate of 40% compared with a 5% relapse rate in HCV GT2.

Table 1: FISSION Primary Efficacy Results and Relapse Rates (All Treated[1])

Efficacy Parameter	**SOF+RBV 12 Weeks N=256**	**PEG+RBV 24 Weeks N=243**
Sustained Virologic Response		
Overall SVR12	67% (171/256)	67% (162/243)
Proportion Difference SOF+RBV 12 Weeks vs. PEG+RBV 24 Weeks [95% CI]	0.1% [-8%, 8%]	
SVR12 in Genotype 2	95% (69/73)	78% (52/67)
Proportion Difference SOF+RBV 12 Weeks vs. PEG+RBV 24 Weeks [95% CI]	17% [6%, 28%]	
SVR12 in Genotype 3	56% (102/183)	63% (110/176)
Proportion Difference SOF+RBV 12 Weeks vs. PEG+RBV 24 Weeks [95% CI]	-7% [-17%, 3%]	
Relapse Rates at Posttreatment Week 12		
Overall Relapse Rate	30% (76/252)	21% (46/217)
Relapse Rate in Genotype 2	5% (4/73)	15% (9/62)
Relapse Rate in Genotype 3	40% (72/179)	24% (37/155)

[1]All Treated was defined as all randomized subjects who received at least one dose of study medication, based on the intention-to-treat (ITT) principle, including three subjects in the SOF+RBV arm with misclassified HCV genotype. These subjects were excluded from the primary efficacy analysis by the Applicant; hence, there are some numerical differences based on these two analyses.
The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits
SOF=sofosbuvir; PEG=pegylated interferon alfa; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

Fewer sofosbuvir-treated subjects discontinued treatment due to an adverse event (AE): 1% in the sofosbuvir/ribavirin group versus 11% in the PEG/RBV group.

2. *Efficacy in HCV Genotype 2 and 3 interferon intolerant, interferon ineligible or unwilling to take interferon population (POSITRON)*

This Phase 3, randomized, double-blind, placebo-controlled, multicenter trial enrolled subjects with chronic genotype 2 or 3 HCV infection who were interferon (IFN) intolerant, interferon ineligible, or unwilling to take interferon. Subjects must be intolerant to IFN as demonstrated

during a prior course of treatment, ineligible to receive IFN due to medical history or unwilling to receive IFN (documented more than three months prior to signing of the informed consent). Eligible subjects were randomized in a 3:1 ratio to one of two treatment arms:

- SOF+RBV for 12 weeks
- Placebo for 12 weeks

Randomization was stratified by presence/absence of cirrhosis at screening. A total of 278 subjects received treatment (207 subjects in the SOF+RBV group and 71 subjects in the placebo group), including 16% with compensated cirrhosis. The primary efficacy endpoint was SVR12. The SOF+RBV 12 Week regimen was superior to placebo with SVR12 rates of 78% and 0%, respectively (Table 2). The difference (95% CI) in proportions was 78% (72% to 83%). No sofosbuvir-treated subject had on-treatment virologic failure.

In the SOF+RBV group, HCV GT2 subjects had higher SVR12 rates compared with HCV GT3 subjects, 93% versus 61%, respectively. Within each genotype, relapse accounted for most treatment failures with HCV GT3 having a relapse rate of 38% compared with a 5% relapse rate in HCV GT2.

Table 2: POSITRON Primary Efficacy Results and Relapse Rates (All Treated[1])

Efficacy Parameter	**SOF+RBV 12 Weeks N=207**	**Placebo 12 Weeks N=71**
Sustained Virologic Response		
Overall SVR12	78% (161/207)	0 (0/71)
Proportion Difference SOF+RBV 12 Weeks vs. Placebo 12 Weeks [95% CI]	78% [72%, 83%]	
SVR12 in Genotype 2	93% (101/109)	0 (0/34)
Proportion Difference SOF+RBV 12 Weeks vs. Placebo 12 Weeks [95% CI]	93% [88%, 98%]	
SVR12 in Genotype 3	61% (60/98)	0 (0/37)
Proportion Difference SOF+RBV 12 Weeks vs. Placebo 12 Weeks [95% CI]	61% [52%, 71%]	
Relapse Rates at Posttreatment Week 12		
Overall Relapse Rate	20% (42/205)	n/a
Relapse Rate in Genotype 2	5% (5/107)	n/a
Relapse Rate in Genotype 3	38% (37/98)	n/a

[1]All Treated was defined as all randomized subjects who received at least one dose of study medication;
The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits
SOF=sofosbuvir; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

Few sofosbuvir-treated subjects discontinued treatment due to an AE (2%) compared to 4% in the placebo arm.

3. Efficacy in HCV Genotype 2 and 3 treatment-experienced population (FUSION)

This Phase 3, randomized, double-blind, multicenter trial enrolled subjects with chronic genotype 2 or 3 HCV who had failed prior treatment with an IFN-based regimen. This trial assessed the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment. Eligible subjects were randomized in a 1:1 ratio to either:

- SOF+RBV 12 Week group
- SOF+RBV 16 Week group

Randomization was stratified by the presence or absence of cirrhosis and HCV genotype (2 or 3) at screening. A historical response rate of 25% was set based on the assumption that the SVR rate would be low had HCV GT2/3 treatment-experienced subjects been retreated with PEG+RBV.

