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APPLICATION NUMBER:

204671Orig1s000

MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

Date	November 20, 2013
From	Poonam Mishra, M.D. Medical Officer Division of Antiviral Products
Subject	Clinical Review Addendum
NDA #	204671
Applicant	Gilead Sciences, Inc.
Date of Additional Data Submission	October 09, 2013
PDUFA Goal Date	December 08, 2013
Established Name/ Proprietary Name	Sofosbuvir (GS-7977)/ SOVALDI
Therapeutic Class	Hepatitis C virus NS5B polymerase inhibitor
Dosage forms / Strength	400mg tablet for oral use
Proposed Indication(s)	Treatment of chronic hepatitis C in adults
Recommended:	Approval with recommended revisions in the dosing regimen for patients with genotype 3 HCV infection; proposed treatment option for Interferon-ineligible HCV genotype 1 patients; and indication in HCV/HIV-1 co-infected patient population

This memorandum is an addendum to the Primary Clinical Review archived on September 06, 2013.

1 Recommendations/Risk Benefit Assessment

From a clinical reviewer's perspective, the approval of sofosbuvir is recommended for the treatment of chronic hepatitis C infection in adults. Please refer to Primary Clinical Review (dated September 06, 2013) for detailed assessment of the data from four Phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110) submitted in the original NDA application. This addendum includes review of additional interim data submitted from two ongoing Phase 3 trials (GS-US-334-0123 and GS-US-334-0133) evaluating sofosbuvir in combination with ribavirin. The overall risk benefit assessment for sofosbuvir remains favorable. No deficiencies in the submitted/reviewed data preclude recommendation for approval of sofosbuvir at this time.

2 Introduction and Regulatory Background

Sofosbuvir (SOF) is a nucleotide inhibitor of hepatitis C virus NS5B RNA-dependent RNA polymerase inhibitor. Sofosbuvir is the first-drug-in class submitted for marketing application in the United States. The original NDA Application was submitted on April 06, 2013 and is currently under priority review. Breakthrough therapy designation was granted for sofosbuvir on October 10, 2013 under the IND 106739.

An Antiviral Drugs Advisory Committee Meeting was convened on October 25, 2013 to discuss NDA 204671. The committee members unanimously voted to support approval of sofosbuvir in combination with ribavirin for treatment of chronic hepatitis C in adult patients with genotypes 2 and 3 infection and to support approval of sofosbuvir in combination with pegylated interferon and ribavirin for treatment of chronic hepatitis C in treatment-naïve adult patients with genotypes 1 and 4 infection. Please refer to AC transcripts for detailed information.

At the time of Primary Clinical Review, the primary clinical data supporting the use of sofosbuvir (SOF) in combination with ribavirin (RBV) for the treatment of genotypes 2 and 3 HCV infection was derived from three registrational Phase 3 trials.

- P7977-1231 (FISSION) evaluated 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

Please refer to Primary Clinical Review archived in DARRTS on September 06, 2013 for detailed efficacy and safety analyses of these trials.

The primary efficacy endpoint (sustained virologic response, SVR12) and relapse rates for these trials are summarized in Table 1 below.

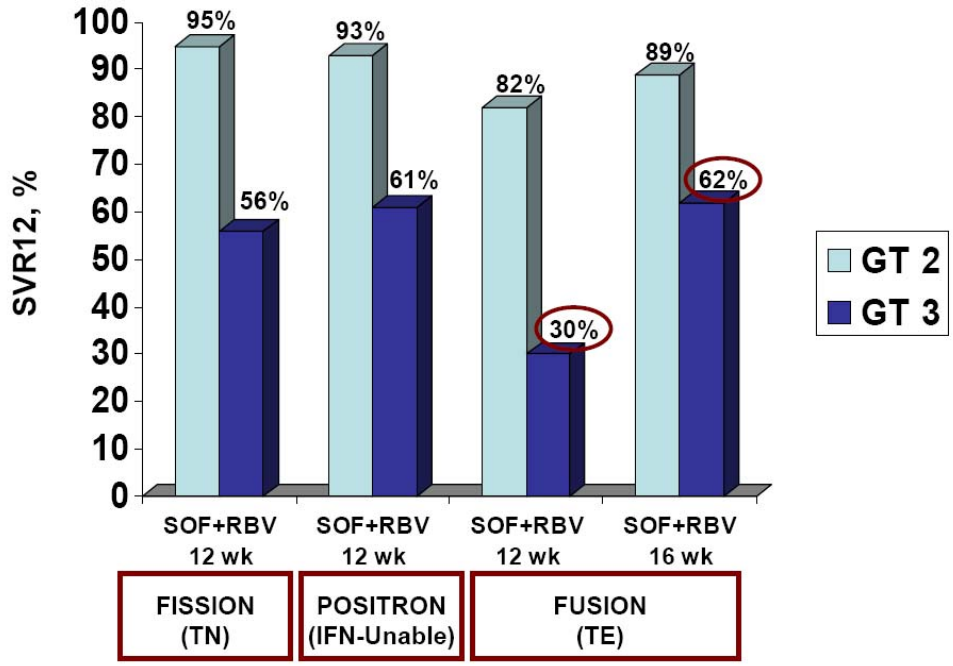
Table 1: Efficacy Data for Genotypes 2 and 3 (Phase 3 Trials - Original NDA Submission)

Trial	Treatment Regimens	n/N	SVR12
Trials in Subjects with Genotype 2 or 3 HCV Infection			
FISSION (P7977-1231) (Treatment-naive)	**SOF+RBV 12 weeks**		
	Genotype 2	69/73	95%
	Genotype 3	102/183	56%
	Relapse Rates GT 2	**4/73**	**5%**
	Relapse Rates GT 3	**72/179**	**40%**
POSITRON (GS-US-334-0107) (Intolerant, ineligible, or unwilling to take interferon)	**SOF+RBV 12 weeks**		
	Genotype 2	101/109	93%
	Genotype 3	60/98	61%
	Relapse Rates GT 2	**5/107**	**5%**
	Relapse Rates GT 3	**37/98**	**38%**
FUSION (GS-US-334-0108) (Treatment-experienced)	**SOF+RBV 12 weeks**		
	Genotype 2	32/39	82%
	Genotype 3	19/64	30%
	Relapse Rates GT 2	**7/39**	**18%**
	Relapse Rates GT 3	**42/64**	**66%**
	SOF+RBV 16 weeks		
	Genotype 2	31/35	89%
	Genotype 3	39/63	62%
	Relapse Rates GT 2	**4/35**	**11%**
	Relapse Rates GT 3	**24/63**	**38%**

Source: Clinical Review (Archived September 06, 2013)

Figure 1 shows the differences in SVR12 between genotypes 2 and 3 across three Phase 3 trials submitted in original NDA submission.

Figure 1: SVR12 Rates for Genotypes 2 and 3



Source: FDA Presentation, Antiviral Drugs Advisory Committee Meeting October 25, 2013

As shown in Figure 1, SVR12 rates for GT3 subjects were consistently lower than GT2 subjects across all three trials. FUSION trial (shown on the right most side of the figure) demonstrated that 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.

Reviewer's Comments

SVR12 rates for HCV genotype 3 subjects were consistently lower than HCV genotype 2 subjects across all three trials submitted for original NDA review. Reduced response rates in genotype 3 subjects were driven by high relapse rates, indicating that extending the duration of therapy may improve SVR. FUSION demonstrated genotype 3 treatment-experienced subjects receiving SOF+RBV for 16 weeks had significantly increased SVR12 rates compared with the SOF+RBV regimen for 12 weeks, 62% versus 30%, respectively, as well as lower relapse rates (38% versus 66%, respectively). The collective evidence from the Phase 3 trials indicated that 12 or 16 weeks of SOF+RBV is not the optimal regimen for HCV genotype 3 patients and the SVR12 rates can be further optimized by longer treatment duration in genotype 3 patient population.

Subsequent to the Primary Clinical Review, the Applicant made us aware of the emerging data from ongoing trials and their plans to present the data at the American Association for the Study of Liver Diseases (AASLD) annual Meeting to be held November 1st – November 5th, 2013 in Washington D.C.

The highlights of the GS-US-334-0133 (VALENCE) data shared by the Applicant appeared promising and supported longer treatment duration (24 weeks of SOF+RBV) for genotype 3 subjects. From a public health perspective, approving a suboptimal regimen when the emerging data is already available for 24 week treatment duration would not be beneficial for patients and would unduly expose patients to a suboptimal therapy. Taking these factors into consideration, a decision was made to review the currently available data from VALENCE trial during current review cycle rather than waiting for the trial completion and subsequent submission of data as an efficacy supplement.

The highlights of the GS-US-334-0123 (PHOTON-1) data supported a treatment option (24 weeks of SOF+RBV) for interferon-ineligible genotype 1 patients and provided safety and efficacy data in the HCV/HIV co-infected patient population.

These assessments led to submission and review of data from the two ongoing trials, GS-US-334-0133 (VALENCE) and GS-US-334-0123 (PHOTON-1) discussed in this review.

3 Ethics and Good Clinical Practices

As noted in the Clinical Review signed on September 06, 2013, the Applicant noted that all trials conducted in the sofosbuvir development program met the requirement for International Conference on Harmonization (ICH) guidelines.

One of the trials included in this review is a non-IND trial (GS-US-334-0133) being conducted in Europe. The Applicant (Gilead) confirmed that Study GS-US-334-0133 (VALENCE) has met the requirements outlined under 21 CFR § 312.120(a)(1). Please refer to Cross Discipline Team Leader (CDTL) Memo by Dr. Sarah Connelly (signed November 08, 2013) which addresses the applicability of available clinical data from trial GS-US-334-0133 (VALENCE) to U.S. population.

The Applicant noted that a FDA Form 3455 was not included in submission dated October 09, 2013 for Study GS-US-334-0133 (VALENCE) as there are no Principal Investigators or Subinvestigators who have a financial interest with Gilead Sciences, Inc.

4 Significant Efficacy/Safety Issues Related To Other Review Disciplines

Please refer to CDTL Memo by Dr. Sarah Connelly which summarizes the pertinent issues related to other review disciplines. Please refer to respective discipline review addenda for detailed assessments.

5 Sources of Clinical Data

Additional data from two ongoing Phase 3 trials were submitted during the current review cycle. These trials are:

- GS-US-334-0133 (VALENCE)
- GS-US-334-0123 (PHOTON-1)

The key elements of the study design for each trial are described in Section 6.

6 Review of Efficacy

The trial design and the efficacy results for the two ongoing Phase 3 trials (GS-US-334-0133 and GS-US-334-0123) reviewed in this addendum are summarized in this section.

The treatment regimen evaluated in both trials was SOF+RBV for 12 or 24 weeks in duration. SOF 400 mg was administered once daily and weight-based RBV (total daily dose of 1000 or 1200 mg) was administered in a divided daily dose.

The primary efficacy endpoint in both trials was defined as the proportion of subjects who attained SVR12 defined as HCV RNA < lower limit of quantitation (LLOQ) (i.e., < 25 IU/mL) at 12 weeks after study drug cessation.

Nomenclature Used for Virologic Failures

On-treatment virologic failure (breakthrough, rebound, and nonresponse) and relapse was defined as follows:

- On treatment failure
  - — Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with two consecutive values (note, second confirmation value could be posttreatment), or last available on-treatment measurement with no subsequent follow up values
  - — Rebound: > 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment, confirmed with two consecutive values (note, second confirmation value could be posttreatment), or last available on-treatment measurement with no subsequent follow up values

  - — Nonresponse: HCV RNA persistently ≥ LLOQ through the treatment (definition of non response varied between the four phase 3 trials based on treatment regimen and duration)

- Relapse
  - — HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at the last observed HCV RNA measurement on treatment, confirmed with two consecutive values or last available posttreatment measurement

GS-US-334-0133 (VALENCE)

Trial Design

GS-US-334-0133 (VALENCE) is an ongoing Phase 3 non-IND European trial evaluating SOF+RBV for the treatment of HCV genotypes 2 or 3 infection in treatment-naïve or treatment-experienced subjects, including subjects with compensated cirrhosis, with treatment durations of 12 or 24 weeks, depending on HCV genotype.

The primary objectives of this study are as follows:

- To determine the efficacy of treatment with SOF+RBV as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)

- To assess the safety and tolerability of SOF+RBV as measured by review of the accumulated safety data

The protocol was originally designed as a comparison between SOF+RBV or placebo for 12 weeks with the primary endpoint of SVR12. The original trial design for Study GS-US-334-0133 is shown in Figure 2.

Following review of the sofosbuvir Phase 3 data from Study GS-US-334-0108 (FUSION) demonstrating the benefit of the longer treatment duration, GS-US-334-0133 was amended so that all subjects with HCV GT3 who had not already completed treatment had their treatment duration extended to 24 weeks (Figure 3). At this stage, the trial was also unblinded, and subjects initially randomized to receive placebo were discontinued from the trial and offered treatment under a separate protocol (GS-US-334-0109).

Figure 2: Original Study Design for GS-US-334-0133

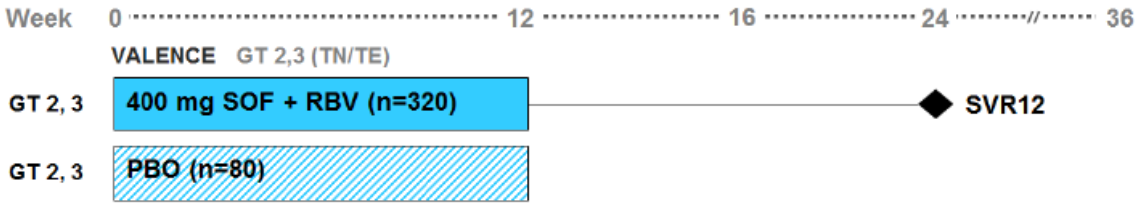
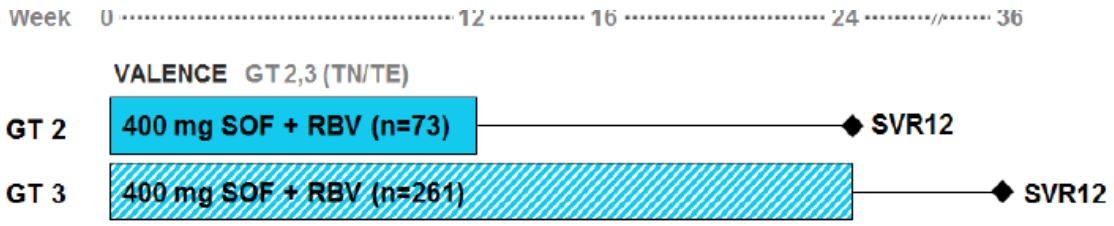


Figure 3: Amended Study Design for GS-US-334-0133*



* Placebo subjects (n=85) and GT 3 subjects who completed 12 weeks of SOF+RBV prior to the amendment (n=11) not shown.
Source: Adapted from NDA Submission

Disposition

All genotype 2 subjects (N=73) who received SOF+RBV for 12 weeks completed the treatment as planned. Eleven HCV genotype 3 subjects who were originally randomized to the 12-week SOF+RBV group completed 12 weeks of treatment as planned and did not extend the treatment duration. Two hundred fifty genotype 3 subjects who were originally randomized to the SOF+RBV 12 Week group and were still receiving treatment had the treatment duration extended to 24 weeks. Only 2% of the 250 HCV genotype 3 subjects who received SOF+RBV for 24 weeks discontinued the study medication.

Table 2: Disposition of Subjects in Study GS-US-334-0133

	Genotype 2 12 Week SOF+RBV (N=73)	Genotype 3 24 Week SOF+RBV (N=250)	Genotype 3 12 Week SOF+RBV (N=11)	Genotype 2/3 Placebo (N=85)
Number of enrolled and treated	73 (100%)	250 (100%)	11 (100%)	85 (100%)
Discontinued study treatment	0	4 (2%)	3 (27%)	81 (95%)
Adverse event	0	1 (<1%)	1 (9%)	1 (1%)
Terminated by sponsor	0	0	0	79 (93%)
Subject withdrew consent	0	2 (1%)	2 (18%)	0
Lost to follow-up	0	1 (<1%)	0	1 (1%)
Discontinued study				
Adverse event	0	1 (<1%)	1 (9%)	1 (1%)
Efficacy failure	0	17 (7%)	3 (27%)	0
Terminated by sponsor	0	1 (<1%)	0	83 (98%)
Subject withdrew consent	0	0	2 (18%)	0
Lost to follow-up	0	1 (<1%)	0	1 (1%)

Source: FDA Statistical Reviewer; Table 1 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Demographics and Baseline Characteristics

Table 3 summarizes the demographic and baseline characteristics for all subjects in the safety analysis set. Overall the mean age (SD) was 50 (11) years old. The majority of subjects were male (60%), white (94%), non-Hispanic (83%). The mean (SD) baseline BMI was 26 (4) kg/m^2.

Among the 73 HCV genotype 2 subjects who received 12 weeks of SOF+RBV, the mean age (SD) was 58 (10) years old. Fifty-five percent of the subjects were male, 89% were white, and 89% were non-Hispanic. The mean BMI (SD) at baseline was 26 (4) kg/m^2.

Among the 250 HCV genotype 3 subjects who received 24 weeks of SOF+RBV, the average age (SD) was 48 (10) years old. The majority of subjects were male (62%), white (94%) and non-Hispanic (81%). The mean BMI (SD) was 25 (4) kg/m^2.

Table 3: Demographics and Baseline Characteristics for Study GS-US-334-0133 (All Treated)

	Genotype 2/3 Placebo (N=85)	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3* 24-Week SOF+RBV (N=250)	Total (N=419)
Age (years)				
Mean (SD)	49 (10)	58 (10)	48 (10)	50 (11)
<50 years	37 (44%)	13 (18%)	117 (47%)	175 (42%)
≥50 years	48 (56%)	60 (82%)	133 (53%)	244 (58%)
Sex				
Male	59 (58%)	40 (55%)	155 (62%)	250 (60%)
Female	36 (42%)	33 (45%)	95 (38%)	169 (40%)
Race				
Black	1 (1%)	5 (7%)	0	6 (1%)
White	81 (95%)	65 (89%)	236 (94%)	393 (94%)
Asian	3 (4%)	1 (1%)	9 (4%)	13 (3%)
Not permitted	0	2(3%)	5 (2%)	7 (2%)
Ethnicity				
Hispanic	10 (12%)	6 (8%)	36 (14%)	53 (13%)
Non-Hispanic	71 (84%)	65 (89%)	203 (81%)	349 (83%)
Not permitted	4 (5%)	2 (3%)	11 (4%)	17 (4%)
Baseline body mass index (kg/m^2)				
Mean (SD)	26 (5)	26 (4)	25 (4)	26 (4)
< 30 kg/m^2,	66 (78%)	61 (84%)	220 (88%)	354 (84%)
≥ 30 kg/m^2,	19 (22%)	12 (16%)	30 (12%)	65 (16%)

* Data on subjects with genotype 3 (N=11) who received 12 weeks of SOF+RBV is not shown separately in this table but is included in the total number
Source: FDA Statistical Reviewer; Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Baseline disease characteristics of the subjects in trial GS-US- 334-0133 are shown in Table 4. Overall, 58% were treatment-experienced and 42% were treatment-naïve. Approximately 21% of the subjects had cirrhosis at baseline, and 68% had non-CC IL28B. The majority of subjects (73%) had baseline viral load ≥ 6 $\log_{10}$ IU/mL.

Table 4: Baseline Disease Characteristics for Study GS-US-334-0133

	Genotype 2/3 Placebo (N=85)	Genotype 2 12-Week SOF+RBV (N=73)	Genotype 3 24-Week SOF+RBV (N=250)	Total (N=419)
HCV genotype				
Genotype 2	18 (21%)	73 (100%)		91 (22%)
Genotype 3*	67 (79%)		250 (100%)	328 (78%)
Prior HCV treatment experience and interferon (IFN) classification				
Experienced	50 (59%)	41 (56%)	145 (58%)	245 (58%)
IFN intolerant	0	3 (4%)	10 (4%)	13 (3%)
Non-response	18 (21%)	10 (14%)	41 (16%)	73 (17%)
Relapse/Breakthrough	32 (38%)	28 (38%)	94 (38%)	159 (38%)
Naïve	35 (41%)	32 (44%)	105 (42%)	174 (42%)
IFN-eligible	30 (35%)	27 (37%)	94 (38%)	153 (37%)
IFN-ineligible	5 (6%)	5 (7%)	11 (4%)	21 (5%)
Baseline cirrhosis				
No	67 (79%)	63 (86%)	192 (77%)	331 (79%)
Yes	18 (21%)	10 (14%)	58 (23%)	88 (21%)
IL28B				
CC	22 (26%)	24 (33%)	86 (34%)	136 (32%)
non-CC	63 (74%)	49 (67%)	164 (66%)	283 (68%)
Baseline HCV RNA (log_{10} IU/mL)				
Mean (SD)	6.5 (0.7)	6.5 (0.7)	6.3 (0.7)	6.4 (0.7)
< 6 log_{10} IU/mL	21 (25%)	16 (22%)	72 (29%)	113 (27%)
≥ 6 log_{10} IU/mL	64 (75%)	57 (78%)	178 (71%)	306 (73%)
Baseline ALT				
≤ 1.5 x ULN	32 (38%)	39 (53%)	64 (26%)	139 (33%)
> 1.5 x ULN	53 (62%)	34 (47%)	186 (74%)	280 (67%)

* Data on subjects with genotype 3 (N=11) who received 12 weeks of SOF+RBV is not shown separately in this table but is included in the total number.
Source: FDA Statistical Reviewer; Table 2 in Study GS-US-334-0133 Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Efficacy Results

A total of 73 genotype 2 subjects received treatment in the SOF+RBV 12 Week group and 250 genotype 3 subjects received treatment in the SOF+RBV 24

Week group, including approximately 21% (68/323) with compensated cirrhosis in these two groups.

The overall SVR12 rate for genotype 2 subjects was 93%, with treatment-naïve subjects achieving an SVR12 rate of 97% and treatment-experienced subjects an SVR12 rate of 90% (Table 5). The observed high SVR rates in genotype 2 subjects in this trial are consistent with those observed in other three Phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108) which evaluated subjects with genotype 2 HCV who received 12 weeks of SOF+RBV treatment.

The overall SVR12 rate for genotype 3 subjects was 84%, with treatment-naïve subjects achieving an SVR12 rate of 93% and treatment-experienced subjects an SVR12 rate of 77% (Table 5). Extending the treatment duration to 24 weeks in genotype 3 subjects resulted in improved SVR rates compared to shorter treatment durations (i.e., 12 or 16 weeks) evaluated in previous trials (P7977-1231, GS-US-334-0107, GS-US-334-0108).

Table 5: Primary Efficacy Results and Relapse Rates (Study GS-US-334-0133)

	Genotype 2 SOF+RBV 12 Weeks N=73	**Genotype 3 SOF+RBV 24 Weeks N=250**
Overall SVR12	**93% (68/73)**	**84% (210/250)**
Treatment-Naïve	97% (31/32)	93% (98/105)
Treatment-Experienced	90% (37/41)	77% (112/145)
Overall Relapse Rate	**7% (5/73)**	**14% (34/249)**
Treatment-Naïve	3% (1/32)	5% (5/105)
Treatment-Experienced	10% (4/41)	20% (29/144)

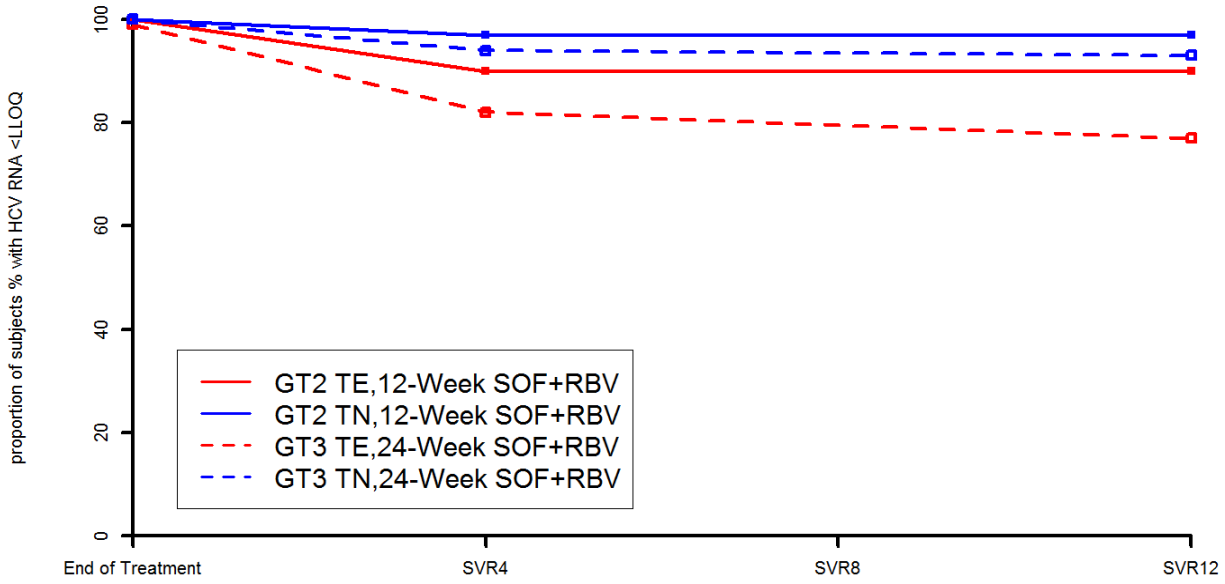
Data on subjects with genotype 3 (N=11) who received 12 weeks of SOF+RBV is not shown in this table.
Source: FDA Statistical Reviewer

The overall relapse rate in GT2 subjects was 7%, with relapse rates of 3% and 10% in treatment-naïve and treatment-experienced subjects, respectively. GT3 relapse rates were 14% overall, and 5% and 20% in treatment-naïve and treatment-experienced subjects, respectively.

Figure 4 displays the virologic responses at End-of-Treatment (EOT) and posttreatment visits for SOF+RBV 12 Weeks for genotype 2 subjects and

SOF+RBV 24 Weeks for genotype 3 subjects. Almost all subjects achieved HCV RNA below LLOQ at the EOT. Most treatment failures were attributed to relapse.

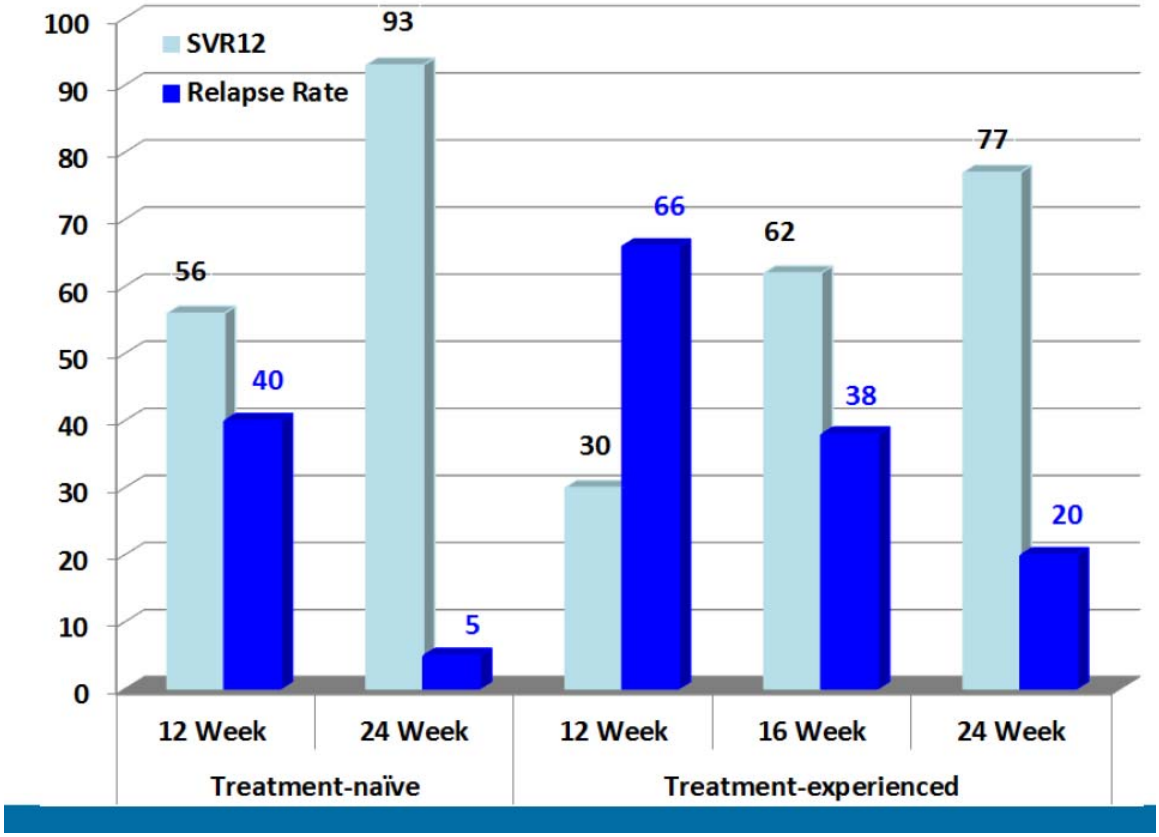
Figure 4: Virologic responses at EOT and Posttreatment Visits for 12-Week SOF+RBV for Genotype 2 Subjects and 24-Week SOF+RBV for Genotype 3 Subjects (All Treated)



Source: FDA Statistical Reviewer

Extending the SOF+RBV treatment duration to 24 weeks in GT3 subjects improved SVR12 rates primarily by decreasing relapse. This point is further illustrated in the bar graph shown in Figure 5.

Figure 5: SVR12 and Relapse Rates for Genotype 3 across Phase 3 Trials



Source: FDA Presentation, Antiviral Drugs Advisory Committee Meeting October 25, 2013

In treatment-naïve genotype 3 subjects, the SVR12 rate was 56% and relapse rate was 40% with 12 weeks of SOF+RBV treatment. Extending the treatment duration to 24 weeks improved the SVR12 rates to 93% and decreased the relapse rates to 5%.

In treatment-experienced genotype 3 subjects, SVR12 rate with 12 weeks of therapy was 30% and relapse rate was 66%. Increasing the duration to 16 weeks resulted in SVR rate of 62% and relapse rate of 38% which was still very high. In the VALENCE trial, treatment duration was 24 weeks which resulted in SVR rate of 77% and relapse rate of 20%.

In conclusion, by extending the treatment duration from 12 weeks to 24 weeks in treatment-experienced genotype 3 subjects, relapse rate decreased from 66% to 20%.

The SVR12 rates for selected subgroups in genotype 3 subjects receiving 24 weeks of SOF+RBV are shown in Table 6. This table illustrates that treatment response varies based on baseline host factors such as presence or absence of cirrhosis.

Table 6: SVR12 Rates for Selected Subgroups in Genotype 3 Subjects Receiving 24 Weeks of SOF+RBV

	Genotype 3 TE, 24-Week SOF+RBV	
	SVR12 (n/N)	**95% CI[1]**
IFN intolerant, non-cirrhotic	100% (5/5)	(48%, 100%)
cirrhotic	100% (5/5)	(48%, 100%)
Relapse/breakthrough non-cirrhotic	84% (56/67)	(73%, 92%)
cirrhotic	59% (16/27)	(39%, 78%)
Null response non-cirrhotic	86% (24/28)	(67%, 96%)
cirrhotic	46% (6/13)	(19%, 75%)

[1]based on Clopper-Pearson method
Source: FDA Statistical Reviewer

Reviewer's Comments

Based on the available data from the ongoing VALENCE trial, sofosbuvir in combination with ribavirin for 24 weeks is recommended for all genotype 3 patients.

The following treatment recommendations can be made:

- *SOF+RBV 12 Week Treatment Regimen is recommended for chronic hepatitis C patients with genotype 2 HCV infection*
- *SOF+RBV 24 Week Treatment Regimen is recommended for chronic hepatitis C patients with genotype 3 HCV infection*

GS-US-334-0123 (PHOTON-1)

An estimated 4 to 5 million people worldwide are coinfected with HCV/HIV. About 25% of individuals infected with HIV in the US are also infected with HCV (http://www.cdc.gov/hiv/resources/factsheets/hepatitis.htm accessed May 14, 2013). HCV/HIV coinfection leads to increased rates of liver fibrosis progression and hepatic decompensation. As HIV-related morbidity and mortality has decreased due to use of highly active antiretroviral therapy (HAART), liver-related complications associated with HCV infection have become a leading cause of non-AIDS-related deaths in the HCV/HIV-coinfected population. Hence, availability of effective and safe drugs with better tolerated side effect profile for this patient population remains a priority for the Division.

In the original NDA submission, the Applicant had provided interim efficacy and safety data for this trial which was limited and was considered insufficient to support a full indication in this population.

Trial Design

Study GS-US-334-0123 (PHOTON-1) is an ongoing Phase 3, open-label, multicenter trial to evaluate the efficacy and safety of SOF+RBV in subjects with genotype 1, 2, or 3 HCV infection and HIV, type 1 (HIV-1) coinfection.

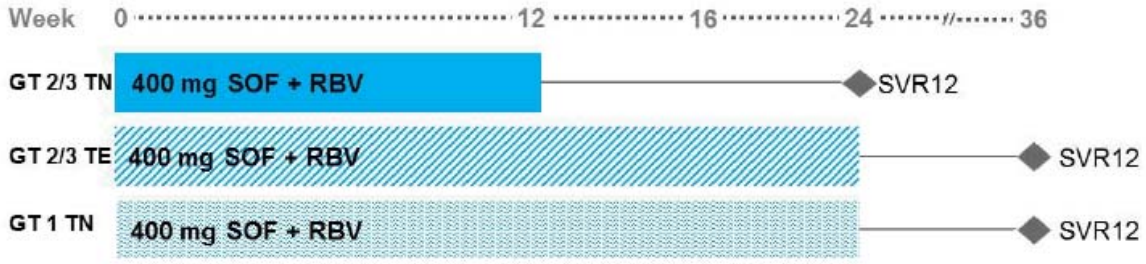
Primary objectives of this study are as follows:

- To determine the efficacy of treatment with SOF+RBV by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)

- To evaluate the safety and tolerability of SOF+RBV as assessed by review of the accumulated safety data, including human immunodeficiency virus (HIV) RNA and CD4 T-lymphocyte percent

Trial design is shown in Figure 6.

Figure 6: GS-US-334-0123: Study Design



GT = genotype; TE = treatment experienced; TN = treatment naive

Source: Study GS-US-334-0123 Second Interim Synoptic Clinical Study Report submitted on October 09, 2013

A total of 223 subjects were enrolled to the following three groups depending on their HCV genotypes and prior treatment experience with PEG+RBV:

- Group 1: SOF+RBV 12 Week Treatment-naïve HCV Genotype 2/3

- Group 2: SOF+RBV 24 Week Treatment-experienced HCV Genotype 2/3

- Group 3: SOF+RBV 24 Week Treatment-naïve HCV Genotype 1

Disposition

As of the data collection date, treatment-naive genotype 1, 2, and 3 HCV-infected subjects completed posttreatment follow-up through the primary endpoint of SVR12 or prematurely discontinued the trial. Of the 41 treatment-experienced genotype 2 or 3 HCV-infected subjects enrolled, 28 have completed posttreatment follow-up through posttreatment Week 12 or prematurely discontinued the trial. These subjects were included in the efficacy analysis (full analysis set), whereas all 41 subjects were included in the safety analysis (safety analysis set).

Table 7 displays subject disposition in Study GS-US-334-0123. Approximately 10% of subjects discontinued the study drug in the two groups for the treatment-naïve subjects, i.e., Group 1 (SOF+RBV 12 Weeks) in HCV genotype 2 or 3 treatment-naïve subjects and Group 3 (SOF+RBV 24 Weeks) in HCV genotype 1 treatment-naïve subjects. The most common reason for discontinuation in the two groups was adverse event (3-4%). For Group 2 (SOF+RBV 24 Weeks) in HCV genotype 2 or 3 treatment-experienced subjects, only one subject discontinued the study treatment. Approximately 20% subjects in Groups 1 and 3 withdrew from the trial due to lack of efficacy.

Table 7: Disposition of Subjects in Study GS-US-334-0123

	Group 1 GT 2/3 TN SOF+RBV 12 Weeks	Group 2 GT 2/3 TE SOF+RBV 24 Weeks	Group 3 GT 1 TN SOF+RBV 24 Weeks
Subjects in Safety Analysis Set	68	41	114
Subjects in Full Analysis Set	68	28	114
Discontinued Study Treatment	6 (9%)	1 (2%)	11 (10%)
Efficacy failure	0	0	1 (1%)
Adverse event	3 (4%)	1 (2%)	3 (3%)
Protocol violation	0	0	4 (4%)
Investigator decision	1 (1%)	0	1 (1%)
Subject withdrew consent	1 (1%)	0	2 (2%)
Lost to follow-up	1 (1%)	0	0
Discontinued Study	21 (31%)	2 (5%)	27 (24%)
Death	1 (1%)	0	0
Efficacy failure	13 (19%)	1 (2%)	24 (21%)
Subject withdrew consent	2 (3%)	0	1 (1%)
Lost to follow-up	5 (7%)	1 (2%)	2 (2%)

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
Source: FDA Statistical Reviewer; Table 1 in Study GS-US-334-0123 Second Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Demographics and Baseline Characteristics

Eligible subjects were males or nonpregnant females aged ≥ 18 years with chronic genotype 1, 2, or 3 HCV infection and confirmed HIV-1 coinfection. Subjects were treatment-naïve (TN) or treatment-experienced (TE); had documentation of the presence or absence of cirrhosis; and had a body mass index (BMI) of ≥ 18 kg/m^2. Subjects who were on antiretroviral (ARV) treatment were required to have been on a stable regimen for > 8 weeks prior to screening, have an HIV-1 RNA < 50 copies/mL, and have a CD4 T-lymphocyte count > 200 $cells/mm^3$. Regimens containing emtricitabine/tenofovir, atazanavir/ritonavir, darunavir/ritonavir, efavirenz, raltegravir, or rilpivirine were permitted. Subjects not on ARV treatment must have had a CD4 T-lymphocyte count > 500 $cells/mm^3$ at screening.

Table 8 summarizes subject demographics and baseline characteristics. The majority of subjects were male (83%), white (69%), and non-Hispanic/Latino (76%). There was a higher proportion of black or African American subjects in the SOF+RBV 24 Week GT 1 group (32%).

Table 8: Demographics and Baseline Characteristics in Study GS-US-334-0123

	Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68	Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=41	Group 3 GT 1 TN SOF+RBV 24 Weeks N=114	Total N=223
Age (years)				
Mean (SD)	49 (10)	54 (6)	48 (8)	49 (9)
Sex				
Male	55 (81%)	37 (90%)	93 (82%)	185 (83%)
Female	13 (19%)	4 (10%)	21 (18%)	38 (17%)
Race				
Black	8 (12%)	7 (17%)	37 (32%)	52 (23%)
White	52 (76%)	32 (78%)	69 (61%)	153 (69%)
Asian	1 (1%)	1 (2%)	1 (1%)	3 (1%)
Other	6 (9%)	1 (2%)	6 (5%)	13 (6%)
Ethnicity				
Hispanic	19 (28%)	10 (24%)	25 (22%)	54 (24%)
Non-Hispanic	49 (72%)	31 (76%)	89 (78%)	169 (76%)
Country				
USA	65 (96%)	39 (95%)	113 (99%)	217 (97%)
Puerto Rico	3 (4%)	2 (5%)	1 (1%)	6 (3%)
Baseline body mass index (kg/m^2)				
Mean (SD)	27 (4)	27 (5)	27 (5)	27 (5)
< 30 kg/m^2	53 (78%)	31 (76%)	88 (77%)	172 (77%)
≥ 30 kg/m^2	15 (22%)	10 (24%)	26 (23%)	51 (23%)

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
Source: FDA Statistical Reviewer; Table 2 in Study GS-US-334-0133 Second Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Table 9 displays the baseline disease characteristics in Study GS-US-334-0123. The majority of subjects (78%) had a baseline HCV RNA ≥6 log_{10} IU/mL and had an IL28B non-CC genotype (66%). Only 10% of subjects had cirrhosis. The baseline mean (SD) CD4 count was 625 (267) cells/mm^3, and 95% of subjects were receiving ARV treatment at enrollment. In the SOF+RBV 12 Week TN GT2/3 and SOF+RBV 24 Week TN GT1 groups, the majority of subjects were interferon eligible (72% and 75%, respectively). It should be noted that the majority of the HCV genotype 1 treatment-naïve subjects in Group 1 did not have cirrhosis at baseline.

Table 9: Baseline Disease Characteristics for Study GS-US-334-0123

	Group 1 12-Week SOF+RBV GT 2/3 TN N=68	Group 2 24-Week SOF+RBV GT 2/3 TE N=41	Group 3 24-Week SOF+RBV GT 1 TN N=114	Total N=223
HCV genotype				
1	0	0	114 (100%)	114 (51%)
1a	0	0	90 (79%)	90 (40%)
1b	0	0	24 (21%)	24 (11%)
2	26 (38%)	24 (59%)	0	50 (22%)
3	42 (62%)	17 (41%)	0	59 (26%)
Baseline HCV RNA				
< 6 $\log_{10}$ IU/mL	21 (31%)	7 (17%)	22 (19%)	50 (22%)
≥ 6 $\log_{10}$ IU/mL	47 (69%)	34 (83%)	92 (81%)	173 (78%)
Cirrhosis				
No	61 (90%)	31 (76%)	109 (96%)	201 (90%)
Yes	7 (10%)	10 (24%)	5 (4%)	22 (10%)
IL28B genotype				
CC	25 (37%)	20 (49%)	30 (26%)	75 (34%)
CT	37 (54%)	17 (41%)	57 (50%)	111 (50%)
TT	6 (9%)	4 (10%)	26 (23%)	36 (16%)
Missing	0	0	1 (1%)	1 (<1%)
Prior PEG+RBV Treatment				
Naïve	68 (100%)	0	114 (100%)	182 (82%)
Experienced	0	41 (100%)	0	41 (18%)
Breakthrough/relapse	0	25 (61%)	0	25 (11%)
Partial/null responders	0	7 (17%)	0	7 (3%)
Interferon intolerant	0	9 (22%)	0	9 (22%)
Interferon classification				
Interferon eligible	49 (72%)	0	85 (75%)	134 (60%)
Interferon ineligible	19 (28%)	0	29 (25%)	48 (22%)
On ARV treatment at enrollment				
No	7 (10%)	2 (5%)	2 (2%)	11 (5%)
Yes	61 (90%)	39 (95%)	112 (98%)	212 (95%)
Tenofovir/Emtricitabine +				
Efavirenz	20 (29%)	16 (39%)	42 (37%)	78 (35%)
Atazanavir/ritonavir	7 (10%)	8 (20%)	24 (21%)	39 (17%)
Darunavir/ritonavir	17 (25%)	2 (5%)	15 (13%)	34 (15%)
Raltegravir	8 (12%)	7 (17%)	21 (18%)	36 (16%)

Other†	9 (13%)	6 (15%)	10 (9%)	25 (11%)
Baseline HIV-1 RNA				
< 50 copies/mL	60 (88%)	40 (98%)	108 (95%)	208 (93%)
≥ 50 copies/mL	8 (12%)	1 (2%)	6 (5%)	15 (7%)
Baseline CD4 (Cells/mm^3)^3				
Mean (SD)	585 (246)	658 (333)	636 (251)	625 (267)
Median (Q1, Q3)	562 (395, 723)	579(482, 744)	583 (455, 812)	579 (442, 753)

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
† Other ART regimens included tenofovir/emtricitabine/atazanavir/raltegravir/ritonavir; tenofovir/emtricitabine/atazanavir; tenofovir/emtricitabine/darunavir/raltegravir/ritonavir; tenofovir/emtricitabine/darunavir/raltegravir/ritonavir/rilpivirine; tenofovir/darunavir/raltegravir/ritonavir; tenofovir/emtricitabine/rilpivirine
Source: FDA Statistical Reviewer; Table 2 in Study GS-US-334-0123 Second Interim Synoptic Clinical Study Report (submitted on October 09, 2013)

Efficacy Results

All safety and efficacy data collected up to September 30, 2013 were included by the Applicant in this interim analysis. Preliminary SVR12 efficacy data are available for 210 subjects. A total of 13 subjects in the SOF+RBV 24 Week TE GT2/3 group have not reached the posttreatment Week 12 visit at the time of the data cut off.

The full analysis set included subjects who were enrolled into the study and received at least 1 dose of study drug. In this interim synoptic CSR, the full analysis set included the following subjects:

- Treatment-naive subjects with genotype 1, 2, or 3 HCV infection (all have completed the posttreatment Week 12 visit or prematurely discontinued from study)
- Treatment-experienced subjects with genotype 2 or 3 infection who have completed the posttreatment Week 12 visit or prematurely discontinued from study

The primary efficacy endpoint was the proportion of subjects who attained SVR12 defined as HCV RNA < LLOQ (i.e., < 25 IU/mL) at 12 weeks after study drug cessation. Table 10 shows the overall SVR12 rate for the three treatment groups and the SVR12 rate by HCV genotype in each group in Study GS-US-334-0123.

Table 10: Primary Efficacy Results (GS-US-334-0123)

	Group 1 GT 2/3 TN SOF+RBV 12 Week (N=68)	Group 2 GT 2/3 TE SOF+RBV 24 Week (N=28)	Group 3 GT1 TN SOF+RBV 24 Week (N=114)
Overall			
SVR12	75% (51)	93% (26)	76% (87)
95% CI	(63%, 85%)	(77%, 99%)	(67%, 84%)
Genotype 1a			
SVR12	n/a	n/a	82% (74/90)
95% CI			(73%, 89%)
Genotype 1b			
SVR12	n/a	n/a	54% (13/24)
95% CI			(33%, 74%)
Genotype 2			
SVR12	88% (23/26)	93% (14/15)	n/a
95% CI	(70%, 98%)	(68%, 99.8%)	
Genotype 3			
SVR12	67% (28/42)	92% (12/13)	n/a
95% CI	(50%, 80%)	(64%, 99.8%)	

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
CI based on the Clopper-Pearson method
Source: FDA Statistical Reviewer

In Group 1 (SOF+RBV 12 Weeks) for HCV genotype 2 or 3 treatment-naïve subjects, the overall SVR12 rate was 75%. The SVR12 rate was lower in HCV genotype 3 treatment-naïve subjects as compared to HCV genotype 2 treatment-naïve subjects, i.e., 67% vs. 88%. The findings were consistent with what had been observed in Studies P7977-1231, GS-US-334-0107 and GS-US-334-0133 where SOF+RBV for 12 weeks was evaluated in treatment-naïve subjects mono-infected with genotype 2/3 HCV.

In Group 2 (SOF+RBV 24 Weeks) for HCV genotype 2 or 3 treatment-experienced subjects, only two-thirds of the subjects (N=28) had their SVR12 data available in this submission including 15 HCV genotype 2 and 13 HCV genotype 3 subjects. The overall SVR12 rate was 93% for the 28 subjects. Although the sample size for each genotype was small, the SVR12 rate in the 15 genotype 2 subjects was 93% which was comparable to the rate seen in Study GS-US-334-0133 in which GT 2 treatment-experienced subjects received 12 weeks of SOF+RBV. The SVR12 rate for the 13 genotype 3 subjects was 92% which was numerically larger than the 77% SVR12 rate in the treatment-experienced subjects mono-infected with genotype 3 HCV in Study GS-US-334-

0133. No definitive conclusions can be drawn from this observation due to small number of GT3 subjects in Group 2.

In Group 3 (SOF+RBV 24 Weeks) for HCV genotype 1 treatment-naïve subjects, the overall SVR12 rate was 76%. A total of 90 (79%) subjects in Group 1 had HCV genotype 1a HCV and 24 (21%) subjects had HCV genotype 1b infection. The SVR12 rates were 82% in HCV genotype 1a subjects and 54% in HCV genotype 1b subjects. The above noted difference in SVR rates between GT1a vs. GT1b subjects was more compared to that in Study GS-US-334-0110 where the 12-week SOF+PEG+RBV was evaluated in the HCV genotype 1 mono-infected subjects. The observed SVR12 rates in genotype 1a subjects was 10% higher than genotype 1b subjects in Study GS-US-334-0110.

Relapse accounted for all virologic failures across the groups except for two subjects (one in Group 1 and one in Group 3).

- One subject with genotype 2 infection experienced on-treatment virologic failure likely due to study drug non-adherence as assessed by serum sofosbuvir levels, hematologic parameters (as a surrogate for ribavirin use), and investigator report.
- The other subject with genotype 1 infection experienced on-treatment virologic failure with hematologic parameters suggestive of inconsistent RBV adherence; sofosbuvir pharmacokinetic data are pending.

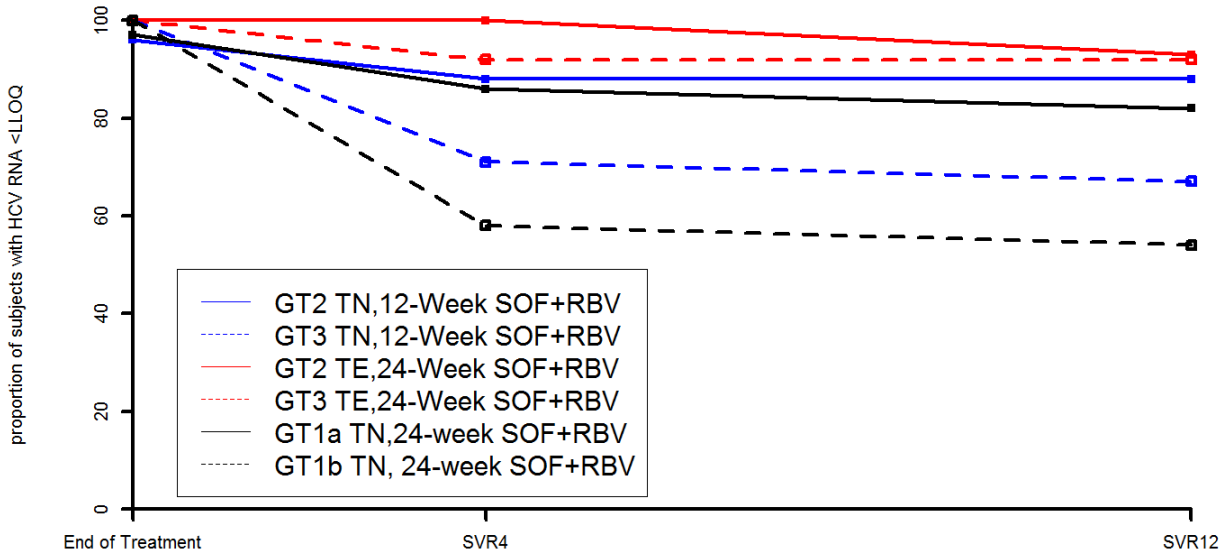
Table 11: Relapse Rates (GS-US-334-0123)

	Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68	**Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=28**	**Group 3 GT 1 TN SOF+RBV 24 weeks N=114**
Overall Relapse Rates			
% (n/N)	18% (12/67)	7% (2/28)	22% (25/113)

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
Source: FDA Statistical Reviewer

Figure 7 displays virologic responses at EOT and posttreatment visits. Almost all subjects had HCV RNA below LLOQ at the end of treatment regardless of different HCV genotypes and prior PEG+RBV treatment experience. However, the SVR rates varied based on genotype and prior PEG+RBV treatment experience. The relapses attributed to the decrease in the response rates from the EOT to posttreatment visits.

Figure 7: Virologic Responses at EOT and Posttreatment Visits by Treatment Group and Genotype in Study GS-US-334-0123



Source: FDA Statistical Reviewer

The relapse rate at Week 12 posttreatment in GT3 TN subjects who received 12 weeks of SOF+RBV was 29%. These higher relapse rates further support conclusions from prior Phase 3 trials that 12 weeks of SOF+RBV is suboptimal for genotype 3 subjects. The relapse rate at Week 12 posttreatment in GT1b TN subjects who received 24 weeks of SOF+RBV was higher (42%) compared to GT1a TN subjects.

Reviewer's Comments

Based upon these interim efficacy results, SVR12 rates in genotype 2 and 3 appear comparable to the results observed in the HCV mono-infected population with 12 weeks and 24 weeks of treatment. These results in genotype 2 and 3 subjects suggest that treatment regimens for these genotypes can be similar to those in mono-infected patients.

The observed SVR12 results in genotype 1 subjects support an indication in HCV/HIV co-infected patients as well as HCV mono-infected patients who are interferon-ineligible and thus have no currently available treatment options. This therapeutic option for genotype 1 subjects is further discussed later.

7 Review of Safety

The safety results for the two ongoing Phase 3 trials presented in this addendum are summarized in this section.

GS-US-334-0133 (VALENCE)

The safety analysis set included subjects who received at least 1 dose of study drug. Safety data included all data collected on or after the first dose date of study regimen through the last dose date of study regimen plus 30 days for subjects who have permanently discontinued all study drugs. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0. All AEs discussed in this section are treatment emergent and are referred to as AEs for the purposes of this review.

As noted by the Applicant, most subjects in each of the treatment groups experienced at least 1 AE, with the incidence of AEs being higher in the active treatment groups (86−91%) compared with the Placebo group (72%) as shown in Table 12. Treatment was discontinued for Placebo group subjects and these subjects were treated with SOF placebo once daily+RBV placebo BID for a median exposure of 8.0 weeks.

Table 12: Overall Summary of Adverse Events (Study GS-US-334-0133)

	GT 2/3 Placebo 12 weeks N=85	**GT 2/3 SOF+RBV 12 Weeks** N=84	**GT 3 SOF+RBV 24 Weeks** N=250
Number of Subjects (%)			
Any AE	61 (72)	72 (86)	228 (91)
Serious AE	2 (2)	0	10 (4)
Grade 3 or 4 AE	4 (5)	3 (4)	17 (7)
AE leading to Discontinuation	1 (1)	1 (1)	1 (<1)
Death	0	0	0

SOF=sofosbuvir; RBV=ribavirin; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

Across treatment groups, 3 subjects (0.7%) discontinued study drug due to AEs: 1 subject (1.2%) in the Placebo group due to Grade 3 abnormal liver tests; 1 subject (1.2%) in the SOF+RBV 12 Week group due to Grade 2 events of malaise and headache; and 1 subject (0.4%) in the SOF+RBV 24 Week group due to a Grade 4 suicide attempt. There were no deaths reported in this trial.

Serious Adverse Events

Serious adverse events reported in this trial are shown in Table 13 by system organ class and preferred terms. No SAE was reported by more than one subject in any treatment group.

Table 13: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Study GS-US-334-0133)

System Organ Class MedDRA Preferred Term	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 24 Weeks
	N=85	N=84	N=250
Number of subjects with any SAE (%)	2 (2.4)	0	10 (4.0)
CARDIAC DISORDERS			
Arrhythmia	0	0	1 (0.4)
GASTROINTESTINAL DISORDERS			
Adenocarcinoma of Colon	1 (1.2)	0	0
Haemorrhoidal Haemorrhage	0	0	1 (0.4)
HEPATOBILIARY DISORDERS			
Biliary Colic	0	0	1 (0.4)
INFECTIONS AND INFESTATIONS			
Gastroenteritis	1 (1.2)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Road Traffic Accident	0	0	1 (0.4)
INVESTIGATIONS			
Amylase Increased	0	0	1 (0.4)
Lipase Increased	0	0	1 (0.4)
METABOLISM AND NUTRITION DISORDERS			
Hyperglycaemia	0	0	1 (0.4)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
Hepatocellular Carcinoma	0	0	1 (0.4)
Invasive Ductal Breast Carcinoma	0	0	1 (0.4)
NERVOUS SYSTEM DISORDERS			
Complex Regional Pain Syndrome	0	0	1 (0.4)
PSYCHIATRIC DISORDERS			
Suicide Attempt	0	0	1 (0.4)

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

Grade 3 or 4 Adverse Events

Most AEs were reported as Grade 1 or Grade 2 in severity. Anemia and fatigue were the only Grade 3 events that occurred in more than 1 subject in the active

treatment groups, occurring in 3 (1.3%) and 2 (0.9%) subjects, respectively as shown in Table 14.

Table 14: Adverse Events of Toxicity Grade ≥ 3 by Preferred Term (≥ 1 subjects) in Study GS-US-334-0133

MedDRA Preferred Term	**Placebo 12 weeks** N=85	**SOF+RBV 12 Weeks** N=84	**SOF+RBV 24 Weeks** N=250
Anaemia	0	1 (1.2)	2 (0.8)
Fatigue	0	0	2 (0.8)
Headache	0	0	1 (0.4)
Asthenia	0	0	1 (0.4)
Insomnia	0	0	1 (0.4)
Abdominal Pain	0	0	1 (0.4)
Vomiting	0	0	1 (0.4)
Influenza	0	0	1 (0.4)
Pyrexia	0	0	1 (0.4)
Upper Respiratory Tract Infection	0	0	1 (0.4)
Hyperglycaemia	1 (1.2)	0	1 (0.4)
Night Sweats	0	0	1 (0.4)
Lipase Increased	0	0	1 (0.4)
Arrhythmia	0	0	1 (0.4)
Pneumonia	0	0	1 (0.4)
Road Traffic Accident	0	0	1 (0.4)
Amylase Increased	0	0	1 (0.4)
Hepatocellular Carcinoma	0	0	1 (0.4)
Invasive Ductal Breast Carcinoma	0	0	1 (0.4)
Psychomotor Retardation	0	0	1 (0.4)
Suicide Attempt	0	0	1 (0.4)
Sarcoidosis	0	1 (1.2)	0
Pityriasis Rosea	0	1 (1.2)	0
Gastroenteritis	1 (1.2)	0	0
Adenocarcinoma of Colon	1 (1.2)	0	0
Liver Function Test Abnormal	1 (1.2)	0	0

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

One Grade 4 AE was reported: a suicide attempt by a subject in the SOF+RBV 24 Week group. This event was also reported as an SAE and is briefly described below.

Subject ID: [GS-US-334-0133] 4991-2052
Suicide attempt

> Subject is a 54-year-old white, non-Hispanic male with chronic genotype 3a HCV infection and no cirrhosis. The subject's medical history included stress, alcohol dependence, polytoxicomania, liver hemangioma, herpes simplex, sleeplessness, morbus werlhof 2, and facial paresis. Concomitant medications included lorazepam (sleeplessness) and valacyclovir (herpes simplex). The subject experienced a Grade 4 suicide attempt by taking 40mg lorazepam on Day 143. The subject was hospitalized for observation and SOF+RBV was discontinued on the same day. Hospital records indicate the subject was experiencing substantial family and work-related social stressors as well as worsened insomnia in the days preceding the suicide attempt. The AE was considered resolved on posttreatment Day 6. The investigator assessed this event as related to SOF+RBV given the temporal association of his symptoms with SOF+RBV treatment and their resolution with SOF+RBV discontinuation.

Reviewer's Comment

As noted in Primary Clinical Review, the incidence of adverse events of completed suicide, suicidal ideation or suicide attempt in sofosbuvir trials is low and is mostly observed in subjects with pre-existing psychiatric conditions and/or accompanied by major life stressors.

*The Applicant has now proposed a subsection titled "**Less Common Adverse Reactions Reported in Clinical Trials (<1%)**" under Section 6 ADVERSE REACTIONS of the prescribing information, which includes adverse reactions that occurred in <1% of subjects receiving sofosbuvir in a combination regimen in any one trial. The following events have been included:*

> *Psychiatric Disorders:* severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide.

The proposal seems reasonable and is acceptable.

Common Adverse Events

The most frequently reported AEs occurring in greater than or equal to 10% of subjects in any treatment group is shown in Table 15.

Table 15: Treatment-Emergent Adverse Events in ≥10% of subjects in any treatment group in Study GS-US-334-0133 (Safety Analysis Set)

MedDRA Preferred Term	GT 2/3 Placebo 12 weeks N=85	GT 2/3 SOF+RBV 12 Weeks N=84	GT 3 SOF+RBV 24 Weeks N=250
Number of subjects with any AE (%)	61 (72)	72 (86)	228 (91)
Fatigue	16 (19)	19 (23)	75 (30)
Headache	23 (27)	24 (29)	74 (30)
Pruritus	8 (9)	20 (24)	67 (27)
Asthenia	5 (6)	21 (25)	53 (21)
Insomnia	2 (2)	9 (11)	41 (16)
Nasopharyngitis	9 (11)	4 (5)	36 (14)
Nausea	9 (11)	26 (31)	32 (13)
Dry Skin	5 (6)	7 (8)	31 (12)
Diarrhoea	4 (5)	4 (5)	30 (12)
Dyspnoea	1 (1)	12 (14)	27 (11)
Cough	4 (5)	8 (10)	26 (10)
Irritability	3 (4)	4 (5)	26 (10)

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

The incidence of pruritus, asthenia, insomnia, dry skin, dyspnea, and cough were similar in the SOF+RBV 12 Week and SOF+RBV 24 Week treatment groups. The Applicant noted that the increased incidence of the preferred term “asthenia” reported in Study GS-US-334-0133 as compared to the other Phase 3 trials of SOF+RBV is likely due to the regional differences in the description and reporting of AEs. In the largely US-based Phase 3 trials, P7977-1231, GS-US-334-0107 and GS-US-334-0108, fatigue was reported at a higher incidence than in Study GS-US-334-0133. The combined incidence of fatigue and asthenia is similar when comparing GS-US-334-0133 to the other trials. Diarrhea and irritability were approximately twice as frequent in the SOF+RBV 24 week treatment group compared with the SOF+RBV 12 Week treatment group. Nausea was more commonly reported with SOF+RBV for 12 weeks (31%) compared with either placebo treatment (11%) or SOF+RBV 24 weeks (13%).

Cardiac Disorder Adverse Events

As previously done for other Phase 3 trials, a comprehensive review of AEs based on MedDRA System Organ Class (SOC) for Cardiac Disorders was done for Study GS-US-334-0133 (Table 16).

Table 16: GS-US-334-0133: Overall Summary of Cardiac Disorder Adverse Events (SOC)

N (%)	Placebo (N=85)	SOF+RBV 12 Weeks (N=84)	SOF+RBV 24 Weeks (N=250)
≥1 AE	1 (1.2)	2 (2.4)	10 (4)
Grade 1	1 (1.2)	2 (2.4)	8 (3.2)
Grade 2	0	0	1 (<1)
Grade 3	0	0	1 (<1)
Grade 4	0	0	0
SAE	0	0	1 (<1)

SOF=sofosbuvir; RBV=ribavirin; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

There were no Grade 4 cardiac AEs or cardiac AEs leading to treatment discontinuation in any of the treatment arms. The only Grade 3 cardiac AE was also an SAE and occurred in the SOF+RBV 24 Weeks group.

Subject ID: [GS-US-334-0133] 1065-2244
Cardiac Arrhythmia

> Subject was a 51 year old female with a family history of Wolff Parkinson White disease and a medical history relevant for palpitations. On Day 37 of SOF + RBV treatment, the subject experienced a “feeling of lump in throat, awareness of heart beat that was out of rhythm, breathlessness, cough and inability to sleep”. These symptoms were identical to episodes she had experienced in the past, prior to study participation. She was admitted to the hospital. Her vital signs were stable (per investigator report) and ECG demonstrated ventricular ectopics. She was started on bisoprolol (5mg qd) and zoplicone (7.5mg qpm) and discharged the following day. While in the hospital, she missed one dose of RBV but otherwise study drugs were not interrupted or altered. She completed 24 weeks of treatment per protocol and achieved SVR12. The investigator assessed the event as not related to study drugs.

Grade 1 palpitations was the most common cardiac AE, occurring in 1% of placebo subjects, 1% of SOF + RBV 12 Week subjects, and 2% of SOF + RBV 24 Week subjects (Table 17). Tachycardia was reported in the active treatment groups only, reported in 1% of subjects in the SOF + RBV 12 Week group and 2% of subjects in the SOF + RBV 24 Week group (Table 17).

Table 17: GS-US-334-0133: Adverse Events by Preferred Term in Cardiac Disorders (SOC)

MedDRA Preferred Term	Placebo 12 Weeks N=85		SOF+RBV 12 Weeks N=84		SOF+RBV 24 Weeks N=250	
	Toxicity Grade		Toxicity Grade		Toxicity Grade	
	All Grades	All Grades	All Grades	Grades ≥ 3	All Grades	Grades ≥ 3
Arrhythmia	0	0	0	0	1 (0.4)	1 (0.4)
Palpitations	1 (1.2)	0	1 (1.2)	0	5 (2.0)	0
Tachycardia	0	0	1 (1.2)	0	4 (1.6)	0

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

No cases of cardiomyopathy were reported in Study GS-US-334-0133.

Laboratory Findings

As reported by the Applicant, the mean hemoglobin change from baseline at the end of treatment was −2.1 g/dL for the SOF+RBV 24 Week group and −2.3 g/dL for the SOF+RBV 12 Week group, suggesting that extending treatment from 12 to 24 weeks does not substantially increase the hematologic toxicity of the SOF+RBV regimen.

Table 18: Hemoglobin Values

Lowest Hemoglobin	Placebo	SOF+RBV 12 weeks	SOF+RBV 24 weeks
Subjects in Analysis*	85	84	250
Hemoglobin <10 g/dL	1 (1.2%)	6 (7.1%)	15 (6%)
Hemoglobin <8.5 g/dL	0	1 (1.2%)	1 (0.4%)

SOF=sofosbuvir; RBV=ribavirin
Source: NDA Submissions dated October 09 and October 17, 2013

No increase in graded laboratory abnormalities was noted on extending SOF+RBV treatment from 12 to 24 weeks (Table 19).

Table 19: GS-US-334-0133: Grade 3 and 4 Laboratory Abnormalities Reported for > 1 Subject in Any Treatment Group (Safety Analysis Set)

Laboratory Parameter	GT 2/3 Placebo (N = 85)	GT 2/3 SOF+RBV 12 Weeks (N = 84)	GT 3 SOF+RBV 24 Weeks (N = 250)
Maximum Post-Baseline Toxicity Grade	85	84	250
Grade 3	7 (8.2%)	16 (19.0%)	43 (17.2%)
Grade 4	2 (2.4%)	1 (1.2%)	2 (0.8%)
Hematology			
Hemoglobin	85	84	250
Grade 3	1 (1.2%)	7 (8.3%)	28 (11.2%)
Lymphocytes	85	84	250
Grade 3	0	1 (1.2%)	5 (2.0%)
Neutrophils	85	84	250
Grade 3	1 (1.2%)	1 (1.2%)	0
Platelets	84	84	250
Grade 3	0	0	3 (1.2%)
Chemistry			
ALT	85	84	250
Grade 3	2 (2.4%)	0	3 (1.2%)
Grade 4	2 (2.4%)	1 (1.2%)	0
AST	85	84	250
Grade 3	4 (4.7%)	1 (1.2%)	0
Lipase	85	84	250
Grade 3	1 (1.2%)	3 (3.6%)	3 (1.2%)
Grade 4	0	0	2 (0.8%)
Serum Glucose (Hyperglycemia)	85	84	250
Grade 3	3 (3.5%)	1 (1.2%)	2 (0.8%)
Total Bilirubin (Hyperbilirubinemia)	85	84	250
Grade 3	0	5 (6.0%)	7 (2.8%)

Source: Applicant's Interim Synoptic Clinical Study Report Submitted on October 09, 2013

Grade 4 laboratory abnormalities occurred in 3 subjects (0.9%) receiving SOF+RBV.

- One subject (# 5528-2236) experienced a Grade 4 ALT elevation and concomitant Grade 3 aspartate aminotransferase (AST) elevation at the posttreatment Week 4 visit in the setting of virologic relapse.
- Two subjects (0.8%) in the SOF+RBV 24 Week group experienced Grade 4 lipase elevations, one at Week 6 of treatment and one at Week 16 of treatment. Both subjects had elevated lipase values at baseline, and the Grade 4 elevations were not associated with any symptoms of pancreatitis; both subjects continued treatment without interruption or dose reduction and completed therapy per protocol.

Creatine Kinase was not assessed in Study GS-US-334-0133.

Reviewer's Comments

Based on the available data at the time of this review, the safety profile of 12 and 24 weeks of sofosbuvir in combination with ribavirin seems comparable. No apparent difference in safety profile is noted on extending the treatment duration from 12 to 24 weeks. The noted safety profile is consistent with the safety review of the clinical data in the Primary Clinical Review.

GS-US-334-0123 (PHOTON-1)

The safety analysis set included subjects who received at least 1 dose of study drug. Safety data included all data collected on or after the first dose date of study regimen through the last dose date of study regimen plus 30 days for subjects who have permanently discontinued all study drugs (except HIV RNA and CD4 data, which was collected through the end of study). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 16.0. All AEs discussed in this section are treatment emergent and are referred to as AEs for the purposes of this review.

Of the 41 treatment-experienced genotype 2 or 3 HCV-infected subjects enrolled in group 2, only 28 subjects have completed posttreatment follow-up through posttreatment Week 12 or prematurely discontinued the trial and were included in the efficacy analysis (full analysis set), whereas all 41 subjects were included in the safety analysis (safety analysis set).

Most subjects in all treatment groups experienced at least one AE (Table 20). Most AEs were Grade 1 or 2 in severity.

Table 20: Overall Summary of Adverse Events (Study GS-US-334-0123)

Number (%) of Subjects Experiencing	Group 1 GT 2/3 TN SOF+RBV 12 Weeks (N=68)	Group 2 GT 2/3 TE SOF+RBV 24 Weeks (N=41)	Group 3 GT 1 TN SOF+RBV 24 weeks (N=114)
Any Adverse Event	57 (84)	37 (90)	106 (93)
Grade 3 or 4 AE	7 (10)	3 (7)	15 (13)
SAE	5 (7)	1 (2)	8 (7)
AE leading to Discontinuation	3 (4)	1 (2)	3 (3)
Death	1 (1.5)	0	0

GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
SOF=sofosbuvir; RBV=ribavirin; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

SAEs or AEs leading to discontinuation were similar in SOF+RBV 24 weeks and 12 weeks groups (Table 20). Among all groups, 25 subjects (11%) had at least one Grade 3 or 4 AE. Grade 3 or 4 AEs and SAEs occurred with similar frequency across all treatment groups, with the lowest incidence in the SOF+RBV 24 Week TE GT2/3 group (7%). Low rates of AEs leading to treatment discontinuation occurred in all treatment groups (2% to 4%).

One subject had an SAE (death) of completed suicide; Subject # 3317-8735 (Group 1; SOF+RBV 12 Week TN GT2/3 group) committed suicide 9 days after the last dose of study drug; the SAE was considered not related to study procedures, study drug, or ARV treatment. Please refer to Primary Clinical Review (Section 7.3.5) for clinical summary.

Reviewer's Comments

There was no apparent difference in safety profile for subjects who received 24 weeks of SOF+RBV compared with those who received only 12 weeks of SOF+RBV.

Serious Adverse Events

Fourteen subjects (6.3%) experienced at least 1 SAE, only one of which was considered related to RBV by the investigator (gastroenteritis salmonella). The only SAEs reported in > 1 subject in any treatment group were acute renal failure (3 subjects), cellulitis, pneumonia, and intentional overdose (2 subjects each). Seven subjects (3.1%) discontinued treatment with SOF+RBV due to AEs. There was no individual AE that led to treatment discontinuation in more than one subject.

Table 21: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Study GS-US-334-0123)

System Organ Class MedDRA Preferred Term	**Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68**	**Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=41**	**Group 3 GT 1 TN SOF+RBV 24 weeks N=114**
Number (%) of Subjects Experiencing Any SAE	5 (7.4)	1 (2.4)	8 (7.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia	0	0	1 (0.9)
Leukocytosis	0	0	1 (0.9)
CARDIAC DISORDERS			
Atrial Fibrillation	0	0	1 (0.9)
Atrial Flutter	0	0	1 (0.9)
Acute Myocardial Infarction	1 (1.5)	0	0

GASTROINTESTINAL DISORDERS			
Abdominal Pain	0	0	1 (0.9)
Colitis	0	0	1 (0.9)
Enteritis	0	0	1 (0.9)
GENERAL DISORDERS AND ADMINISTRATION SITE			
Chest Pain	0	0	1 (0.9)
INFECTIONS AND INFESTATIONS			
Cellulitis	0	0	2 (1.8)
Pneumonia	1 (1.5)	1 (2.4)	0
Gastroenteritis Salmonella	0	0	1 (0.9)
Respiratory Tract Infection	0	0	1 (0.9)
Incision Site Infection	1 (1.5)	0	0
Septic Shock	1 (1.5)	0	0
Staphylococcal Bacteremia	1 (1.5)	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
Intentional Overdose	1 (1.5)	0	1 (0.9)
Fracture	1 (1.5)	0	0
METABOLISM AND NUTRITION DISORDERS			
Diabetic Ketoacidosis	0	0	1 (0.9)
NERVOUS SYSTEM DISORDERS			
Altered State of Consciousness	0	0	1 (0.9)
Encephalopathy	1 (1.5)	0	0
PSYCHIATRIC DISORDERS			
Bipolar Disorder	0	0	1 (0.9)
Completed Suicide	1 (1.5)	0	0
Drug Abuse	1 (1.5)	0	0
Suicide Attempt	1 (1.5)	0	0
RENAL AND URINARY DISORDERS			
Renal Failure Acute	1 (1.5)	0	2 (1.8)
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS			
Chronic Obstructive Pulmonary Disease	0	1 (2.4)	0
Pulmonary Embolism	1 (1.5)	0	0
Respiratory Failure	1 (1.5)	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Leukocytoclastic Vasculitis	0	1 (2.4)	0

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

Grade 3 or 4 Adverse Events

Grade 3 or 4 AEs reported in > 1 subject in any treatment group included fatigue (3 subjects) and acute renal failure (3 subjects). As reported by the Applicant, each event of acute renal failure was associated with an SAE:

- One subject had an episode of staphylococcal pneumonia and sepsis in the setting of intravenous methamphetamine use,
- One subject had salmonella gastroenteritis, and
- One subject was hospitalized for diabetic ketoacidosis.

In addition, Grade 3 or 4 AEs of chest pain, hyperbilirubinemia, intentional overdose, and depression occurred in 2 subjects each.

Table 22: Adverse Events of Toxicity Grade ≥ 3 in ≥ 1 subjects in Study GS-US-334-0123

MedDRA Preferred Term	**Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68**	**Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=41**	**Group 3 GT 1 TN SOF+RBV 24 weeks N=114**
Number (%) of Subjects Experiencing Any Grade 3 or 4 AE	7 (10.3)	3 (7.3)	15 (13.2)
Anemia	0	0	1 (0.9)
Leukocytosis	0	0	1 (0.9)
Atrial Fibrillation	0	0	1 (0.9)
Atrial Flutter	0	0	1 (0.9)
Acute Myocardial Infarction	1 (1.5)	0	0
Abdominal Pain	0	0	1 (0.9)
Colitis	0	0	1 (0.9)
Enteritis	0	0	1 (0.9)
Fatigue	2 (2.9)	1 (2.4)	0
Chest Pain	0	0	2 (1.8)
Hyperbilirubinemia	0	1 (2.4)	1 (0.9)
Jaundice	0	1 (2.4)	1 (0.9)
Gastroenteritis	0	1 (2.4)	0
Gastroenteritis Salmonella	0	0	1 (0.9)
Respiratory Tract Infection	0	0	1 (0.9)
Staphylococcal Infection	0	0	1 (0.9)
Pneumonia	1 (1.5)	0	0
Septic Shock	1 (1.5)	0	0
Staphylococcal Bacteremia	1 (1.5)	0	0
Intentional Overdose	1 (1.5)	0	1 (0.9)
Fracture	1 (1.5)	0	0
Lower Limb Fracture	1 (1.5)	0	0
Diabetic Ketoacidosis	0	0	1 (0.9)
Abnormal loss of weight	1 (1.5)	0	0
Decreased Appetite	1 (1.5)	0	0
Fracture Pain	1 (1.5)	0	0
Altered State of Consciousness	0	0	1 (0.9)

Encephalopathy	1 (1.5)	0	0
Headache	1 (1.5)	0	0
Depression	1 (1.5)	1 (2.4)	0
Agitation	0	0	1 (0.9)
Anger	0	0	1 (0.9)
Insomnia	0	0	1 (0.9)
Mental Status Changes	0	1 (2.4)	0
Mood Swings	0	0	1 (0.9)
Stress	0	0	1 (0.9)
Completed Suicide	1 (1.5)	0	0
Drug Abuse	1 (1.5)	0	0
Suicide Attempt	1 (1.5)	0	0
Renal Failure Acute	1 (1.5)	0	2 (1.8)
Pulmonary Embolism	1 (1.5)	0	0
Respiratory Failure	1 (1.5)	0	0

SOF=sofosbuvir; RBV=ribavirin
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

Common Adverse Events

Table 23 presents the most commonly reported AEs reported in greater than 10% of subjects in any treatment group. Overall, the most frequently reported AEs were fatigue (38%, 84 subjects), insomnia (17%, 37 subjects), nausea (16%, 36 subjects) and headache (13%, 30 subjects).

Table 23: Treatment-Emergent Adverse Events by Preferred Term (in ≥10% of Subjects in Any Treatment Group) in Study GS-US-334-0123

Preferred Term	Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68	Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=41	Group 3 GT 1 TN SOF+RBV 24 weeks N=114
Number (%) of Subjects Experiencing Any AE	57 (84)	37 (90)	106 (93)
Fatigue	24 (35)	19 (46)	41 (36)
Insomnia	14 (21)	8 (20)	15 (13)
Nausea	12 (18)	6 (15)	18 (16)
Headache	9 (13)	5 (12)	16 (14)
Upper Respiratory Tract Infection	8 (12)	5 (12)	13 (11)
Diarrhoea	6 (9)	5 (12)	12 (11)
Irritability	7 (10)	2 (5)	14 (12)
Anaemia	6 (9)	3 (7)	13 (11)
Cough	4 (6)	4 (10)	14 (12)
Dizziness	1 (2)	5 (12)	7 (6)

GT 1 = genotype 1, GT 2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
SOF=sofosbuvir; RBV=ribavirin; N = number of subjects
Source: NDA Submissions dated October 09 and October 17, 2013

The frequency of most commonly occurring AEs was similar between the 12- and 24-week arms with the exception of cough and dizziness, which were more common with the longer treatment duration. However, this difference was present in the first 12 weeks of treatment. The rates of cough and dizziness in the Phase 3 trials of SOF+RBV in monoinfected subjects for 12 Week and 24 Week, are similar to the rates observed in the 24 Week treatment groups of GS-US-334-0123.

Reviewer's Comments

The most frequently reported AEs in this trial were fatigue, insomnia, nausea and headache which are similar to those reported in trials done in HCV-monoinfected subjects. The incidence of AEs is comparable to those observed in other Phase 3 trials with 12, 16 or 24 weeks of SOF+RBV.

Cardiac Disorder Adverse Events

A comprehensive review of AEs based on MedDRA System Organ Class (SOC) for Cardiac Disorders was done for Study GS-US-334-0123 by the Applicant (NDA Submission 0044).

As per Applicant, in Study GS-US-334-0123 (PHOTON-1), treatment-emergent cardiac AEs were mostly mild in severity (Grade 1 or 2). Grade 1 events in the SOF+RBV 24 week arm were palpitations (N=4), sinus tachycardia (N=2) and Grade 2 event in the SOF+RBV 24 week arm was arrhythmia (N=1).

> Subject # 6612-8838 experienced a Grade 2 AE of arrhythmia on Day 105 for which no action was taken with respect to study drugs or treatment for the AE. The subject reported he received a 24-hour holter monitor through his primary care physician for complaints of an "irregular heartbeat". According to the patient, he had an arrhythmia that required no treatment or additional follow up. On physical exam he was noted to have "extra beats" with normal vital signs (heart rate 80 beats per minute). The symptoms, though recorded as ongoing at the time of the data cut, were reported as resolved on post-treatment Day 8.

There were no Grade 3 cardiac AEs in either of the treatment arms. There were 2 subjects with Grade 4 cardiac AEs that were also SAEs (Table 21).

- Subject # 0843-8722 experienced a Grade 4 myocardial infarction in the setting of intravenous methamphetamine overdose leading to hospitalization for multiorgan failure, septic shock, and staphylococcal bacteremia.
- Subject #0843-8852 was a 37 year old male with a relevant medical history of aortic valve disorder, bacterial endocarditis, poorly controlled diabetes mellitus, hypertension, and multiple psychiatric diagnoses including psychosis who completed 24 weeks of SOF+RBV treatment per protocol. He was admitted to the hospital on post-treatment Day 23 in severe diabetic ketoacidosis with acute renal failure and altered level of consciousness precipitated by an episode of binge drinking. In this setting, he was noted to have atrial fibrillation and atrial flutter which resolved following treatment of his underlying acute medical issues.

Reviewer's Comments

In the SAEs reported under CARDIAC DISORDERS, the subject either had a prior history of cardiovascular disease or had cardiovascular risk factors. There were no cases of cardiomyopathy reported.

Laboratory Findings

Treatment-emergent laboratory abnormalities were defined as values that increase by at least 1 toxicity grade from baseline at any time postbaseline up to the last dose of study regimen plus 30 days. Laboratory results were assigned toxicity grades (Grade 0, Grade 1 [mild], Grade 2 [moderate], Grade 3 [severe],

or Grade 4 [potentially life-threatening]) based on the Gilead Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

A total of 41 subjects (18.4%) had a Grade 3 or 4 laboratory abnormality. No Grade 3 or 4 hematological laboratory abnormalities were observed.