A total of 201 subjects received treatment (103 subjects in the SOF+RBV 12 Week group and 98 subjects in the SOF+RBV 16 Week group), including 34% with compensated cirrhosis, a higher percentage than enrolled in the other Phase 3 trials. Approximately 25% subjects had prior nonresponse to an IFN-based regimen, and 75% had prior relapse/breakthrough. The SVR12 rate in the SOF+RBV 12 Week group was 50% and in the SOF+RBV 16 Week group was 71%, each statistically significantly higher ($p < 0.001$) compared to the null rate of 25% (Table 3). In addition, treatment with SOF+RBV for 16 weeks resulted in statistically significant higher SVR12 rates compared with the shorter treatment duration of 12 weeks. No subject in either treatment group had on-treatment virologic failure.

In both the SOF+RBV 12 Week and 16 Week groups, HCV GT2 subjects had higher SVR12 rates compared with HCV GT3 subjects, and within each genotype, relapse accounted for most treatment failures. Extending the treatment duration by 4 weeks increased SVR12 rates in HCV GT2 subjects from 82% to 89%, and in HCV GT3 subjects from 30% to 62%.

Table 3: FUSION Primary Efficacy Results and Relapse Rates (All Treated[1])

Efficacy Parameter	**SOF+RBV 12 Weeks N=103**	**SOF+RBV 16 Weeks N=98**
Sustained Virologic Response		
Overall SVR12 Rate	50% (51/103)	71% (70/98)
Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]	-22% [-35%, -9%]	
SVR12 in Genotype 2	82% (32/39)	89% (31/35)
Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]	-7% [-23%, 9%]	
SVR12 in Genotype 3	30% (19/64)	62% (39/63)
Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]	-32% [-49%, -16%]	
Relapse Rates at Posttreatment Week 12		
Overall Relapse Rate	48% (49/103)	29% (28/98)
Relapse Rate in Genotype 2	18% (7/39)	11% (4/35)
Relapse Rate in Genotype 3	66% (42/64)	38% (24/63)

[1]All Treated was defined as all randomized subjects who received at least one dose of study medication, based on the intention-to-treat (ITT) principle, including six subjects (three in each arm) with misclassified HCV genotype. These subjects were excluded from the primary efficacy analysis by the Applicant; hence, there are some numerical differences based on these two analyses.
The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits
SOF=sofosbuvir; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

Few sofosbuvir-treated subjects (≤ 1%) discontinued treatment due to an AE in either treatment duration arm.

4. HCV Genotype 2 and 3 Subgroup Analyses

a. Response Rates in Genotype 2 and 3 Subjects

Across the Phase 3 trials, higher SVR12 rates occurred in HCV GT2 subjects compared with HCV GT3 subjects.

- FISSION (treatment-naïve): HCV GT2 subjects had a significantly higher SVR12 rate than HCV GT3 subjects in the SOF+RBV 12 Week group (95% and 56% of HCV GT2 and 3 subjects, respectively) (p-value <0.0001).
- POSITRON (IFN-intolerant, ineligible, unwilling): HCV GT2 subjects had significantly higher SVR12 rates than HCV GT3 subjects in the SOF+RBV 12 Week group (93% and 61%, respectively) (p-value < 0.0001).
- FUSION (treatment-experienced): the SVR12 rate difference between HCV GT2 and 3 subjects was significant within each treatment duration group.

- *SOF+RBV for 12 weeks*: SVR12 rates were 82% and 30% for HCV GT2 and 3 subjects, respectively (p-value < 0.0001).
- *SOF+RBV for 16 weeks*: SVR12 rates were 89% and 62% for HCV GT2 and 3 subjects, respectively (p-value = 0.0052).

The HCV GT3 relapse rate in the 16 Week arm was still as high as 38% even though much lower than 66% in the 12 Week arm. This observation suggests the efficacy could potentially be further improved with longer treatment duration or an additional antiviral agent (e.g., PEG or another direct acting antiviral).

b. Bridging Analyses to Explore Treatment Duration in Treatment-Naïve Genotype 3 Subjects

The collective evidence from the Phase 3 trials indicates 12 weeks of SOF+RBV is not the optimal regimen for HCV GT3 patients. Reduced response rates in HCV GT3 subjects were driven by relapse, indicating extending the duration of therapy may improve SVR. FUSION demonstrated HCV GT3 treatment-experienced subjects receiving SOF+RBV for 16 weeks had significantly increased SVR12 rates compared with the same regimen for 12 weeks, 62% versus 30%, respectively, as well as lower relapse rates (38% versus 66%, respectively). Additionally, response rates for HCV GT3 subjects were consistently lower than HCV GT2 subjects across all three trials. These observations suggest that a longer treatment duration may also be beneficial in the HCV GT3 treatment-naïve population; however, the available Phase 3 trials only evaluated SOF+RBV for 12 weeks. Due to the overall lower SVR12 rate observed in HCV GT3 patients, the FDA requested the Applicant to provide analyses justifying a treatment duration for HCV GT3 treatment-naïve patients based on the available Phase 3 data. These analyses, which are included in the Applicant's background package, show their bridging analysis to estimate the SVR12 rate for 16 weeks of SOF+RBV in HCV GT3 treatment-naïve patients using the GT3 data from FISSION and FUSION.