Table 24: GS-US-334-0123: Grade 3 or 4 Laboratory Abnormalities Occurring in > 1 Subject in Any Treatment Group (Safety Analysis Set)

	Group 1	Group 2	Group 3	Groups 2 and 3
Laboratory Parameter	SOF+RBV 12 Weeks GT 2/3 TN (N = 68)	SOF+RBV 24 Weeks GT 2/3 TE (N = 41)	SOF+RBV 24 Weeks GT 1 TN (N = 114)	SOF+RBV 24 Weeks (N = 155)
Maximum Postdose Toxicity Grade				
Grade 3	7 (10.3%)	5 (12.2%)	15 (13.2%)	20 (12.9%)
Grade 4	1 (1.5%)	2 (4.9%)	11 (9.6%)	13 (8.4%)
Lipase				
Grade 3	0	0	3 (2.6%)	3 (1.9%)
Grade 4	0	0	0	0
Total Bilirubin (Hyperbilirubinemia)				
Grade 3	3 (4.4%)	4 (9.8%)	13 (11.4%)	17 (11.0%)
Grade 4	1 (1.5%)	2 (4.9%)	9 (7.9%)	11 (7.1%)

GT= genotype; TE = treatment experienced; TN = treatment naive
Source: Study GS-US-334-0123 Second Interim Synoptic Clinical Study Report Submitted on October 09, 2013

Elevated total bilirubin was the most frequent Grade 3 (20 subjects, 9.0%) and Grade 4 (12 subjects, 5.4%) laboratory abnormality. These elevations occurred mostly (30 of 32 subjects, 93.8%) in subjects receiving atazanavir (ATV) as part of the ARV regimen and were consistent with RBV-induced hemolysis in the setting of UGT1A1 inhibition by ATV.

As noted by the Applicant, none of the elevations in total bilirubin were associated with elevations in direct bilirubin or transaminitis. Consistent with RBV-induced hemolysis, total bilirubin elevations peaked at Week 1 or 2 with subsequent decreases observed thereafter. All subjects had improvement in total bilirubin to near baseline by the posttreatment Week 12 visit.

Among subjects not taking ATV, Grade 3 or 4 elevated total bilirubin was observed in 2 subjects (1.5%) which is similar to the rate (2.0%) observed with HCV-monoinfected subjects receiving SOF+RBV in registrational Phase 3 studies included in the Primary Safety Population of the original NDA submission.

Reviewer's Comments

Information regarding increased incidence of elevated total bilirubin levels in HCV/HIV-1 co-infected subjects receiving concomitant atazanavir should be included in the prescribing information.

Grade 3 lipase elevations were the only other Grade 3 or 4 laboratory abnormalities to occur in more than 1 subject, occurring in 3 subjects in the SOF+RBV 24 Week TN GT 1 group.

- Two of the subjects had asymptomatic elevations of lipase (one subject at Week 12 and one subject at Week 20).
- The third subject (#1961-8812) had Grade 1 or 2 lipase elevations at each on-treatment study visit and had Grade 3 lipase elevation (346 U/L) at Week 8. This was reported as a Grade 1 AE of pancreatitis by the investigator and was considered related to study drug. Additional information was subsequently requested and the investigator noted that the subject was asymptomatic with respect to findings suggestive of pancreatitis. The only other concomitant AE was "pain secondary to tooth extraction". The subject completed scheduled dosing without interruption and lipase values returned to within the reference range by posttreatment Week 4. The incidental finding of elevated lipase was reconsidered as clinically insignificant and has been removed from the database as an AE by the investigator.

Reviewer's Comments

Overall, the incidence of elevated lipase values in Study GS-US-334-0123 is similar to that observed in other sofosbuvir Phase 3 trials.

Creatine Kinase was not evaluated in Study GS-US-334-0123.

Effects of SOF+RBV Therapy on HIV

HIV-1 Viral Load at Baseline and End of Treatment

The majority of the subjects in the study had HIV-1 RNA < 50 copies/mL at baseline. Almost all the subjects with baseline HIV-1 RNA < 50 copies/mL were on HIV antiretroviral therapy (ARV). The snapshot algorithm was applied by Dr. Karen Qi to calculate the proportion of subjects with HIV-1 RNA <50 copies/mL at EOT. The algorithm is usually used to compute the primary efficacy endpoint of percent of subjects with HIV-1 RNA < 50 copies/mL in the HIV trials. Table 25 shows the HIV viral load at EOT by the baseline viral load (< 50 or ≥ 50 copies/mL). In all three treatment groups, above 90% of the subjects who had

baseline viral load below 50 copies/mL maintained their viral load suppressed <50 copies/mL at EOT.

Table 25: HIV-1 Viral Load at Baseline and End of Treatment (Study GS-US-334-0123)

	Group 1 GT 2/3 TN SOF+RBV 12 Weeks N=68	Group 2 GT 2/3 TE SOF+RBV 24 Weeks N=28	Group 3 GT 1 TN SOF+RBV 24 weeks N=114
Baseline HIV-1 RNA < 50 copies/mL	60 (100%)	40 (100%)	108 (100%)
HIV RNA at EOT			
Virologic success – HIV RNA <50 copies/mL	54 (90%)	38 (95%)	99 (92%)
Virologic failure	3 (5%)	1 (3%)	5 (5%)
No virologic data at EOT window	3 (5%)	1 (3%)	4 (4%)
Discontinued SOF+RBV due to AE or death	1 (2%)	1 (3%)	1 (1%)
Discontinued SOF+RBV for other reasons	1 (2%)	0	2 (2%)
Missing data during window but on SOF+RBV	1 (2%)	0	1 (1%)
Baseline HIV-1 RNA ≥ 50 copies/mL	8 (100%)	1 (100%)	6 (100%)
HIV RNA at EOT			
Virologic success – HIV RNA <50 copies/mL	2 (25%)	1 (100%)	4 (67%)
Virologic failure*	5 (63%)	0	1 (17%)
No virologic data at EOT window	1 (13%)	0	1 (17%)
Discontinued SOF+RBV due to AE or death	0	0	1 (17%)
Discontinued SOF+RBV for other reasons	0	0	0
Missing data during window but on SOF+RBV	1 (13%)	0	0

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
* including subjects who discontinued study drug due to lack of efficacy and subjects who had HIV RNA ≥ 50 copies in the EOT window
Source: FDA Statistical Reviewer

It should be noted that the nine subjects classified as "virologic failure" include two subjects with confirmed rebound (see HIV Virologic Rebound), one subject not receiving ARV and six subjects with sporadic, isolated virologic blips. Review team believes that these six subjects did not have treatment failure of their HIV regimen due to SOF-based treatment. Instead, they had "blips" which can be seen in patients on stable ART. These isolated blips are not thought to

necessarily predict virologic failure. As stated in the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, "isolated blips (viral loads transiently detectable at low levels, typically <400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure."[1]

HIV-1 Virologic Rebound

According to the protocol, the subjects who met the following criteria were considered to have HIV-1 virologic rebound:

- at any visit, having at least two consecutive plasma HIV-1 RNA ≥ 50 copies/mL (at least two weeks apart)
- currently on ARV treatment and had HIV-1 RNA < 50 copies/mL

Only two subjects met the virologic rebound criteria (Subject # 4262-8725 in Group 1 and Subject # 0843-8852 in Group 3) during SOF+RBV therapy.

One subject in the HCV GT 2/3 treatment-naïve SOF+RBV 12 Week group on raltegravir plus tenofovir/emtricitabine had detectable HIV-1 RNA at Week 12. Poor adherence to both antiretroviral and study drug medication was suspected by the investigator, and this subject also experienced HCV relapse. One subject in the HCV GT 1 SOF+RBV 24 Week group on atazanavir/ritonavir plus tenofovir/emtricitabine had HIV-1 RNA ranging between <20 to 75 copies/mL on-treatment, and 491 and 32 copies/mL at the posttreatment Week 4 and 12 visits, respectively. Poor adherence with antiretroviral treatment was reported by the investigator.

Subject #1692-8915 in Group 2 had HIV-1 RNA < 50 copies/mL at baseline, but had ≥ 50 copies/mL at Weeks 20 and 24 visits. However the subject was not on ARV treatment.

CD4+ T-Lymphocytes

Table 26 displays the total CD4+ counts at baseline and the change from baseline in the total CD4+ cells at EOT and post-treatment follow-up visits in the three treatment groups.

[1] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/Adultand AdolescentGL.pdf Accessed on November 19, 2013

Table 26: Total CD4+ Cell Counts in Study GS-US-334-0123

	Group 1 12-Week SOF+RBV GT 2/3 TN[1] (N=68)	Group 2 24-Week SOF+RBV GT 2/3 TE[1] (N=41)	Group 3 24-Week SOF+RBV GT 1 TN[1] (N=114)
Baseline			
n	68	41	114
Mean (SD)	585 (246)	658 (333)	636 (251)
Median (Q1, Q3)	562 (395, 723)	579 (482, 744)	583 (455, 812)
Change from baseline at EOT			
n	68	41	114
Mean (SD)	-94 (141)	-99 (156)	-79 (175)
Median (Q1, Q3)	-81 (-167, 5)	-73 (-161, -13)	-88 (-186, -4)
Change from baseline at 4 weeks post-treatment			
n	64	39	111
Mean (SD)	-71 (175)	-64 (153)	-35 (173)
Median (Q1, Q3)	-65 (-158, 26)	-55 (-161, 34)	-52 (-131, 34)
Change from baseline at 12 weeks post-treatment			
n	51	27	93
Mean (SD)	-4 (134)	-46 (138)	64 (171)
Median (Q1, Q3)	-13 (-111, 106)	-52 (-129, 45)	52 (-56, 164)

GT 1 = genotype 1; GT 2/3 = genotype 2/3; TN = treatment-naïve; TE = treatment-experienced
Source: FDA Statistical Reviewer

In all groups, the CD4+ counts decreased at the end of SOF+RBV treatment. However, the percentage of CD4+ cells stayed fairly consistent at EOT and post-treatment follow-up visits as noted in the analyses done by Dr. Karen Qi.

Safety Summary

The observed safety profile of sofosbuvir and ribavirin (SOF+RBV) regimens is consistent with the previously noted adverse event profile in Primary Clinical Review based on the evaluation of data submitted at the time of original NDA. In addition, no new adverse events were identified. No clustering of adverse events and no trends in any specific adverse event type were noted.

In conclusion, based on the review of the additional data submitted, no major safety issues associated with sofosbuvir use have been identified to date. The noted safety profile of sofosbuvir is acceptable.

8 Other Efficacy Considerations

8.1 Evidence to Support IFN-Free Regimen for Treatment of HCV Genotype 1 Infection in Patients Who Are IFN-Ineligible

A comprehensive assessment of the collective evidence to support a 24 week SOF+RBV regimen as an alternative therapeutic option for genotype 1 subjects who are ineligible to receive an IFN-based therapy was done.

The primary clinical data supporting the use of SOF+RBV for 24 weeks for the treatment of HCV genotype 1 infection is derived from Study GS-US-334-0123 (PHOTON-1) which is an ongoing Phase 3 trial evaluating SOF+RBV for the treatment of HCV genotypes 1-3 in HIV-infected subjects, including subjects with compensated cirrhosis with treatment durations of 12 or 24 weeks, depending on HCV genotype and treatment history.

As described earlier, in PHOTON-1, SOF+RBV regimen was studied for 24 weeks in 114 HCV genotype 1 treatment-naïve subjects co-infected with HIV-1. Out of these 114 subjects, 76% (87 subjects) have achieved SVR12 (Table 10). Relapse accounted for all HCV genotype 1 virologic failures except for one subject who experienced on-treatment virologic failure with hematologic parameters suggestive of inconsistent RBV adherence. The number of GT1 subjects with cirrhosis in this trial was small (n=5) and the observed SVR12 was 60% (3/5) based on these limited number of subjects. A substantial difference in SVR12 results was noted between GT1a vs. GT1b subjects (82% vs. 54% respectively) as shown in Table 10. The small number of subjects in these subgroups should be noted.

As noted by the Applicant, Phase 2 data from the NIAID-sponsored trial (11-I-0258) and the re-treatment arm of Study P2938-0721 (QUANTUM) further support the results obtained in PHOTON-1 with SVR12 response rates of 68% and 66% in genotype 1 HCV-infected patients who are not co-infected with HIV, and who were treated with SOF+RBV for 24 weeks, respectively. The data from NIAID-sponsored trial (11-I-0258) and the re-treatment arm of Study P2938-0721 (QUANTUM) have not been independently reviewed.

These Phase 2 and 3 data collectively demonstrate HCV genotype 1 treatment-naïve SVR rates between 66 and 76% following SOF+RBV for 24 weeks, which is similar to the current HCV genotype 1 standard of care of a PI (boceprevir or telaprevir) plus PEG/RBV with SVR rates between 66% and 75%, after 24-48 weeks of therapy. SOF+RBV offers an all oral, interferon-free, low pill burden option to HCV genotype 1 patients who may be unable to take interferon.

Reviewer's Comments

Clinical evidence available to date suggests sofosbuvir in combination with ribavirin for 24 weeks duration may represent a therapeutic option for the treatment of HCV genotype 1 infected patients who are ineligible to receive interferon-based regimens which are the only approved regimens currently available for treatment of genotype 1 patients. In addition, sofosbuvir and ribavirin combination is simpler to take due to low pill burden, no weekly injections, and has an overall improved safety profile compared to current standard of care treatment.

8.2 Exploratory Evidence to Support SOF+PEG+RBV 12 Week Regimen in Prior P/R Nonresponders

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). The observed high overall SVR rate in HCV GT1 treatment-naïve subjects from Study GS-US-334-0110 (NEUTRINO) led the review team to use a similar approach to explore whether the data may support use of SOF+PEG+RBV for 12 weeks in patients who have failed a prior PEG/RBV regimen.

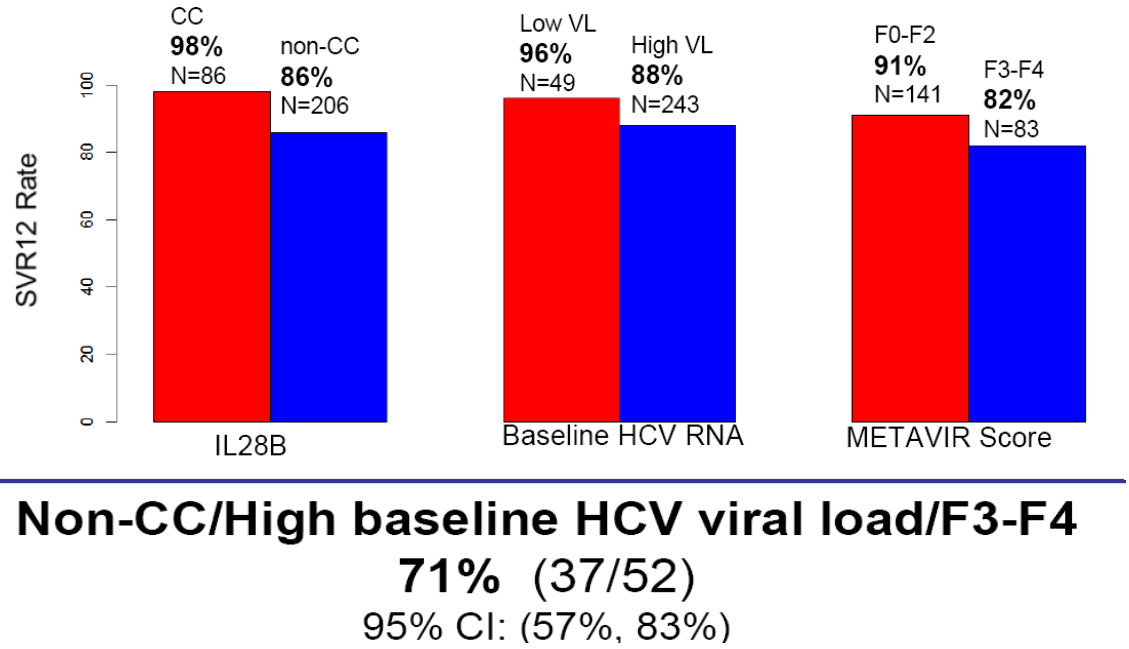
Exploratory analyses were performed by the review team and were presented at the Advisory Committee meeting in a collaborative presentation from Drs. Karen Qi and Jeffry Florian. Please refer to their respective reviews for details of the analyses performed.

One of the exploratory analyses performed predicted the SVR rate based on the observed SVR rate for PEG/RBV treatment in the historical trials, which ranges from 40% to 50%. As a conservative assessment, it was assumed that 50% of the HCV genotype 1 treatment-naïve subjects in NEUTRINO could be PEG/RBV treatment failures and that all 11% of subjects who failed to respond SOF+PEG+RBV in NEUTRINO can also be classified as PEG/RBV treatment failures. This implied that 39% (i.e., 50% -11%) of the potential PEG/RBV treatment failures responded to the SOF+PEG+RBV treatment. Thus, based on these assumptions, the predicted SVR rate in HCV genotype 1 treatment-experienced population is 78% (i.e., 39/50).

Another analysis was done using selected baseline factors which are known to be associated with lower response to PEG/RBV therapy. These baseline factors

were: IL28B non-CC genotype, baseline HCV RNA viral load >800,000 IU/mL and METAVIR score of F3-F4. Using NEUTRINO data, subjects with all three of these baseline factors had an observed SVR12 rate of 71%, with a 95% confidence interval of 57-83% (Figure 8).

Figure 8: SVR12 Rates in Harder-to-Treat GT 1 Treatment-Naïve Subjects (NEUTRINO)



Source: FDA Presentation, Antiviral Drugs Advisory Committee Meeting October 25, 2013

Acknowledging the lack of clinical data directly obtained in the HCV GT1 patients who have failed a prior PEG/RBV regimen, the review team believes that the SOF+PEG+RBV shorter treatment duration and improved tolerability profile can provide a therapeutic option for this patient population.

Please refer to AC transcripts for detailed discussion by the committee members on the FDA analyses and the proposed treatment regimen.

9 Labeling Recommendations

Labeling recommendations based on the review of the additional data include:

- The trial results from VALENCE AND PHOTON-1 should be included in the Prescribing information (Section 14 CLINICAL STUDIES).
- SOF+RBV for 12 weeks is recommended for patients with genotype 2 HCV infection

- SOF+RBV for 24 weeks is recommended for patients with genotype 3 HCV infection

- Similar dosing regimens are recommended for HCV-Monoinfected and HCV/HIV-1 Co-infected patients.

- SOF+PEG+RBV for 12 weeks can be considered as a treatment option for genotype 1 patients who have failed a previous course of pegylated interferon and ribavirin therapy based on estimated response rate in genotype 1 subjects (NEUTRINO) with multiple baseline factors traditionally associated with a lower response to interferon-based treatment.

- SOF+RBV for 24 weeks can be considered as a therapeutic option for CHC patients with genotype 1 infection who are ineligible to receive interferon-based regimen. Treatment decision should be guided by an assessment of the potential benefits and risks for the individual patient.

- The following points have been added to guide health care providers regarding treatment regimens and response.
    - Treatment regimen and duration are dependent on both viral genotype and patient population.
    - Treatment response varies based on baseline host and viral factors.

- A subsection titled "***Less Common Adverse Reactions Reported in Clinical Trials (<1%)***" has been added under Section 6 ADVERSE REACTIONS to include less frequent adverse events of clinical significance noted in the clinical trials.

Labeling discussions are ongoing with the Applicant and have not been finalized at the time of this review.

10 Errata to the Primary Clinical Review

This section includes errata to the Primary Clinical Review signed September 06, 2013 in DARRTS under NDA 204671 for sofosbuvir

The following errors have been identified and corrected:

1. On page 55, "Table 12: Serious Adverse Events in Study GS-US-334-010 (Safety Analysis Set)" should include the SAE of Abdominal Pain:

MedDRA Preferred Term	Study Day/ Start of AE	Study Day/ End of AE	Subject ID	Treatment Group
Abdominal Pain	51	56	2760-6598	SOF+PEG+RBV 12 Weeks
Anaemia	48	56		
Cryoglobulinaemia	48	69		

2. On page 74, Table 26: Primary Efficacy Results and Relapse rates in Study GS-US-334-0107 (All Treated), the row "Proportion Difference SOF+RBV 12 Weeks vs. Placebo 12 Weeks [95% CI]" listed under Overall SVR12, 95% CI should be read as follows:

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%]	

3. On page 77, Title of "Table 28: Primary Efficacy Results and Relapse Rates in Study GS-US-334-0110 (FAS)" should read:

   Table 28: Primary Efficacy Results in Study GS-US-334-0110 (FAS)

4. On page 78, subsection Response Rates based on Gender (Section 6.1.7 Subpopulations), the first sentence should read as:

   The post-hoc analyses showed that the female subjects with genotype 3 infection had higher SVR12 rates than male subjects in all of the SOF+RBV treatment groups in the three pivotal trials (P7977-1231, GS-US-334-0107 and GS-US-334-0108).

5. On page 79, subsection Response Rates in Subjects with Cirrhosis (Section 6.1.7 Subpopulations), the last bullet should read as:

   - In GS-US-334-0110, it was found that a higher SVR12 rate was observed in the noncirrhotic subjects than the cirrhotic subjects (92% [252/273] with 95% CI: 87% to 95% for noncirrhotic subjects, 80% [43/54] with 95% CI: 66% to 89% for cirrhotic subjects).

6. On page 94, Table 32 header row should be replaced with the following to indicate that cells in the table contain n (%):

   Table 32 header row should read:

	SOF+RBV 12 Weeks N=256 n (%)	**PEG+RBV 24 Weeks** N=243 n (%)

7. On page 102, the last row of "Table 35: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in the Primary Safety Population (Integrated Data)" should read as follows:

MedDRA Preferred Term	**Placebo 12 weeks**	**SOF+RBV 12 Weeks**	**SOF+RBV 16 Weeks**	**PEG+SOF+RBV 12 Weeks**	**PEG+RBV 24 Weeks**
	N=71	N=566	N=98	N=327	N=243
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Eczema	0	1 (0.2)	0	0	0

8. On Page 140, foot note regarding Milan criteria* should read as follows:

* 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.

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

/s/

POONAM MISHRA
11/20/2013

SARAH M CONNELLY
11/20/2013
I concur with Dr. Mishra's assessments and conclusions in this review.

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	204671
Priority or Standard	Priority
Submit Date(s)	April 06, 2013
Received Date(s)	April 08, 2013
PDUFA Goal Date	December 08, 2013
Division / Office	Division of Antiviral Products/Office of Antimicrobial Products
Reviewer Name(s)	Poonam Mishra, MD
Review Completion Date	September 06, 2013
Established Name	Sofosbuvir (GS-7977)
(Proposed) Trade Name	
Therapeutic Class	Hepatitis C virus NS5B polymerase inhibitor
Applicant	Gilead Sciences, Inc.
Formulation(s)	Tablets for oral use
Dosing Regimen	400 mg once daily
Indication(s)	Treatment of chronic hepatitis C in adults
Intended Population(s)	Adult patients (18 years and older) with chronic hepatitis C

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical reviewer's perspective, the approval of sofosbuvir is recommended for the treatment of chronic hepatitis C infection in adults. This recommendation is based on the review of the data presented in the marketing new drug application (NDA 204671). The efficacy and safety of sofosbuvir was demonstrated in the four pivotal Phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110). The currently available data supports a favorable risk benefit assessment for the use of sofosbuvir in combination with ribavirin in treatment-naïve and treatment-experienced subjects with genotype 2 or 3 hepatitis C virus (HCV) infection and sofosbuvir in combination with pegylated interferon and ribavirin in treatment-naïve subjects with genotype 1 or 4 HCV infection.

No deficiencies in the submitted/reviewed data preclude recommendation for approval of sofosbuvir at this time.

1.2 Risk Benefit Assessment

The overall risk benefit assessment is markedly favorable for sofosbuvir. This assessment is based on the demonstrated efficacy results, observed safety profile, shorter treatment duration and simpler treatment regimens compared to currently available therapeutic regimens for the treatment of chronic hepatitis C (CHC).

Efficacy

The efficacy of sofosbuvir in subjects with chronic HCV infection was established in four Phase 3 pivotal trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110). The primary efficacy endpoint was sustained virologic response defined as HCV RNA < LLOQ 12 weeks after the discontinuation of treatment or active therapy (SVR12). The overall efficacy results for each of the pivotal trials are briefly summarized below and details are further discussed in Section 6 (Review of Efficacy).

- The efficacy and safety of sofosbuvir and ribavirin (SOF+RBV) for 12 weeks compared with pegylated interferon and ribavirin (PEG+RBV) for 24 weeks was evaluated in treatment-naive subjects with genotype 2 or 3 HCV infection (Study P7977-1231). The overall SVR12 rate in the SOF+RBV group was 67%, which was noninferior to the SVR12 rate of 67% in the PEG+RBV group. The difference (95% CI) in proportions 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 greater than the prespecified noninferiority margin of -15%.

- The efficacy and safety of SOF+RBV for 12 weeks versus placebo was evaluated in subjects with genotype 2 or 3 HCV infection who were interferon (IFN) intolerant, IFN ineligible, or unwilling to take IFN (Study GS-US-334-0107). A statistically significant proportion of subjects ($p < 0.001$) in the SOF+RBV group achieved SVR12 (78%) compared with placebo (0%).

- The efficacy and safety of SOF+RBV for 12 weeks or 16 weeks was evaluated in treatment-experienced subjects with genotype 2 or 3 HCV infection (Study GS-US-334-0108). The SVR12 rates in the SOF+RBV 12 Week group was 50% and in the SOF+RBV 16 Week group was 71%, which were each statistically significantly higher ($p < 0.001$) compared to the prespecified null rate of 25%.

- The efficacy and safety of a SOF+PEG+RBV treatment regimen for 12 weeks was evaluated in treatment-naïve subjects with genotype 1, 4, 5, or 6 HCV infection (Study GS-US-334-0110). A statistically significant higher proportion of subjects achieved SVR12 (90%, $p < 0.001$) compared with an historical SVR12 rate of 60%. It should be noted that few subjects with genotype 5 (N=1) and genotype 6 (N=6) were included in the clinical trial and the available data are insufficient to make any definite dosing recommendations for patients with genotype 5 or 6.

In summary, two Phase 3 trials demonstrated efficacy in treatment-naive CHC subjects: Study GS-US-334-0110 demonstrated the efficacy of a SOF+PEG+RBV treatment regimen for 12 weeks in subjects with genotype 1 or 4 HCV infection and Study P7977-1231 demonstrated the efficacy of a SOF+RBV treatment regimen for 12 weeks in subjects with genotype 2 or 3 HCV infection; one Phase 3 trial (Study GS-US-334-0107) demonstrated the efficacy of a SOF+RBV-treatment regimen for 12 weeks in subjects with genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible, or unwilling to take IFN thus addressing an unmet need for therapy in these patients, and one Phase 3 trial (Study GS-US-334-0108) demonstrated the efficacy of a SOF+RBV treatment regimen for 12 or 16 weeks in treatment-experienced subjects with genotype 2 or 3 HCV infection. All four Phase 3 trials included a subset of subjects with compensated cirrhosis which represents a harder to treat subgroup.

Safety

The safety evaluation focused on overall safety as well as adverse events of special interest. The data derived from the four pivotal Phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110) constitute the primary safety population. The data from Phase 1 trials, Phase 2 trials and other ongoing trials constitute the supporting safety data. The notable safety findings have been discussed in relevant sections throughout the review and the details are provided in Section 7 (Review of Safety).

Safety data for the SOF+RBV regimen in subjects with genotype 2 and 3 HCV infection were evaluated from trials P7977-1231, GS-US-334-0107, and GS-US-334-0108. The most frequently reported AEs in subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups were: fatigue (SOF+RBV 12 Week: 40%; SOF+RBV 16 Week: 47%), headache (SOF+RBV 12 Week: 23%; SOF+RBV 16 Week: 33%), insomnia (SOF+RBV 12 Week: 16%; SOF+RBV 16 Week: 29%), and nausea (SOF+RBV 12 Week: 20%; SOF+RBV 16 Week: 20%). No notable difference in safety profile was observed between the two durations (SOF+RBV 12 weeks vs. SOF+RBV 16 weeks) evaluated in GS-US-334-0108. No additional safety issues were identified by extending the treatment duration of sofosbuvir and ribavirin by 4 weeks.

Safety data for the SOF+PEG+RBV regimen in subjects with genotype 1, 4, 5, and 6 HCV infection were evaluated from trial GS-US-334-0110. The three most common adverse events in subjects in the SOF+PEG+RBV group were: fatigue (59%), headache (36%), and nausea (34%).

An improved safety profile for all-oral SOF+RBV regimens was noted as compared to interferon based treatment regimens. Overall, the observed incidences of adverse events (any grade), Grade 3 or higher adverse events, and adverse events leading to permanent discontinuation, interruption or dose modification of the study drugs was lower in sofosbuvir-containing treatment regimens. The incidence of treatment-emergent adverse events reported as related to study drug (by investigator's causality assessment) was low. No clustering of adverse events and no trends in any specific adverse event type were noted.

Based on the review of available clinical data at this time, a detailed safety evaluation focusing on cardiac disorders revealed no potential safety concerns in regards to cardiac toxicity associated with sofosbuvir use. No renal adverse events of concern have been identified to date. Mild elevations of serum creatine kinase values were noted without any associated clinical symptoms of concern. Mild elevations of lipase values were noted which were not associated with clinical signs and symptoms of acute pancreatitis. No obvious safety concern of gastrointestinal toxicity associated with sofosbuvir use was identified. Elevated bilirubin levels consistent with hemolytic anemia associated with ribavirin therapy were noted. No safety signals related to hepatotoxicity was identified in the sofosbuvir treated groups. No acute hypersensitivity reactions such as Stevens - Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) were reported. No safety signals related to bone marrow suppression were identified in the sofosbuvir treated groups.

In conclusion, the observed safety profile of sofosbuvir and ribavirin (SOF+RBV) regimens is consistent with the known safety profile of ribavirin. The safety profile of pegylated interferon and ribavirin containing sofosbuvir regimen (SOF+PEG+RBV) is similar to the well documented adverse event profile of pegylated interferon and ribavirin containing treatment regimens. In addition, the known toxicities of ribavirin or expected

side effects associated with pegylated interferon use do not seem to be exacerbated when used in combination with sofosbuvir. No major safety issues associated with sofosbuvir use have been identified to date.

Overall Risk Benefit Assessment

Sofosbuvir and ribavirin combination regimen provides a first all-oral treatment option for chronic hepatitis C patients with genotype 2 or 3 infection. The SOF+RBV regimen offers a shorter duration of treatment with an improved safety profile compared to interferon based regimen. In addition, SOF+RBV regimen provides therapeutic option for patients who are ineligible, intolerant or non-willing to take interferon-based regimens, thus addressing an unmet need in this patient population.

Sofosbuvir in combination with pegylated interferon and ribavirin (SOF+PEG+RBV) provides improved efficacy and shorter duration of treatment for chronic hepatitis C patients with genotype 1 or 4 infection. The shorter duration of interferon and ribavirin based regimen translates into a better tolerated side effect profile which in turn leads to less treatment discontinuations and contributes to improved rates of sustained virologic response. The observed safety profile is consistent with the well-documented safety profile of interferon and ribavirin.

An advisory committee meeting has been scheduled on October 25, 2013 to discuss this application. The expert opinion and recommendations from the committee will be considered before the final regulatory decision is made regarding approval of sofosbuvir for treatment of adult patients with chronic hepatitis C.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this NDA submission for sofosbuvir at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

The pediatric trials to assess safety and efficacy of sofosbuvir for the treatment of chronic hepatitis C in pediatric subjects will be required under Pediatric Research Equity Act (PREA).

Additional post-marketing commitments or requirements may be proposed at a later time based on the discussions and recommendations at the advisory committee meeting scheduled on October 25, 2013.

2 Introduction and Regulatory Background

HCV is a small, enveloped, single-stranded ribonucleic acid (RNA) virus of the family Flaviviridae. Globally, it is estimated that 170-200 million persons are infected with HCV, and it affects about 3-5 million people in the United States (US). (http://www.epidemic.org/thefacts/theepidemic/worldPrevalence/)
HCV infection is a major public health problem and a leading cause of chronic liver disease in the US. The natural history of chronic hepatitis C (CHC) involves progression to cirrhosis, hepatocellular carcinoma, liver failure, and death. CHC is currently the most common reason for liver transplantation in the US. By 2007, there were more yearly deaths in the US related to HCV than human immunodeficiency virus (HIV) infection (Ly 2012). Without effective treatment interventions, significant increases in CHC-associated morbidity, mortality, and health care costs are predicted (Kim 2002). 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 hepatocellular carcinoma.

HCV is classified into different genotypes based on genetic (RNA sequence) variability. The most common genotype in the US (70-75%) is genotype 1 followed by genotype 2 and genotype 3. Genotype 4, 5, and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively.

The current application requests approval of sofosbuvir for the proposed indication for the treatment of chronic hepatitis C in adults.

2.1 Product Information

Generic (trade) name:	Sofosbuvir
Chemical class:	New molecular entity
Pharmacological class:	Hepatitis C virus NS5B polymerase inhibitor
Proposed indication:	Treatment of chronic Hepatitis C Virus (HCV) infection
Dosing regimens:	400 mg tablet orally once daily
Dosage form:	Tablet

Sofosbuvir is a nucleotide inhibitor of HCV NS5B RNA-dependant RNA polymerase.

The Applicant completed a clinical development plan to assess the efficacy and safety of sofosbuvir in adult patients with chronic hepatitis C infection.

No trade name for sofosbuvir has been approved at this time.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current standard of care treatment for chronic hepatitis C genotype 1 infection is the triple therapy with NS3/4A protease inhibitor in combination with pegylated interferon alfa and ribavirin for a total duration of 24 to 48 weeks based on on-treatment response. The current standard of care treatment for chronic hepatitis C genotype 2 and 3 infection is the combination therapy with pegylated interferon alfa and ribavirin for a total duration of 24 weeks. The recommended treatment duration for genotype 4 HCV infection is the combination therapy with pegylated interferon alfa and ribavirin for a total duration of 48 weeks. The currently approved drugs for the treatment of HCV infection are listed in Table 1.

Table 1: Currently Approved Drugs for the Treatment of Chronic Hepatitis C

Generic Name	Trade Name
Pegylated interferons	
Peginterferon alfa-2a	Pegasys®
Peginterferon alfa-2b	PegIntron®
Interferons	
Interferon alfa-2a	Roferon-A®*
Interferon alfa-2b	Intron-A®
Consensus interferon	Infergen®
Ribavirin	Rebetol®, Copegus®
Boceprevir	Victrelis
Telaprevir	Incivek

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns

The currently available therapeutic regimens have decreased the morbidity and mortality associated with HCV infection. However, the tolerability of these regimens is still a major issue. It is imperative that safe and effective treatment options are available to minimize the impact of this major public health problem. Therefore, the development of new therapeutic modalities that are more efficacious, are better tolerated with improved safety profiles, have less associated pill and injection burden and can be administered with simple treatment and management algorithms are much needed for the optimal management of patients chronically infected with HCV.

2.3 Availability of Proposed Active Ingredient in the United States

The proposed active ingredient is a new molecular entity and is not currently marketed in the United States or elsewhere.

2.4 Important Safety Issues With Consideration to Related Drugs

Currently, no pharmacologically related products have received FDA approval and this is the first drug in the pharmacologic class of HCV NS5B polymerase inhibitor filed for the marketing licensure in US.

The development of an investigational agent labeled BMS-986094 (formerly known as INX-189), a nucleotide polymerase (NS5B) inhibitor in Phase 2 clinical development for the treatment of hepatitis C was halted by Bristol-Myers Squibb Company in August, 2012 after nine patients in a clinical trial had to be hospitalized and one of them died of heart failure. In a Press Release dated August 23, 2012, Bristol-Myers Squibb stated that "While the cause of these unexpected events, which involve heart and kidney toxicity, has not been definitively established, the Company has determined that it is in the best interest of patients to halt development of BMS-986094." (http://www.bms.com/News/press_releases/Pages/default.aspx)

Although sofosbuvir is structurally different (GS-7977 is a 2'-F, 2'-Me uridine monophosphate analogue prodrug and BMS-986094 is a 2'-Me guanosine monophosphate analogue prodrug), a detailed safety evaluation focused on cardiac disorders was done to identify any potential safety signal. No safety issues related to cardiac toxicity have been noted in clinical development program of sofosbuvir to date. Please see Section 7.2.6 for full assessment.

The proposed indication for sofosbuvir use is in combination with pegylated interferon and ribavirin or with ribavirin (based on genotype); hence the safety profile of these drugs is discussed briefly in this section.

Almost all patients treated with pegylated interferons and ribavirin experience one or more adverse events during the course of therapy. The most commonly reported adverse events are influenza-like side effects such as fatigue, headache, myalgia, fever and rigors. Other common adverse events are anorexia, nausea and vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, actual suicide, and homicide. Adverse events are a major reason that patients decline or stop HCV therapy altogether. The currently approved alpha-interferon product labels carry Warnings and Precautions regarding potential toxicities in a substantial number of organ systems. All the approved interferon products carry a Pregnancy Category rating of C.

The most common and concerning adverse events related to ribavirin are hemolytic anemia and rash. The hemolytic anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Ribavirin is genotoxic and teratogenic and is classified as Pregnancy Category X.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

An Investigational New Drug application (IND) was submitted on November 13, 2009 by Pharmasset, Inc. After 30-day safety review, it was concluded that the Sponsor may proceed with the proposed clinical investigation under IND 106,739. Additional comments were provided to the Sponsor for consideration in regards to proposed clinical protocol/development plan in a letter signed December 10, 2009.

The clinical protocols and the development plan were reviewed by the Division of Antiviral Products (DAVP) throughout the clinical development program and feedback was provided addressing the issues involving dose, durations, and optimization of treatment regimens.

Two End-of-Phase 2 (EOP2) meetings were held with DAVP. Agreements were reached on the study design of pivotal trials in different patient populations to support the New Drug Application (NDA) for sofosbuvir (Pharmasset EOP2 meeting held August 18, 2011 and Gilead EOP2 meeting held on June 05, 2012).

A Type C Meeting (teleconference) was held on October 17, 2012 to discuss the strategy related to the format and content of the sofosbuvir NDA. The following excerpts from the official meeting minutes are included below to highlight one of the key agreements reached as the result of this meeting which is relevant to the current submission:

> **Sponsor's Question: Does the Agency agree that the data available in treatment-naïve genotype 2 and 3 HIV/HCV co-infected subjects at the time of the NDA filing supports the proposed indication?**
>
> *FDA Response:*
> *At this time, SVR4 data are not sufficient to support an indication in HIV/HCV treatment-naive genotype 2 and 3 subjects; however, we do expect these data to be submitted with the initial NDA. SVR12 data are needed to support an indication. Fewer than 300 HIV/HCV subjects may be acceptable for a future indication in the setting of favorable safety and efficacy data, and we encourage further discussion with the Division to reach agreement on the details of such a proposal.*
>
> **Discussion at the Meeting:**
> Gilead stated they no longer plan for an HIV/HCV treatment-naïve genotype 2 and 3 indication with the original NDA submission; however, the submission would include SVR4 data for 31 HIV/HCV treatment-naïve genotype 2 and 3 subjects enrolled through the end of September 2012. Gilead had difficulty getting the expected enrollment for the genotype 2/3 co-infected population as agreed upon at the End-of-Phase 2 meeting held in June 2012. Logistical issues related to biopsies were the biggest contributor to the delay, because HIV physicians were not used to requesting this type of test.

Gilead expects to submit a supplemental NDA to support the HIV/HCV co-infection indication following the approval of the original NDA.

Pre-NDA Meeting: A Pre-NDA meeting was held on March 14, 2013 to seek agreement on key aspects related to the content and format of the application, to seek agreement on key phase 3 data and to discuss the proposed indication for sofosbuvir, specifically for genotype 3 subjects. The key outcomes of this meeting pertaining to current submission are noted below:

- Gilead presented summary data supporting 12-week treatment duration for genotype 2 treatment-naïve and treatment-experienced HCV-infected patients. Their rationale for the 12-week duration is based on the high response rates in genotype 2 across multiple trials, overlapping confidence intervals, and small numbers in subgroups such as cirrhosis which therefore affect the differences observed. Gilead stated that they were cautious about over-interpreting results given the small numbers across the subgroups. Therefore, Gilead has no plans to change the 12 week treatment duration for all genotype 2 patients in the proposed label.

- Gilead agreed with the Agency's recommendation that longer treatment duration (16 weeks) would be more beneficial for all genotype 3 treatment-naïve and treatment-experienced HCV-infected patients.

- Gilead referenced discussion with European Medicines Agency (EMA), and their view that the label would be similar to HIV drug labels with broader indication statements. The Agency responded that this issue will also be a topic for discussion during the NDA review and the Advisory Committee meeting.

- Gilead is committed to doing an additional trial in HCV-infected subjects with severe renal impairment and will work with the Agency to design the trial.