FDA analyses were also conducted to estimate the treatment response of 16 weeks of SOF+RBV treatment in HCV GT3 treatment-naïve subjects. Instead of applying the Applicant's model to estimate the SVR12 rate, the FDA analyses extrapolated the SVR12 rate from the observed SVR12 rates in FISSION and FUSION based on an assumption of equivalent odds ratios of SOF+RBV 16 Weeks over SOF+RBV 12 Weeks compared to SOF+RBV 12 Weeks in both treatment-naïve and treatment-experienced HCV GT3 subjects. This odds ratio analysis predicted an SVR12 rate of 83% for 16 weeks of SOF+RBV in HCV GT3 treatment-naive subjects (Table 4). Alternative calculations based on using either relative risk (RR) or proportion difference (PD) were also evaluated and resulted in estimated SVR12 rates of 76% and 88%, respectively. Thus, these exploratory post-hoc analyses determined the estimated SVR12 rate for 16 weeks in HCV GT3 treatment-naive subjects ranges from 76% to 88% depending on the extrapolation approach used, and suggest 16 weeks of SOF+RBV treatment in HCV GT3 treatment-naïve subjects would lead to a higher SVR12 rate than the 56% SVR12 rate observed for 12 weeks of SOF+RBV treatment in the FISSION trial.

Table 4: FDA Bridging Analysis Results for Estimated SVR12 Rate for 16 Weeks of SOF+RBV in HCV Genotype 3 Treatment-Naïve Subjects Based on Extrapolation Approach

	Estimated SVR12 rate for 16-week SOF+RBV in HCV Genotype 3 treatment-naive subjects (95% CI)
Odds ratio	83% (69%, 92%)
Relative risk	76% (65%, 84%)
Proportion difference	88% (70%, 100%)

SOF=sofosbuvir; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

c. Subgroup Analyses to Explore Treatment Duration in HCV Genotype 2 Subjects

Although higher overall SVR12 rates are observed in HCV GT2 subjects compared with HCV GT3 subjects, FDA performed post-hoc analyses to determine if particular HCV GT2 subpopulations may benefit from a longer treatment duration. Treatment-experienced subjects with HCV GT2 showed a numerical improvement in SVR rates following a longer duration of 16 weeks SOF+RBV compared to 12 weeks SOF+RBV (89% vs. 82%) (Table 5). In particular, treatment-experienced HCV GT2 null and partial responders and treatment-experienced HCV GT2 cirrhotic subjects had numerically higher SVR rates following 16 weeks of treatment compared to 12 weeks of treatment.

Table 5: FDA Subgroup Analysis in HCV Genotype 2 Subjects with Prior Treatment-Experience (FUSION)[1]

	SOF + RBV 12 Weeks	SOF + RBV 16 Weeks
Overall SVR12 Rate	82% (32/39)	89% (31/35)
Prior Treatment-Experience		
P/R Breakthrough or Relapser	86% (25/29)	89% (24/27)
P/R Null or Partial Responder	70% (7/10)	88% (7/8)
Cirrhosis Status		
Cirrhosis Yes	60% (6/10)	78% (7/9)
No	90% (26/29)	92% (24/26)

[1]Based on the intention-to-treat (ITT) principle, including six subjects (three in each arm) with misclassified HCV genotype.
P/R = pegylated interferon/ribavirin; SOF=sofosbuvir; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment

Although the treatment-experienced nulls/partial-responders and treatment-experienced cirrhotic subgroups were small, the numerical differences suggest a longer duration of 16 weeks SOF+RBV for HCV GT2 treatment-experienced patients may improve SVR in this subgroup.

B. HCV Genotype 1, 4, 5 and 6 Population

1. Efficacy in HCV Genotype 1, 4, 5 and 6 treatment-naïve population (NEUTRINO)

This Phase 3, multicenter, open-label trial enrolled treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection. Subjects received SOF (400 mg once daily) + PEG (180 µg/week) + RBV (1000 or 1200 mg/day) for 12 weeks. A total of 327 subjects received study drugs, including 17% with compensated cirrhosis.

Overall, a statistically significant proportion of subjects achieved SVR12 (90%, $p < 0.0001$) compared with a historical SVR12 rate of 60% (Table 6). Relapse accounted for most treatment failures, with an overall rate of 9%. No subject had on-treatment virologic failure. Subjects with GT1 (N=292) had an SVR12 rate of 89%, with a GT1a and GT1b subtype difference noted (SVR12 92% and 82%, respectively). Subjects with GT4 (N=28) had an SVR12 rate of 96%. It should be noted that few subjects with GT5 (N=1) and GT6 (N=6) were included in the clinical trial and the available data are believed to be insufficient to make definitive dosing recommendations for patients with HCV GT5 or 6 infection.

Table 6: NEUTRINO Primary Efficacy Results (FAS)[1]

Efficacy Parameter	**SOF+PEG+RBV 12 Weeks (N=327)**
Overall SVR12 Rate [95% CI] (n/N)	90% [86%, 93%] (295/327)
Genotype 1 (1a, 1b, 1a/1b)	89% [85%, 93%] (261/292)
Genotype 1a	92% [87%, 95%] (206/225)
Genotype 1b	82% [70%, 90%] (54/66)
Genotype 4	96% (27/28)
Genotype 5	100% (1/1)
Genotype 6	100% (6/6)

[1]FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication; SOF=sofosbuvir; PEG=pegylated interferon alfa; RBV=ribavirin; CI=confidence interval
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

Few sofosbuvir-treated subjects (<2%) discontinued treatment due to an AE.