- There will be no late submissions for this NDA submission.

- The sofosbuvir NDA will have an Advisory Committee Meeting.

- The meeting minutes from the October 17, 2012 Type C teleconference and the March 14, 2013 pre-NDA meeting will serve as an agreement between Gilead Sciences and the Agency (FDA/DAVP) as to what constitutes a complete NDA package for sofosbuvir.

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

2.6 Other Relevant Background Information

Gilead Sciences, Inc. (Gilead) is the Applicant of this NDA. On January 17, 2012, Gilead completed its acquisition of Pharmasset, Inc. making Pharmasset a wholly owned subsidiary of Gilead. The name Pharmasset is used throughout this NDA review for historical reasons. In addition, references to sofosbuvir in this review include GS-7977 and PSI-7977.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A consult request for clinical site inspections was submitted to the Division of Good Clinical Practice Compliance (DGCPC) in the Office of Scientific Investigations (OSI)/ Office of Compliance on May 09, 2013, in response to the NME NDA submission under PDUFA timeline. The site selection process involved the NDA review team and Dr. Antoine El-Hage from OSI.

The overall assessment of findings and general recommendations from the Clinical Inspection Summary document are noted here. Six clinical investigator sites were inspected in support of this application. The inspection of the six clinical investigators revealed no regulatory violations. The final classification for one site is No Action Indicated (NAI) and the pending classification for the other five inspections is NAI. Preliminary classification is based on e-mail communication from the field; the Establishment Inspectional Report (EIR) has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

Please refer to OSI Consult Review (signed 08/21/13 in DARRTS) for further details.

3.2 Compliance with Good Clinical Practices

The Applicant noted that all trials conducted in the sofosbuvir development program met the requirement for International Conference on Harmonization (ICH) guidelines. In addition, for trials conducted under a US Investigational New Drug (IND) application, investigators were required to ensure that the basic principles of “Good Clinical Practice” were adhered to, as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, “Responsibilities of Sponsors and Investigators,” 21 CFR, part 50, “Protection of Human Subjects,” and 21 CFR, part 56, “Institutional Review Boards.”

In addition, the FDA OSI inspected the clinical sites, and the available data from the site audits were considered acceptable (see Section 3.1). For a more detailed discussion of the OSI audit, please refer to the Clinical Inspection Summary, by Dr. Antoine El-Hage.

3.3 Financial Disclosures

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

There are seven investigators listed who are participating or have participated in the clinical trials and who have financial interest or arrangements as described in 21 CFR 54.4(a)(3). Six of the investigators have significant payments of other sorts greater than $25,000 and one investigator disclosed equity interest greater than $50,000. The Form FDA 3455 for each investigator was provided.

Overall, the number of investigators with a financial interest is low. Moreover, due to the global multicenter nature of these trials, the potential bias by any one investigator is minimized. In addition, the efficacy endpoints are determined using objective measurements of HCV-RNA PCR by (b) (4) and hence will not be vulnerable to bias on the part of the investigator. Hence, the likelihood that trial results were biased based on financial interests is minimal.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The significant efficacy and safety issues noted in other review disciplines have been summarized in this section. For detailed assessments, please refer to Primary Review for the particular discipline.

4.1 Chemistry Manufacturing and Controls

Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥ 2 mg/mL across the pH range of 2-7.7 at 37°C and is slightly soluble in water. Sofosbuvir tablets are for oral administration. Each tablet contains 400 mg of sofosbuvir. The tablets include the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, mannitol, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: polyethylene glycol, polyvinylalcohol, talc, titanium dioxide, and yellow iron oxide.

As noted by the Applicant, the sofosbuvir [redacted] (b) (4) was administered in Studies P7977-1231 and GS-US-334-0107 and the sofosbuvir [redacted] (b) (4) was administered in Studies GS-US-334-0108 and GS-US-334-0110. The equivalence of sofosbuvir tablets with [redacted] (b) (4) was evaluated by the Applicant using PK results from Phase 3 trials. Please refer to CMC and Clinical Pharmacology Reviews for detailed assessment.

Please refer to Primary Quality Review for full assessment of the data provided by the Applicant on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product.

4.2 Clinical Microbiology

Please refer to the Clinical Virology Review by Dr. Lisa Naeger and Dr. Eric Donaldson for detailed assessment. Key findings are noted below.

Sofosbuvir showed no clear evidence of mitochondrial toxicity. Sofosbuvir showed no decrease in mitochondrial DNA following a 10-to 14-day treatment of multiple cell lines. Sofosbuvir and its metabolites showed no inhibition of mitochondrial biogenesis (mitochondrial DNA replication, RNA transcription and protein expression) with $mtCC_{50}$ values >100 μM in PC3 and HepG2 cells. The active triphosphate form of sofosbuvir did not inhibit RNA polymerase II at concentrations up to 200 μM, mitochondrial RNA polymerase at concentrations up to 500 μM, or DNA polymerases α, β, or γ at concentrations up to 200 μM, RNA polymerase II at concentrations up to 200 μM, or mtRNAP at concentrations up to 500 μM. In addition, the active metabolite of sofosbuvir is a poor substrate for mitochondrial RNA polymerase with an incorporation rate into RNA of <0.5% relative to UTP.

Sofosbuvir had EC_{50} values ranging from 14-110 nM in stable full-length replicon cells of genotype 1a, 1b, 2a, 3a and 4a, chimeric GT1b con-1 replicons carrying NS5B coding sequences from genotype 2b, 5a, or 6a and NS5B amplified from individual patient plasma samples and cloned into the replicon-based shuttle vectors. Interestingly, the EC_{50} values were slightly higher for GT1b and GT3a replicons than other genotypes/subtypes replicons which may provide some supportive evidence for why subjects with GT1a and GT2 HCV had higher overall clinical efficacy compared to subjects with GT1b and GT3a HCV.

Sofosbuvir showed no antiviral activity at the highest concentration tested (100 μM) against other non-HCV viruses: HIV, human rhinovirus (HRV) types 10 and 14, respiratory syncytial virus (RSV), and influenza A viruses. Sofosbuvir showed no antagonism when combined with other classes of direct acting antivirals for HCV, i.e. NS5A inhibitors (GS-5885, GS-5816), nonnucleoside inhibitors (GS-9190, GS-9669),

NS3/4A protease inhibitors, NS3 inhibitors (boceprevir, telaprevir, GS-9451), with RBV, with IFN or with HIV-1 NRTIs (ABC, AZT, ddI, d4T, FTC, TDF, 3TC).

The NS5B S282T substitution was selected in GT1b, 2a, 3a and 4a subgenomic replicons when the replicon cells were treated with SOF concentrations of 10 to 30 times the wild-type EC_{50} value. Detection of the S282T substitution was associated with a 4- to 24- fold decrease in susceptibility to sofosbuvir for all four genotypes. The S282T substitution was not cross-resistant with the NS5A inhibitor, GS-5885, or RBV. SOF remained fully active against all NS5B nucleoside and nonnucleoside inhibitor mutants, NS5A resistance mutants, and NS3 PI resistance associated mutants tested indicating that these mutants are not cross-resistant to sofosbuvir.

No S282T substitutions were identified at baseline or at time of relapse in any of the subjects from any of the Phase 3 trials in either the Gilead or FDA analyses.

4.3 Preclinical Pharmacology/Toxicology

Please refer to Pharmacology/Toxicology Review by Dr. Christopher Ellis for full assessment. Key findings from Dr. Ellis's Review are provided below:

The nonclinical safety profile of sofosbuvir has been evaluated in: safety pharmacology studies in rats and dogs with GS-9851 (GS-9851 comprises 2 diastereomers, SOF and GS-491241, in an approximate 1:1 ratio); single- and repeat-dose toxicology studies in mice, rats and dogs with GS-9851 and/or sofosbuvir alone for up to 3, 6 and 9 months duration, respectively; up to 1-month repeat-dose toxicology studies with sofosbuvir to qualify impurities; fertility and pre- and post-natal developmental studies in rats and embryo-fetal developmental studies in rats and rabbits with sofosbuvir; and genetic toxicology studies (Ames, *in vitro* chromosomal aberration and *in vivo* mouse micronucleus assays) with GS-9851. In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies, evaluating the absorption, distribution, metabolism and excretion of sofosbuvir, have been conducted.

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 estimated AUC exposure for sofosbuvir-derived GS-331007 is ~14-fold that in humans at the recommended sofosbuvir dose, since GS-9851 consists of 50% sofosbuvir. Heart toxicity was not observed in rats administered oral doses of sofosbuvir up to 500 mg/kg/day (AUC_{last}~66 μg.h/ml for GS-331007) for 6 months, or in dogs and mice administered sofosbuvir at up to 500 and 1000 mg/kg/day (AUC_{last}~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 ~9 (rat), 27 (dog) and 41 (mouse)-fold that in humans at the recommended sofosbuvir dose.

Gastrointestinal (GI) hemorrhage occurred in male dogs administered oral sofosbuvir doses of 500 mg/kg/day (AUC_{last}~209 to 278 μg.h/ml for GS-331007 at 6 & 3 months, respectively), corresponding to AUC exposures ~29 to 39-fold that in humans at the recommended sofosbuvir dose. Increased frequency and incidence of emesis and diarrhea also occurred at this dose level. These GI-related toxicities are most likely sofosbuvir-related; however, they also appear consistent with idiopathic hemorrhagic gastroenteritis of spontaneous origin. The NOEL for GI toxicity is 100 mg/kg/day (AUC_{last}~90 μg.h/ml for GS-331007) in dogs administered oral doses of sofosbuvir for up to 9 months, corresponding to AUC exposure ~13-fold that in humans at the recommended sofosbuvir dose. GI hemorrhage has not been observed in rats or mice.

4.4 Clinical Pharmacology

This section provides a brief summary of the clinical pharmacology of sofosbuvir. The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA to support a recommendation of approval of sofosbuvir. Please refer to the Clinical Pharmacology Review by Dr. Jenny Zheng and Dr. Jeffry Florian for additional information.

4.4.1 Mechanism of Action

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by HCV NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotypes 1b, 2a, 3a and 4a with IC50 values ranging from 0.7 to 2.6 μM. GS-461203 is not an inhibitor of human DNA and RNA polymerases or an inhibitor of mitochondrial RNA polymerase.

4.4.2 Pharmacodynamics

- In vitro studies indicated that sofosbuvir and its metabolites:
  - are not inhibitors (IC50 > 50−100 μM) of human cytochrome P450 (CYP) isozymes CYP3A4, CYP1A2, CYP2C19, CYP2C9, CYP2C8, and CYP2D6.
  - show no significant inhibition (IC50 >50 μM) of UGT1A1
  - show no induction of CYP enzymes
  - show no inhibition of the transport of probe substrates by P-gp, breast cancer resistance protein (BCRP), OATP1B1, OATP1B3, OCT1, and BSEP

- GS-331007 showed little or no inhibition of the renal transporters OAT1, OAT3, OCT2, and MATE1 (IC50 values > 100 μM).

- Sofosbuvir and its metabolites GS-566500 and GS-331007 were minimally metabolized by FMO, UGT, or CYP. In human liver microsomes, CYP- and UGT-related metabolism represents a minor contribution to SOF and GS-606965 (nucleotide analog monophosphate) disappearance.

Please refer to Clinical Pharmacology Review for detailed assessment of exposure-response.

4.4.3 Pharmacokinetics

A comprehensive range of clinical trials was conducted to characterize the pharmacokinetics of sofosbuvir and its predominant circulating metabolite GS-331007. The results are summarized below:

Absorption

- Following oral administration of sofosbuvir, sofosbuvir was absorbed quickly and the peak plasma concentration was observed ~0.5-2 hours post-dose, regardless of dose level. Peak plasma concentration of GS-331007 was observed between 2 and 4 hours post-dose.

- Steady-state GS-331007 and sofosbuvir pharmacokinetic (PK) parameters after once-daily administration of sofosbuvir are similar between HCV-infected subjects and healthy subjects.

Effect of Food

- Relative to fasting conditions, the administration of a single dose of sofosbuvir with a standardized high fat meal slowed the rate of absorption of sofosbuvir but did not substantially affect the extent of absorption. The exposure of GS-331007 was not altered in the presence of a high-fat meal. Therefore, sofosbuvir can be administered without regard to food (as instructed in phase 3 trials).

Distribution

- Sofosbuvir is approximately 61-65% bound to human plasma proteins and the binding is independent of drug concentration over the range of 1 μg/mL to 20 μg/mL. Protein binding of GS-331007 was minimal in human plasma. After a single 400 mg dose of [^{14}C]-SOF in healthy subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately 0.7.

Metabolism

- Sofosbuvir is extensively metabolized in the liver to form the pharmacologically active, intracellular nucleoside analog triphosphate GS-461203. The metabolic activation pathway involves sequential hydrolysis of the carboxyl ester moiety catalyzed by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and phosphoramidate cleavage by histidine triad nucleotide-binding protein 1 (HINT1) followed by phosphorylation by the pyrimidine nucleotide biosynthesis pathway. 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.

- After a single 400 mg oral dose of [^{14}C]-SOF, 4%, 7.0% and 91% of the mean circulating plasma total radioactivity (24,979 ng eq·h/g) were accounted for by sofosbuvir, GS-566500 and GS-331007, respectively. These results indicate GS-331007 is the major circulating metabolite of sofosbuvir.

Elimination

- Following a single 400 mg oral dose of [^{14}C]-SOF, mean total recovery of the dose was greater than 92%, consisting of approximately 80%, 14%, and 2.5% recovered in urine, feces, and expired air, respectively. The majority of the sofosbuvir dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as sofosbuvir. These data indicate that 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.

5 Sources of Clinical Data

Sofosbuvir has been evaluated by the Applicant in 18 Phase 1/2 trials, five Phase 2 clinical trials: P7977-0221, P7977-0422 (PROTON), P7977-0523 (ELECTRON), P7977-0724 (ATOMIC), and P2938-0721 (QUANTUM) and four Pivotal Phase 3 clinical trials: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO). The data from the four pivotal Phase 3 trials formed the principal basis for characterizing the safety and efficacy of sofosbuvir in patients with chronic hepatitis C infection.

The primary safety population is represented by the integrated data from four Phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110). The secondary safety population includes the safety data from Phase 1/2 short-term dose-ranging trials and the Phase 2 trials.

5.1 Tables of Studies/Clinical Trials

Phase 1 Trials

A total of 13 Phase 1 trials were performed in healthy volunteers, subjects with renal impairment, and HCV-infected subjects including one hepatic impairment trial in subjects with varying degrees of hepatic impairment. An overview of Phase 1 trials is provided in Table 2.

Table 2: Overview of Phase 1 Trials

Trial	Trial Design and Objective(s)	Number of Subjects
Healthy Subjects		
P7977-0111	Randomized, single-dose, 3-way crossover study to compare the rates and extent of absorption of GS-9851 200 mg and SOF 200 mg and estimate the effect of a high-fat meal on the PK of SOF and its metabolites in healthy subjects	24
P7977-0312	Open-label, single-dose, mass balance study to explore the routes and rates of elimination of [^{14}C]-SOF (1 × 400-mg capsule)	7
P7977-0613	Single-dose, randomized, blinded, placebo- and positive-controlled, 4-period crossover study in healthy subjects to demonstrate lack of effect of SOF administration on cardiac repolarization as determined by the baseline-adjusted QTcF effect of each active regimen relative to placebo following a single oral dose targeting therapeutic (400 mg) and supratherapeutic (1200 mg) exposures	60
P7977-1318	Randomized, single-dose, 3-way crossover study to compare the rate and extent of absorption of 2 formulations of SOF ((b) (4) tablet vs. 1 × 400-mg tablet) administered following an overnight fast and estimate the effect of a high-fat meal on the PK of SOF and its metabolites	40
P7851-1101	Randomized, double-blind, placebo-controlled, parallel, single-ascending-dose study of the PK, safety, and tolerability of GS-9851 25, 50, 100, 200, 400, and 800 mg and its metabolites	42
HCV-infected Subjects		
P7851-1102	Randomized, double-blind, placebo-controlled, parallel, multiple-ascending-dose study of the PK, safety, and tolerability of GS-9851 50, 100, 200, and 400 mg	40
P2938-0212	Randomized, double-blind, placebo-controlled, 2-part, parallel multiple-ascending-dose study in treatment-naive subjects with genotype 1 HCV infection to assess the PK, PD, safety, and tolerability of GS-0938 alone (100−300 mg) and in combination with SOF 400 mg	30 (cohorts 2-4)
Drug-Drug Interaction (DDI) Trials		
P7977-0814	Open-label, single-sequence, DDI study to evaluate the effect of steady-state SOF 400 mg on the steady-state PK of (R)- and (S)-methadone (30−130 mg)	15
P7977-1819	Randomized, open-label, 3-period crossover, DDI study to evaluate the effect of SOF 400 mg coadministration on single-dose PK of CsA 600 mg and tacrolimus 5 mg and the effect of CsA and tacrolimus coadministration on single-dose PK of SOF and its metabolites	40
P7977-1910	Open-label, single-sequence study to evaluate whether SOF 400 mg significantly influences the PK parameters of ATV/r 400/100 mg, DRV/r 800/100 mg, EFV 600 mg, TDF 300 mg, FTC 200 mg, RAL 400 mg, ZDV 300 mg, and 3TC 150 mg	Interim data on 34 subjects

Trial	Trial Design and Objective(s)	Number of Subjects
GS-US-334-0131	Open-label, multiple-dose, fixed-sequence, single-center, PK, DDI study to evaluate the PK of SOF 400 mg on coadministration with EFV 600 mg/FTC 200 mg/TDF 300 mg, DRV/r 800/100 mg, RAL 400 mg, and RPV 25 mg relative to SOF 400 mg alone; the PK of TFV, FTC, EFV, DRV, RTV, RAL, RPV on coadministration with SOF relative to administration of these agents alone; the safety and tolerability of coadministration of SOF and HIV medications; and the single-dose PK of a tablet containing SOF (b) (4) 400 mg	88
Renal Impairment Trial		
P7977-0915	Single-dose study to characterize the PK of SOF 400 mg and metabolites following single doses of SOF in subjects with normal renal function; mild, moderate and severe chronic renal impairment; and end-stage renal disease compared with matched healthy subjects	30
Hepatic Impairment Trial		
P2938-0515	PK/PD study to characterize the PK of SOF 400 mg and metabolites over 7 days of dosing in HCV-infected subjects with varying degrees of hepatic impairment compared with historical PK data	17 subjects (Groups B and C)
3TC = lamivudine, ATV = atazanavir, CsA = cyclosporine (cyclosporine A), DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, RAL = raltegravir, RTV = ritonavir, /r = boosted with ritonavir, TDF = tenofovir disoproxil fumarate, TFV = tenofovir, ZDV = zidovudine GS-9851 comprises 2 diastereomers, SOF and GS-491241, in an approximate 1:1 ratio. The diastereomeric mixture GS-9851 was used in early nonclinical and clinical studies		

Source: Adapted from Applicant's Summary of Clinical Safety (Table 4; pages 21-22)

Please refer to Clinical Pharmacology Review by Dr. Jenny Zheng for detailed assessment of Phase 1 trials.

Phase 2 Trials

Dose, duration, and combination regimens of SOF were explored in five Phase 2 clinical trials: P7977-0221, P7977-0422 (PROTON), P7977-0523 (ELECTRON), P7977-0724 (ATOMIC), P2938-0721 (QUANTUM), and NIAID-sponsored Phase 1/2a trial 11-I-0258. An overview of these Phase 2 trials is provided in Table 3.

Table 3: Overview of Phase 2 Clinical Trials

Trial Number	Trial Design	Regimen and Duration	Trial Status and Data
P7977-0221	Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study of the efficacy, PK, PD, safety, and tolerability of SOF+PEG+RBV for 28 days in treatment-naïve subjects with chronic genotype 1 HCV infection	SOF 100 mg+PEG+RBV group: SOF 100 mg QD on Days 0–27 and PEG+RBV Weeks 1–48 SOF 200 mg+PEG+RBV group: SOF 200 mg QD on Days 0–27 and PEG+RBV Weeks 1–48 SOF 400 mg+PEG+RBV group: SOF 400 mg QD on Days 0–27 and PEG+RBV Weeks 1–48 Placebo+PEG+RBV group: SOF-matching placebo QD on Days 0−27 and PEG+RBV Weeks 1−48 Treatment duration was 48 weeks (SOF+PEG+RBV for 4 weeks followed by 44 weeks of PEG+RBV).	Completed study
P7977-0422 (PROTON)	Phase 2b, placebo-controlled, dose-ranging, multicenter study in treatment-naïve subjects with chronic genotype 1 HCV infection and an open-label assessment in subjects with genotype 2 or 3 HCV infection of the efficacy, PK, PD, safety and tolerability of SOF administered with PEG+RBV for 12 weeks	**Randomized, Double-Blind Groups (Genotype 1):** SOF 200 mg+PEG+RBV group: SOF 200 mg QD+PEG+RBV for 12 weeks followed by PEG+RBV for up to 36 weeks SOF 400 mg+PEG+RBV group: SOF 400 mg QD+PEG+RBV for 12 weeks followed by PEG+RBV for up to 36 weeks Placebo+PEG+RBV group: SOF-matching placebo QD+PEG+RBV for 12 weeks followed by PEG+RBV for up to 36 weeks **Open-Label Group (Genotype 2/3):** SOF 400 mg+PEG+RBV group: SOF 400 mg QD+PEG+RBV 800 mg/day (divided daily dose) for 12 weeks	Completed study
P7977-0724 (ATOMIC)	Phase 2b, randomized, open-label, treatment duration-finding, multicenter study of the efficacy, PK, PD, safety, and tolerability of treatment with SOF+PEG+RBV for 12 or 24 weeks in	Group A: SOF 400 mg QD +PEG+RBV for 12 weeks Group B: SOF 400 mg QD +PEG+RBV for 24 weeks Group C: SOF 400 mg QD PEG+RBV for 12 weeks Subjects in Group C were then rerandomized to 1 of 2 groups to	Completed study

Trial Number	Trial Design	Regimen and Duration	Trial Status and Data
	treatment-naive subjects with genotype 1, 4, 5, 6, or genotype indeterminate HCV infection	receive another 12 weeks of treatment: Group C1: SOF 400 mg QD for 12 weeks Group C2: SOF 400 mg QD+RBV for 12 weeks	
P7977-0523 (ELECTRON)	Phase 2a, open-label, multicenter study of the efficacy, PK, PD, safety, and tolerability of SOF 400 mg for 8 or 12 weeks administered with and without RBV and/or PEG in subjects with genotype 1, 2, or 3 HCV infection	**Part 1 (Treatment-Naive Subjects with Genotype 2/3 HCV):** Group 1: SOF+RBV 12 weeks Group 2: SOF+PEG+RBV for 4 weeks then SOF+RBV for 8 weeks Group 3: SOF+PEG+RBV for 8 weeks then SOF+RBV for 4 weeks Group 4: SOF+PEG+RBV for 12 weeks **Part 2 (Treatment-Naive Subjects with Genotype 2/3 HCV in Groups 5 and 6 and Null Responders with Genotype 1 HCV in Group 7):** Group 5: SOF for 12 weeks Group 6: SOF+PEG+RBV for 8 weeks Group 7: SOF+RBV 12 weeks **Part 3 (Treatment-Naive Subjects with Genotype 1 HCV in Group 8 and Treatment-Experienced Subjects with Genotype 2/3 in Group 9):** Groups 8 and 9: SOF+RBV 12 weeks	Ongoing study
P2938-0721 (QUANTUM)	Phase 2, randomized, double-blind, multicenter study of the efficacy, PK, PD, safety, and tolerability of regimens containing SOF and RBV in treatment-naïve subjects with chronic genotype 1−6 HCV infection. For this submission, only data for the SOF 400 mg + RBV treatment regimens	Group C: SOF 400 mg QD PO+RBV PO for 12 weeks Group G: SOF 400 mg QD PO+RBV PO for 24 weeks	Completed study for Groups C and G.

Trial Number	Trial Design	Regimen and Duration	Trial Status and Data
	(Groups C and G) are included		
11-I-0258 (NIAID sponsored)	Phase 1/2a, randomized, open-label, prospective, multicenter study to assess the efficacy, safety, and tolerability of SOF administered in combination with full- or low-dose RBV for 24 weeks in treatment-naïve, subjects monoinfected with genotype 1 HCV	**Part 1:** SOF 400 mg QD+RBV for 24 weeks **Part 2:** Group A: SOF 400 mg QD+RBV for 24 weeks Group B: SOF 400 mg QD+RBV 600 mg QD for 24 weeks	Study completed. Interim abbreviated CSR for 60 subjects

For all subjects, PEG dose was 180 µg/week subcutaneous injections and RBV dose was 1000 or 1200 mg/day (divided daily dose) unless indicated otherwise.
For subjects who weighed < 75 kg, the RBV dose was 1000 mg/day, and for subjects who weighed ≥ 75 kg, the RBV dose was 1200 mg/day.
For Study P7977-0422, genotype 1 HCV-infected subjects with HCV RNA below the limit of detection (LOD) on Day 28 through Week 12 (i.e., extended rapid virologic response [eRVR]) received an additional 12 weeks of PEG+RBV after the SOF/placebo treatment period. Genotype 1 HCV-infected subjects with HCV RNA not below the LOD on Day 28 or with HCV RNA above the LOD at any time from Day 28 through Week 12 received an additional 36 weeks of PEG+RBV after treatment with SOF and PEG+RBV. Genotype 1 HCV-infected subjects who received SOF placebo and achieved an eRVR received an additional 36 weeks of PEG+RBV.
Source: Adapted from Applicant's Summary of Clinical Safety (pages 17-19)

Pivotal Phase 3 Trials

The key clinical trials analyzed for the assessment of the clinical efficacy and safety are the four pivotal Phase 3 trials: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO). These trials are summarized in Table 4.

Table 4: Overview of Pivotal Phase 3 Trials

Trial Number	Trial Design	Regimen and Duration	Trial Status and Data
P7977-1231 (FISSION)	Phase 3, randomized, open-label study of the efficacy and safety of 12 weeks of SOF+RBV or 24 weeks of PEG+RBV in treatment-naïve subjects with genotype 2 or 3 HCV infection (enrolled in approximately a 1:3 ratio of genotype 2 to genotype 3) Up to 20% of subjects may have had the presence of cirrhosis	SOF+RBV group: SOF 400 mg QD +RBV 1000 or 1200 mg/day for 12 weeks PEG+RBV group: PEG+RBV 800 mg/day for 24 weeks	SVR12 interim analysis for 499 subjects
GS-US-334-0107 (POSITRON)	Phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 12 weeks of SOF+RBV in subjects with genotype 2 or 3 HCV infection who are IFN-intolerant, IFN-ineligible, or unwilling to take IFN Up to 20% of subjects may have had the presence of cirrhosis	SOF+RBV group: SOF 400 mg QD +RBV 1000 or 1200 mg/day for 12 weeks Placebo group: SOF placebo QD +RBV placebo for 12 weeks	SVR12 interim analysis for 278 subjects
GS-US-334-0108 (FUSION)	Phase 3, randomized, double-blind study of the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment in subjects with chronic genotype 2 or 3 HCV infection who had failed prior treatment with an IFN-based regimen Up to 30% of subjects may have had the presence of cirrhosis	SOF+RBV 12-week group: SOF 400 mg QD +RBV 1000 or 1200 mg/day for 12 weeks followed by placebo for 4 weeks SOF+RBV 16-week group: SOF 400 mg QD +RBV 1000 or 1200 mg/day for 16 weeks	SVR12 Interim analysis for 201 subjects
GS-US-334-0110 (NEUTRINO)	Phase 3, open-label study of the efficacy and safety of 12 weeks SOF+PEG+RBV in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection Up to 20% of subjects may have had the presence of cirrhosis	SOF 400 mg QD +PEG+RBV 1000 or 1200 mg/day for 12 weeks	SVR12 interim analysis for 327 subjects

For all subjects, PEG dose was 180 µg/week subcutaneous injections
For all subjects, who weighed < 75 kg, the RBV dose was 1000 mg/day, and for subjects who weighed ≥ 75 kg, the RBV dose was 1200 mg/day (divided into 2 doses) except for subjects in PEG+RBV group of trial P7977-1231 in which RBV dose was 800 mg/day (divided into 2 doses)
Source: Adapted from Applicant's Summary of Clinical Safety (page 15)

Cirrhosis determination in Gilead Phase 3 trials was done using the following criteria:

a) Cirrhosis is defined as any one of the following:
   - Liver biopsy showing cirrhosis
   - Fibroscan (in countries where locally approved) showing cirrhosis or results >12.5 kPa
   - A FibroTest® score of >0.75 AND an AST:platelet ratio index (APRI) of >2 performed during screening

b) Absence of cirrhosis is defined as any one of the following:
   - Liver biopsy within 2 years of Screening showing absence of cirrhosis
   - Fibroscan (in countries where locally approved) with a result of ≤12.5 kPa within ≤ 6 months of Baseline/Day 1
   - A FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 performed during Screening

Biopsy results were considered to be definitive and superseded results obtained by other detection methods. If biopsy results were not available for a given subject and results from transient elastography and blood tests were conflicting for that subject, then the subject was deemed cirrhotic.

The Applicant was asked to provide the numbers and percentages of subjects in Phase 3 trials categorized by each method of cirrhosis determination. The data submitted by the Applicant on September 04, 2013 is noted below.

Subjects, N (%)	FISSION (P7977-1231) (N=499)	POSITRON (GS-US-334-0107) (N=278)	FUSION (GS-US-334-0108) (N=201)	NEUTRINO (GS-US-334-0110) (N=327)
Liver biopsy	247 (49%)	167 (60%)	116 (58%)	232 (71%)
Transient Elastography	139 (28%)	38 (14%)	34 (17%)	0
Serum biomarkers[1]	108 (22%)	73 (26%)	50 (25%)	91 (28%)
Missing	5 (1%)	0	1 (.5%)	4 (1%)

[1] FibroTest® score of > 0.75 AND an AST:platelet (APRI) ratio of > 2 performed during screening indicated cirrhosis; FibroTest® score of ≤ 0.48 AND APRI of ≤ 1 performed during screening indicated the absence of cirrhosis.

The majority of the subjects (who received at least one dose) in the pivotal Phase 3 trials had cirrhosis determination based on liver histology.

5.2 Review Strategy

This reviewer, Dr. Poonam Mishra, is the primary clinical reviewer for this NDA. The clinical and statistical reviewer collaborated extensively during the review process, and a number of the analyses included in this review were performed by the FDA Statistical Reviewer (Statistical Review by Dr. Karen Qi/ Division of Biometrics). In addition, there were significant interactions with the FDA clinical pharmacology, clinical microbiology,

toxicology, and product evaluation groups. Their assessments are summarized in this document in the relevant sections, but complete descriptions of their findings are available in their respective discipline reviews.

This NDA application was part of a pilot project "JumpStart" being undertaken by Computational Science Center (CSC) at Center for Drug Evaluation and Research (CDER). The data quality fitness and some of the analyses outputs for the pivotal trials were provided by the project team and the CSC staff.

5.3 Discussion of Individual Studies/Clinical Trials

This section describes the individual Phase 2 and pivotal Phase 3 trials. The pertinent efficacy and safety results from dose-ranging and duration-finding Phase 2 trials; and from three non-Gilead sponsored trials are included in this section. The safety data on the four individual pivotal Phase 3 trials are also discussed in this section. The efficacy results from pivotal Phase 3 trials are discussed in Section 6 (Review of Efficacy). The integrated safety data from the four pivotal Phase 3 clinical trials are presented in Section 7 (Review of Safety). The results for trials in HCV special populations are discussed in Section 7.4.5 (Special Safety studies/Clinical Trials).

Phase 2 Trials

Dose, duration, and combination regimens of sofosbuvir were explored in five Phase 2 clinical trials: P7977-0221, P7977-0422 (PROTON), P7977-0523 (ELECTRON), P7977-0724 (ATOMIC), and P2938-0721 (QUANTUM). The results for these trials have been summarized from the review of clinical study reports provided in the NDA submission. No independent analyses of safety or efficacy were done for the data from Phase 2 trials.

Study P7977-0221

This Phase 2a, multicenter, randomized, double-blind trial evaluated the safety of sofosbuvir (SOF) in combination with PEG+RBV in treatment-naive subjects with genotype 1 HCV infection.

Sixty-four subjects were randomized to parallel treatment groups to receive one of three SOF doses (100, 200, or 400 mg) or matching placebo once daily based upon stratification for IL28B genotype (CC or non-CC). Subjects received SOF or placebo on Days 0 to 27. Subjects also received treatment with PEG 180 µg weekly + RBV 1000 or 1200 mg (divided daily dose) starting on Day 0 of the trial which continued for 48 weeks. Subjects were followed for 24 weeks after the end of treatment to assess SVR at 12 and 24 weeks (SVR12 and SVR24).

A total of 63 subjects received at least one dose of study drug: SOF 100 mg (16 subjects), SOF 200 mg (18 subjects), SOF 400 mg (15 subjects), or placebo (14 subjects) in combination with PEG+RBV. Of the 63 dosed subjects, 17 subjects did not complete 48 weeks of PEG+RBV treatment. Reasons for study discontinuation were generally similar and distributed across the four treatment groups. Overall, demographic and baseline characteristics were similar among the four treatment groups with no notable differences. Most subjects (82.5%) had baseline HCV RNA levels > 800,000 IU/mL, genotype 1a infection (81%), and IL28B non-CC allele (73%).

SVR12 and SVR24 rates were greatest in the SOF 200 mg+PEG+RBV (72% and 83%, respectively) and 400 mg+PEG+RBV (87% and 80%, respectively) groups versus the SOF 100 mg+PEG+RBV (56% and 56%, respectively) and placebo+PEG+RBV groups (50% and 43%, respectively).

No viral breakthrough was observed in any subject in any of the SOF dose groups through the 28 days of SOF dosing. Eight subjects (6 SOF+PEG+RBV subjects and 2 placebo+PEG+RBV subjects) had viral breakthrough during the PEG+RBV treatment period. For the 6 SOF+PEG+RBV subjects, breakthrough occurred relatively soon after discontinuing SOF (at Week 6 or 8). Ten subjects (7 SOF+PEG+RBV and 3 placebo+PEG+RBV subjects) relapsed during follow-up visits. Of the 7 relapsed SOF+PEG+RBV subjects, 5 received SOF 100 mg+PEG+RBV, 1 received SOF 200mg+PEG+RBV, and 1 received SOF 400 mg+PEG+RBV.
No deaths, serious adverse events (SAEs), pregnancies, or discontinuations of study drug due to adverse events (AEs) were reported in the SOF treatment period of this trial. All AEs were reported as Grade 1 (mild) or 2 (moderate) in severity, and were consistent with the known safety profile of PEG+RBV.

As SVR12 and SVR24 rates were lowest, and breakthrough and relapse rates were highest, in the SOF 100 mg+PEG+RBV group, SOF 200 mg+PEG+RBV and 400 mg+PEG+RBV were the therapeutic doses carried forward for further evaluation in Study P7977-0422 over a longer treatment duration.

Study P7977-0422 (PROTON)

This Phase 2b trial evaluated the safety of SOF+PEG+RBV in noncirrhotic, treatment-naive subjects with genotypes 1, 2, and 3 HCV infection. A total of 122 subjects with genotype 1 HCV infection, stratified for IL28B genotype (CC or non-CC) and baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL) were randomized to receive SOF 200 or 400 mg or matching placebo once daily in combination with PEG 180 µg weekly + RBV 1000 or 1200 mg daily (divided dose) for 12 weeks. Subjects with genotype 1 HCV infection were randomized in a 2:2:1 ratio. Subjects with genotype 1 HCV infection who achieved an extended rapid virologic response (eRVR; HCV RNA < lower limit of detection [LOD] at Weeks 4 through 12) received an additional 12 weeks of PEG+RBV. Subjects with genotype 1 HCV infection who did not achieve an eRVR received an

additional 36 weeks of PEG+RBV. Subjects with genotype 1 HCV infection who received Placebo+PEG+RBV and achieved an eRVR still received an additional 36 weeks of PEG+RBV.

In addition, 25 treatment-naive subjects with genotype 2 (n = 15) or 3 (n = 10) HCV infection received open-label SOF 400 mg once daily in combination with PEG+RBV for 12 weeks, with no PEG+RBV follow-up.

Subjects were followed for 24 weeks after the end of treatment to assess SVR at 12 and 24 weeks (SVR12 and SVR24).

A total of 121 genotype 1 HCV-infected subjects received at least one dose of study drug: SOF 200 mg (48 subjects), SOF 400 mg (47 subjects), and placebo (26 subjects) in combination with PEG+RBV. A total of 25 genotype 2 or 3 HCV-infected subjects were enrolled and received open-label SOF 400 mg in combination with PEG+RBV. Overall, the demographic and baseline characteristics were comparable between the four treatment groups. Most subjects (76%) had a baseline HCV RNA ≥ 800,000 IU/mL, had genotype 1a HCV infection (63%), and had IL28B non-CC allele. Most subjects (77%) had portal fibrosis based on the liver biopsy. No subject had cirrhosis.

SVR 24 rates of 90-92% were observed with sofosbuvir 200 and 400 mg, in combination with PEG and RBV, in subjects infected with HCV genotype 1, 2, or 3. In genotype 1 HCV-infected subjects, virologic breakthroughs during treatment with PEG+RBV following treatment with SOF+PEG+RBV were more common in the SOF 200 mg+PEG+RBV group compared with the SOF 400 mg+PEG+RBV group, suggesting that the SOF 400 mg dose may provide greater suppression of viral activity.

Seven treatment-emergent SAEs were reported in five subjects in the SOF/placebo treatment period of this trial: retinal vein occlusion (SOF 200 mg+PEG+RBV), lymphangitis (SOF 400 mg+PEG+RBV), acute myocardial infarction (SOF 400 mg+PEG+RBV), depression and suicidal ideation (SOF 400 mg+PEG+RBV), and chest pain and ST segment elevation on ECG (placebo+PEG+RBV). Except for one SAE (lymphangitis) that was considered to be unrelated to all drugs, all of these SAEs were considered to be related to PEG, and/or RBV, but not SOF or placebo. No subjects in the genotype 2 or 3 SOF 400 mg+PEG+RBV group experienced an SAE. The retinal vein occlusion was the only treatment-emergent SAE that did not resolve. Seventeen treatment-emergent AEs leading to discontinuation of any drug were reported in 8 subjects. Three subjects, all in the SOF 400 mg+PEG+RBV group, had AEs leading to discontinuation of SOF: SAE of acute myocardial infarction (subject had an ongoing history of atypical chest pain, further discussed in Section 7.2.6), depression and suicidal ideation (SAEs, subject had a history of ongoing depression), and aphthous stomatitis. These four events were considered by the investigator to be unrelated to SOF or placebo, but related to PEG and/or RBV. There were no deaths reported in the trial and one subject (placebo+PEG+RBV group) had a confirmed ongoing pregnancy

during the trial. Overall, the AE and laboratory profile observed was consistent with that previously reported for PEG and RBV.

Study P7977-0724 (ATOMIC)

This Phase 2b, multicenter, open-label, randomized, duration-finding trial evaluated the efficacy and safety of two treatment durations (12 and 24 weeks) of SOF 400 mg in combination with PEG+RBV in noncirrhotic, treatment-naive subjects with genotypes 1, 4, 5, or 6 HCV infection. A total of 332 subjects with genotype 1 HCV infection were randomized in a 1:2:3 ratio into one of three open-label treatment groups to receive SOF 400 mg once daily + PEG 180 µg weekly + RBV 1000 or 1200 mg (divided daily dose) for 12 (Groups A and C) or 24 weeks (Group B). Randomization was stratified by IL28B genotype (CC or non-CC) and baseline HCV RNA levels (< 800,000 or ≥ 800,000 IU/mL). No subjects with genotype 5 or indeterminate genotype HCV infection were enrolled.

To investigate the therapeutic role of RBV in the absence of PEG, subjects in Group C were randomized again after the initial 12 weeks of treatment to receive further treatment with either SOF 400 mg monotherapy for 12 weeks or SOF 400 mg once daily + RBV 1000 or 1200 mg (divided daily dose) for 12 weeks (Groups C1 or C2). In addition, 17 subjects with genotype 4 or 6 HCV infection were enrolled into Group B and received SOF 400 mg once daily + PEG 180 µg weekly + RBV 1000 or 1200 mg daily (divided dose) for 24 weeks.

Subjects were followed for 24 weeks after discontinuation of therapy to determine if an SVR24 was achieved, as well as to determine the presence of any drug-resistant variants. To evaluate the primary efficacy endpoint of SVR24, point estimates and 2-sided 95% CIs of the between-treatment-group differences in SVR24 (Group B – Group A; Group C – Group A) were constructed using stratum-adjusted Mantel-Haenszel (MH) proportions.