2. Response Rates in HCV Genotype 1a and 1b Subjects

In NEUTRINO, HCV GT1a treatment-naïve subjects had 10% higher SVR12 rates than GT1b subjects. Post-hoc analyses between the two genotype subtypes across demographics and baseline characteristic subgroups found HCV GT1a subjects had numerically higher SVR12 rates than HCV GT1b subjects in almost all subgroups (Table 7). Thus, the HCV GT1 subtype SVR12 rate differences are not clearly explained by such factors. Cell culture replicon data with sofosbuvir demonstrates EC_{50} values are slightly higher for GT1b (110 nM) and GT3a (50 nM) replicons compared to GT1a (40 nM) and GT2b (15 nM) replicons, which may offer some supportive evidence for why subjects infected with HCV GT1b and GT3a had lower overall clinical efficacy compared to subjects infected with HCV GT1a and GT2 HCV.

Table 7: NEUTRINO FDA Subgroup Comparisons between HCV Genotype 1a and Genotype 1b (All Treated)

	12-Week SOF+PEG+RBV		
	Genotype 1a (n=225)	**Genotype 1b (n=66)**	**Genotype 1a vs. Genotype 1b Prop Diff (95% CI)**
Age (years)			
<50 years old	94% (76/81)	92% (11/12)	2% (-14%, 19%)
>=50 years old	90% (130/144)	80% (43/54)	11% (-1%, 22%)
Sex			
Male	90% (128/143)	78% (35/45)	12% (-1%, 25%)
Female	95% (78/82)	91% (19/21)	5% (-9%, 18%)
Race			
Black	91% (30/33)	77% (13/17)	14% (-8%, 37%)
Non-black	92% (176/192)	84% (41/49)	8% (-3%, 19%)
Ethnicity			
Hispanic	92% (33/36)	83.3% (5/6)	8% (-23%, 39%)
Non-Hispanic	92% (173/189)	82% (49/60)	10% (-1%, 20%)
Baseline body mass index			
<30 kg/m^2	95% (127/134)	85% (33/39)	10% (-2%, 22%)
>=30 kg/m^2	87% (79/91)	78% (21/27)	9% (-8%, 26%)
Cirrhosis[1]			
No	93% (168/180)	84% (47/56)	9% (-1%, 20%)
Yes	84% (36/43)	67% (6/9)	17% (-16%, 50%)
IL28 B			
CC	99% (71/72)	92% (12/13)	6% (-8%, 21%)
CT or TT	88% (135/153)	79% (42/53)	9% (-3%, 21%)
Baseline HCV RNA			
<6 $\log_{10}$ IU/mL	96% (44/46)	100% (9/9)	-4% (-2%, 10%)
>=6 $\log_{10}$ IU/mL	91% (162/179)	79% (45/57)	12% (0.1%, 23%)
Baseline ALT			
<=1.5 x ULN	91% (89/98)	82% (31/38)	9% (-4%, 23%)
>1.5 x ULN	92% (117/127)	82% (23/28)	10% (-5%, 25%)

[1]Subjects with missing data are excluded from the cirrhosis subgroup comparisons.
The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limit
SOF=sofosbuvir; PEG=pegylated interferon alfa; RBV=ribavirin
Prop Diff=proportion difference
SVR12= sustained virologic response at 12 weeks after the end of treatment
Source: FDA Statistical Reviewer

3. HCV Genotype 1 Infection, Prior Pegylated Interferon Nonresponders: Exploratory Analyses

HCV GT1 patients who failed prior treatment with PEG+RBV were not specifically studied in the SOF development program. Clinical HCV trials have generally categorized patients as treatment-naïve or treatment-experienced based upon their prior virologic response to a PEG+RBV regimen. Previous FDA analyses have demonstrated that PEG+RBV nonresponders

are represented within the treatment-naïve population (Liu et al. Hepatology 2013, Liu et al. CID 2012, Florian et al. Hepatology 2013). Other baseline factors or patient characteristics such as cirrhosis status and viral load have been shown to predict response to a PEG+RBV regimen. The observed high overall SVR rate in HCV GT1 treatment-naïve subjects from NEUTRINO led the Division to use a similar approach to explore if the data may support use of SOF+PEG+RBV for 12 weeks in patients who have failed a prior PEG+RBV regimen. During the Advisory Committee meeting, analyses will be presented addressing use of SOF+PEG+RBV in this population, including limitations of this approach such as the NEUTRINO single arm trial design and potential subpopulations in which this 12 week regimen may not be optimal (e.g., prior null responders). Acknowledging the lack of data directly obtained in this patient population, we believe that the SOF+PEG+RBV shorter treatment duration and improved tolerability profile warrants consideration by the Committee for use in HCV GT1 patients who have failed a prior PEG+RBV regimen.

As more DAA-based therapies emerge, the patient population who failed a prior PEG+RBV regimen is anticipated to diminish over time, and the traditional PEG+RBV-based treatment-naïve and treatment-experienced definitions may not be optimal. In addition, we recognize the baseline predictors identified from the long experience with PEG+RBV treatment may be different from those identified with DAA-based regimens.

III. SUMMARY OF SAFETY

The Division's primary safety analyses evaluated treatment-emergent adverse events (AEs), serious AEs (SAEs), severe and life-threatening AEs, AEs leading to discontinuation, deaths and laboratory abnormalities in the Phase 3 trials. Safety review from non-pivotal trials provides supportive data. In general, the Division agrees with the Applicant's safety assessments. Accounting for higher RBV dosing in sofosbuvir-containing regimens, there does not appear to be additive hematologic toxicities associated with sofosbuvir use. Extending treatment duration of the sofosbuvir and ribavirin combination regimen from 12 to 16 weeks does not appear to increase AEs associated with sofosbuvir use. Please refer to the Applicant's safety assessment in these trials.

A. Cardiac Safety Analyses

FDA conducted a detailed safety evaluation focused on cardiac disorders to identify any potential cardiac toxicity signals in the sofosbuvir development program.

Non-clinical
GS-9851 is a 1:1 mixture of sofosbuvir and its stereoisomer. GS-331007 is the main circulating metabolite in both animals and humans, accounting for the majority of total drug-related exposure. Myocardial inflammation and degeneration occurred in rats administered oral GS-9851 doses of 2000 mg/kg/day (AUC_{last}~206 μg.h/ml for GS-331007) in a 7-day toxicology study. The AUC exposures for GS-9851- and sofosbuvir-derived GS-331007 are approximately 29- and 14-fold higher, respectively, than human exposure at the recommended sofosbuvir dose. Cardiac toxicity was not observed in rats administered oral doses of sofosbuvir up to 500 mg/kg/day (AUC_{last} approximately 66 μg.h/ml for GS-331007) for 6 months, or in dogs and mice

administered sofosbuvir at doses up to 500 and 1000 mg/kg/day (AUC_{last} approximately 195 and 293 μg.h/ml for GS-331007), the highest doses examined in 9 and 3 month studies in dogs and mice, respectively, corresponding to AUC exposures approximately 9 (rat), 27 (dog) and 41 (mouse)-fold higher than human exposure at the recommended sofosbuvir dose.

Clinical

There were no serious or severe cardiac AEs reported in sofosbuvir-treated subjects, and no treatment discontinuations due to cardiac AEs. Furthermore, no clustering of cardiac-related AEs was observed. The only Grade 2 event observed in the SOF+RBV group was palpitations. Grade 1 events noted in the SOF+RBV group were: palpitations (N=5), tachycardia (N=3), sinus bradycardia (N=1), extrasystoles (N=1), and ventricular extrasystoles (N=1). These AEs could be confounded by the concomitant administration of ribavirin in all subjects treated in Phase 3 trials, which is known to cause hemolytic anemia. Some of the symptoms of anemia include fatigue, dyspnea, dizziness, headache, tachycardia, and chest pain. As noted by the Applicant, there have been no cases of cardiomyopathy reported in sofosbuvir-containing trials to date.

Table 8: Adverse Events by Preferred Term in Cardiac Disorders (SOC) in the Primary Safety Population (Integrated Data)

MedDRA Preferred Term	Treatment Group Toxicity Grade		Treatment Group Toxicity Grade	
	All Grades n (%)	Grades ≥ 3 n (%)	All Grades n (%)	Grades ≥ 3 n (%)
FISSION				
	SOF+RBV 12 Weeks N=256		**PEG+RBV 24 Weeks** N=243	
Atrioventricular Block	0	0	1 (0.4)	1 (0.4)
Extrasystoles	1 (0.4)	0	0	0
Palpitations	2 (0.8)	0	6 (2.5)	0
Pulmonary Valve Incompetence	0	0	1 (0.4)	0
Sinus Bradycardia	1 (0.4)	0	1 (0.4)	0
Tachycardia	1 (0.4)	0	3 (1.2)	0
POSITRON				
	SOF+RBV 12 Weeks N=207		**Placebo** N=71	
Atrial Fibrillation	0	0	1 (1.4)	0
Palpitations	2 (1.0)	0	0	0
Tachycardia	2 (1.0)	0	0	0
Ventricular Extrasystoles	1 (0.5)	0	0	0
FUSION				
	SOF+RBV 12 Weeks + Placebo 4 Weeks N=103		**SOF+RBV 16 Weeks** N=98	
Palpitations	2 (1.9)	0	0	0
NEUTRINO				
	SOF+PEG+RBV 12 Weeks N=327		NA	
Coronary Artery Disease	1 (0.3)	0		
Palpitations	3 (0.9)	0		

SOF=sofosbuvir; PEG=pegylated interferon alfa; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
n (%) is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, MedDRA system organ class, and preferred term
Source: FDA Analysis. Integrated Datasets (FISSION, POSITRON, FUSION, NEUTRINO)

Three cardiac-related SAEs occurred in Phase 2 trials: acute myocardial infarction (Day 72), atrial fibrillation (post-treatment Day 8), angina (post-treatment Day 24). Each subject was receiving sofosbuvir plus pegylated interferon and ribavirin, and each subject had either a prior history of cardiac disease or cardiac risk factors.

Based on the review of submitted data to date, no obvious safety issue related to cardiac toxicity has been identified in sofosbuvir clinical development program.

B. Special Populations: Pre-Transplant Population

Recurrence of HCV infection after liver transplantation is almost universal. The rate of fibrosis progression in these patients is accelerated compared to non-transplant HCV patients with approximately 10-25% developing cirrhosis within 5 to 10 years of transplantation (Burra P. Seminars in Liver Disease 2009). There are currently no approved therapies to prevent recurrence of HCV infection post liver transplant. Hence, therapies administered pre-transplant to prevent HCV recurrence represent an area of unmet medical need.