The demographics of the five treatment groups were comparable. The disease characteristics were also comparable among treatment groups. The majority of subjects in all groups had the IL28B CT allele (50−64%). The relative proportion of subjects with the IL28B CC versus non-CC allele was similar among groups.

SVR24 rates of > 90% in genotype 1 HCV-infected subjects were achieved in all treatment groups. There was no clinically meaningful difference in SVR24 rates between Groups C1 and C2. No subject experienced relapse between SVR12 and SVR24. The SVR24 rate in genotype 4 and 6 subjects (14 of 16 subjects [87.5%]) was similar to that in genotype 1 HCV-infected subjects (101 of 109 [92.7%]). All five subjects with genotype 6 HCV infection completed 24 weeks of study drug treatment and achieved SVR4, SVR12, and SVR24. Nine of the 11 subjects with genotype 4 HCV

infection completed 24 weeks of study drug treatment and achieved SVR4, SVR12, and SVR24.

Twelve weeks of SOF 400 mg+PEG+RBV was as effective as 24 weeks SOF 400 mg+PEG+RBV for the treatment of genotype 1 HCV-infected subjects as evidenced by SVR12 and SVR24 rates > 90%. No subject relapsed between SVR12 and SVR24, showing the durability of SVR12.

Mean duration of exposure to study drug was 11.4 weeks for Group A; 21.3 weeks for Group B; and 23.1 weeks for Group C and showed that most subjects were exposed to study drug for planned duration of treatment for the treatment group (Group A = 12 weeks and Groups B/C = 24 weeks).The majority of subjects in all groups had at least one AE. Most AEs were Grade 1 or 2 in severity, and were typical of the expected safety profile of PEG+RBV.

Grade 3 or higher AEs were reported by < 18% of subjects in all treatment groups and the frequency was comparable among treatment groups. Grade 4 AEs were reported by Subject #1040-7223 in Group A (road traffic accident, SAE), Subject #1009-7421 in Group B (pyelonephritis, SAE) and by two subjects in Group C1 (#1033-7090 and #1008-7428; neutropenia). Besides neutropenia, fatigue was the only other Grade 3 AE that was reported in ≥3 subjects in any treatment group. The majority of Grade 3 AEs of neutropenia, fatigue, and anemia were considered related to at least PEG+RBV study drug. No Grade 3 AEs of neutropenia, fatigue, and anemia were considered related to sofosbuvir only.

Thirteen treatment-emergent SAEs were reported in 12 subjects: two subjects (3.8%) in Group A, six subjects (4.8%) in Group B, and four subjects (2.6%) in Group C (two subjects each in both Groups C1 and C2). Nine SAEs were considered unrelated to study drug treatment (arrhythmia – details in Section 7.2.6, colitis ischemic, chest pain, cholecystitis acute, cholelithiasis, alcohol poisoning, road traffic accident, costochondritis, and hip arthroplasty). Four SAEs of anemia, autoimmune hepatitis (details in Section 7.4.2), pyelonephritis, and pancytopenia were reported as related to PEG+RBV study drug (but unrelated to sofosbuvir). Two SAEs (autoimmune hepatitis and chest pain) led to permanent discontinuation of study drug. No deaths were reported.

Study P7977-0523 (ELECTRON)

This Phase 2a, open-label trial evaluated different treatment regimens of SOF alone and in combination with RBV with and without PEG. This submission includes the data for Parts 1, 2, and 3 (Groups 1−9). In Part 1 (Groups 1−4) and 2 (Group 6) of this trial, the potential to achieve SVR following treatment with SOF 400 mg once daily + RBV 1000 or 1200 mg daily (divided dose) with shortened PEG therapy (180 µg weekly) or the absence of PEG was evaluated in noncirrhotic, treatment-naive subjects with

genotype 2 or 3 HCV infection. In Part 2 (Group 5), SOF 400 mg once daily alone was evaluated in noncirrhotic, treatment-naive subjects with genotype 2 or 3 HCV infection. In Part 2 (Group 7), SOF 400 mg once daily + RBV 1000 or 1200 mg daily (divided dose) was evaluated in noncirrhotic subjects with genotype 1 HCV infection who demonstrated null response (defined as < 2 $\log_{10}$ IU/mL decrease from baseline in HCV RNA) following previous PEG+RBV therapy. For Part 3, two treatment groups were added to evaluate SOF 400 mg once daily + RBV 1000 or 1200 mg daily (divided dose) for 12 weeks in treatment-experienced subjects with genotype 2 or 3 HCV infection and treatment-naive subjects with genotype 1 HCV infection. In this trial, SOF 400 mg was administered orally once daily for 8 or 12 weeks, according to treatment group assignment. This trial was not designed to evaluate formal statistical hypotheses.
All but one subject completed the trial as assigned by treatment group. One subject (Subject 1030-5047) discontinued PEG at Day 29 due to an AE of depression; but completed treatment with SOF+RBV for 12 weeks (Group 4). The event was considered probably related to PEG, unlikely related to SOF, and not related to RBV.

No deaths were reported. Three SAEs were reported: angina pectoris (Subject #1031-5070 - details in Section 7.2.6), urethral injury (Subject #1030-5137), and furuncle (Subject #1030-5039). Only urethral injury occurred during treatment in a treatment-naive subject with genotype 1 HCV infection who received SOF+RBV for 12 weeks (Group 8). The two other SAEs occurred during follow-up. All SAEs were considered not related to SOF.

Hematology laboratory abnormalities were more common among subjects who received PEG than in subjects who did not receive PEG. For subjects who received SOF in combination with PEG+RBV (Groups 2−4 and 6), the most frequently reported Grade 3 and 4 laboratory abnormalities were decreased hemoglobin levels and neutrophil counts. No Grade 4 laboratory abnormality of decreased hemoglobin levels was reported. For subjects who received SOF alone and in combination with RBV (Groups 1, 5, and 7−9) one Grade 4 laboratory abnormality of decreased lymphocytes was reported in a subject receiving SOF monotherapy (Group 5). The most frequently reported Grade 3 hematology laboratory abnormality was decreased hemoglobin levels. Three Grade 3 chemistry laboratory abnormalities were reported in subjects receiving SOF alone or in combination with RBV: elevated creatine kinase, elevated ALT, and elevated total bilirubin. No AE was associated with these laboratory abnormalities.

Study P2938-0721 (QUANTUM)

This Phase 2 blinded trial evaluated the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of SOF+RBV in subjects with chronic HCV infection. For this submission, only data for the SOF 400 mg + RBV treatment regimens (Groups C and G) through follow-up Week 12 are included. Following screening, 50 treatment-naive subjects with genotype 1, 2, or 3 HCV infection (genotype 1, 38 subjects and genotype 2 or 3, 12 subjects) were randomized to Groups C and G in

equal ratios. Randomization was stratified by genotype (i.e., genotype 1a vs genotype 1b vs other), baseline HCV RNA (< 6 $\log_{10}$ or ≥ 6 $\log_{10}$ IU/mL), and cirrhosis (present or absent). Three subjects had cirrhosis at screening: 1 of 25 subjects (4%) in Group C and 2 of 25 subjects (8%) in Group G. Subjects in Group C received SOF 400 mg once daily + RBV 1000 or 1200 mg (divided daily dose) for 12 weeks and subjects in Group G received SOF 400 mg once daily + RBV 1000 or 1200 mg (divided daily dose) for 24 weeks. The primary efficacy endpoint was SVR12.

Sofosbuvir 400 mg in combination with RBV given for 12 weeks was shown to be as effective as 24 weeks of treatment in achieving SVR in subjects with genotypes 1 through 3 HCV (56% versus 52%, respectively). Virologic relapse occurred in a similar proportion of subjects who received either 12 or 24 weeks of sofosbuvir+RBV treatment (i.e., 39% and 44%, respectively).

Similar safety profile was observed in the 12- and 24-week treatment groups. The majority of subjects in all groups had at least 1 AE and 1 laboratory abnormality, generally Grade 1 or Grade 2 in severity, and comparable within the sofosbuvir+RBV groups. In the sofosbuvir+RBV groups the most frequent AEs (and AEs considered related to study drug) were fatigue, nausea, headache, and insomnia. In the 24-week sofosbuvir+RBV group, two of 25 subjects (8%) experienced four Grade 3 AEs. Two of these events (bronchitis and chest pain) were also considered SAEs and unrelated to study drug. No other Grade 3 or 4 AEs or SAEs were reported in the sofosbuvir+RBV groups. Adverse events that led to study drug discontinuation of sofosbuvir+RBV included decreased appetite (Grade 2, 1 subject) reported in the 12-week treatment group.

Brief Description of Non-Gilead Sponsored Trials

National Institute of Allergy and Infectious Diseases (NIAID)-Sponsored Study 11-I-0258

This NIAID-sponsored Phase 1/2a, randomized, controlled trial evaluated the efficacy, safety, and tolerability of SOF in combination with full- or low-dose RBV in treatment-naïve subjects with genotype 1 HCV infection. The trial was divided into 2 parts. In Part 1, 10 subjects received SOF 400 mg once daily + RBV 1000 or 1200 mg (divided daily dose) for 24 weeks. In Part 2 of the trial, 50 subjects were randomized in a 1:1 ratio to receive either 24 weeks of SOF 400 mg once daily +RBV 1000 or 1200 mg (divided daily dose) (Group A) or 24 weeks of SOF 400 mg once daily + RBV 600 mg (Group B). Randomized subjects were predominantly black (82%), obese (52%), IL28 CT/TT genotype (84%), genotype-1a (72%), high HCV RNA (60%) and 26% had advanced liver disease.

The abbreviated clinical study report was included in the current NDA submission and the results were also recently published (*JAMA*. 2013; 310(8):804-811). In the first part

of the trial, SVR24 was 90% (95% CI, 55%-100%). In the second part, SVR24 rates were 68% (95% CI, 46%-85%) in the weight-based ribavirin group and 48% (95% CI, 28%-69%) in the low-dose ribavirin group. The most frequent adverse events reported were headache, anemia, fatigue, and nausea. There were seven grade 3 adverse events including anemia, neutropenia, nausea, hypophosphatemia, and cholelithiasis or pancreatitis. No one discontinued treatment due to adverse events.

Janssen-Sponsored Study HPC2002 (COSMOS)

This Janssen-sponsored Phase 2, multicenter, randomized, open-label trial is evaluating the efficacy and safety of SOF and the nonstructural protein 3/4A (NS3/4A) PI simeprevir (SMV; TMC435) with or without RBV for 12 or 24 weeks in treatment-naive subjects with genotype 1 HCV infection or subjects with genotype 1 HCV infection who had a null response with prior PEG+RBV treatment. Two cohorts were sequentially enrolled. Cohort 1 (N=80) included subjects without advanced hepatic fibrosis/cirrhosis who were null responders to prior PEG+RBV therapy, and Cohort 2 (N=87) included subjects with advanced hepatic fibrosis/cirrhosis who were null responders to prior PEG+RBV therapy or treatment-naïve subjects. All subjects received a treatment regimen of SOF 400 mg once daily + SMV 150 mg once daily + RBV 1000 or 1200 mg daily (divided dose). In each cohort, subjects were randomized in a 2:1:2:1 ratio to receive SOF+SMV+RBV for 24 weeks; SOF+SMV for 24 weeks; SOF+SMV+RBV for 12 weeks; and SOF+SMV for 12 weeks, respectively. The primary efficacy endpoint was the number of subjects with SVR12. This submission only includes available preliminary data from a subset of Cohort 1.

Interim SVR4 results from Cohort 2, including treatment naïve or previous null responder HCV patients all with METAVIR score F3-F4 were reported in a press release by the company Medivir on August 28, 2013. It was noted that the treatment for 12 weeks with simeprevir and sofosbuvir, with or without ribavirin, led to SVR4 rates of 96% (26/27) and 100% (14/14), respectively. Interim results from Cohort 1 of the COSMOS trial, which include only prior null responder HCV patients (METAVIR F0-F2) demonstrated SVR8 rates of 96% (26/27) and 93% (13/14) after 12 weeks treatment simeprevir and sofosbuvir with and without ribavirin, respectively. (http://www.medivir.se/v5/en/uptodate/pressrelease.cfm).

BMS-Sponsored Study AI444040

This BMS-sponsored Phase 2a, randomized, open-label, 2-stage, parallel-group trial evaluated the efficacy and safety of the combination of SOF and daclatasvir (DCV; BMS-790052; an NS5A inhibitor) with or without RBV for 12 or 24 weeks in noncirrhotic, treatment-naïve subjects with genotype 1, 2, or 3 HCV infection or 12 weeks in subjects with genotype 1 HCV infection who have failed therapy with telaprevir or boceprevir.

Subjects received SOF 400 mg once daily + DCV 60 mg once daily with or without RBV (1000 or 1200 mg daily [divided dose] for subjects with genotype 1 HCV infection or 800 mg twice a day (BID) for subjects with genotype 2 or 3 HCV infection). In Groups A (N=15) and B (N=16), treatment-naive subjects with genotype 1 HCV infection or genotype 2 or 3 HCV infection received a lead-in of SOF 400 mg once daily for 7 days (lead-in) then SOF+DCV for 23 weeks, respectively. In Groups C (N=14) and E (N=15) and Groups D (N=14) and F (N=14), treatment-naive subjects with genotype 1 HCV infection and genotype 2 or 3 HCV infection received SOF+DCV with or without RBV for 24 weeks, respectively. In Groups G (N=41) and H (N=41), treatment-naive subjects with genotype 1 HCV infection received SOF+DCV with or without RBV for 12 weeks. In Group I and J, subjects with genotype 1 HCV infection who had previously failed treatment with telaprevir or boceprevir received SOF+DCV or without RBV for 24 weeks, respectively. The primary efficacy endpoint was the percentage of subjects with SVR12. This submission includes currently available efficacy and safety data from Groups A through H only.

For the treatment-naive subjects with genotype 2 or 3 HCV infection, the SVR12 rates were 88%, 93%, and 86% following treatment with SOF+DCV with SOF Lead-in, SOF+DCV, and SOF+DCV+RBV for 24 weeks, respectively. For the treatment-naive subjects with genotype 1 HCV infection, the SVR12 rates were 100% following treatment with SOF+DCV with SOF Lead-in, SOF+ DCV, and SOF+DCV+RBV for 24 weeks. For the treatment-naive subjects with genotype 1 HCV infection, the SVR4 rates were 98% and 95% following treatment with SOF+DCV and SOF+DCV+RBV for 12 weeks, respectively.

Treatment with SOF+DCV with or without RBV for 12 or 24 weeks was generally well tolerated. A total of 9 SAEs were reported (4 overdoses classified as SAEs were also reported). Two subjects discontinued treatment due to AE: 1 subject who received SOF+DCV and 1 subject who received SOF+DCV+RBV. Overall, the most frequently reported AEs were fatigue, headache, and nausea. Grade 3 or 4 anemia was only reported in subjects who received RBV: six subjects (21%) and five subjects (12%) who received SOF+DCV+RBV for 12 or 24 weeks, respectively.

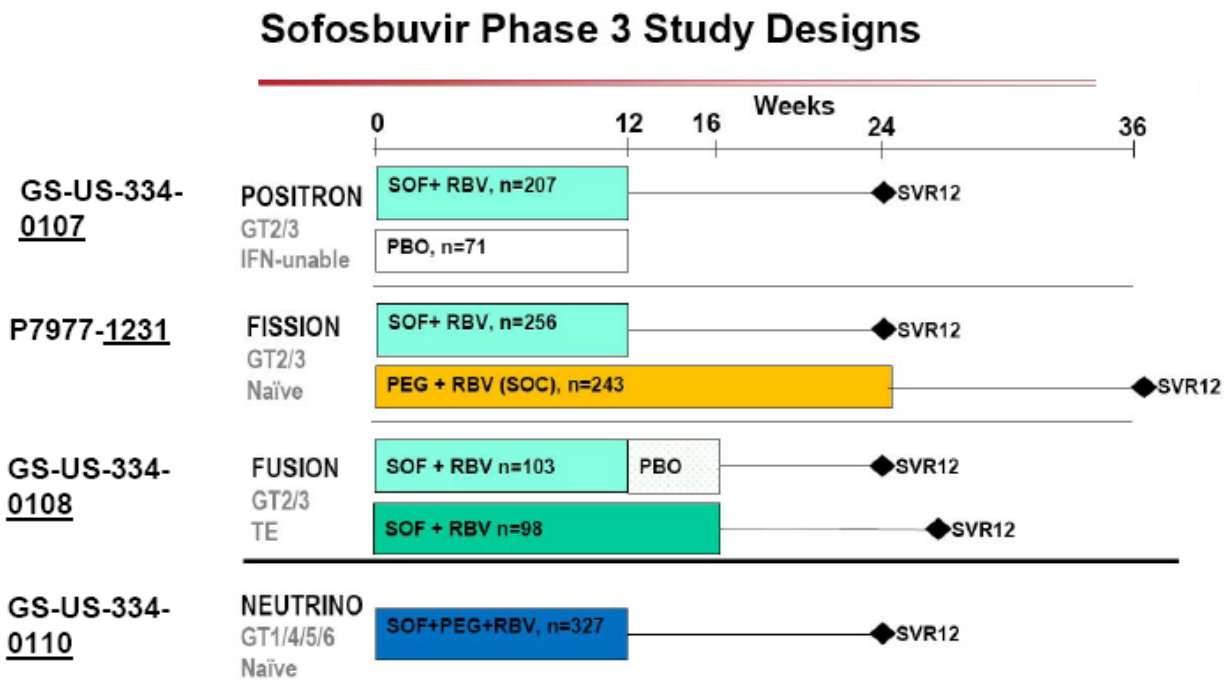
Reviewer's Comment:

The data noted above from three non-Gilead sponsored trials provides supportive evidence of safety and efficacy for sofosbuvir use. However, the complete data from non-Gilead sponsored trials has not been submitted and reviewed as part of this NDA review. Hence, no definite conclusions regarding safety and efficacy of the above noted combination regimens can be made at this time.

Pivotal Phase 3 Trials

The trial designs and the safety results for the four pivotal Phase 3 trials are described in this section. The notable safety events and the integrated safety analyses are discussed in detail in Section 7.3. The efficacy results of Phase 3 trials are discussed in Section 6. The trial designs for four Phase 3 trials: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO) are shown in Figure 1.

Figure 1: Study Schematic of Pivotal Phase 3 trials



Source: Adapted from Gilead's Slide Set (Sofosbuvir Clinical Update FDA Teleconference February 1, 2013)

Study P7977-1231 (FISSION)

Study Title: A Phase 3, Multicenter, Randomized, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 Weeks Compared to Pegylated Interferon and Ribavirin for 24 Weeks in Treatment-Naïve Patients with Chronic Genotype 2 or 3 HCV Infection

The primary objective of this trial as noted by the Applicant was the following:

- To determine the efficacy of sofosbuvir ([SOF] GS-7977; formerly PSI-7977) in combination with ribavirin (RBV) administered for 12 weeks compared with pegylated interferon (PEG)+RBV administered for 24 weeks in treatment-naive subjects with genotype 2 or 3 hepatitis C virus (HCV) infection as assessed by

the rate of sustained virologic response 12 weeks after cessation of therapy (SVR12; HCV RNA less than the limit of quantitation [LLOQ] 12 weeks after cessation of therapy)

Trial Design

This was a Phase 3, randomized, multicenter, open-label active-controlled trial in treatment-naive subjects with genotype 2 or 3 HCV infection. The subjects were enrolled in approximately 1:3 ratio and 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). Approximately 20% of the subjects enrolled had evidence of cirrhosis. Eligible subjects were randomized in a 1:1 ratio to one of following treatment groups:

- SOF+RBV: SOF 400 mg + RBV 1000 mg or 1200 mg (based on baseline body weight) daily for 12 weeks

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

A total of 527 subjects were randomized (263 subjects in SOF+RBV group; 264 subjects in PEG+RBV group). All randomized subjects were enrolled at 90 sites: 61 in the US (including 1 in Puerto Rico), 14 in Australia, 6 in New Zealand, 5 in Canada, 2 in Sweden, 1 in Italy, and 1 in the Netherlands. A total of 499 randomized subjects received treatment in this trial (256 subjects in the SOF+RBV group; 243 subjects in the PEG+RBV group).

Overall, the SOF+RBV treatment regimen seems to be better tolerated than the comparator PEG+RBV treatment regimen. The overall summary of adverse event profile in Study P7977-1231 is shown in Table 5.

Table 5: Overall Summary of Adverse Events in Study P7977-1231 (Safety Analysis Set)

	SOF+RBV 12 Weeks N=256	PEG+RBV 24 Weeks N=243
Number (%) of Subjects Experiencing Any		
Adverse Event (AE)	220 (86)	233 (96)
Treatment-Related AE	183 (72)	228 (94)
Serious Adverse Event (SAE)	7 (3)	3 (1)
Treatment-Related SAE	1 (<1)	0
Grade 3 & 4 AE	17 (7)	45 (19)
Treatment-Related Grade 3 & 4 AE	8 (3)	39 (16)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	3 (1)	29 (12)
AE Leading to Permanent Discontinuation from All Study Drugs	3 (1)	26 (11)
AE Leading to Modification or Interruption of Study Drug	25 (10)	65 (27)
Death	1 (<1)	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

There were a decreased number of treatment-emergent as well as treatment-related AEs observed in the SOF+RBV group compared to the PEG+RBV group (86% vs. 96% and 72% vs. 94% respectively). The frequency of Grade 3 and Grade 4 events, AEs leading to permanent discontinuation of study drugs, and AEs leading to modification or interruption of study drugs were also lower in SOF+RBV group compared to active control group (Table 5). Three subjects discontinued due to AEs in SOF+RBV group. MedDRA preferred terms were: decreased appetite, weight decreased, depression, abnormal dreams, agitation, apathy in one subject; increased CPK (n=1) and chest pain (n=1). The most frequently reported AEs leading to dose modification or interruption of study drug in SOF+RBV group were: anemia (16 subjects), decreased Hgb (3 subjects), and fatigue, nausea, dizziness, dyspnea, and myalgia (2 subjects each). Although the number of subjects with SAE was higher in the SOF+RBV group (n=7) compared to PEG+RBV group (n=3); only one SAE (anemia) was reported as treatment-related (RBV was interrupted). The causality assessments of the investigators seem reasonable. The observed SAEs are shown in Table 6.

Table 6: Serious Adverse Events in Study P7977-1231

MedDRA Preferred Term	Study Day/ Start of AE	Study Day/ End of AE	Subject ID	Treatment Group
Osteomyelitis Chronic	14	23	1224-310678	SOF+RBV 12 Weeks
Allergy To Arthropod Sting	102	102	1226-310481	SOF+RBV 12 Weeks
Cellulitis	38	54	1231-310483	SOF+RBV 12 Weeks
Chest Pain	110	111	1241-310504	SOF+RBV 12 Weeks
Toxicity To Various Agents*	1		1276-310535	SOF+RBV 12 Weeks
Anaemia	20	25	1073-310378	SOF+RBV 12 Weeks
Urinary Tract Infection	48	59	1073-310378	SOF+RBV 12 Weeks
Chronic Obstructive Pulmonary Disease	63	66	1085-310217	SOF+RBV 12 Weeks
Clavicle Fracture	60	116	1188-310524	PEG+RBV 24 Weeks
Rib Fracture	60	116	1188-310524	PEG+RBV 24 Weeks
Pneumothorax	60	116	1188-310524	PEG+RBV 24 Weeks
Infection	67	116	1188-310524	PEG+RBV 24 Weeks
Atrioventricular Block	106	112	1008-310146	PEG+RBV 24 Weeks
Breast Cancer In Situ	29		1002-310443	PEG+RBV 24 Weeks

* Details are provided in Section 7.3.1 (Deaths)
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

There was no life threatening AE reported in the SOF+RBV group. There was only one treatment-emergent death (Subject ID: 1276-310535) observed in this trial (SOF+RBV group). The cause of death in this subject was reported as acute cocaine and heroin intoxication on Study Day 1. The details are provided in Section 7.3.1.

Study GS-US-334-0107

Study Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 Weeks in Subjects with Chronic Genotype 2 or 3 HCV Infection who are Interferon Intolerant, Interferon Ineligible or Unwilling to Take Interferon.

The primary objectives of this trial as noted by the Applicant were the following:

- To determine the efficacy of treatment with GS-7977 + RBV compared to treatment with GS-7977 placebo + RBV placebo as measured by the rate of sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of GS-7977 + RBV compared to placebo control as assessed by review of the accumulated safety data

Trial Design

This is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in subjects with chronic genotype 2 or 3 HCV infection who were interferon intolerant, interferon ineligible, or unwilling to take interferon. Subjects must be unwilling to receive IFN (documented more than 3 months prior to signing of the informed consent), intolerant to IFN as demonstrated during a prior course of treatment, or be ineligible to receive IFN due to medical history.

Eligible subjects were randomized in a 3:1 ratio to one of two treatment arms:

- Arm 1: SOF 400 mg administered once daily + RBV total daily dose of 1000 to 1200 mg administered in a divided daily dose (SOF+RBV)

- Arm 2: SOF placebo administered once daily + RBV placebo administered in a divided daily dose

Randomization was stratified by presence/absence of cirrhosis at screening. Approximately 16% of the subjects enrolled had evidence of cirrhosis.

A total of 280 subjects were randomized: 209 to the SOF+RBV group and 71 to the placebo group. All randomized subjects were enrolled at 54 sites: 43 in the US (including 1 in Puerto Rico), 5 in Canada, 4 in Australia, and 2 in New Zealand. Most of the subjects (228) were enrolled in US, followed by Canada (23), Australia (21), and New Zealand (6). A total of 278 subjects were included in the safety analysis set (207 subjects in the SOF+RBV group and 71 subjects in the placebo group).

The treatment period duration was 12 weeks for all subjects. Subjects assigned to receive placebo who completed the 12-week treatment period and the posttreatment Week 4 visit were offered treatment with SOF+RBV for 12 weeks in Study GS-US-334-0109 (open-label trial of GS-7977+ RBV with or without PEG in subjects who participated in prior SOF-containing Gilead HCV trials).

The majority of subjects in the trial experienced at least 1 treatment-emergent AE; 89% in the SOF+RBV group and 78% in the placebo group respectively (Table 7).

Table 7: Overall Summary of Adverse Events in Study GS-US-334-0107 (Safety Analysis Set)

	SOF+RBV 12 Weeks N=207	Placebo N=71
Number (%) of Subjects Experiencing Any		
Adverse Event (AE)	185 (89)	55 (78)
Treatment-Related AE	150 (73)	40 (56)
Serious Adverse Event (SAE)	11 (5)	2 (3)
Treatment-Related SAE	1 (<1)	0
Grade 3 & 4 AE	17 (8)	1 (1)
Treatment-Related Grade 3 & 4 AE	3 (1)	0
AE Leading to Permanent Discontinuation from Any of the Study Drugs	5 (2)	3 (4)
AE Leading to Permanent Discontinuation from SOF/SOF Placebo	4 (2)	3 (4)
AE Leading to Modification or Interruption of Study Drugs (Any Study Drug)	29 (14)	0
Death	0	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

Adverse events such as fatigue, insomnia, anemia, and dyspnea were observed at a higher rate in the SOF+RBV group. These AEs could be attributed to anemia secondary to RBV therapy. Most AEs were graded as either Grade 1 (mild) or Grade 2 (moderate) in severity. No subjects in the SOF+RBV group had a Grade 4 AE.

The observed SAEs are shown in Table 8 below. Only one subject experienced a treatment-related SAE (peripheral edema and eczema, 28 days after the last dose of study drug). The causality assessments of the investigators seem reasonable. The summary of the narrative is provided in Section 7.

Table 8: Serious Adverse Events in Study GS-US-334-0107

MedDRA Preferred Term	Study Day/ Start of AE	Study Day/ End of AE	Subject ID	Treatment Group
Hepatic Neoplasm Malignant	57		1055-7271	SOF+RBV 12 Weeks
Hypoglycaemia*	44	45	1069-7352	SOF+RBV 12 Weeks
Hypersensitivity*	22	23	1069-7371	SOF+RBV 12 Weeks
Eczema*	112	119	2074-7398	SOF+RBV 12 Weeks
Oedema Peripheral*	112	119		
Drug Withdrawal Syndrome	20	27	2728-7332	SOF+RBV 12 Weeks
Overdose	20	27		
Non-Cardiac Chest Pain*	104	107	2760-7374	SOF+RBV 12 Weeks
Injury	72	88	4262-7292	SOF+RBV 12 Weeks
Road Traffic Accident	72	72		
Fall	38	39	4322-7257	SOF+RBV 12 Weeks
Spinal Compression Fracture	38	39		
Spinal Compression Fracture	53	55		
Abdominal Abscess*	68	121	4323-7310	SOF+RBV 12 Weeks
Cellulitis*	96	99	4434-7432	SOF+RBV 12 Weeks
Pyrexia*	96	99		
Abnormal Behaviour	32	36	5498-7435	SOF+RBV 12 Weeks
Bile Duct Stone	9		5586-7268	Placebo
Pancreatitis	1	9		
Bronchitis	79	81	5730-7447	Placebo

* Details provided in Section 7.3.2 (Nonfatal Serious Adverse Events)
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

Seventeen (8%) subjects in the SOF+RBV group had a Grade 3 (severe) AE; no subjects in the placebo group had a Grade 3 AE. Fatigue, peripheral edema, and pyrexia were the only Grade 3 AEs reported in more than one subject, each of these AEs occurred in 2 (1%) subjects. Two SOF+RBV subjects experienced one AE each that led to discontinuation and was considered related to study drug;

- Subject #0530-7404 discontinued study drug due to insomnia and
- Subject #0773-7357 discontinued RBV on Day 70, due to a Grade 2 AE of anemia, but completed treatment with SOF and achieved SVR12.

A total of 29 (14%) subjects in the SOF+RBV group had AEs leading to modification or interruption of study drug compared to none of the subjects in the placebo group. The most frequently reported AEs leading to modification or interruption of study drug in the SOF+RBV group were anemia (6%), decreased hemoglobin (2%), and fatigue (2%).

No treatment-emergent deaths were reported in this trial. Two deaths occurred that were not treatment emergent (i.e., did not occur during the study drug treatment period plus 30 days).

- Subject #2074-7350 in the SOF+RBV group died of cardiogenic shock secondary to aortic stenosis 47 days after the last dose of SOF+RBV.
- Subject #5586-7322 in the SOF+RBV group died of metastatic lung cancer 63 days after the last dose of SOF+RBV.

The details of the above noted two death cases are provided in Section 7.3.1.

Reviewer's Comments

The adverse events profile reported in trial GS-US-334-0107 is consistent with what has been previously observed in ribavirin containing regimens. No clustering of events was noted. No specific safety issues are identified to date based on these trial findings.

Study GS-US-334-0108

Study Title: A Phase 3, Multicenter, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of GS-7977 + Ribavirin for 12 or 16 Weeks in Treatment Experienced Subjects with Chronic Genotype 2 or 3 HCV Infection

The primary objectives of this trial as noted by the Applicant were the following:

- To determine the efficacy of treatment with sofosbuvir + ribavirin (SOF+RBV) in each treatment group as measured by the proportion of subjects with sustained virologic response (SVR) 12 weeks after discontinuation of active therapy (SVR12)
- To evaluate the safety and tolerability of SOF+RBV in each treatment group as assessed by review of the accumulated safety data

Trial Design

This is an ongoing Phase 3, randomized, double-blind, multicenter trial. This trial assessed the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment in subjects with chronic genotype 2 or 3 HCV infection who had failed prior treatment with an interferon-based regimen.

Eligible subjects with chronic genotype 2 or 3 HCV infection had screening HCV RNA levels ≥ 10^4 IU/mL, had documentation of the presence or absence of cirrhosis, and had failed prior treatment with an interferon-based regimen. Eligible subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups.

- SOF+RBV 12 Week group: SOF 400 mg administered once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg or 1200 mg for subjects

weighing ≥ 75 kg administered in a divided daily dose for 12 weeks, followed by SOF placebo administered once daily + RBV placebo administered in a divided daily dose for 4 weeks

- SOF+RBV 16 Week group: SOF 400 mg administered once daily + RBV total daily dose of 1000 mg for subjects weighing < 75 kg or 1200 mg for subjects weighing ≥ 75 kg administered in a divided daily dose for 16 weeks

Randomization was stratified by the presence or absence of cirrhosis and HCV genotype (2 or 3) at screening. Approximately 34% of subjects with cirrhosis were enrolled.

A total of 202 subjects were randomized in the trial: 103 subjects to the SOF+RBV 12 Week group and 99 subjects to the SOF+RBV 16 Week group. All randomized and treated subjects were enrolled at a total 57 sites: 43 sites in the US (including 1 in Puerto Rico), 12 sites in Canada, and 2 sites in New Zealand. Sites in the US randomized and treated the majority of subjects (150 subjects), followed by Canada (43 subjects), and New Zealand (8 subjects). A total of 201 subjects were included in the safety analysis set (103 subjects in the SOF+RBV 12 Week group and 98 subjects in the SOF+RBV 16 Week group).

The treatment period duration was 16 weeks in both treatment groups, with the SOF+RBV 12 Week group receiving matching placebos between Weeks 12 and 16.

Majority of the subjects in the Study GS-US-334-0108 experienced at least one treatment-emergent AE as shown in Table 9.

Table 9: Overall Summary of Adverse Events in Study GS-US-334-0108 (Safety Analysis Set)

	SOF+RBV 12 Weeks + Placebo 4 weeks N=103	SOF+RBV 16 Weeks N=98
Number (%) of Subjects Experiencing Any		
Adverse Event (AE)	92 (89)	86 (88)
Treatment-Related AE	75 (73)	75 (77)
Serious Adverse Event (SAE)	5 (5)	3 (3)
Treatment-Related SAE	0	0
Life Threatening AE	0	1
Grade 3 & 4 AE	8 (8)	4 (4)
Treatment-Related Grade 3 & 4 AE	4 (4)	2 (2)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	1 (1)	0
AE Leading to Permanent Discontinuation from SOF/SOF Placebo	1 (1)	0
AE Leading to Modification or Interruption of Study Drug	9 (9)	7 (7)
Death	0	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

The incidence of AEs was comparable between the two treatment groups (89% in the SOF+RBV 12 Weeks + Placebo 4 Weeks group vs. 88% in SOF+RBV 16 Weeks group). Majority of the AEs reported in the Study GS-US-334-0108 were Grade 1 (mild) or Grade 2 (moderate) in severity. No treatment-emergent deaths were reported in this trial. No subjects in the SOF+RBV 12 Week group had a Grade 4 (life-threatening) AE. Only one subject (Subject #0519-1532) in the SOF+RBV 16 Week group had a Grade 4 AE (opiate overdose), which was reported as serious. The observed serious adverse events in the trial are shown in Table 10 below. None of the reported serious adverse events were considered treatment-related.

Table 10: Serious Adverse Events in Study GS-US-334-0108 (Safety Analysis Set)

MedDRA Preferred Term	Study Day/ Start of AE	Study Day/ End of AE	Subject ID	Treatment Group
Overdose*	126	127	0519-1532	SOF+RBV 16 Weeks
Suicide Attempt	24	43	1069-1587	SOF+RBV 16 Weeks
Non-Cardiac Chest Pain	44	45	2493-1422	SOF+RBV 16 Weeks
Oesophageal Varices Haemorrhage	143	145	0521-1499	SOF+RBV 12 Weeks
Basal Cell Carcinoma	58	121	1055-1438	SOF+RBV 12 Weeks
Hepatic Neoplasm Malignant	131			
Abdominal Pain	87	139	1071-1492	SOF+RBV 12 Weeks
Hepatic Neoplasm Malignant	92			
Pyrexia	87	91		
Upper Limb Fracture	108	110	5367-1489	SOF+RBV 12 Weeks
Hepatic Neoplasm Malignant	113		5586-1449	SOF+RBV 12 Weeks
Portal Vein Thrombosis	113			

* Details provided in Section 7.3.2 (Nonfatal Serious Adverse Events)
SOF=sofosbuvir; RBV=ribavirin
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

A total of 8 subjects (8%) in the SOF+RBV 12 Week group and 3 subjects (3%) in the SOF+RBV 16 Week group were reported to have a Grade 3 (severe) AE. Malignant hepatic neoplasm and anemia were the only Grade 3 AEs reported in more than one subject. Grade 3 malignant hepatic neoplasm was reported for three subjects (2.9%) in the SOF+RBV 12 Week group and none of the subjects in the SOF+RBV 16 Week group. Grade 3 anemia was reported for two subjects (1.9%) in the SOF+RBV 12 Week group and none of the subjects in the SOF+RBV 16 Week group. The incidence of Grade 3 or 4 AEs that were considered related to study drug by the investigator was low (four subjects (3.9%) in the SOF+RBV 12 Week group and two subjects (2%) in the SOF+RBV 16 Week group). See Section 7 (Review of Safety) for further details.

Reviewer's Comment

The overall safety profile of two regimens (i.e. SOF+RBV 12 Weeks + Placebo 4 Weeks compared to SOF+RBV 16 Weeks) evaluated in GS-US-334-0108 was similar. No additional safety issues were identified by extending the treatment duration of sofosbuvir and ribavirin by 4 weeks.

Study GS-US-334-0110

Study Title: A Phase 3, Multicenter, Open-Label Study to Investigate the Efficacy and Safety of GS-7977 with Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naive Subjects with Chronic Genotype 1, 4, 5, or 6 HCV Infection

The primary objectives of this trial as noted by the Applicant were the following:

Primary Objectives

- To determine the efficacy of treatment with sofosbuvir (SOF) + pegylated interferon (PEG) + ribavirin (RBV) as measured by the proportion of subjects with sustained viral response 12 weeks after discontinuation of therapy (SVR12)
- To evaluate the safety and tolerability of SOF+PEG+RBV as assessed by review of the accumulated safety data

Trial Design

This is an ongoing Phase 3, multicenter, open-label trial in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection. Approximately 17% of subjects with cirrhosis were enrolled.

A total of 328 subjects were enrolled at 55 sites in the US; 327 subjects received study drugs and were included in both the safety analysis set and the full analysis set. One subject was enrolled but never returned for the Baseline/Day 1 visit.

Subjects were treated with SOF (400 mg once daily) + PEG (180 µg/week) + RBV (1000 or 1200 mg/day). Treatment duration was 12 weeks.

Table 11 represents an overall summary of treatment-emergent adverse events reported in Study GS-US-334-0110.

Table 11: Overall Summary of Adverse Events in Study GS-US-334-0110 (Safety Analysis Set)

	SOF+PEG+RBV 12 Weeks (N=327)
Number (%) of Subjects Experiencing Any	n (%)
Adverse Event (AE)	310 (95)
Treatment-Related AE	304 (93)
Serious Adverse Event (SAE)	4 (1)
Treatment-Related SAE	2 (<1)
Life Threatening (Grade 4) AE	0
Grade 3 AE	48 (15)
Treatment-Related Grade 3 AE	42 (13)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	8 (2)
AE Leading to Permanent Discontinuation from All Study Drugs	5 (2)
AE Leading to Modification or Interruption of Study Drugs (Any Study Drug)	109 (33)
Death	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

The majority of subjects (95%) had at least one treatment-emergent AE. Ninety three percent subjects had an AE considered to be related to SOF, PEG, or RBV. The three most frequently reported AEs were fatigue (59%, 192 subjects), headache (36%, 118 subjects), and nausea (34%, 112 subjects). Most reported AEs were either Grade 1 (mild) or Grade 2 (moderate) in severity. No Grade 4 AEs were reported in this trial. Grade 3 AEs were reported in 48 subjects (15%) and in 42 of these subjects (13% of all subjects) the AE was considered related to a study drug by the investigator. The most frequently reported Grade 3 AEs were neutropenia (7%, 23 subjects), anemia (2%, 7 subjects), and fatigue and headache (1.5%, 5 subjects each).

Eight SAEs were reported in four subjects (1.2%). Four of these SAEs were assessed as related to a study drug: anemia and cryoglobulinemia (both in Subject #2760-6598) and leukopenia and pyrexia (both in Subject #4308-6454). SAEs are listed in Table 12 and details for Subject #4308-6454 are provided in Section 7.3.2.

Table 12: Serious Adverse Events in Study GS-US-334-0110 (Safety Analysis Set)

MedDRA Preferred Term	Study Day/ Start of AE	Study Day/ End of AE	Subject ID	Treatment Group
Anaemia	48	56	2760-6598	SOF+PEG+RBV 12 Weeks
Cryoglobulinaemia	48	69		
Laryngeal Cancer	114		2760-6606	SOF+PEG+RBV 12 Weeks
Spinal Compression Fracture	93		4139-6404	SOF+PEG+RBV 12 Weeks
Leukopenia*	53	116	4308-6454	SOF+PEG+RBV 12 Weeks
Non-Cardiac Chest Pain*	53	57		
Pyrexia*	53	56		

* Details provided in Section 7.3.2 (Nonfatal Serious Adverse Events)
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Data Tabulation and Analysis Datasets (demo.xpt; adae.xpt)

Five subjects (1.5%) had an AE that led to discontinuation of all study drugs and eight subjects (2.4%) had an AE that led to discontinuation of any study drug. Adverse events that led to a study drug interruption or dose modification of a study drug were reported in 109 subjects (33.3%). There were no deaths reported in this trial.