1. P7977-2025

This ongoing Phase 2, open-label trial is evaluating the efficacy of SOF+RBV administered pre-transplant in preventing HCV recurrence post liver transplant in subjects with HCV GT1 through 6 infection and hepatocellular carcinoma (HCC) specifically meeting the Milan criteria[1] prior to undergoing liver transplantation with an anticipated time until transplantation within one year. The original protocol-specified treatment duration was for a maximum of 24 weeks and later extended via protocol amendment to 48 weeks, or until transplant, whichever comes first. Treatment is discontinued within 24 hours prior to liver transplant if it occurs before the subject has completed their treatment course, as appropriate. Prevention of post-transplant reinfection is determined by a sustained post-transplant virological response (HCV RNA < LLOQ) at 12 weeks post-transplant (pTVR12). Please refer to the Applicant's background package for further trial details.

The majority of the subjects had HCV GT1 infection (73.8%, GT1; 39.3%, GT1a and 34.4%, GT1b) while 13.1%, 11.5%, and 1.6% had GT 2, 3, and 4 HCV infection, respectively. Most subjects had a baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL (67.2%) and an IL28B non-CC allele (78.3%). Baseline Child-Pugh-Turcotte (CPT) scores ranged from 5 to 8. Baseline MELD score ranged from 6 to 14, with approximately half of subjects (49.2%) having a score of 7 or 8. About 75% of subjects had prior HCV treatment experience.

A total of 61 subjects received at least one dose of study drugs at the time of the data cutoff for updated data submission to FDA. The trial status of these subjects is as follows:

- 6 subjects prematurely discontinued treatment
- 9 subjects were on treatment
- 29 subjects underwent liver transplantation while on treatment
- 8 subjects completed 24 weeks of treatment and then underwent a liver transplantation
- 7 subjects relapsed after completing 24 weeks of treatment and were retreated with SOF+RBV in a substudy

[1] Milan criteria were defined as the presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinomas and no more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors. There should be no extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor.

- 2 subjects completed 24 weeks of treatment and were prematurely terminated from the trial due to disease progression (were no longer transplant candidates)

Pre Liver Transplant Phase

A total of 11 of 15 subjects (73%) who completed 24 weeks of SOF+RBV treatment relapsed in the pre-transplant phase. Ten of these subjects had HCV GT1 infection (7 GT1a, 3 GT1b) and one subject had GT2b infection. The rate of virologic relapse after 24 weeks of treatment in this patient population suggested a longer treatment duration may be indicated to achieve HCV RNA < LLOQ at the time of transplant. This finding led to a protocol amendment to extend the treatment duration from 24 weeks to 48 weeks or to the time of transplant.

Post Liver Transplant Phase

A total of 41 subjects with any SOF+RBV treatment duration have undergone liver transplantation at the time of the updated submission. Thirty-seven subjects had HCV RNA <LLOQ at the time of liver transplantation and 36 have been followed to post-transplant Week 12. Of those subjects, 63.9% achieved sustained pTVR12. Of the approximately two-thirds of subjects (N=24) reaching post-transplant Week 24, 71% (17/24) achieved sustained pTVR24 (data not shown).

HCV GT2 and GT3 infected subjects had improved virologic outcomes (75-100%) compared with HCV GT1 subjects (54%). The lower overall HCV GT1 rate compared to NEUTRINO data can be explained by the lack of pegylated interferon use, with possible additional contributions of poorer baseline predictors such as cirrhosis. Among HCV GT1 subjects, those with HCV GT1a had improved pTVR12 rates compared with HCV GT1b subjects, 62% versus 46%, respectively.

Table 9: Transplanted Subjects Followed to Post-Transplant Week 12, by Genotype

HCV Genotype	SOF+RBV, (N=36)
Overall pTVR12	23/36 (63.9)
90% CI	48.8-77.1
1a, n (%)	8/13 (61.5)
90% CI	35.5-83.4
1b, n (%)	6/13 (46.2)
90% CI	22.4-71.3
2, n (%)	5/5 (100.0)
90% CI	54.9-100.0
3, n (%)	3/4 (75.0)
90% CI	24.9-98.7
4, n (%)	1/1 (100.0)

pTVR = post-transplant virologic response

Source: Applicant's Submission

A total of 28% subjects (10/36) experienced recurrent HCV infection post-transplant. By genotype, GT1b had the highest recurrence rates (54%, 7/13) followed by GT1a (15%, 2/13). A single GT3a subject had recurrence as well. Five subjects had on-treatment virologic failure: 3 breakthroughs (1 GT1a, 1 GT1b and 1 GT2b) and 2 non-responders (both GT1a).

Safety

Higher rates of Grade 3 or 4 AEs, SAEs, and deaths were reported in this pre-transplant population compared to the adverse event profile in the Phase 3 trials. This difference in safety profile can be attributed to the more advanced stage of liver disease and/or due to underlying disease progression (cirrhosis with HCC) in these subjects. Some of the AEs noted were associated with liver transplant. After accounting for these factors, the safety profile in this subpopulation does not appear to differ from the overall safety profile of a sofosbuvir and ribavirin regimen in subjects not undergoing transplantation.

The demonstrated efficacy (as measured by pTVR12 of 63.9%, 23/36) coupled with a generally well-tolerated safety profile in this pre-transplant population addresses an unmet medical need. Moreover, the sustained virologic response post-transplantation was maintained through Week 24 in a subset of subjects (pTVR24 of 71%, 17/24). However, it should be noted that the number of subjects evaluated so far is limited and the population studied was a subpopulation of pre-transplant patients (those with HCC). These patients were eligible to undergo liver transplants due to an upgrade in their MELD scores due to HCC and not necessarily because of worsening liver disease.

IV. VIROLOGY SUMMARY

The NS5B S282T substitution was selected in GT1b, 2a, 3a and 4a subgenomic replicons when the replicon cells were treated with sofosbuvir concentrations of 10 to 30 times the wild-type EC_{50} value. The S282T substitution is associated with a 4- to 24- fold decrease in susceptibility to sofosbuvir for all tested genotypes, and it is not cross-resistant with the NS5A inhibitor, GS-5885, or RBV.

In the Phase 3 trials, there were no significant differences between baseline sequences of subjects who achieved SVR12 and those who relapsed. Notably, S282T was not present in any of the baseline samples or at the time of relapse.

The S282T substitution was detected by next generation sequence (NGS) analysis in one GT2b infected subject from the Phase 2 trial P7977-0523 (ELECTRON) who received sofosbuvir monotherapy for 12 weeks and relapsed at Week 4 post-treatment. The sample from this subject with detectable S282T had a mean 13.5-fold reduced susceptibility to sofosbuvir. The S282T substitution was no longer detectable at Week 12 post-treatment by NGS analysis with an assay cut off of 1%.

An independent assessment of the NGS data by the Division identified some treatment-emergent NS5B substitutions that occurred frequently in the virus of subjects who relapsed, including L159F and E341D. The L159F substitution emerged in 6 relapse subjects infected with HCV GT3a and is a previously identified NS5B substitution shown, along with L320F, to confer reduced susceptibility to HCV nucleotide inhibitors (Tong X et al., AASLD 2012). Substitution E341D emerged in 13 relapse subjects infected with HCV GT3a in two clinical trials (FISSION, n=10; POSITRON, n=3) and it was only found in the virus of subjects who relapsed. The L159F and E341D substitutions emerged together in one HCV GT3a relapse subject. Both L159F and E341D occur at conserved amino acid positions. Phenotypic data for the L159F substitution alone did not show detectable decreased susceptibility to SOF. The E341D has not been analyzed phenotypically. Therefore, the Division has requested that the Applicant characterize the E341D substitution and the combination of L159F + E341D in phenotypic assays to determine if they contribute to decreased sofosbuvir susceptibility.

The available resistance data from both population and deep sequencing of subjects who had on treatment failure (N=5) and subjects who relapsed (N=20) in the pre-transplant trial P7977-2025 provided supportive information for the FDA resistance findings in the sofosbuvir Phase 3 trials. The presence of substitution L159F at baseline was associated with sofosbuvir breakthrough and relapse in 4 subjects infected with HCV GT1b and this substitution emerged on treatment in 2 subjects who were infected with HCV GT1a (one breakthrough and one relapse) and 1 subject infected with HCV GT2b (breakthrough). In addition, an S282R and L320F substitution were detected by deep sequencing in the on-treatment sample from a subject infected with HCV GT1a who did not respond to sofosbuvir.

V. CLINICAL PHARMACOLOGY SUMMARY

Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). A comprehensive range of clinical studies was conducted to characterize the pharmacokinetics (PK) of sofosbuvir and its predominant circulating metabolite, GS-331007, as GS-461203 is not measureable in plasma. Select clinical pharmacology points are summarized below. For a more complete discussion of the clinical pharmacology of sofosbuvir, please refer to the Applicant's background document.

A. Metabolism and Elimination

The metabolic activation pathway to form the pharmacologically active triphosphate metabolite, GS-461203, is mediated by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and histidine triad nucleotide-binding protein 1 (HINT1). Dephosphorylation of the active metabolite results in the formation of the nucleoside metabolite, GS-331007, which cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. GS-331007 is the major circulating metabolite of sofosbuvir. The majority of the sofosbuvir dose is recovered in urine as GS-331007 (78%). Therefore, renal clearance is the major elimination pathway for GS-331007. The median terminal half-lives of sofosbuvir and GS-331007 were 0.4 and 27 hours, respectively.

B. Intrinsic factors

Population PK analysis in HCV-infected subjects indicated that race, gender, or age (19 to 75 years) had no clinically relevant effect on the exposures of sofosbuvir or GS-331007.

The PK of sofosbuvir was studied in HCV-negative subjects with mild (estimated glomerular filtration rate [eGFR] $\geq$ 50 and < 80 mL/min/1.73m^2), moderate (eGFR $\geq$30 and <50 mL/min/1.73m^2), severe renal impairment (eGFR < 30 mL/min/1.73m^2) and subjects with end stage renal disease (ESRD) requiring hemodialysis following a single 400 mg dose of sofosbuvir. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the sofosbuvir $AUC_{0\text{-}inf}$ was 61%, 107% and 171% higher in subjects with mild, moderate and severe renal impairment, while the GS-331007 $AUC_{0\text{-}inf}$ was 55%, 88% and 451% higher, respectively. In subjects with ESRD (relative to subjects with normal renal function), sofosbuvir and GS-331007 $AUC_{0\text{-}inf}$ was 28% and 1280% higher when sofosbuvir was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when sofosbuvir was dosed 1 hour after hemodialysis. No dose adjustment is required for patients with mild or moderate renal impairment. The safety of sofosbuvir has not been established in patients with severe renal impairment or ESRD and a dose recommendation cannot be provided for these populations at this time.