Reviewer's Comments

The safety profile is consistent with the well documented adverse event profile of pegylated interferon and ribavirin combination regimen. No trends in any specific AE type were observed.

6 Review of Efficacy

Efficacy Summary

Four Phase 3 pivotal trials evaluated the efficacy of sofosbuvir in subjects with chronic HCV infection.

- Study P7977-1231 evaluated the efficacy and safety of SOF+RBV for 12 weeks compared with PEG+RBV for 24 weeks in treatment-naive subjects with genotype 2 or 3 HCV infection. The primary efficacy endpoint was SVR12 and the prespecified non-inferiority margin was met. The overall SVR12 rate in the SOF+RBV group was 67%, which was noninferior to the SVR12 rate of 67% in the PEG+RBV group. The difference (95% CI) in proportions 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 greater than the prespecified noninferiority margin of -15%.

- Study GS-US-334-0107 evaluated the efficacy and safety of SOF+RBV for 12 weeks versus placebo in subjects with genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible, or unwilling to take IFN. A statistically significant proportion of subjects ($p < 0.001$) in the SOF+RBV group achieved SVR12 (78%) compared with placebo (0%).

- Study GS-US-334-0108 evaluated the efficacy and safety of SOF+RBV for 12 or 16 weeks in treatment-experienced subjects with genotype 2 or 3 HCV infection. The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of active therapy. The SVR12 rates in the SOF+RBV 12 Week group was 50% and in the SOF+RBV 16 Week group was 71%, which were each statistically significantly higher ($p < 0.001$) compared to the prespecified null rate of 25%.

- Study GS-US-334-0110 evaluated the efficacy and safety of a SOF+PEG+RBV treatment regimen for 12 weeks in treatment-naïve subjects with genotype 1, 4, 5, or 6 HCV infection. A statistically significant higher proportion of subjects achieved SVR12 (90%, $p < 0.001$) compared with an historical SVR12 rate of 60%.

In summary, two Phase 3 trials demonstrated efficacy in treatment-naive chronic hepatitis C subjects: Study GS-US-334-0110 demonstrated the efficacy of a SOF+PEG+RBV treatment regimen for 12 weeks in subjects with genotype 1 or 4 HCV infection and Study P7977-1231 demonstrated the efficacy of a SOF+RBV treatment regimen for 12 weeks in subjects with genotype 2 or 3 HCV infection; one Phase 3 trial (Study GS-US-334-0107) demonstrated the efficacy of a SOF+RBV-treatment regimen for 12 weeks in subjects with genotype 2 or 3 HCV infection who were IFN intolerant, IFN ineligible, or unwilling to take IFN thus addressing an unmet need for therapy in these patients, and one Phase 3 trial (Study GS-US-334-0108) demonstrated the efficacy of a SOF+RBV treatment regimen for 12 or 16 weeks in treatment-experienced subjects with genotype 2 or 3 HCV infection. All four Phase 3 trials included a subset of subjects with compensated cirrhosis which represents a harder to treat subgroup.

Sofosbuvir and ribavirin combination regimens provide a shorter, interferon-free, more convenient, all oral regimen option for chronic hepatitis C patients with genotype 2 and 3 infection. Sofosbuvir in combination with pegylated interferon and ribavirin provides a shorter 12 week regimen for chronic hepatitis C patients with genotype 1 and 4 infection. A shorter HCV treatment regimen translates into less pegylated interferon and ribavirin associated adverse events, less discontinuation and overall improved sustained virologic response rates. It should be noted that few subjects with genotype 5 (N=1) and genotype 6 (N=6) were included in the clinical trial and the available data are insufficient to make any definite dosing recommendations for patients with genotype 5 or 6.

6.1 Indication

The proposed indication by the Applicant is the following:

> [TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults.

6.1.1 Methods

The efficacy data for the four Phase 3 pivotal trials; P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO) were reviewed in support of the proposed indication.

In general, the following definitions are used to define the treatment experience of chronic hepatitis C patients, which are based on previous responses to PEG-Interferon/RBV.

Treatment Naïve: received no prior therapy for HCV (including interferon or pegylated interferon monotherapy)

Treatment Experienced: who have failed prior therapy with peg-Interferon/RBV (PEG/RBV) with any one of the following treatment response:

- Null Responder: less than 2 $\log_{10}$ reduction in HCV RNA at week 12 of a Peg Interferon/RBV
- Partial Responder: greater than or equal to 2 $\log_{10}$ reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with a Peg-Interferon/RBV
- Responder Relapser: HCV RNA undetectable at end of treatment with a pegylated interferon-based regimen, but HCV RNA detectable within 24 weeks of treatment follow-up.

Statistical Methods

This section describes the statistical methods used by the Applicant and the FDA for the efficacy analysis of the pivotal trials.

Some of the key concepts used by the Applicant are described below:

Imputation for missing values of HCV RNA data

For analyses of categorical HCV RNA data, if a data point was missing and was preceded and followed in time by values that were "< LLOQ TND" then the missing data point was set to "< LLOQ TND." If a data point was missing and preceded and followed

by values that were "< LLOQ detected," or preceded by "< LLOQ detected" and followed by "< LLOQ TND," or preceded by "< LLOQ TND" and followed by "< LLOQ detected," then the missing value was set to "< LLOQ detected;" otherwise the data point was considered a failure (i.e., ≥ LLOQ detected).

Nomenclature Used for Virologic Failures

On-treatment virologic failure (breakthrough, rebound, and nonresponse) and relapse was defined as follows:

- On treatment failure
  - — Breakthrough: HCV RNA ≥ LLOQ after having previously had HCV RNA < LLOQ, while on treatment, confirmed with two consecutive values (note, second confirmation value could be posttreatment), or last available on-treatment measurement with no subsequent follow up values
  - — Rebound: > 1 $\log_{10}$ IU/mL increase in HCV RNA from nadir while on treatment, confirmed with two consecutive values (note, second confirmation value could be posttreatment), or last available on-treatment measurement with no subsequent follow up values
  - — Nonresponse: HCV RNA persistently ≥ LLOQ through the treatment (definition of non response varied between the four phase 3 trials based on treatment regimen and duration)

- Relapse
  - — HCV RNA ≥ LLOQ during the posttreatment period having achieved HCV RNA < LLOQ at the last observed HCV RNA measurement on treatment, confirmed with two consecutive values or last available posttreatment measurement

P7977-1231

The trial hypothesis was that SOF+RBV administered for 12 weeks was noninferior/superior to PEG+RBV administered for 24 weeks. A closed testing procedure was utilized whereby the noninferiority of SOF+RBV to PEG+RBV was tested first. Noninferiority was assessed using a conventional 95% CI approach, with a delta of 0.15. If the lower bound of the 2-sided 95% CI on the difference (SOF+RBV treatment group minus PEG+RBV treatment group) in the response rate was > -15%, then it was to be concluded that SOF+RBV was noninferior to PEG+RBV. If the noninferiority null hypothesis was rejected, then the p-value associated with the test of superiority was to be calculated.

GS-US-334-0107

The primary efficacy analysis assessed whether the proportion of subjects with SVR12 who received SOF+RBV was superior to the proportion of subjects with SVR12 who received placebo. The SVR12 rates between the SOF+RBV and placebo groups were compared using a Cochran-Mantel- Haenszel (CMH) test stratified by the absence or presence of cirrhosis. Superiority was demonstrated if the 2-sided CMH p-value associated with the test of superiority was < 0.05.

GS-US-334-0108

The 2 primary statistical hypotheses of the trial were that the SVR12 rates in both treatment groups were higher than 25%. The 2-sided 95% exact confidence interval (CI) using the Clopper-Pearson method was provided for the SVR12 rate in each of the 2 treatment groups.

GS-US-334-0110

The primary efficacy analysis assessed whether subjects who were administered SOF+PEG+RBV for 12 weeks achieved an SVR12 rate higher than 60%. The p-value associated with the test of superiority was demonstrated if the 2-sided one-sample exact test p-value was less than the 0.05 significance level. The basis for this 60% SVR null rate, as noted by the Applicant, was derived from: 1) an historical SVR rate of approximately 65% calculated from the telaprevir (ADVANCE trial) and boceprevir (SPRINT2 trial) data after adjusting for the targeted proportion of subjects with cirrhosis (approximately 20%) in this trial; and 2) a 5% trade-off in efficacy exchanged for an expected improved safety profile and shorter duration of treatment.

All statistical comparisons for the primary and key secondary efficacy analyses were carried out using the two-sided Cochran-Mantel Haenszel (CMH) chi-square test (adjusted for the baseline stratification factors).

Please refer to Statistical Review by Dr. Karen Qi for detailed assessment of Statistical Methods used by FDA for analyses.

6.1.2 Demographics

P7977-1231

The demographics and baseline characteristics for the subjects in Study P7977-1231 are shown in Table 13. Overall, the demographics and baseline characteristics, such as age, sex, race and BMI, were comparable between the two treatment groups and no major differences were noted.

Table 13: Demographics and Baseline Characteristics for Study P7977-1231 (Safety Analysis Set)

	SOF+RBV 12 Weeks (N=256)	PEG+RBV 24 Weeks (N=243)
Age (Years)		
Mean (SD)	48 (11)	48 (11)
Sex		
Male	171 (67%)	156 (64%)
Female	85 (33%)	87 (36%)
Race		
Black or African American	12 (5%)	5 (2%)
White	223 (87%)	212 (87%)
Asian	14 (6%)	15 (6%)
Others	7 (3%)	11 (5%)
Ethnicity		
Hispanic or Latino	41 (16%)	31 (13%)
Not Hispanic or Latino	215 (84%)	212 (87%)
Region		
North America	180 (70%)	175 (72%)
Canada	15 (6%)	24 (10%)
USA	165 (65%)	151 (62%)
Australia/New Zealand	61 (24%)	59 (24%)
Australia	32 (13%)	29 (12%)
New Zealand	29 (11%)	30 (12%)
Europe	15 (6%)	9 (4%)
Italy	8 (3%)	4 (2%)
Netherlands	3 (1%)	1 (<1%)
Sweden	4 (2%)	4 (2%)
Baseline Body Mass Index (kg/m^2)		
Mean (SD)	28 (5)	28 (6)
Median (Q1, Q3)	27 (24, 31)	27 (24, 31)

Source: FDA Statistical Reviewer

The mean (SD) age was 48 (11.0) years, with an overall age range of 19 to 77 years. The majorities of subjects were white (87%), males (66%) and were recruited in the North America region (71%).

Table 14 shows a summary of baseline disease characteristics for the safety analysis set in Study P7977-1231. The majority of subjects (72%) were genotype 3. The proportion of subjects with genotype 2 or genotype 3 HCV infections was well balanced between the two treatment groups. Most subjects did not have cirrhosis at baseline (80%).

Table 14: Baseline Disease Characteristics for Study P7977-1231 (Safety Analysis Set)

	SOF+RBV 12 weeks (N=256)	PEG+RBV 24 Weeks (N=243)
HCV Genotype		
Genotype 2[1]	73 (28%)	67 (28%)
Genotype 3	183 (72%)	176 (72%)
Cirrhosis[2]		
No	205 (80%)	189 (78%)
Yes	50 (20%)	50 (21%)
Missing	1 (<1%)	4 (2%)
IL28B[2]		
CC	108 (42%)	106 (44%)
CT	121 (47%)	98 (40%)
TT	25 (10%)	38 (16%)
Missing	2 (1%)	1 (<1%)
Baseline HCV RNA (log_{10} IU/mL)		
Mean (SD)	6 (0.8)	6 (0.8)
Median (Q1, Q3)	6 (5.5, 6.7)	6 (5.5, 6.7)
<6 log_{10} IU/mL	108 (42%)	106 (44%)
≥6 log_{10} IU/mL	148 (58%)	137 (56%)
Baseline ALT		
≤1 x ULN	54 (21%)	47 (19%)
>1 x ULN	202 (79%)	196 (81%)
≤1.5 x ULN	118 (46%)	97 (40%)
>1.5 x ULN	138 (54%)	146 (60%)

Source: FDA Statistical Reviewer
[1]There were three subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by population sequencing.
[2] The Applicant did not count the subjects with missing data when calculating the percentage of subjects in each category. The statistical reviewer re-calculated the percentage of subjects in each category including all subjects, i.e., the denominator was the randomized and treated subjects in each treatment group.

GS-US-334-0107

Table 15 represents a summary of the demographics and baseline characteristics for the subjects in the Study GS-US-334-0107. Overall, the demographics and baseline characteristics were generally balanced between the two treatment groups.

Table 15: Demographics and Baseline Characteristics for Study GS-US-334-0107 (Safety Analysis Set)

	SOF+RBV 12 Week (N=207)	Placebo (N=71)
Age (Years)		
Mean (SD)	52 (10)	52 (8)
Sex		
Male	117 (57%)	34 (48%)
Female	90 (44%)	37 (52%)
Race		
Black or African American	9 (4%)	4 (6%)
White	188 (91%)	66 (93%)
Asian	7 (3%)	1 (1%)
Others	3 (2%)	0
Ethnicity		
Hispanic or Latino	19 (9%)	11 (16%)
Not Hispanic or Latino	188 (91%)	60 (85%)
Region		
North America	183 (88%)	68 (96%)
Canada	15 (7%)	8 (11%)
USA	168 (81%)	60 (85%)
Australia/New Zealand	24 (12%)	3 (4%)
Australia	18 (9%)	3 (4%)
New Zealand	6 (3%)	0
Baseline Body Mass Index (kg/m^2)		
Mean (SD)	28 (6)	28 (6)
Median (Q1, Q3)	28 (24, 31)	27 (23, 32)

Source: FDA Statistical Reviewer

The mean (SD) age was 52 (9) years. The majorities of subjects were white (91%) and were recruited in the North America region (88% in the SOF+RBV group and 96% in the placebo group).

Table 16 shows a summary of baseline disease characteristics for the subjects in Study GS-US-334-0107. There were no notable imbalances between the two treatment groups for the baseline disease characteristics.

Table 16: Baseline Disease Characteristics for Study GS-US-334-0107 (Safety Analysis Set)

	SOF+RBV 12 Week (N=207)	Placebo (N=71)
HCV Genotype		
Genotype 2	109 (53%)	34 (48%)
Genotype 3	98 (47%)	37 (52%)
Cirrhosis		
No	176 (85%)	58 (82%)
Yes	31 (15%)	13 (18%)
IL28B		
CC	97 (47%)	29 (41%)
CT	84 (41%)	36 (51%)
TT	26 (13%)	6 (9%)
Baseline HCV RNA (log_{10} IU/mL)		
Mean (SD)	6.3 (0.77)	6.3 (0.76)
Median (Q1, Q3)	6.4 (5.8, 6.8)	6.5 (6.1, 6.8)
<6 log_{10} IU/mL	67 (32%)	17 (24%)
≥6 log_{10} IU/mL	140 (68%)	54 (76%)
Baseline ALT		
≤1 x ULN	52 (25%)	15 (21%)
>1 x ULN	155 (75%)	56 (79%)
≤1.5 x ULN	90 (44%)	29 (41%)
>1.5 x ULN	117 (57%)	42 (59%)
Duration on Prior HCV Treatment		
No	170 (82%)	56 (79%)
≤12 weeks	21 (10%)	8 (11%)
>12 weeks	16 (8%)	7 (10%)
Interferon Classification		
Ineligible	88 (43%)	33 (47%)
Intolerant	17 (8%)	8 (11%)
Unwilling	102 (49%)	30 (42%)

Source: FDA Statistical Reviewer

GS-US-334-0108

The subject demographics and baseline characteristics were comparable between the two treatment groups as displayed in Table 17. The mean (SD) age was 54 (8) years. The majority of the subjects were male (70%), white (87%), non-Hispanic (91%), and from USA sites (76%). The mean BMI (SD) was around 29 (5) kg/m^2.

Table 17: Demographics and Baseline Characteristics for Study GS-US-334-0108 (Safety Analysis Set)

	SOF+RBV 12 Weeks + Placebo 4 Weeks (N=103)	SOF+RBV 16 Weeks (N=98)
Age (Years)		
Mean (SD)	54 (7.7)	54 (7.8)
Sex		
Male	73 (71%)	67 (68%)
Female	30 (29%)	31 (32%)
Race		
Black or African American	5 (5%)	1 (1%)
White	88 (85%)	86 (88%)
Asian	7 (8%)	5 (5%)
Others	3 (3%)	6 (6%)
Ethnicity		
Hispanic or Latino	10 (10%)	8 (8%)
Not Hispanic or Latino	93 (90%)	89 (91%)
Declined to Disclose	0	1 (1%)
Country		
Canada	26 (25%)	17 (17%)
USA	74 (72%)	76 (78%)
New Zealand	3 (3%)	5 (5%)
Baseline Body Mass Index (kg/m^2)		
Mean (SD)	28 (5)	29 (5)
Median (Q1, Q3)	27 (25, 31)	29 (26, 32)

Source: FDA Statistical Reviewer

The baseline disease characteristics were quite similar between the two treatment arms (Table 18). In general, the majority of the subjects (63%) had genotype 3 HCV infection. Approximately 75% of subjects were categorized as having relapse/breakthrough during the prior HCV treatment and 25% were classified as nonresponders to the previous HCV therapy. The majority of the subjects (70%) had non-CC IL28B alleles at baseline.

There were six subjects who were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis instead of genotype 2 HCV infection as determined by LiPA at screening.

Table 18: Baseline Disease Characteristics for Study GS-US-334-0108 (Safety Analysis Set)

	SOF+RBV 12 Weeks + Placebo 4 Weeks (N=103)	SOF+RBV 16 Weeks (N=98)
HCV Genotype		
Genotype 2[1]	39 (38%)	35 (36%)
Genotype 3	64 (62%)	63 (64%)
Cirrhosis		
No	66 (65%)	66 (67%)
Yes	36 (35%)	32 (33%)
IL28B		
CC	31 (30%)	30 (31%)
CT	53 (52%)	56 (57%)
TT	19 (18%)	12 (12%)
Response To Prior HCV Treatment		
Nonresponse	25 (24%)	25 (26%)
Relapse/Breakthrough	78 (76%)	73 (75%)
Baseline HCV RNA (log_{10} IU/mL)		
Mean (SD)	6.5 (0.7)	6.5 (0.6)
Median (Q1, Q3)	6.6 (6.0, 7.0)	6.6 (5.9, 7.1)
<6 log_{10} IU/mL	26 (25%)	29 (30%)
≥6 log_{10} IU/mL	77 (75%)	69 (70%)
Baseline ALT		
≤1 x ULN	23 (22%)	20 (20%)
>1 x ULN	80 (78%)	78 (80%)
≤1.5 x ULN	40 (39%)	42 (43%)
>1.5 x ULN	63 (61%)	56 (57%)

Source: FDA Statistical Reviewer
[1]There were six subjects who were found to have genotype 2 infection as determined by LiPA at screening but were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis.

GS-US-334-0110

Table 19 summarizes the demographics and baseline characteristics for all subjects in the safety analysis set. Overall the mean age (SD) was 52 years (10). The majority of subjects were male (64%), white (79%), non-Hispanic (86%). The mean (SD) baseline BMI was 29 (7) kg/m^2.

Table 19: Demographics and Baseline Characteristics for Study GS-US-334-0110 (Safety Analysis Set)

	SOF+PEG+RBV 12 Weeks (N=327)
Age (Years)	
Mean (SD)	52 (10)
Sex	
Male	209 (64%)
Female	118 (36%)
Race	
Black or African American	54 (17%)
White	257 (79%)
Asian	7 (2%)
Others	9 (3%)
Ethnicity	
Hispanic or Latino	46 (14%)
Not Hispanic or Latino	281 (86%)
Country	
USA	327 (100%)
Baseline Body Mass Index (kg/m^2)	
Mean (SD)	29 (7)

Source: FDA Statistical Reviewer

Baseline disease characteristics for subjects in GS-US-334-0110 are summarized in Table 20. The majority of subjects (89%) had genotype 1 HCV infection. There was only one subject with genotype 5 HCV infection and six subjects with genotype 6 HCV infection. Most subjects (83%) did not have cirrhosis. More than two-thirds of the subjects had non-CC IL28B allele. The majority of subjects had a baseline HCV RNA ≥6 $\log_{10}$ IU/mL (78%).

Table 20: Baseline Disease Characteristics for Study GS-US-334-0110 (Safety Analysis Set)

	SOF+PEG+RBV 12 Weeks (N=98)
HCV Genotype	
Genotype 1a/1b	1 (<1%)
Genotype 1a	225 (69%)
Genotype 1b	66 (20%)
Genotype 4	28 (9%)
Genotype 5	1 (<1%)
Genotype 6	6 (2%)
Cirrhosis	
No	270 (83%)
Yes	54 (17%)
Missing	3 (1%)
IL28B	
CC	95 (29%)
CT	181 (55%)
TT	51 (16%)
Baseline HCV RNA (log_{10} IU/mL)	
Mean (SD)	6.4 (0.67)
Median (Q1, Q3)	6.6 (6.1, 6.9)
<6 log_{10} IU/mL	71 (22%)
≥6 log_{10} IU/mL	256 (78%)
Baseline ALT	
≤1 x ULN	68 (21%)
>1 x ULN	259 (79%)
≤1.5 x ULN	161 (49%)
>1.5 x ULN	51% (166)

Source: FDA Statistical Reviewer

Reviewer's comment:

Demographic and baseline characteristics that have been shown to predict a lower SVR rate with pegylated interferon and ribavirin treatment include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), obesity, older age, and African American race. A genetic polymorphism near the IL28B gene is a strong predictor of SVR in patients receiving therapy with peginterferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

6.1.3 Subject Disposition

P7977-1231

A total of 527 subjects were randomized (263 subjects in SOF+RBV group; 264 subjects in PEG+RBV group). As noted by the Applicant, 28 of the 527 randomized subjects discontinued the trial during the 7-day period between randomization and initiation of study drug and hence, never received study drugs (SOF+RBV 2.7%, 7 subjects; PEG+RBV 8.0%, 21 subjects). Thus, a total of 499 randomized subjects received treatment in this trial (SOF+RBV 256 subjects; PEG+RBV 243 subjects). Three randomized subjects (all in the SOF+RBV group) were found to have HCV genotype 1 infection on NS5B sequencing at baseline and were therefore excluded from the FAS by the Applicant (n = 496; SOF+RBV 253 subjects; PEG+RBV 243 subjects).
The disposition is shown in Table 21 below.

Table 21: Subject Disposition in Study P7977-1231 (Randomized Subjects)

Randomized	PEG+RBV N=264		SOF+RBV N=263	
Randomized but Never Treated	21		7	
Safety Analysis Set	N=243		N=256	
Reason for Premature Discontinuation of Study				
Disposition Event	n	%	n	%
Virologic Failure	28	11.5	0	0
Lost to Follow-Up	9	3.7	6	2.3
Consent Withdrawn	6	2.5	4	1.6
Other	4	1.6	5	2.0
Initiated Non-Protocol HCV Treatment	0	0	4	1.6
Death	1	0.4	1	0.4
Completed Study Treatment	189	77.8	245	95.7
Reason for Premature Discontinuation of Study Treatment				
Adverse Event	26	10.7	3	1.2
Virologic Failure	17	7.0	1	0.4
Lost to Follow-Up	5	2.1	2	0.8
Other	4	1.6	3	1.2
Consent Withdrawn	2	0.8	1	0.4
Death	0	0	1	0.4

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Analysis performed by JumpStart Team

Eighty seven percent (434/499) subjects in the safety analysis set completed study treatment as planned (SOF+RBV 95.7%, 245 subjects; PEG+RBV 77.8%, 189 subjects). The predominant difference noted between treatment groups in the rate of premature discontinuation of study treatment was lower rates of discontinuations due to

AEs (1.2%, 3 subjects) and virologic failure (0.4%, 1 subject) in the SOF+RBV group compared with the PEG+RBV group (10.7% [26 subjects] and 7.0% [17 subjects], respectively).

GS-US-334-0107

Eligible subjects were ≥ 18 years old with chronic genotype 2 or 3 HCV infection; had screening HCV RNA level of ≥ 10^4 IU/mL; required documentation of the presence or absence of cirrhosis; were interferon intolerant, interferon ineligible or unwilling to take interferon; and had a body mass index (BMI) ≥ 18 kg/m^2.

A total of 280 subjects were randomized: 209 to the SOF+RBV group and 71 to the placebo group. Of the 280 randomized subjects, 278 were included in the safety analysis set and FAS (207 in the SOF+RBV group and 71 in the placebo group); 2 subjects were erroneously randomized to the SOF+RBV group, but did not receive study drug. The subject disposition is shown in Table 22 below.

Table 22: Subject Disposition in Study GS-US-334-0107

Safety Analysis Set		Placebo N=71		SOF+RBV N=207	
	Disposition Event	n	%	n	%
Study Completion	Lack of Efficacy	71	100	38	18.4
	Death	0	0	2	1.0
	Lost to Follow-Up	0	0	2	1.0
	Withdrawal By Subject	0	0	1	0.5
Study Drug Completion	Completed	68	95.8	201	97.1
	Adverse Event	3	4.2	4	1.9
	Lost to Follow-Up	0	0	2	1.0

Source: Analysis performed by JumpStart Team

Efficacy was evaluated by measuring HCV RNA levels at Day 1 (baseline); during treatment at Weeks 1, 2, 4, 6, 8, 10, and 12/end of treatment (EOT); and posttreatment Weeks 4, 12, and 24. Safety assessments included monitoring of adverse events (AEs) and concomitant medications, clinical laboratory analyses, physical examinations, and vital signs measurements.

This NDA includes an interim clinical study report which summarizes the results from the primary efficacy endpoint analysis for SVR12, when all subjects had completed the posttreatment Week 12 visit or had prematurely discontinued from the trial. All the data collected by the data finalization date (November 20, 2012) were included in this interim analysis. The final analysis will be conducted when all subjects have completed the posttreatment Week 24 visit or prematurely discontinued from the trial.

GS-US-334-0108

A total of 202 subjects were randomized in the trial: 103 subjects to the SOF+RBV 12 Week group and 99 subjects to the SOF+RBV 16 Week group. The disposition of all the randomized subjects is shown in Table 23 below.

Table 23: Subject Disposition in Study GS-US-334-0108

Randomized		SOF+RBV 12 Weeks N=103		SOF+RBV 16 Weeks N=98	
	Disposition Event	n	%	n	%
Study Completion	Lack of Efficacy	49	47.6	28	28.6
	Lost to Follow-Up	2	1.9	0	0
	Withdrawal by Subject	1	1.0	0	0
Study Drug Completion	Completed	102	99.0	98	100
	Adverse Event	1	1.0	0	0

Source: Analysis performed by JumpStart Team

Of the 202 randomized subjects, 201 were included in the safety analysis set (103 in the SOF+RBV 12 Week group and 98 in the SOF+RBV 16 Week group) and 195 were included in the full analysis set (100 in the SOF+RBV 12 Week group and 95 in the SOF+RBV 16 Week group). One subject (Subject 1543-1551) was randomized to the SOF+RBV16 Week group but did not receive study drug, and was excluded from both the safety and full analysis sets. A total of six subjects in the safety analysis set (Subjects 0057-1480, 0451-1507, 0521-1542, 0530-1405, 0535-1412, and 5852-1500) were excluded from the full analysis set because they were subsequently found to have genotype 1 HCV infection as determined by NS5B sequence analysis and not genotype 2 HCV infection as determined by LiPA at screening.

GS-US-334-0110

Of the 328 subjects enrolled, 327 subjects were treated with at least one dose of study drug and these treated subjects were included in both the safety analysis set and the full analysis set (Table 24).

Table 24: Subject Disposition in Study GS-US-334-0110

Randomized	Disposition Event	SOF+PEG+RBV N=327	
		n	%
Study Completion	Lack of Efficacy	26	8.0
	Lost to Follow-Up	2	0.6
	Withdrawal by Subject	1	0.3
Study Drug Completion	Completed	320	97.9
	Adverse Event	5	1.5
	Protocol Violation	1	0.3
	Withdrawal by Subject	1	0.3

Source: Analysis performed by JumpStart Team

Subjects enrolled in this trial were males and nonpregnant females ≥ 18 years old who had chronic genotype 1, 4, 5, or 6 HCV infection with a screening HCV RNA level ≥ 104 IU/mL; were naive to HCV antiviral treatment; had documentation of the presence or absence of cirrhosis; and had a body mass index (BMI) ≥ 18 kg/m^2.

6.1.4 Analysis of Primary Endpoint(s)

The ultimate goal of CHC treatment is to reduce the occurrence of end-stage liver disease and its complications including decompensated cirrhosis, liver transplantation, hepatocellular carcinoma, and death. Evaluating clinical outcomes from prospective, randomized controlled clinical trials 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 virological parameter for treatment of chronic hepatitis C has been the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy. The attainment of SVR has been proven to be a reliable predictor of long-term clearance of hepatitis C infection and is generally regarded as a “virological cure”. Multiple observational cohorts show correlations between SVR and improvements in clinical outcomes such as development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (Yoshida 1999; Shiratori 2005; Veldt 2007; Manos 2009; Singal, 2010; Backus 2011; van der Meer 2012). Use of SVR24 has been the primary efficacy endpoint in trials evaluating CHC treatments.

The Division of Antiviral Products in collaboration with the Division of Pharmacometrics examined whether assessing SVR at week 12 (SVR12) could be used as a primary efficacy endpoint by examining the correlation between SVR12 and SVR 24 in over 13,000 subjects pooled from multiple clinical trials of peg-IFN-based regimens. In brief, there was a high rate of concordance between SVR12 and SVR24. Sensitivity and

specificity for SVR12 were 99% and 98%, respectively; hence, SVR12 is now being used as a primary endpoint for registrational trials (Gastroenterology. 2013 Jun;144(7):1450-1455).

Primary Efficacy Results in Study P7977-1231

The primary efficacy endpoint was the proportion of subjects in the FAS with SVR12, defined as HCV RNA < LLOQ 12 weeks after the last dose of study drug. The SVR12 rate in the SOF+RBV 12 Weeks treatment group was similar to the SVR12 rate in the PEG+RBV 24 Weeks treatment group (Table 25). The strata-adjusted difference (95% CI) in the proportions was 0.1% (-8% to 8%).

Table 25: Primary Efficacy Results and Relapse Rates in Study P7977-1231 (All Treated)

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)

All Treated was defined as all randomized subjects who received at least one dose of study medication including those with misclassified HCV genotype.
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment.
Source: FDA Statistical Reviewer

It should be noted that there were three subjects who were classified as having genotype 2 infection at screening (determined by LiPA testing) but were subsequently found to have genotype 1 HCV infection as determined by population sequencing.

These subjects were excluded from the primary efficacy analysis by the Applicant; however, these three subjects were included in the efficacy analyses performed by FDA statistical reviewer based on the intention-to-treat (ITT) principle.

Reviewer's Comments

No final decision regarding whether FDA or Applicant's analyses will be presented in the sofosbuvir prescribing information has been made. Discussions are ongoing at this time.

The primary trial endpoint of non inferiority was met as the lower bound of the 2-sided 95% CI for the difference between groups (i.e., SOF+RBV − PEG+RBV) was greater than the prespecified noninferiority margin of -15%. Hence, the efficacy of SOF+RBV for 12 weeks was demonstrated to be noninferior to PEG+RBV for 24 weeks.

Overall relapse rate at posttreatment Week 12 was 30% in the SOF+RBV 12 Week treatment group compared to 21% in the PEG+RBV 24 Week treatment group. Within the SOF+RBV 12 Week treatment group, the relapse rate in genotype 2 subjects was low (5%) compared to high relapse rate (40%) in genotype 3 subjects.

Reviewer Comments

Even though the primary efficacy results are comparable between the two treatment groups (prespecified noninferiority margin was met) and the superiority of SOF+RBV over PEG+RBV treatment was not demonstrated, SOF+RBV treatment regimen provides an all oral IFN-free regimen of shorter duration with better tolerated adverse event profile compared to PEG+RBV therapy.

Higher rates of relapse and lower rates of on-treatment virologic failure on SOF+RBV treatment may partly be due to shorter treatment duration of 12 weeks. Extending the treatment duration may potentially improve the overall efficacy results in the SOF+RBV treatment regimen. Moreover, high relapse rates observed in the subgroup of genotype 3 subjects further indicates that treatment duration needs to be optimized in this patient population. Historically genotype 3 is harder-to-treat compared to genotype 2.

Primary Efficacy Results in Study GS-US-334-0107

In trial GS-US-334-0107, the SOF+RBV 12 Weeks regimen was superior to placebo. The primary efficacy results and relapse rates are shown in Table 26.

Table 26: Primary Efficacy Results and Relapse Rates in Study GS-US-334-0107 (All Treated)

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% [71%, 84%]	
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		
Relapse Rate in Genotype 2	5% (5/107)	n/a
Relapse Rate in Genotype 3	38% (37/98)	n/a

All Treated was defined as all randomized subjects who received at least one dose of study medication; SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment.
Source: FDA Statistical Reviewer

The relapse rates for genotype 2 subjects was low (5%) compared to a much higher relapse rate (38%) observed in genotype 3 subjects treated with the SOF+RBV 12 Weeks regimen.

Primary Efficacy Results in Study GS-US-334-0108

The primary efficacy endpoint was SVR12, defined as HCV RNA < LLOQ 12 weeks after discontinuation of active therapy.

The SVR12 rates in the SOF+RBV 12 Week group was 50% and in the SOF+RBV 16 Week group was 71%, which were each statistically significantly higher ($p < 0.001$) compared to the null rate of 25%.

Treatment with SOF+RBV for 16 weeks resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks. The difference in the percentage of subjects who achieved SVR12 between the 2 treatment groups (SOF+RBV 12 Week group −

SOF+RBV 16 Week group) was −22% (95% CI: −35% to −9%) in favor of the SOF+RBV 16 Week group. This difference was statistically significant (p = 0.0015).

No subject in either treatment group had on-treatment virologic failure. Among all randomized and treated subjects in the SOF+RBV 12 Week group, a total of 49 subjects (48%) relapsed; 45 subjects did so within 4 weeks of stopping active treatment, and 4 subjects did so between posttreatment Week 4 and posttreatment Week 12. Similarly, in the SOF+RBV 16 Week group, a total of 28 subjects (29%) relapsed; 24 subjects did so by posttreatment Week 4, and 4 subjects did so between posttreatment Week 4 and posttreatment Week 12.

Table 27: Primary Efficacy Results and Relapse Rates in Study GS-US-334-0108 (All Treated)

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)

All Treated was defined as all randomized subjects who received at least one dose of study medication including those with misclassified HCV genotype
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment.
Source: FDA Statistical Reviewer

It should be noted that there were six subjects (3 subjects in each arm) who were classified as having genotype 2 infection at screening (determined by LiPA testing) but were subsequently found to have genotype 1 HCV infection as determined by population sequencing. These subjects were excluded from the primary efficacy

analysis by the Applicant; however, these three subjects were included in the efficacy analyses performed by FDA statistical reviewer based on the ITT principle. Hence, there is some difference in the overall SVR rates based on these two analyses. The Applicant's results reported SVR rate of 50% (50/100) in SOF+RBV 12 Weeks vs. SVR rate of 73% (69/95) in SOF+RBV 16 Weeks group.

Improved SVR rates for HCV GT3 subjects were noted with longer treatment duration in GS-US-334-0108, the only pivotal trial where different durations were explored. These data, combined with the approximately 40% relapse rate in the treatment-naïve trials, indicate that a longer treatment duration should be considered in all GT3 subjects. However, the SOF+RBV 16 Weeks treatment regimen was not evaluated in treatment naïve GT3 subjects in any of the pivotal Phase 3 trials submitted for review in this NDA. This poses a dilemma for a regulatory recommendation of 16 weeks of sofosbuvir and ribavirin therapy in all genotype 3 patients. Several bridging analyses were conducted by the Applicant and the FDA statistical review team to explore if this recommendation is reasonable or not. This is further discussed in Section 6.1.10.

Based on subgroup analyses from Study GS-US-334-0108, a numerical trend toward improved SVR12 rates with longer SOF/RBV duration (16 weeks) was observed in certain subgroups (e.g., cirrhosis, prior nonresponders) of genotype 2 subjects. We do acknowledge the small subgroup sample size; however, the improved efficacy outcome in this subgroup of patients with no potential additional safety risk due to tolerable safety profile warrants a longer duration of therapy in this population to maximize the outcome of therapy.

Reviewer's Comments

The relapse rate in genotype 2 treatment-experienced subjects was lower in subjects treated with SOF+RBV 16 weeks regimen compared to 12 week regimen. This information supports recommending 16 week treatment duration for all treatment-experienced genotype 2 subjects to optimize the potential benefit of attaining SVR.

Primary Efficacy Results in Study GS-US-334-0110

In trial GS-US-334-0110, a statistically significant proportion of subjects achieved SVR12 (90%, $p < 0.0001$) compared with an historical SVR12 rate of 60%.

Table 28: Primary Efficacy Results and Relapse Rates in Study GS-US-334-0110 (FAS)

Efficacy Parameter	SOF+PEG+RBV 12 Weeks (N=327)
Overall SVR12 Rate [95% CI]	90% [86%, 93%]
Genotype 1	89% (260/291)
Genotype 1a	92% (206/225) [87%, 95%]
Genotype 1b	82% (54/66) [70%, 90%]
Genotype 4	96% (27/28)
Genotype 5	100% (1/1)
Genotype 6	100% (6/6)

FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication;
SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
SVR12= sustained virologic response at 12 weeks after the end of treatment.
Source: FDA Statistical Reviewer

HCV genotype 1a treatment-naïve subjects had higher SVR12 rate than the genotype 1b subjects in GS-US-334-0110 (i.e., 92% vs. 82%). Historically, the subjects infected with genotype 1a HCV are harder- to-treat compared to the subjects with genotype 1b HCV infection. The Applicant attributed the observed treatment difference to the findings that the subjects with genotype 1a had a lower percentage of IL28B CC subjects, black subjects, non-cirrhotic subjects and had a lower mean age as compared to the subjects infected with genotype 1b HCV in the trial. However, the statistical reviewer compared the SVR12 rates between the two sub genotypes across the subgroups defined by the demographics and baseline characteristics, and found that the genotype 1a subjects had numerically higher SVR12 rate than the genotype 1b subjects in all subgroups. It should be noted that these analyses were post-hoc and the lack of a control group in this trial makes it challenging to derive any definitive conclusion whether the observed differences between the two sub genotypes were due to chance. The labeling implications of this observation are ongoing at this time.

6.1.5 Analysis of Secondary Endpoints(s)

Other secondary efficacy endpoints analyzed were:

- Proportion of subjects with HCV RNA <LLOQ by study visit
- Time to first HCV RNA < LLOQ and time to first HCV RNA < LLOQ Target Not Detected
- On-treatment virologic failure
- Relapse

Please refer to FDA Statistical and Clinical Microbiology Reviews for details of analyses performed.

6.1.6 Other Endpoints

Several other analyses were done by the FDA Reviewers. Please refer to FDA Clinical Pharmacology, Clinical Microbiology and Statistical Reviews.

6.1.7 Subpopulations

Response Rates in Genotypes 2 or 3

The observed SVR12 rates based on the results of the pre-specified subgroup analyses in Studies P7977-1231, GS-US-334-0107 and GS-US-334-0108 were different in subjects with genotype 2 or 3 HCV infection.

- In Study P7977-1231, the difference in the SVR12 rate between genotypes 2 and 3 was more evident in the SOF+RBV 12 Week group (95% and 56% of genotypes 2 and 3 subjects respectively) compared to the PEG+RBV 24 Week group (78% and 63% of genotypes 2 and 3 subjects respectively).
- In Study GS-US-334-0107, in the SOF+RBV 12 Week group, the HCV genotype 2 subjects had significantly higher SVR12 rate than the HCV genotype 3 subjects (i.e., 93% vs. 61%).
- In Study GS-US-334-0108, in which two treatment durations of SOF+RBV were evaluated, the difference in SVR12 rates between the genotypes 2 and 3 subjects were significant within each treatment duration group. In the 12-week SOF+RBV group, 82% of the HCV genotype 2 subjects achieved SVR12 compared with 30% of the HCV genotype 3 subjects (p-value < 0.0001 based on Chi-Square test). In the 16-week SOF+RBV group, the SVR12 rates were 89% and 62% for the genotypes 2 and 3 subjects, respectively (p-value = 0.0052 based on Chi-Square test).

The collective evidence from the three trials indicates that 12 weeks of SOF+RBV treatment regimen is not the optimal regimen for the genotype 3 patients.

Response Rates based on Gender

The post-hoc analyses showed that the female subjects with genotype 3 infection had higher SVR12 rates than male subjects in all of the SOF+RBV treatment groups in the three pivotal trials (P7977-1231, GS-US-334-0107 and GS-US-334-0108) except for the SOF+RBV 12 Week treatment group in Study GS-US-334-0108 where the sample sizes were small. In addition, compared with the 24-week PEG+RBV group, the gender difference was more notable for the 12-week SOF+RBV in Study P7977-1231. These post-hoc exploratory analyses show that gender appears to affect the SVR rate for SOF+RBV among the HCV genotype 3 subjects.

Response Rates in Subjects with Cirrhosis

- In P7977-1231, as compared to the PEG+RBV treatment, the SOF+RBV treatment resulted in 2% lower SVR12 rate in non-cirrhotic subjects but 8% higher among cirrhotic subjects.
- In GS-US-334-0107, the overall SVR12 rate in cirrhotic subjects was around 20% lower than in non-cirrhotic subjects (61% [19/31] for cirrhotic subjects, 81% [142/176] for non-cirrhotic subjects). In genotype 2 HCV infected subjects, the SVR12 rates were unaffected by the cirrhosis status. However, genotype 3 HCV infected subjects had notably lower SVR12 rates in cirrhotic versus non-cirrhotic subjects.
- In GS-US-334-0108, genotype 2 subjects with cirrhosis had lower SVR12 rates (60% [6/10]). The 16-week duration of SOF+RBV improved SVR12 rates for genotype 2 subjects with cirrhosis to 78% (7/9). The 16-week duration of SOF+RBV improved SVR12 rates for genotype 3 subjects with cirrhosis to 61% (14/23) similar to 63% (25/40) for genotype 3 subjects without cirrhosis. The 16-week duration improved SVR12 rates for genotype 3 subjects with cirrhosis three times better than the 12-week duration (61% [14/23] vs. 19% [5/26]).
- In GS-US-334-0110, it was found that a higher SVR12 rate was observed in the noncirrhotic subjects than the cirrhotic subjects (92% [252/273] with 95% CI: 88.5% to 95% for noncirrhotic subjects, 80% [43/54] with 95% CI: 66% to 89% for cirrhotic subjects).

Additional subgroup analyses evaluating response rates based on documented response to prior course of HCV treatment were also evaluated by Statistical and Virology reviewers.

Please refer to Statistical and Clinical Microbiology Reviews for detailed assessment of subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Study GS-US-334-0108 was the only pivotal trial which evaluated SOF+RBV 16 Weeks treatment duration. In Study GS-US-334-0108, treatment with SOF+RBV for 16 weeks resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks. The difference in the percentage of subjects who achieved SVR12 between the 2 treatment groups (SOF+RBV 12 Week group − SOF+RBV 16 Week group) was −22% (95% CI: −35% to −9%) in favor of the SOF+RBV 16 Week group. This difference was statistically significant ($p < 0.001$). However the relapse rate in the 16-week arm was still as high as 38% even though it was much lower than 66% in the 12-week arm. This suggested that the efficacy could potentially be further improved with longer treatment duration or additional of a third antiviral agent (PEG or DAA).

Exposure-response analyses were conducted by Dr. Florian for genotype 3 subjects based on the sparse pharmacokinetic data from GS-US-334-0108 (treatment-experienced; SOF/RBV 12 weeks: n=64; SOF/RBV 16 weeks: n=63). These analyses

demonstrated that increasing the treatment duration improved SVR12 from 45% to 78% in subjects with GS-331007 exposures greater than the median (7062 ng·hr/mL) though only marginal benefit was observed in subjects with GS-331007 exposures less than the median (7062 ng·hr/mL) (from 28 to 31%). Given the improvement in response observed by extending treatment to 16-weeks and the observation that all the treatment failures in both durations were relapsers, it is likely that extending the treatment duration in genotype 3 subjects even longer (e.g., 24 weeks) may result in further SVR12 improvements in this population.

Reviewer's Comments

The Phase 3 efficacy results show decreased response rates in genotype 3 subjects compared to genotype 2 subjects for a similar duration of therapy. Moreover, the reduced response rates in genotype 3 subjects seems to be driven by the high relapse rate which indicates that extending the duration of therapy may optimize the treatment regimen by potentially increasing the overall response rates.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

SVR12 and SVR24 Concordance

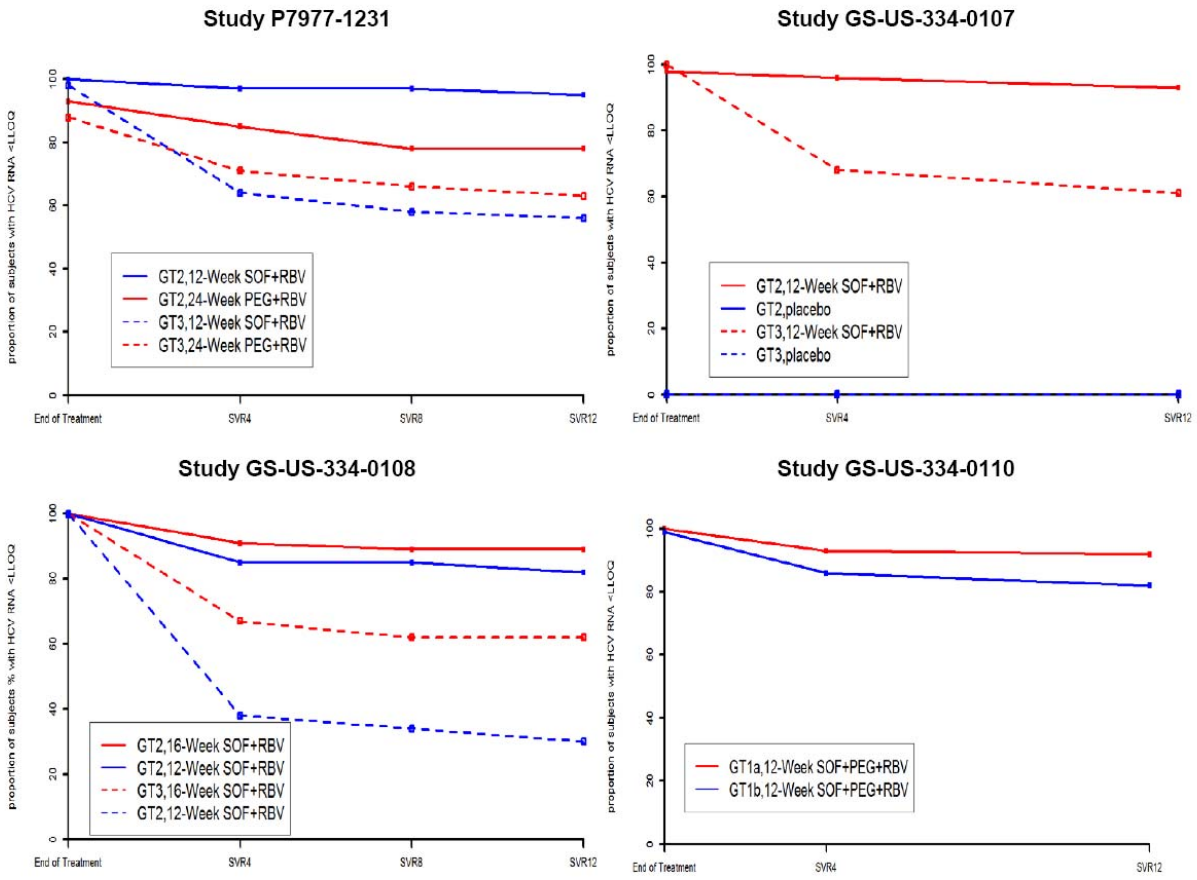
Evaluation of SVR at 24 weeks (SVR24) post-treatment cessation has been the universally accepted time point to assess virologic response. With peg-IFN and RBV based therapy, viral relapse usually occurs in the first several weeks following treatment cessation and measurement of SVR at an earlier time point could yield greater trial efficiency. FDA reviewers examined whether SVR12 could be used as a primary efficacy endpoint by evaluating the correlation between SVR12 and SVR 24 in over 13,000 subjects pooled from multiple clinical trials of peg-IFN-based regimens. In brief, there was a high rate of concordance between SVR12 and SVR24. Sensitivity and specificity for SVR12 was 99% and 98%, respectively; therefore, SVR12 is now used as a primary endpoint for registrational trials.

In clinical trials of sofosbuvir, data is being collected for SVR24 in addition to SVR12 to further evaluate the persistence of treatment effects and concordance between SVR12 and SVR24 in non-IFN based regimens. Data from trials P7977-1231 and GS-US-334-0107 was evaluated by Dr. Florian. SVR24 data was unavailable from GS-US-334-0108 or GS-US-334-0110, so no concordance assessments could be performed for those two trials. Overall, assessments at week 12 of follow-up (SVR12) were concordant with those at week 24 of follow-up (SVR24). The positive predictive value based on data from the SOF+RBV treatment arm in P7977-1231 was 98.8% (161/163). The SOF+RBV treatment arm in GS-US-334-0107 showed 100% concordance between SVR12 and SVR24 in subjects with data available for both time points. The overall positive predictive value between SVR12 and SVR24 in SOF+RBV treatment arms was

99.4% (314/316). This data further supports the use of SVR12 as the primary endpoint in interferon-free trials.

The figure 2 below further demonstrates that most of the relapses occur early after discontinuation of therapy.

Figure 2: End of Treatment and Post Treatment Response Rates in Phase 3 Trials



Source: FDA Statistical Reviewer

The figure 2 above also illustrates that relapse rates is higher in genotype 3 subjects compared to genotype 2 subjects as was previously discussed in Section 6.1.4.

6.1.10 Additional Efficacy Issues/Analyses

Bridging Analyses to Explore Treatment Duration in Treatment-naïve Genotype 3 Subjects

SOF+RBV for 12 weeks is the only sofosbuvir regimen studied in treatment-naïve genotype 3 subjects in the pivotal Phase 3 trial (P7977-1231). However, GS-US-334-0108 demonstrated treatment-experienced genotype 3 subjects receiving SOF+RBV for 16 weeks had clinically significant increased SVR12 compared with the same regimen for 12 weeks. Therefore, the Applicant conducted a bridging analysis to estimate the SVR12 rate for 16 weeks of SOF+RBV in treatment-naïve genotype 3 subjects using the genotype 3 data in Studies P7977-1231 and GS-US-334-0108. Based on these results, the Applicant proposed a 16-week SOF+RBV regimen for all patients with genotype 3 infection.

Additional analyses were also done by the FDA Statistical Reviewer to determine whether the statistical methods in the Applicant's bridging analyses were appropriate. Also, in the statistical reviewer's opinion, instead of applying the model to estimate the SVR12 rate, the SVR12 rate could be extrapolated directly from the observed rates in Studies P7977-1231 and GS-US-334-0108 based on the assumption of the same odds ratios of 16-week SOF+RBV over 12-week SOF+RBV between treatment-naïve and treatment-experienced subjects. For details of statistical analyses please refer to FDA Statistics Review.

The statistical reviewer obtained an SVR12 rate of 83% for the 16-week SOF+RBV in treatment-naïve genotype 3 subjects based on the extrapolation which was very close to the Applicant's. The reviewer also used relative risk (RR) and proportion difference (PD) to extrapolate the SVR rate. The estimated SVR12 rate was 76% based on RR and 88% based on PD. All these post-hoc analyses suggested that the 16 weeks of SOF+RBV treatment in genotype 3 treatment-naïve subjects would lead to a higher SVR12 rate than 56% rate for the 12 weeks of SOF+RBV treatment seen in Study P7977-1231. From the statistical perspective, these bridging analyses were based on the assumptions (with no available clinical trial data to validate) and the lack of 16 week trial data makes it difficult to determine the optimal treatment duration for genotype 3 treatment-naïve patients.

Optimal Duration of Therapy in Genotype 2 Subjects with Poor Baseline Predictors

Efficacy issues which are under discussion at this time are:

- Optimum duration of therapy in genotype 2 who are nonresponders to previous pegylated interferon and ribavirin therapy.

- Optimum duration of therapy in genotype 2 treatment naïve who have poor baseline predictors such as cirrhosis, non-CC IL28B genotype.

The response rates in subjects with genotype 2 HCV infection were analyzed by baseline factors and selected subgroup analyses are shown in Table 29. For treatment-naïve subjects with genotype 2, SVR12 rates were 93-95% following 12 weeks of SOF+RBV treatment (Table 29). SVR12 rates were also high for subjects with prior PR breakthrough or relapse following both 12 and 16 weeks of SOF+RBV (86% for 12 weeks; 89% for 16 weeks). Response rates after 12 weeks of SOF+RBV for subjects who were prior PR null or partial responders were 70% (Table 29). A longer duration of 16 weeks SOF+RBV improved SVR12 rates for prior PR nulls and partial responders to 88%.

Table 29: Selected Subgroup Analyses in Genotype 2 Subjects

	GS-US-334-0107		GS-US-334-0108*		P7977-1231*	
	SOF+RBV 12 weeks	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+RBV 12 Weeks	PEG+RBV 24 Weeks
GT2 (n=357)	93% (101/109)	0/34	82% (32/39)	89% (31/35)	95% (69/73)	78% (52/67)
Prior PR			82% (32/39)	94% (30/32)		
PR Breakthrough or Relapser			86% (25/29)	89% (24/27)		
PR Null or Partial Responder			70% (7/10)	88% (7/8)		
Naive	93% (101/109)	0/34			95% (69/73)	78% (52/67)
IL28B CC	89% (40/45)	0/17	88% (7/8)	71% (10/14)	97% (32/33)	82% (28/34)
IL28B CT	98% (49/50)	0/14	75% (15/20)	100% (19/19)	94% (30/32)	77% (17/22)
IL28B TT	86% (12/14)	0/3	91% (10/11)	100% (2/2)	88% (7/8)	64% (7/11)
IL28B CT/TT	95% (61/64)	0/17	86% (25/29)	100% (21/21)	93% (37/40)	73% (24/33)
Cirrhosis Yes	94% (16/17)	0/3	60% (6/10)	78% (7/9)	83% (10/12)	62% (8/13)
No	92% (85/92)	0/31	90% (26/29)	92% (24/26)	97% (59/61)	81% (44/54)

* Analyses includes 9 subjects that screened GT2 but were determined GT1a or 1b by NS5B sequencing
Source: FDA Clinical Microbiology Reviewer (Dr. Lisa Naeger)

SVR12 rates were 71-100% for both treatment-naïve and experienced subjects with GT2 HCV regardless of IL28B genotype (Table 29). Subgroups were too small to make any definitive conclusions regarding differences in response by IL28B genotype. However, in treatment-experienced GT2 subjects in GS-US-334-0108, response rates

were in general better with the longer 16-week duration for IL28B genotype compared to the 12- week duration although again subgroups were small.

For treatment-naïve cirrhotic GT2 subjects, SVR12 rates were 83%-94% following 12 week SOF+RBV treatment (Table 29). For treatment-experienced cirrhotic GT2 subjects, SVR12 rates were lower (60%) following 12 weeks of SOF+RBV treatment. The 16-week duration of SOF+RBV improved SVR12 rates for cirrhotic treatment-experienced subjects to 78%.

Please refer to Statistical and Clinical Microbiology Reviews for details on subgroup analyses.

Reviewer's Comments

Numerical trends of improved SVR rates were observed in the above noted subgroups of genotype 2 patients. There are ongoing discussions regarding whether extending the treatment duration to 16 weeks in these subgroups of genotype 2 patients will optimize the SVR rates. No final decisions have been made at this time.

Analyses to Support Potential Treatment Recommendations for Subjects with Genotype 1 HCV Infection who are PEG/RBV-Nonresponders

SOF+PEG+RBV regimen was not evaluated in PEG/RBV-nonresponders with genotype 1 HCV infection in sofosbuvir clinical development program. The Applicant has not proposed an indication in PEG/RBV-nonresponders with genotype 1, 4, 5 or 6 HCV infection.

Previous experience with the treatment-naïve and the PEG/RBV- nonresponders population (Florian J et al. *Hepatology 2012*, Liu J et al. *Clinical Infectious Diseases 2012*, and Liu J et al. *Hepatology 2012*) has indicated that nonresponders to pegylated interferon and ribavirin were included in the treatment-naïve population (e.g., up to 50% of the treatment-naïve genotype 1 subjects fail PEG+RBV therapy and are subsequently categorized as PEG/RBV- nonresponders). Given this previous observation, the high overall SVR rate identified in the Applicant's treatment-naïve trial (GS-US-334-0110), and analyses performed by the Pharmacometrics group (see Clinical Pharmacology Review), the currently available evidence supports the effectiveness of SOF+PEG+RBV regimen in genotype 1 PEG/RBV- nonresponders.

Data from GS-US-334-0110 suggests that subjects with detectable HCV RNA at Treatment Week 2 (TW 2) were less likely to achieve SVR12 compared to subjects with HCV RNA target not detected at TW 2. Also, treatment-naïve subjects with multiple poor baseline predictive factors (such as high baseline viral load, non-CC IL28B, advanced fibrosis/cirrhosis) were more likely to have HCV RNA detectable at TW 2 compared to other treatment-naïve genotype 1 subjects. As the primary reason for

treatment failure was relapse, this observation supports that a subset of genotype 1 subjects (treatment-naïve with poor baseline predictive factors and PEG/RBV-nonresponders) may benefit from a longer SOF+PEG+RBV treatment duration.

While these analyses provide supportive evidence that SOF+PEG+RBV is likely to be an effective therapeutic option for prior PEG/RBV-nonresponders, the available data is not sufficient to estimate the SVR12 response rates in specific PEG/RBV-nonresponder subgroups, such as prior null responders and prior partial responders. Moreover, the optimal regimen and treatment duration in this harder-to-treat population can not be determined by these analyses.

Please refer to Clinical Pharmacology Review for detailed assessment.

Reviewer's Comments

Internal discussions are still ongoing. Please refer to CDTL Review for any labeling considerations based on these analyses.

7 Review of Safety

Safety Summary

The observed safety profile of sofosbuvir and ribavirin (SOF+RBV) regimens is consistent with known safety profile of ribavirin. The safety profile of pegylated interferon and ribavirin containing sofosbuvir regimen (SOF+PEG+RBV) is similar to the well documented adverse event profile of pegylated interferon and ribavirin containing treatment regimens. In addition, the known toxicities of ribavirin or expected side effects associated with pegylated interferon use do not seem to worsen when used in combination with sofosbuvir. No clustering of adverse events and no trends in any specific adverse event type were noted.

- An improved safety profile for all-oral SOF+RBV regimens was noted as compared to interferon based treatment regimens. Overall, the observed incidences of adverse events (any grade), Grade 3 or higher adverse events, and adverse events leading to permanent discontinuation, interruption or dose modification of the study drugs was lower in SOF containing treatment regimens. The incidence of treatment-emergent adverse events reported as related to study drug (by investigator's causality assessment) was low.

- Based on the review of available clinical data at this time, a detailed safety evaluation focusing on cardiac disorders revealed no potential safety concerns in regards to cardiac toxicity associated with sofosbuvir use.

- No renal adverse events of concern have been identified to date.
- Mild elevations of serum creatine kinase values were noted without any associated clinical symptoms of concern.
- Mild elevations of lipase values were noted which were not associated with clinical signs and symptoms of acute pancreatitis.
- No obvious safety concern of gastrointestinal toxicity associated with sofosbuvir use was identified.
- Elevated bilirubin levels consistent with hemolytic anemia associated with ribavirin therapy were noted.
- No safety signals related to hepatotoxicity were identified in the sofosbuvir treated groups.
- No acute hypersensitivity reactions such as SJS or TEN were reported.
- No safety signals related to bone marrow suppression were identified in the sofosbuvir treated groups.

In summary, sofosbuvir and ribavirin combination regimen provides a first all-oral treatment option for chronic hepatitis C patients with genotype 2 and 3 infections. The SOF+RBV regimen offers a shorter duration of treatment with improved safety profile compared to interferon based regimen. In addition, SOF+RBV regimen provides therapeutic option for patients who are ineligible, intolerant or non-willing to take interferon-based regimens, thus addressing an unmet need in this patient population.

Sofosbuvir in combination with pegylated interferon and ribavirin (SOF+PEG+RBV) provides improved efficacy and shorter duration of treatment for chronic hepatitis C patients with genotype 1 or 4 infection. The number of subjects with genotype 5 or 6 infection evaluated in pivotal trials is very small to make any conclusive decisions regarding dosing recommendations in this subpopulation. The shorter duration of interferon and ribavirin based regimen translates into a better tolerated side effect profile which in turn leads to less treatment discontinuations and contributes to improved rates of sustained virologic response. The observed safety profile is consistent with the well-documented safety profile of interferon and ribavirin. Some of the adverse events noted such as hepatocellular carcinoma or signs/symptoms of hepatic decompensation are consistent with the patient population under study and may be related to the underlying liver disease progression.

In conclusion, based on the review of the submitted data, no major safety issues associated with sofosbuvir use have been identified to date. The noted safety profile of sofosbuvir is acceptable.

7.1 Methods

Safety data for this NDA were submitted by the Applicant as clinical overview, summary of clinical safety, final clinical study reports, and electronic datasets. The ISS includes information on deaths, SAEs, discontinuations due to AEs and pertinent other significant adverse events (e.g. liver-related events, pancytopenia). Narrative summaries and CRFs are provided for all subjects who died, developed a serious adverse event (SAE), or discontinued from the trial because of an adverse event (AE).

Summary results of the individual trials are presented followed by relevant integrated safety analysis in the following sections. Minor differences between the Applicant's results and FDA's results can be attributed to the differences in the methods for conducting the analyses and do not significantly alter the final conclusions. Medical Dictionary for Regulatory Activities (MedDRA) terms are used in the analyses of the adverse event tables in this review; however American English spelling is used in the tables and text of this review instead of British English spelling.

Each AE is listed only once in summary tables, regardless of the number of times it occurred for the subject. A subject may report more than one AE; therefore, the total number of AEs reported may be greater than the number of subjects in the trial.

7.1.1 Clinical Trials Used to Evaluate Safety

The safety data derived from the four pivotal phase 3 trials (P7977-1231, GS-US-334-0107, GS-US-334-0108, and GS-US-334-0110) constitute the primary safety population and FDA analyses of key safety signals were performed using this integrated dataset. The data from Phase 1 trials, Phase 2 trials and other ongoing trials constitutes the supporting safety data and has been discussed in relevant sections of this review.

Safety data for the SOF+PEG+RBV regimen in subjects with genotype 1, 4, 5, and 6 HCV infection are presented from trial GS-US-334-0110. Safety data for the SOF+ RBV regimen in subjects with genotype 2 and 3 HCV infection are presented from trials P7977-1231, GS-US-334-0107, and GS-US-334-0108.

7.1.2 Categorization of Adverse Events

MedDRA version 15.0 was used by the Applicant for AE coding. The NDA includes the AE dictionary files that consist of all investigator verbatim and the preferred terms to which they were mapped as SAS transport files for the four pivotal Phase 3 trials. In addition, information describing the current AE coding process at Gilead is also included

in this original NDA application. The Applicant's categorization of closely related events and coding of adverse event verbatim terms to preferred terms was assessed and was found to be appropriate.

An AE was any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. A treatment-emergent AE was defined as any AE that began on or after the treatment start date up to 30 days after the treatment stop date. All AEs noted in AE summary tables and discussed throughout this review were treatment emergent unless indicated otherwise and are referred to as AEs for the purposes of this review. Adverse events related to study drug were defined as AEs for which the investigator assessed the event to be possibly or probably related to the study drug. It should be noted that trials P7977-1231 and GS-US-334-0110 were open-label and hence subject to bias. Events for which the investigator did not record relationship to study drug were considered related to study drug by the Applicant for purpose of analysis.

A serious adverse event (SAE) is any event that results in any one of the following outcomes: death; life-threatening AE; persistent or significant disability/incapacity; required in-patient hospitalization or prolonged hospitalization; congenital anomaly or birth defect; other important medical events that may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes.

The severity grading of AEs and laboratory abnormality was assessed as Grade 1, 2, 3, or 4 using the Gilead Sciences, Inc. (GSI) Toxicity Grading Scale for Severity of Adverse Events and Laboratory Abnormalities except in Study P7977-1231 (FISSION), in which AEs were graded by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) according to criteria specified in Division of AIDS [DAIDS] Toxicity Grading Table. The Applicant noted in their previous correspondence with the Division that these toxicity grading scales are identical with respect to grading of clinical adverse events. For the laboratory toxicity grading in Study P7977-1231 (FISSION), harmonization to the GSI toxicity grading scale was done for safety analyses in the Phase 3 Clinical Study Reports and the ISS. The Gilead-modified toxicity grading scale, September 2011 version, was used to analyze laboratory data.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For subjects with genotypes 2 and 3 HCV infection, the data from SOF+RBV 12 Week regimen groups were pooled across trials P7977-1231, GS-US-334-0107, and GS-US-334-0108 due to similar treatment regimen and duration. All other treatment regimens such as SOF+RBV 16 Week, placebo, PEG+RBV, and SOF+PEG+RBV were not

pooled and were evaluated separately. The safety evaluation was done by comparing the following treatment groups for the integrated safety population:

- Placebo: This group includes subjects who received placebo for 12 weeks in Study GS-US-334-0107
- SOF+RBV 12 Weeks: This group includes subjects who received SOF+RBV for 12 weeks in Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108
- SOF+RBV 16 Weeks: This group includes subjects who received SOF+RBV for 16 weeks in Study GS-US-334-0108
- SOF+PEG+RBV 12 Weeks: This group includes subjects who received SOF+PEG+RBV for 12 weeks in Study GS-US-334-0110
- PEG+RBV 24 Weeks: This group includes subjects who received PEG+RBV for 24 weeks in Study P7977-1231

For Study GS-US-334-0108, AEs that occurred up to 30 days after the last dose of active study drugs (i.e., SOF and RBV) are included in the integrated safety analysis.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The Applicant has presented safety data from a total of 27 clinical trials that comprise 4 pivotal Phase 3 trials, 5 Phase 2 trials, 2 special HCV population trials, 13 Phase 1 trials, 1 NIAID-sponsored trial, 1 BMS-sponsored trial (A144040), and 1 Janssen-sponsored trial (HPC2022). Overall, 2885 subjects were treated in these 27 trials of which 2443 subjects received at least one dose of a sofosbuvir-containing regimen. At the proposed clinical dose of 400 mg once daily in Phase 2 and Phase 3 trials, 1732 HCV-infected subjects have been exposed to sofosbuvir in combination with RBV or PEG+RBV. A total of 1183 subjects have been exposed for 12 weeks, 98 subjects exposed for 16 weeks, and 374 subjects have been exposed for 24 weeks treatment duration (Table 30).

Table 30: Exposures to Sofosbuvir 400mg in Phase 2 and 3 Trials Included in Initial NDA Filing

Study Number	Regimen	Weeks of SOF	N
12 Weeks			
P7977-1231 (FISSION)	SOF+RBV	12	256
GS-US-334-0107 (POSITRON)	SOF+RBV	12	207
GS-US-334-0108 (FUSION)	SOF+RBV	12	103
GS-US-334-0110 (NEUTRINO)	SOF+PEG+RBV	12	327
GS-US-334-0123 (PHOTON-1, Group 1)	SOF+RBV	12	31
P2938-0721 (QUANTUM)	SOF+RBV	12	25

Study Number	Regimen	Weeks of SOF	N
P7977-0422 (PROTON)	SOF+RBV (GT 2/3) SOF+PEG+RBV(GT-1)	12	72
P7977-0523 (ELECTRON)	Multiple	12	110
P7977-0724 (ATOMIC, Group A)	SOF+PEG+RBV	12	52
			1183
16 Weeks			
GS-US-334-0108 (FUSION)	SOF+RBV	16	98
24 Weeks			
2938-0721 (QUANTUM)	SOF+RBV	24	25
7977-0724 (ATOMIC, Group B and C)	SOF+PEG+RBV (24 weeks) SOF+PEG+RBV (12 weeks) + SOF+RBV(12 weeks) SOF+PEG+RBV(12 weeks) + SOF (12 weeks)	24	280**
P7977-2025 (Pre-transplant)	SOF+RBV	24	15
GS-US-334-0112 (NIAID Collaborative study)*	SOF+RBV	24	54
			374
Total			1655

* Datasets were not included in the NDA.
** 5 patients in Group C discontinued from study treatment after 12 weeks of SOF+PEG+RBV.
Source: Information received from Applicant on August 14, 2013

A total of 1337 subjects were randomized into four pivotal clinical trials. Out of these, 1305 received at least one dose of study drug and were evaluated for the primary safety analysis. This safety analysis set included 566 subjects (43.4%) who received at least one dose of the SOF+RBV 12 Week regimen, 327 subjects (25.1%) who received at least one dose of the SOF+PEG+RBV regimen for 12 weeks; 243 subjects (18.6%) who received at least one dose of the PEG+RBV regimen for 24 weeks; 98 subjects (7.5%) who received at least one dose of the SOF+RBV 16 Week regimen; and 71 subjects (5.4%) who received at least one dose of the placebo regimen for 12 weeks.

SOF+RBV Groups

A total of 566 subjects received treatment in the SOF+RBV 12 Week group (Studies P7977-1231, GS-US-334-0107, and GS-US-334-0108), with a mean (standard deviation [SD]) duration of exposure of 12.0 (1.32) weeks. Most subjects (96.8%, 548 subjects) received SOF+RBV for 12 weeks. Two subjects who were randomized to receive 12 weeks of SOF+RBV followed by 4 weeks of matching placebo switched to SOF placebo at Week 12 but continued RBV treatment through Week 16.

A total of 98 subjects received treatment in the SOF+RBV 16 Week group, with a mean (SD) duration of exposure of 16.1 (0.18) weeks. All 98 subjects received SOF+RBV for 16 weeks according to the study protocol.

SOF+PEG+RBV Group
A total of 327 subjects received treatment in the SOF+PEG+RBV group (Study GS-US-334-0110), with a mean (SD) duration of exposure of 11.9 (1.09) weeks. Most subjects (97.9%, 320 subjects) received study regimen for 12 weeks; 7 subjects (2.1%) discontinued study treatment. The reasons for discontinuation were AEs (1.5%, 5 subjects) and protocol violation and withdrawal of consent (each 0.3%, 1 subject).

Control Groups (Placebo and PEG+RBV)

There were 71 subjects in the placebo group (Study GS-US-334-0107), with a mean (SD) duration of exposure of 11.8 (1.60) weeks. Most subjects (95.8%, 68 subjects) received placebo for 12 weeks according to the study protocol.

A total of 243 subjects received study drug in the PEG+RBV group, with a mean (SD) duration of exposure of 21.3 (5.82) weeks. The PEG+RBV group had the lowest rate (77.8%) of study drug completion compared with the SOF-containing or placebo groups mainly driven by the higher rates of discontinuation due to AEs (10.7%, 26 subjects) and virologic failure (7.0%, 17 subjects) in the PEG+RBV group compared with other groups.

Please refer to Section 6.1.2 for demographics of trial participants.

Reviewer's comments:

Overall, an adequate number of subjects and duration of drug exposure was obtained for the target patient population. A substantial number of subjects have also received treatment with sofosbuvir beyond the proposed 16 week treatment duration (i.e. 24 weeks, N=374). Hence an adequate safety data base for the proposed dose and treatment duration exists.

7.2.2 Explorations for Dose Response

The Phase 3 sofosbuvir dose of 400 mg once daily was selected based on on-treatment virologic response data observed from P7977-0221. Subjects were administered one of three sofosbuvir doses (100, 200, and 400 mg once daily) in combination with PEG/RBV and change from baseline in HCV RNA was assessed at Day 3 of treatment. An E_{max} model based on GS-331007 AUC_{tau} fit to the virologic response data supported that change from baseline in HCV RNA at Day 3 increased with increasing sofosbuvir dose up to 400 mg once daily.

In Study P7977-0422 (PROTON), a Phase 2b trial in noncirrhotic, treatment-naive subjects with genotypes 1, 2, or 3 HCV infection, SVR 24 rates of 90-92% were observed with sofosbuvir 200 and 400 mg, in combination with PEG and RBV. In genotype 1 HCV-infected subjects, virologic breakthroughs during treatment with

PEG+RBV (following initial treatment with SOF+PEG+RBV) were more common in the SOF 200 mg+PEG+RBV group compared with the SOF 400 mg+PEG+RBV group, further suggesting that the sofosbuvir 400 mg dose may provide greater suppression of viral activity.
Please refer to Clinical Pharmacology Review for exposure-response analyses.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate nonclinical testing was performed. Please refer to Section 4.3 and Dr. Christopher Ellis' review for details.

7.2.4 Routine Clinical Testing

The routine clinical testing was performed at pre-specified regular intervals during the trials and was adequate. Safety assessments included, but were not limited to, the following; physical examinations, measurement of vital signs, and clinical laboratory tests. Additional testing was performed as indicated during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

The metabolic, clearance, and interaction workup was adequate. Please refer to Section 4.4 and to Clinical Pharmacology Review for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

As mentioned earlier, the development of an investigational agent labeled BMS-986094 (formerly known as INX-189), a nucleotide polymerase (NS5B) inhibitor in Phase 2 clinical development for the treatment of hepatitis C was halted by Bristol-Myers Squibb Company in August, 2012 after nine patients in a clinical trial had to be hospitalized and one of them died of heart failure.

Although sofosbuvir is structurally different, a detailed safety evaluation focused on cardiac disorders was done to identify any potential cardiac toxicity signal due to class effect. In addition, the issue was discussed with the review team members of the investigational drugs in the same class to identify any potential safety signals.

Cardiac Disorder Adverse Events

Cardiac Disorders Adverse Events in Primary Safety Population (Pivotal Trials)

The evaluation of this particular safety concern included detailed assessment of nonclinical data by Dr. Christopher Ellis. Please refer to Pharmacology Toxicology Review for full assessment of the findings. An independent detailed evaluation of the submitted data was done by this reviewer and is provided in this section. The Applicant

was also asked to perform a comprehensive review focusing on cardiac safety. The findings reported by the Applicant (submission dated June 24, 2013) are also summarized in this section.

The comprehensive review based on MedDRA System Organ Class (SOC) for Cardiac Disorders was done for all four pivotal trials.

Table 31: Overall Summary of Cardiac Disorder Adverse Events (SOC) in the Primary Safety Population

N (%)	Placebo (N=71)	SOF+RBV 12 Weeks (N=566)	SOF+RBV 16 Weeks (N=98)	SOF+PEG+RBV 12 Weeks (N=327)	PEG+RBV 24 Weeks (N=243)
≥1 AE	1 (1)	12 (2)	0	4 (1)	11 (5)
Grade 1	0	11 (2)	0	3 (<1)	8 (3)
Grade 2	1 (1)	1 (<1)	0	1 (<1)	2 (<1)
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	1 (<1)
SAE	0	0	0	0	1 (<1)
AE leading to Discontinuation	0	0	0	0	2 (<1)

Source: Submission to NDA dated June 24, 2013

There were no serious or severe cardiac adverse events reported in sofosbuvir-treated subjects. There were no treatment discontinuations due to cardiac AEs in subjects who were treated with sofosbuvir. Table 32 summarizes adverse events by MedDRA preferred term and toxicity grade.

Table 32: 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	Grades 3/4/5	All Grades	Grades 3/4/5
P7977-1231				
	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
GS-US-334-0107				
	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
GS-US-334-0108				
	SOF+RBV 12 Weeks + Placebo 4 Weeks N=103		**SOF+RBV 16 Weeks** N=98	
Palpitations	2 (1.9)	0	0	0
GS-US-334-0110				
	SOF+PEG+RBV 12 Weeks N=327		NA	
Coronary Artery Disease	1 (0.3)	0		
Palpitations	3 (0.9)	0		

n (%) is the number of subjects experiencing at least one adverse event at the stated toxicity grade using the maximum toxicity grade per subject, system organ class, and preferred term
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

The only Grade 2 event observed in the SOF+RBV group was palpitations. The 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).

Table 33 provides an overall summary of adverse events noted in the cardiac disorders SOC in the secondary safety population.

Table 33: Overall Summary of Cardiac Disorder Adverse Events (SOC) in the Secondary Safety Population

N (%)	P7977-0221 (N=63)	P7977-0422 (N=146)	P7977-0742 (N=332)	P7977-0523 (N=120)	P2938-0721 (N=50)
≥1 AE	0	2 (1)	7 (2)	6 (5)	1 (2)
Grade 1	0	1(<1)	5 (2)	5 (4)	1 (2)
Grade 2	0	0	1 (<1)	0	0
Grade 3	0	0	1 (<1)	1 (<1)	0
Grade 4	0	1 (<1)	0	0	0
SAE	0	1 (<1)	1 (<1)	1 (<1)	0
AE leading to Discontinuation	0	1 (<1)	0	0	0

Source: Submission to NDA dated June 24, 2013

Cardiac Events in the Secondary safety Population (5 Phase 2 trials)

One Grade 4 event (SAE) which also led to treatment discontinuation:
Subject ID #1018-1213: A 58 year old man in Study P7977-0422 (PROTON) with past MHx relevant for cardiac stents, hypertension, hypercholesterolemia and tobacco use was randomized to SOF+PEG+RBV experienced acute MI on Day 72. Study drugs were discontinued and the AE resolved without sequelae on posttreatment Day 8.

Two Grade 3 events (both SAEs):
Subject ID #1019-7033 in P7977-0724 (ATOMIC): A 63 year old female with a past MHx significant for hypertension, diabetes and a heart murmur who completed SOF+PEG+RBV therapy for 24 weeks. On post-treatment Day 8, she experienced an SAE of Grade 3 arrhythmia (atrial fibrillation). An echocardiogram showed an ejection fraction of 60%, moderate left ventricular hypertrophy, moderate mitral valve regurgitation, and moderate to severe tricuspid regurgitation. She received a pacemaker for sick sinus syndrome post atrial fibrillation and was placed on digoxin. This event was deemed unrelated to study drugs and resolved on posttreatment Day 13.

Subject ID #1031-5070 in Study P7977-0523 (ELECTRON): A 54 year old female with a past MHx significant for “palpitations—considered benign” and syncopal episode secondary to dehydration completed treatment with SOF+PEG+RBV for 8 weeks (Group 6). On posttreatment Day 24, she experienced Grade 3 angina pectoris. The event was deemed unlikely related to SOF and PEG and unrelated to RBV and resolved on posttreatment Day 25. Further work-up was done and a cardiologist concluded that coronary artery (disease) had been reasonably excluded.

In Study P7977-0422, Grade 1 event was palpitations.
In Study P7977-0724, Grade 1 events were palpitations (N=3), tachycardia (N=2) and the Grade 2 event was coronary artery disease.
In Study P7977-0523, the Grade 1 events were palpitations (N=3) and atrial fibrillation (N=2).

Cardiac Events in Special HCV Populations

Two subjects with cardiac events in Study P7977-2025 (Pre-transplant study).

One subject receiving SOF+RBV experienced Grade 1 palpitations on Day 26, which were assessed as not related to study drugs.

One subject (Subject #0773-7717) was a 63 year old male with a past medical history relevant for paroxysmal atrial fibrillation and hypertension who experienced Grade 2 atrial fibrillation on Day 55 that was assessed as not related to study drugs. The subject was hospitalized and the event was considered resolved without sequelae on Day 56.

One subject (Subject #0843-8722) with acute MI in Study GS-US-334-0123 (PHOTON-1)

The subject was a 44 year old male with HIV/HCV coinfection who was receiving treatment with SOF+RBV for 12 weeks. On Day 68 the subject was found unresponsive by his wife and subsequently admitted with atrial fibrillation, atrial flutter, acute renal failure, respiratory failure, encephalopathy, pneumonia, septic shock and staphylococcal bacteremia. All of these events resolved during the subject's hospitalization. It was subsequently determined that he had experienced a relapse of injection methamphetamine abuse that may have precipitated these events.

There was one event of myocardial infarction in the BMS-sponsored trial AI444040.

The subject was a 55 year old man with a history of prior myocardial infarction, hypertension, hypercholesterolemia, ongoing tobacco use (1.5 packs/day), hypothyroidism, and gastroesophageal reflux disease. The subject completed 6 months of treatment per protocol. At the posttreatment Week 36 visit, he reported that one month prior he had experienced a “heart attack” leading to hospitalization and stent placement. His hemoglobin at that time was 15.7 g/dL and peak troponin was 1.44. The event was assessed as unrelated to study drugs.

The Applicant noted that there have been no cases of cardiomyopathy in sofosbuvir-containing trials. In addition, the Applicant stated that there is no current evidence for sofosbuvir-related cardiotoxicity in the sofosbuvir clinical development program.

Exposure-response safety analyses were also evaluated by Dr. Florian for adverse events of dyspnea and system organ class cardiac disorders (based on MEDRA system organ classification) to identify if the SOF or GS-331007 exposures from the Phase 3 trials were associated with any cardiac adverse events.