The PK of sofosbuvir was studied following 7-day dosing of 400 mg sofosbuvir in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir $AUC_{0\text{-}24}$ was 126% and 143% higher in subjects with moderate and severe hepatic impairment, while the GS-331007 $AUC_{0\text{-}24}$ was 18% and 9% higher, respectively. Population PK analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on the exposure of sofosbuvir and GS-331007. No dose adjustment of sofosbuvir is recommended for patients with mild, moderate and severe hepatic

impairment. However, as PEG is contraindicated for use in patients with decompensated cirrhosis and the safety and efficacy of sofosbuvir have not been established in these patients, sofosbuvir should not be used in this patient population who would receive a PEG-based regimen.

C. Drug Interactions

Sofosbuvir is a substrate of drug transporters P-gp and BCRP, while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) may decrease sofosbuvir plasma concentration leading to reduced therapeutic effect of sofosbuvir and thus should not be used with sofosbuvir. Coadministration of sofosbuvir with drugs that inhibit P-gp and/or BCRP would likely increase sofosbuvir plasma concentration (e.g., cyclosporine). The effects of coadministered drugs on the exposure of SOF and GS-331007 have been studied for cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, raltegravir, rilpivirine, tacrolimus, and tenofovir disoproxil fumarate. No clinically significant effect of sofosbuvir on these drug exposures has been observed. No significant changes in the exposures of sofosbuvir and GS-331007 caused by these coadministered drugs have been observed, with the exception of cyclosporine (CsA).

Coadministration of sofosbuvir with the P-gp and BCRP inhibitor CsA (administered as a single high dose of 600 mg), resulted in an increase (approximately 4.5-fold) in sofosbuvir exposure, but the exposure of GS-331007 was unchanged in the presence of CsA. The safety margins for sofosbuvir and metabolites after coadministration with CsA are adequate (AUC safety margins range from 2.9 to 10.3), when compared with exposures obtained in rat and dog in 3 to 9-month toxicology studies. Furthermore, limited safety data from ongoing post-transplant study (GS-US-334-0126) indicated that the safety of SOF+RBV is similar between subjects not taking CsA (N=30) and subjects taking CsA (N=10). Therefore, no dose modification of sofosbuvir is recommended when coadministered with CsA.

VI. General Summary

The currently available data support a favorable benefit-risk assessment for the use of sofosbuvir as part of a combination regimen for the treatment of chronic hepatitis C. In the HCV GT 2 and 3 populations, the sofosbuvir and ribavirin combination regimen provides the first all-oral, interferon-free treatment, as well as a shorter treatment duration and improved safety profile compared to the current standard of care interferon-based regimen. In addition, SOF+RBV provides a therapeutic option for patients who are ineligible, intolerant or unwilling to take interferon-based regimens, thus addressing an unmet need in this patient population.

In the HCV GT 1 and 4 populations, sofosbuvir in combination with pegylated interferon and ribavirin provides increased efficacy and shorter treatment duration compared with currently approved regimens. The shorter 12 week duration translates into a better tolerated side effect profile with observed treatment discontinuations due to AEs of less than 2%. The available data are believed to be insufficient to make definite dosing recommendations for patients with GT 5 or 6.

No major safety issues associated with sofosbuvir use have been identified to date. The observed safety profile between the two durations (SOF+RBV 12 weeks versus SOF+RBV 16 weeks) evaluated in FUSION is similar.

VII. PRELIMINARY TOPICS FOR THE ADVISORY COMMITTEE

The Division is convening this meeting to solicit the Committee's comments on the following topics. Please note, however, that these are preliminary topics and are still subject to change.

1. **Considering potential risks and benefits do the available data support approval of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in treatment-naïve adult patients with genotype 1 and 4 infection?**

Background Information for Consideration (Issue 1): As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, doesn't mean that one must agree with all of the proposed dosing recommendations or that one must define all labeling recommendations. Questions 3 through 7 that follow the general approval question/vote will give the Committee a chance to provide opinions on more granular issues and labeling recommendations, if there is consensus that the overall risk-benefit is positive and supportive of approval for use in treatment of hepatitis C. If not, please consider what additional studies should be recommended.

2. **Considering potential risks and benefits do the available data support approval of sofosbuvir in combination with ribavirin for treatment of chronic hepatitis C in adult patients with genotype 2 and 3 infection?**

Background Information for Consideration (Issue 2): As the question states, we are asking the committee to weigh all the risks and benefits in the vote for approval. The general background information included in Question 1 applies to this question as well.

3. **Please comment on the strength of evidence for use of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in patients with genotype 1 infection who are nonresponders to a prior course of pegylated interferon and ribavirin. Please comment if additional data are needed in this population.**

4. **Please comment on the strength of evidence (bridging analyses) for use of sofosbuvir and ribavirin for 16 weeks duration in treatment-naïve genotype 3 patients.**

5. **Please comment on the strength of evidence for use of sofosbuvir and ribavirin for 16 weeks duration in subgroups of genotype 2 patients who may benefit from an extended duration of therapy.**

6. **Please comment on the strength of evidence for use of sofosbuvir in combination with ribavirin in HCC patients meeting Milan criteria awaiting liver**

transplantation. Are the available data sufficient for dosing recommendation? If not, what additional studies are recommended?

7. **Please comment on postmarketing studies/trials that are needed to further define the optimal use of sofosbuvir.**