> This analysis was based on the pooled Phase 3 population and identified that any grade dyspnea and any grade cardiac events were more likely in subjects with higher GS-331007 exposures. However, the significance of these adverse events relationships should be interpreted with caution. First, the overall number of cardiac events in the Phase 3 population administered SOF was 19 out of 991 subjects with PK data available (6 of 327 in SOF+PEG+RBV [1.8%] and 13 of 664 in SOF+RBV [1.9%]). This event rate was lower than the cardiac event rate observed in the PEG+RBV control arm from P7977-1231 (11 of 243 [4.2%]). In addition, the adverse event listings under this system organ class were predominantly grade 1 (17 of 19; only two events were grade 2) and include palpitations, tachycardia, bradycardia, and ventricular extrasystoles. These adverse events could also be confounded by 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, insomnia, tachycardia, and chest pain.

Reviewer's Comments

In most of the cases noted above, the subject either had a prior history of cardiovascular disease or had cardiovascular risk factors. No clustering of adverse events was noted. Ribavirin, which causes hemolytic anemia, can result in profound decreases in hemoglobin levels that can contribute to fatigue and possibly worsening of cardiac status.

Based on the review of submitted data to date, no obvious safety issue related to cardiac toxicity has been identified. We will continue to monitor closely in the postmarketing setting for any potential signals.

7.3 Major Safety Results

7.3.1 Deaths

The deaths reported in the sofosbuvir pivotal trials are summarized in Table 34. Deaths reported in the ongoing trials are included in the relevant sections of this review.

Table 34: List of all Deaths in Pivotal Sofosbuvir Trials

Study Number/Subject ID	Age/Sex/ Race (ethnicity)	Treatment Group	Causes of Death (MedDRA Preferred Term)	Days to Death
Pivotal Trials				
P7977-1231/ 1276-310535	52/M/W (Hispanic)	SOF+RBV 12 Week	Toxicity to various agents (cocaine and heroin intoxication)	Study Day (b) (6)
Non-treatment-emergent Deaths (occurred > 30 days after last dose of study drug)				
P7977-1231/ 1225-310184	56/F/W (non-Hispanic)	PEG+RBV	Brain Neoplasm	(b) (6) days after the last dose of study drug (subject discontinued study drugs on Study Day 37)
GS-US-334-0107/ 2074-7350	55/M/W (non-Hispanic)	SOF+RBV 12 Week	Cardiogenic shock secondary to aortic stenosis	(b) (6) days after the last dose of study drug
GS-US-334-0107/ 5586-7322	66/M/W (non-Hispanic)	SOF+RBV 12 Week	Metastatic lung cancer	(b) (6) days after the last dose of study drug

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities

Three deaths occurred during the study follow-up period but > 30 days after last dose of study drug (non-treatment-emergent) in pivotal trials. None of the 3 non-treatment emergent deaths was considered related to the study treatment. Selected clinical summaries are provided below because of their clinical significance.

Subject ID: [P7977-1231] 1276-310535
Acute cocaine and heroin intoxication

A 52-year-old white (Hispanic) male enrolled in SOF+RBV group died due to acute cocaine and heroine intoxication on Study Day (b) (6). It was uncertain to the investigator if the patient had actually ingested any study drug. Concomitant medications included hydrochlorothiazide, quinapril, cyclobenzaprine,

lamotrigine, oxycodone, acetylsalicylic acid, omeprazole and meloxicam. Medical history included intravenous drug abuse (stopped in 1998), bipolar disorder, hypertension, gastroesophageal reflux disease, and arthritis. He reported no illegal drug use or alcohol use during the screening period. Baseline laboratory results at screening included potassium 4.0 mEq/L (reference range (RR): 3.5-5.5 mEq/L), glucose 89 mg/dL (RR: 68-118 mg/dL), AST 48 U/L (RR: 10-45 U/L), ALT 84 U/L (RR: 6-48 U/L), and total CPK 59 U/L (RR: 24-195 U/L). The subject was reported to be well except for the complaint of a very mild sore throat on Day 1 study visit. Abnormal central laboratory results on Day 1 showed potassium 3.1 mEq/L, glucose 122 mg/dL, AST 55 U/L, ALT 97 U/L, and total CPK 266 U/L. An ECG performed on the same day showed normal sinus rhythm. Study drugs were dispensed with instructions to begin taking the first dose of the study drugs when at home. At night of Day (b) (6) the investigator was informed by the police that the subject had passed away. (b) (6) the patient's wife reported that the patient was found dead on the street. She was uncertain as to whether the patient had actually ingested any study medication prior to his death. The police told the investigator that there were two witnesses who saw the patient consume a large amount of alcohol in the hours before his death and the police at the time felt that the death was due to the patient falling onto the street after ingestion of alcohol. An autopsy was performed and the preliminary copy of death certificate listed cause of death as acute cocaine and heroin intoxication. The investigator assessed the event not related to the study drugs. Alternative causality included overdose.

Subject ID: [GS-US-334-0107] 2074-7350
Aortic stenosis, Hypotension, Sepsis-toxic

A 55-year-old Caucasian male patient was treated with SOF+RBV and completed 12 weeks of therapy, per protocol. Medical history included aortic valve stenosis (1991), myocardial infarction (1992), diabetes mellitus (2007), back pain (2000) and high cholesterol (2007). Concomitant medications included metformin, glipizide, acetylsalicylic acid, celecoxib, clopidogrel and Lipidex. Approximately six weeks after completing the treatment, the patient was found collapsed on the street, was resuscitated and admitted to the hospital. The patient underwent coronary artery study due to cardiogenic shock which revealed minor coronary artery disease and aortic stenosis. Further assessment with echocardiogram was recommended to assess degree of aortic stenosis. An intraaortic balloon pump was inserted and the patient underwent aortic valve replacement for severe aortic stenosis and cardiogenic shock. The patient also developed hypotension and sepsis (toxic). Chest x-ray showed widespread airspace opacity consistent with congestive heart failure. Echocardiogram showed severe aortic stenosis with mild aortic regurgitation. The patient died (b) (6) days after the last dose of study drug. According to the patient's spouse, the coroner's reported cause of death was cardiogenic shock due to aortic stenosis.

The investigator assessed the events not related to study drugs. Alternative causality for aortic stenosis included the patient's pre-existing condition. Alternative causality for hypotension and sepsis (toxic) included the patient's intercurrent illness.

Reviewer's comments:

The total number of deaths in these trials is small and the noted cause of death in each of these cases does not raise any safety concerns. No clustering of events was noted. Based on the reported information, I agree with the investigator's assessment of the events that were considered to be unlikely related to study drugs.

7.3.2 Nonfatal Serious Adverse Events

A SAE was defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject was at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other medically significant events that were not be immediately life-threatening or resulted in death or hospitalization, but based upon appropriate medical and scientific judgment, may have jeopardized the subject or may have required medical or surgical intervention to prevent 1 of the outcomes listed above.

In the Integrated Primary Safety Population, ≤ 4% subjects in all treatment groups experienced an SAE (Table 35). The treatment-emergent SAEs reported in the pivotal Phase 3 trials are summarized by system organ class and MedDRA preferred terms in Table 35.

Table 35: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in the Primary Safety Population (Integrated Data)

MedDRA Preferred Term	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+SOF+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Number of subjects with any SAE (%)	2 (2.8)	22 (3.9)	3 (3.1)	4 (1.2)	3 (1.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS					
Anaemia	0	1 (0.2)	0	1 (0.3)	0
Leukopenia	0	0	0	1 (0.3)	0
CARDIAC DISORDERS					
Atrioventricular Block	0	0	0	0	1 (0.4)
GASTROINTESTINAL DISORDERS					
Abdominal Pain	0	1 (0.2)	0	1 (0.3)	0
Pancreatitis	1 (1.4)	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
Non-Cardiac Chest Pain	0	1 (0.2)	1 (1.0)	1 (0.3)	0
Pyrexia	0	2 (0.4)	0	1 (0.3)	0
Chest Pain	0	1 (0.2)	0	0	0
Drug Withdrawal Syndrome	0	1 (0.2)	0	0	0
Oedema Peripheral	0	1 (0.2)	0	0	0
HEPATOBILIARY DISORDERS					
Bile Duct Stone	1 (1.4)	0	0	0	0
Portal Vein Thrombosis	0	1 (0.2)	0	0	0
IMMUNE SYSTEM DISORDERS					
Allergy To Arthropod Sting	0	1 (0.2)	0	0	0
Cryoglobulinaemia	0	0	0	1 (0.3)	0
Hypersensitivity	0	1 (0.2)	0	0	0
INFECTIONS AND INFESTATIONS					
Cellulitis	0	2 (0.4)	0	0	0
Abdominal Abscess	0	1 (0.2)	0	0	0
Bronchitis	1 (1.4)	0	0	0	0
Infection	0	0	0	0	1 (0.4)
Osteomyelitis Chronic	0	1 (0.2)	0	0	0
Urinary Tract Infection	0	1 (0.2)	0	0	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS					

MedDRA Preferred Term	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+SOF+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Overdose	0	1 (0.2)	1 (1.0)	0	0
Spinal Compression Fracture	0	1 (0.2)	0	1 (0.3)	0
Clavicle Fracture	0	0	0	0	1 (0.4)
Fall	0	1 (0.2)	0	0	0
Injury	0	1 (0.2)	0	0	0
Rib Fracture	0	0	0	0	1 (0.4)
Road Traffic Accident	0	1 (0.2)	0	0	0
Toxicity To Various Agents	0	1 (0.2)	0	0	0
Upper Limb Fracture	0	1 (0.2)	0	0	0
METABOLISM AND NUTRITION DISORDERS					
Hypoglycaemia	0	1 (0.2)	0	0	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)					
Hepatic Neoplasm Malignant	0	3 (0.5)	0	0	0
Basal Cell Carcinoma	0	1 (0.2)	0	0	0
Breast Cancer In Situ	0	0	0	0	1 (0.4)
Laryngeal Cancer	0	0	0	1 (0.3)	0
PSYCHIATRIC DISORDERS					
Abnormal Behaviour	0	1 (0.2)	0	0	0
Suicide Attempt	0	0	1 (1.0)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
Chronic Obstructive Pulmonary Disease	0	1 (0.2)	0	0	0
Pneumothorax	0	0	0	0	1 (0.4)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS					
Eczema	0	1 (4.5)	0	0	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

The incidence of SAEs was comparable between the SOF+RBV 12 Week group (4%, 22 subjects) and SOF+RBV 16 Week group (3%, 3 subjects). The incidence of SAEs was very low in the SOF+PEG+RBV group (1.2%, 4 subjects). The incidence of SAEs that were considered related to the study drug by the investigators was very low (four subjects). These SAEs were: anemia; peripheral edema and eczema; anemia and

cryoglobulinemia; leukopenia and pyrexia. The investigator's causality assessment for relatedness seems reasonable for the observed SAEs.

Malignant hepatic neoplasm (0.5%, 3 subjects) and pyrexia and cellulitis (each 0.4%, 2 subjects) were the only SAEs reported in ≥ 2 subjects in the SOF+RBV 12 Week group. No other individual SAEs in the SOF+RBV 12 Week groups were reported in more than 1 subject. There was no apparent clustering of SAEs observed within SOCs.

Reviewer's Comments

Hepatocellular carcinoma (HCC) is a known complication of cirrhosis in this patient population. All three subjects with malignant hepatic neoplasm had documented evidence of baseline cirrhosis either on histology or imaging study.

Selected case narratives of SAEs are summarized below due to their clinical significance.

Subject ID: [GS-US-334-0107] 0407-7218
Acute pancreatitis

> Acute pancreatitis was reported in a 67-year-old Caucasian female patient approximately 6 weeks after study treatment completion. Medical history included back pain. Concomitant medications included ondansetron, ibuprofen, pregabalin, oxycodone/paracetamol and triamcinolone. The patient was admitted with symptoms of severe abdominal pain. Initial lipase level was 3,769 (units not reported). Amylase level was 1000 (no unit reported). CT scan findings were consistent with acute pancreatitis and no gallstones were found. The patient was discharged after 3 days. The event was considered resolved. The investigator assessed the event not related to study drugs. No alternative causality was provided.

Subject ID: [GS-US-334-0107] 1069-7352
Hypoglycemic episode

> A 55-year-old Caucasian male subject was receiving treatment with SOF+RBV. Medical history included: diabetes mellitus type 1, insomnia, GERD and hypertension. Concomitant medications included temazepam, omeprazole, clazapril, amlodipine, aspirin, nova rapid, protophane, and fluvax. Around TW 6, the patient was admitted due to hypoglycemic episode. While shopping, the subject felt faint and ate a Snicker's bar and drank some milk. His blood sugar was found to be 11 (unit not reported) and blood pressure was low. It was reported that the subject had two hypoglycemic episodes in the past two days and has had a recent change of insulin regimen. The investigator assessed the event not related to study drugs. Alternative explanation included the subject's

pre-existing condition (diabetes mellitus type 1). No action was taken with the study drugs and subject completed 12 weeks of therapy, per protocol.

Subject ID: [GS-US-334-0107] 1069-7371
Allergic reaction unclear etiology

A 40 year old Caucasian male subject was receiving SOF+RBV). Concomitant medications included Zoplicone (non-benzodiazepine sedative-hypnotic). Medical history included: insomnia; no known drug allergies. Three weeks after initiation of study treatment, the subject took his usual medications and two tablets of Zoplicone 7.5 mg. After an unspecified interval, he ate apple crumble with ice cream. Approximately one hour later, the patient developed a blotchy, erythematous rash (site not reported) and experienced mild difficulty breathing. Examination revealed heart rate of 110 beats/minute, BP 120/60, and oxygen saturation of 94-96%. No features of anaphylaxis were noted. An ECG and chest x-ray were reported to be normal. Treatment included oral prednisone 40 mg and loratadine 10 mg. The patient was admitted for observation of allergic reaction of unclear etiology. Next day, the event resolved and patient was discharged. No action was taken with the study drug or Zoplicone in regards to the event. The investigator reported causality as not related to study medications, but related to an unspecified intercurrent illness. The subject completed 12 weeks of therapy per protocol.

Reviewer's Comment

I agree with the investigator's causality assessment and Gilead's assessment that "The acute course of the event occurring several weeks after initiation of study drug as well as the resolution of the event with continuation of study drug further suggests alternate etiology."

Subject ID: [GS-US-334-0107] 4323-7310
Early abscess in lower right quadrant (Abdominal abscess)

A 51-year-old Caucasian female subject was receiving treatment with SOF + RBV. After 8 weeks of therapy, the subject complained of abdominal pain, diarrhea and fever over 101 F. A week later, the patient presented to the ER with fever. Low potassium levels were detected and potassium supplement was started. The patient was released on the same date. Two days later, all study drugs were interrupted. The patient was hospitalized with a fever over 104 F. CT scan showed an early abscess on right lower quadrant. She was treated with Zosyn. The patient restarted the study drugs after 10 days of interruption and completed to final week 12 dose per protocol without any new adverse events. The outcome of the event was reported as resolved. The investigator assessed the event not related to the study medications or study procedures. Alternative

causality was reported as unknown. The patient did not have any significant medical history or any risk factors for an intra-abdominal abscess, e.g. perforated viscus, recent surgery or diverticulitis.

Subject ID: [GS-US-334-0107] 2074-7398
Swelling in both lower legs, Worsening Eczema

This 34-year-old Caucasian male patient was treated with SOF+RBV for 12 weeks. Medical history was significant for eczema, asthma and gastric reflux. Concomitant medications included Seretide inhaler for asthma and Nexium for gastric reflux. Four weeks after treatment discontinuation, the patient was hospitalized for worsening eczema, swelling in both lower legs lower, and painful left lower leg. A bilateral lower limb venous Doppler ultrasound showed no evidence of deep vein thrombosis (DVT). X-rays were normal with no evidence of bony or joint abnormality or fracture or dislocation. The patient was started on intravenous cefazolin and prednisolone 50 mg orally, emulsifying ointment; betamethasone valerate 0.01% and 0.05% and wet dressing for exacerbated eczema. The skin biopsies showed spongiotic dermatitis pattern which can be seen in eczema and the presence of occasional eosinophils also raised the possibility of a drug reaction. The investigator assessed the events related to the study drugs (GS-7977 and ribavirin). Alternate causality for worsening eczema was reported as a pre-existing condition and alternate causality for swelling in both lower legs was reported as worsening eczema. The reported events resolved with intervention.

Reviewer's Comment

Worsening of eczema and swelling of legs four weeks after completion of study treatment in a subject with a history of eczema makes the causality assessment challenging. Although, the contribution of study agents (SOF+RBV) can not be fully ruled out, the adverse events seem less likely to be associated with sofosbuvir.

Subject ID: [GS-US-334-0107] 4434-7432
Cellulitis, Fever

58-year-old Caucasian female patient was admitted approximately two weeks after completing 12 weeks of therapy with SOF+RBV. The patient was hospitalized for fever and progressively worsening cellulitis involving both lower extremities and received intravenous antibiotics. The investigator assessed the event not related to the study drugs. The outcomes of the events were reported as resolved. The patient's history of recurrent cellulitis and signs of venous insufficiency were noted by Gilead as a likely explanation for the reported cellulitis.

Subject ID: [GS-US-334-0107] 2760-7374
Noncardiac chest pain

55-year-old Hispanic American female subject completed 12 weeks of therapy with SOF+RBV. The subject's medical history included hypertension, hyperlipidemia, diabetes mellitus, asthma, insomnia, anxiety, peripheral neuropathy, arthritis and cellulitis. Concomitant medications included alprazolam, zolpidem, tramadol, hydrocodone, dicycloverine, benazepril, insulin (Novolog), pregabalin, salbutamol, glyceryl trinitrate, sulfamethoxazole/trimethoprim and insulin glargine (Lantus). More than two weeks after treatment completion, the patient presented with complaints of chest pain. Initial EKG showed sinus tachycardia with heart rate of 111. The patient was admitted to telemetry for monitoring of serial EKG and cardiac enzymes. Next day, EKG was normal and chest x-ray showed no acute process. Laboratory results included creatine kinase 38 U/L, 35 U/L and 27 U/L (RR: 21-232 U/L) and troponin <0.03 ng/ml times three (RR: 0.00-0.06 ng/ml) which were all within normal ranges. Treatment included Nitropaste, acetylsalicylic acid, metroprolol, oxycodone, gabapentin, clonidine and alprazolam. The patient was discharged from the hospital and the event was considered resolved. The investigator assessed the event not related to study drugs. Alternative causality included intercurrent illness of arthritis, neuropathy and anxiety.

Subject ID: [GS-US-334-0107] 4238-7308
Coxsackie pneumonia worsening, pericardial effusion

51-year-old Caucasian male patient completed 12 weeks of therapy with SOF+RBV. Medical history was significant for chronic obstructive pulmonary disease, anemia, fibromyalgia, rheumatoid arthritis (RA), osteoarthritis, muscle spasms, hypertension, GERD, insomnia, anxiety and depression. The patient is a smoker (smoked one pack per day for 20 years) and has a penicillin allergy. He is chronically immunosuppressed (low-dose prednisone daily and plaquenil for RA). More than three weeks after completing study treatment, the patient was diagnosed with pneumonia and was treated with doxycycline. One week later, presented with worsening chest pain on inspiration and had significant exertional dyspnea. He has no history of underlying cardiac disease. A chest angiogram showed the presence of a large pericardial effusion with enhancement of the pericardium concerning for pericarditis. Groundglass opacities throughout bilateral lungs were also seen. Laboratory tests included white count 23.5, hemoglobin 11.5, platelets 371,000, sodium 132, potassium 3.9, troponin less than 0.02 (RR: 0.00-0.07), total CK 40 units/L (RR: 26-308) and CK MB <0.5 (RR: 0.0-3.2 ng/ml). The patient was admitted to intensive care unit and received intravenous antibiotics. He was placed on steroids and received immunoglobulin. Coxsackie virus testing came back positive. Chest x-ray showed cardiomegaly consistent with known pericardial effusion and increasing diffuse right lung

airspace infiltrates consistent with pneumonia. Intravenous antibiotics were continued with slow improvement and patient was to be discharged on several more days of antibiotics as well as a tapering dose of prednisone. A “scan” was done to confirm pneumonia resolution and the event was considered resolved. The investigator assessed the events not related to study drugs.

Subject ID: [GS-US-334-0107] 4139-7279
Adult Onset Stills Disease (Atypical)

This 56-year-old Caucasian female subject received 12 weeks of SOF+RBV therapy, per protocol. The subject reported experiencing recurrent episodes of sore throat, fever, chest congestion, and dyspnea beginning in the posttreatment period (date not specified). The episodes were approximately monthly and approximately 4.5 months after the completion of therapy, the patient experienced fever, fatigue, headaches and myalgias and presented to ED with fever, chest pain and leukocytosis. CK and Troponin were negative. She had an episode of supraventricular tachycardia (SVT) versus atrial fibrillation with rapid ventricular rate (RVR) of 175-205. She also had a five second syncopal episode with her heart rate decreasing to the 60s followed by a rate of around 110. The patient was admitted for atrial fibrillation with RVR, syncope and systemic inflammatory response (SIRS). Echocardiogram revealed pericardial effusion without hemodynamic compromise. She had a protracted clinical course and underwent an extensive diagnostic work-up and was diagnosed with autoimmune pericarditis/adult onset still’s disease several months after treatment completion. It was noted that the patient responded well to corticosteroid and anakinra (anti-inflammatory, IL-1 inhibitor) therapy.

Subject ID: [GS-US-334-0108] 0519-1532
Opiate overdose

This 52-year-old Caucasian male patient received treatment with SOF+RBV for 16 weeks. Concomitant medications included lorazepam, nadolol and quetiapine. Medical history included hepatic cirrhosis, alcoholism and drug abuse. Two weeks after study treatment completion, the patient was found pulseless and apneic on the street. Cardiopulmonary resuscitation was administered for one minute by Emergency Medical Services and was transported to the Emergency Room. The patient was given Narcan with good response. The patient reported taking Percocet and 'had been drinking" and experienced a "blackout." It was reported that the patient was using illicit Percocet. The investigator assessed the event to be not related to study drugs.

Subject ID: [GS-US-334-0110] 4308-6454
Leukopenia, Fever, Noncardiac chest pain

A 52-year-old female subject of African descent was on treatment with SOF+PEG+RBV. Medical history included GERD and smoking (quit 18 years ago). No history of chest pain, chronic renal failure or underlying pulmonary disease. Family history was significant for multiple family members with coronary artery disease and mother who passed away due to myocardial infarction (MI). No known drug allergies. Around TW 8, the subject presented to the ER with complaints of intermittent substernal non-radiating chest pain and shortness of breath that began four days ago. Chest pain was on the left side, described as "pressure-like" and lasting 15 to 20 minutes. The subject had multiple episodes and the symptoms gradually worsened over several days. The subject reported feeling very weak and tired recently and had difficulty walking up a flight of stairs due to shortness of breath. The subject reported a stress test done a year ago was normal. She also reported feeling her throat "closing up" and had some pain while swallowing. She denied any cough, dysuria or rashes. Upon arrival in the ER, her temperature was 100.6 (unit not reported) and had mild shortness of breath at rest. Laboratory results included troponin <0.01 ng/ml (RR: 0.0-0.78), white blood cell count 3.4 K/uL (RR: 4.0-11.0), neutrophils 30% (RR: 45-75) and normal cardiac enzymes. EKG showed normal sinus rhythm. Chest x-ray was normal. Stress test showed mild abnormality (small amount of anterior septal reperfusion noted). The subject underwent a cardiac angiogram. Acute coronary syndrome was ruled out. Sepsis work-up was negative. RBV dose was reduced to 600 mg daily. The event of noncardiac chest pain was reported as resolved two days after ribavirin dose reduction. The investigator assessed the event leukopenia and fever, related to peginterferon alfa-2a, not related to other study drugs, and the event noncardiac chest pain not related to study drugs.

Reviewer's Comment

No definitive conclusions regarding causality assessments can be made due to concomitant use of peginterferon alfa and ribavirin.

7.3.3 Dropouts and/or Discontinuations

Subjects who had virologic failure while receiving SOF+RBV were discontinued from study treatment. In addition, all subjects who met any of the following criteria were discontinued from study treatment:

- Elevation of ALT and/or AST > 5 × baseline value or nadir, confirmed by immediate repeat testing
- Elevation of ALT > 3 × baseline value and total bilirubin > 2 × ULN, confirmed by immediate repeat testing
- Elevation of ALT > 15 × ULN confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 event assessed as related to treatment with SOF or placebo

Table 36: Subject Disposition in the Primary Safety Population (Safety Analysis Set – Integrated Data)

	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
Total Number of subjects	N=71	N=566	N=98	N=327	N=243
Study Discontinuation					
N (%)	71 (100)	115 (20.32)	28 (28.57)	29 (8.87)	48 (19.75)
Reasons for Study Discontinuation					
Efficacy Failure	71 (100)	87 (15.37)	28 (28.57)	26 (7.95)	28 (11.5)
Lost To Follow-Up	0	10 (1.77)	0	2 (0.6)	9 (3.7)
Other	0	9 (1.59)	0	0	4 (1.65)
Consent Withdrawn	0	6 (1.06)	0	1 (0.3)	6 (2.47)
Death	0	3 (0.53)	0	0	1 (0.4)
Study Treatment Discontinuation					
N (%)	3 (4.2)	18 (3.2)		7 (2.1)	54 (22.2)
Reasons for Study Treatment Discontinuation					
Adverse Event	3 (4.2)	8 (1.4)	0	5 (1.5)	26 (10.7)
Virologic Failure	0	1 (0.2)	0	0	17 (7.0)
Lost To Follow-Up	0	4 (0.7)	0	0	5 (2.1)
Other	0	3 (0.5)	0	0	4 (1.6)
Consent Withdrawn	0	1 (0.2)	0	1 (0.3)	2 (0.8)
Death	0	1 (0.2)	0	0	0
Protocol Violation	0	0	0	1 (0.3)	0

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin; N = number of subjects
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

The following table (Table 37) summarizes the adverse events (by MedDRA preferred terms) leading to permanent discontinuation from any study drug in two or more subjects in any treatment group in the pivotal Phase 3 trials. A total of 13 sofosbuvir treated subjects discontinued study treatment due to adverse events in the sofosbuvir containing treatment groups.

Table 37: Adverse Events Leading to Permanent Discontinuation from any Study Drug Occurring in ≥ 2 subjects in any Treatment Group in the Primary Safety Population (Integrated Data)

MedDRA Preferred Term	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Number of Subjects (%)					
Anaemia	0	1 (0.2)	0	2 (0.6)	4 (1.6)
Fatigue	0	0	0	0	6 (2.5)
Depression	0	1 (0.2)	0	0	3 (1.2)
Insomnia	0	1 (0.2)	0	0	3 (1.2)
Alanine Aminotransferase Increased	1 (1.4)	0		0	2 (0.8)
Anxiety	0	1 (0.2)	0	0	2 (0.8)
Nausea	0	0	0	0	3 (1.2)
Neutropenia	0	0	0	1 (0.3)	2 (0.8)
Haemoglobin Decreased	0	0	0	0	2 (0.8)
Irritability	0	0	0	0	2 (0.8)
Loss of Consciousness	0	0	0	0	2 (0.8)
Pain	0	0	0	0	2 (0.8)
Platelet Count Decreased	0	0	0	0	2 (0.8)

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

The summaries of the clinical narratives on the selected subjects are provided below due to their clinical significance.

Subject ID: [P7977-1231] 1031-310130
Blood creatine phosphokinase increased

A 42-year-old native Hawaiian or other Pacific Islander, non-Hispanic male with chronic genotype 3 HCV infection and cirrhosis was randomized to SOF+RBV group. Medical history included narcotic dependence and concomitant medications included methadone. He was noted to have an elevated screening and baseline creatine phosphokinase (CK) which were not deemed clinically significant by the Investigator due to the subject's job as a manual laborer. At baseline, subject's CK value was 394 IU/L (2.0×ULN), normal range for the laboratory noted as 24-195 IU/L. The subject experienced Grade 1 insomnia starting on Day 2, Grade 1 arthralgia, myalgia, and dry mouth starting on Day 3, and Grade 2 muscle twitching localized to the upper arms starting on Day 13. CK

levels were similar to baseline at the Week 1 and Week 2 visits. At the Week 3 visit, the CK had increased to 8759 U/L. He did not report worsening of symptoms at that visit, and noted that he had been feeling so good since starting treatment, the preceding week at work he elected to perform the heaviest manual labor jobs available, and 1 day preceding the Week 3 visit he spent the entire day using a handsaw in both arms to saw wood. Local repeat blood work 2 days after the Week 3 visit demonstrated an elevated CK of 993 U/L, normal creatinine, and normal ECG. Study drugs were continued with a plan for close follow up. He was advised to reduce his physical activity. He returned to the clinic 4 days later (Day 29) for his Week 4 study visit and his CK was elevated at 2225 U/L (central laboratory). Study drugs were discontinued. During the posttreatment follow up period, the subject's symptoms of arthralgia, myalgia, and muscle twitching resolved. MRI of the cervical spine (19 days posttreatment) showed C6 and C7 nerve root compromise with prominent wasting of the distal triceps. On posttreatment Day 28, CK had returned to baseline with a value of 387 IU/L. However, at the posttreatment Week 24 visit, the subject's CK increased to 9121 U/L and he was referred to a rheumatologist for evaluation. An electromyography (EMG) demonstrated myopathic changes, and a muscle biopsy (253 days posttreatment) showed evidence for compensated denervation likely related to previous radiculopathy and no evidence for inflammatory myopathy. Rheumatologist's assessment was that the subject probably had a metabolic myopathy with elevated CK and negative autoimmune profile (ANA, ENA, myositis antibodies). He was noted to not require further follow up.

Subject ID: [P7977-1231] 1068-310203
Chest Pain

A 57-year-old white, non-Hispanic female with chronic genotype 3 HCV infection and no cirrhosis was randomized to SOF+RBV group. Medical history included postmenopausal, insomnia, hypertension, generalized pain/arthritis, neck fusion, thoracostomy, right ankle surgery, right knee replacement, and anxiety/depression. Concomitant medications included dyazide and amlodipine besilate (hypertension), morphine sulfate (generalized pain), tizanidine hydrochloride (insomnia), and alprazolam (anxiety). The subject experienced Grade 1 chest pain starting on Day 2 and was considered by the investigator to be unrelated to SOF and RBV. No treatment was administered. CPK remained within normal range. Concurrent AEs included Grade 1 arthralgia, Grade 1 nausea, Grade 1 insomnia, Grade 1 muscle spasms, Grade 1 dry skin, Grade 1 dehydration, Grade 1 pruritus, Grade 3 headache (continuing), and Grade 2 vomiting. Study drugs were discontinued on Day 44. The AE of chest pain was considered resolved on posttreatment Day 6.

Subject ID: [P7977-1231] 1091-310386

Decreased appetite, abnormal dreams, weight decreased, agitation, apathy, and depression

A 44-year-old white, non-Hispanic male with chronic genotype 3 HCV infection and no cirrhosis was randomized to SOF+RBV group. Medical history included open reduction internal fixation and skin graft on left arm, MRSA infection left leg, and GERD. Concomitant medications included omeprazole. The subject experienced the AEs Grade 2 decreased appetite, abnormal dreams, and weight decreased starting on Day 2 and Grade 2 agitation, apathy and depression starting on Day 12 that led to study drug discontinuation. All of the AEs were considered by the investigator to be related to RBV; decreased appetite, abnormal dreams and weight decreased were also considered to be related to SOF, while agitation, apathy, and depression were considered unrelated to SOF. Although no treatment was administered for the AEs, SOF and RBV were interrupted from Day 3 to Day 14. There were no concurrent AEs reported. Study drugs were discontinued on Day 16. The AEs of agitation, apathy, and depression resolved on Day 16 and the AE of abnormal dreams resolved on posttreatment Day 4. The AEs of decreased appetite and weight decreased were continuing at the early termination (and final) visit on posttreatment Day 20.

Subject ID: [GS-US-334-0107] 0535-7281
Muscle spasms

A 58-year-old white, non-Hispanic male with chronic genotype 3a HCV infection and compensated cirrhosis received treatment with SOF+RBV. Medical history included autoimmune disorder, noninvasive basal cell carcinoma excision, thrombocytopenia, chronic postnasal drip, nearsighted, bigeminy, herpes simplex virus, hypertension, insomnia, interstitial lung disease, colon polyp, esophageal varices and gastroesophageal reflux disease. Concomitant medications included acyclovir (herpes simplex), dexamethasone and PritorPlus (telmisartan/hydrochlorothiazide for hypertension), omeprazole, zolpidem, and multivitamins and vitamin D. The subject experienced Grade 2 muscle spasms starting on Day 76 that was considered not related to study drug by the investigator. Study drugs were discontinued on Day 79 by subject himself. Concurrent AEs included Grade 1 insomnia, Grade 1 fatigue (continuing), Grade 1 dizziness, Grade 1 dry throat, Grade 1 hypoaesthesia, Grade 1 scar, Grade 1 dyspnea, and Grade 1 pain. The AE muscle spasms resolved after 7 days (post-treatment Day 3). Creatine kinase was not assessed in GS-US-334-0107. Chemistry parameters values (ALT, AST, and creatinine) were within normal limits on study Day 71 and posttreatment Day 6.

Subject ID: [GS-US-334-0107] 0530-7404
Insomnia

A 48-year-old white, non-Hispanic, female with chronic genotype 3a HCV infection and no cirrhosis was enrolled in Study GS-US-334-0107 based on interferon ineligibility and received treatment with SOF+RBV. Medical history included bilateral tubal ligation, bilateral oophorectomy, suicide attempts, significant psychiatric disease, depression/bipolar, insomnia, obesity, joint pain, fatigue, and forgetfulness. With the exception of vitamins with iron (general health), the subject did not report the use of any concomitant medications prior to randomization. The subject experienced Grade 2 insomnia starting on Day 13 that was considered related to study drugs by the investigator and resulted in treatment with zolpidem tartrate and Medinite (contains pseudoephedrine hydrochloride). Concurrent AEs included Grade 1 dizziness (continuing), Grade 1 pain (continuing), and Grade 1 pruritus (continuing). Study drugs were discontinued on Day 19. The AE insomnia was continuing at the subject's last visit (Posttreatment Week 4; 37 days after discontinuing treatment).

Subject ID: [GS-US-334-0107] 6833-7405
Abdominal pain upper, anxiety, and chest discomfort

A 60-year-old white, Hispanic female with chronic genotype 2 HCV infection and no cirrhosis received treatment with SOF+RBV. Medical history included cholecystectomy, occasional headaches, myalgias, seasonal allergies, postmenopausal, osteoporosis, significant psychiatric disease, and depression. Concomitant medications included fexofenadine hydrochloride and mometasone furoate (seasonal allergies), carisoprodol (myalgias), ibandronate sodium (osteoporosis), ibuprofen, calcium and vitamin D, and multivitamins and vitamin B12. The subject experienced Grade 3 upper abdominal pain starting on Day 3, Grade 3 anxiety and Grade 2 chest discomfort both starting on Day 6, and all were considered by the investigator not related to study drug. Treatment with omeprazole was started for the upper abdominal pain. No other concurrent AEs were reported. Study drugs were discontinued on Day 6. All AEs were reported as continuing at the subject's last visit (Posttreatment Week 4; 39 days after discontinuing treatment).

Subject ID: [GS-US-334-0110] 6834-6423
Anemia

A 56-year-old white, non-Hispanic female with chronic genotype 1a HCV infection and cirrhosis received treatment with SOF+PEG+RBV. Medical history included opioid withdrawal, anxiety, white coat syndrome, hypothyroidism, hypertension, and intermittent acid reflux. Concomitant medications included methadone, levothyroxine, Co-Diovan (hypertension), and alprazolam (anxiety). The subject experienced anemia starting on Day 29 of treatment that progressed to Grade 3 anemia on Day 64; nadir hemoglobin of 6.8 g/dL on Day 64. The AE anemia was considered related to study drugs by the investigator. Study drugs

were discontinued on Day 66 and the subject underwent a blood transfusion. Hemoglobin increased to 10.0 g/dL at the posttreatment Week 4 visit and the final hemoglobin value was 13.7 g/dL at the follow-up Week 12 visit on posttreatment Day 84.

Subject ID: [GS-US-334-0110] 2493-6464
Anemia

A 60-year-old black or African American, non-Hispanic male with chronic genotype 1b HCV infection and no cirrhosis was on treatment with SOF+PEG+RBV. Medical history included hypertension. Concomitant medications included zestoretic (hypertension), multivitamins (general health), and paracetamol (prophylactic fever reducer for PEG). The subject experienced Grade 2 anemia starting on Day 30 that resulted initially in RBV dose reduction; hemoglobin was 9.7 g/dL on Day 29 and declined to a nadir of 8.6 g/dL, 17 days after discontinuing treatment. The AE anemia was considered related to study drugs by the investigator and study drugs were discontinued on Day 54. Anemia was considered resolved on posttreatment Day 96. At the follow-up Week 12 visit on posttreatment Day 87 the hemoglobin value was 11.2 g/dL.

Subject ID: [GS-US-334-0110] 4308-6656
Blood creatinine increased

A 59-year-old black or African American, non-Hispanic male with chronic genotype 1b HCV infection and no cirrhosis was on treatment with SOF+PEG+RBV. Medical history included seasonal allergies, hypertension, headache, hematuria, and renal dysfunction. Concomitant medications included cetirizine hydrochloride and mometasone furoate (seasonal allergies), multivitamin combinations (general health), nebivolol hydrochloride (hypertension), diphenhydramine hydrochloride and ibuprofen (prePEG injection/prophylaxis). The subject experienced Grade 2 increased blood creatinine starting on Day 11 that was considered related to study drugs by the investigator. Serum creatinine increased from 1.58 mg/dL (1.17 × ULN) at baseline to 1.78 mg/dL (1.32 × ULN) on Day 9. The estimated creatinine clearance (by Cockroft Gault equation) concurrently declined from a baseline value of 77.75 mL/min to 68.64 mL/min. At the early termination visit 10 days after the last dose of study drug, serum creatinine had returned to below baseline level (1.44 mg/dL). Concurrent AEs included Grade 1 fatigue. Study drugs were discontinued on Day 16. The AE creatinine increased was considered resolved after 41 days on posttreatment Day 35.

7.3.4 Significant Adverse Events

The majority of subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups (each approximately 88%) experienced at least one AE. Most subjects (94.8%, 310

subjects) in the SOF+PEG+RBV group had at least one AE. The following Table 38 provides an overall summary of adverse events in the integrated data from pivotal Phase 3 trials.

Table 38: Overall Summary of Adverse Events in the Primary Safety Population (Integrated Data)

	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Number of Subjects (%)					
Any AE	55 (77.5)	496 (87.6)	86 (87.8)	310 (94.8)	233 (95.9)
Treatment-Related AE	40 (56.3)	408 (72.1)	75 (76.5)	304 (93.0)	228 (93.8)
Serious AE	2 (2.8)	22 (3.9)	3 (3.1)	4 (1.2)	3 (1.2)
Treatment-Related SAE	0	2 (0.4)	0	2 (0.6)	0
Grade 3 or 4 AE	1 (1.4)	41 (7.2)	4 (4.1)	48 (14.7)	45 (18.5)
Treatment-Related Grade 3 or 4 AE	0	15 (2.7)	2 (2.0)	42 (12.8)	39 (16.0)
AE Leading to Permanent Discontinuation from Any of the Study Drugs	3 (4.2)	9 (1.6)	0	8 (2.4)	29 (11.9)
AE Leading to Permanent Discontinuation from SOF/ SOF Placebo	3 (4.2)	8 (1.4)	0	5 (1.5)	N/A
AE Leading to Modification or Interruption of Study Drug	0	63 (11.1)	7 (7.1)	109 (33.3)	65 (26.7)
Death	0	1 (0.2)	0	0	0

Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

The incidence of SAEs (< 4%) was low in the SOF+RBV 12 Week and SOF+RBV 16 Week groups. No Grade 4 AEs were reported in subjects in the SOF+RBV 12 Week group. One subject in the SOF+RBV 16 Week group had a Grade 4 AE (opiate overdose). In the SOF+PEG+RBV group, the incidence of SAEs was low (1.2%, 4 subjects). No life-threatening (Grade 4) AEs were reported.

Table 39 summarizes adverse events of toxicity Grade 3 or higher which were reported in two or more subjects.

Table 39: Adverse Events of Toxicity Grade ≥ 3 by Preferred Term (observed in ≥ 2 subjects) in the Primary Safety Population (Integrated Data)

MedDRA Preferred Term	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Neutropenia	0	0	0	23 (7.0)	8 (3.3)
Fatigue	0	5 (0.9)	1 (1.0)	5 (1.5)	5 (2.1)
Anaemia	0	3 (0.5)	0	7 (2.1)	2 (0.8)
Headache	0	2 (0.4)	1 (1.0)	5 (1.5)	2 (0.8)
Thrombocytopenia	0	1 (0.2)	0	1 (0.3)	5 (2.1)
Insomnia	0	0	1 (1.0)	0	3 (1.2)
Migraine	0	2 (0.4)	0	1 (0.3)	1 (0.4)
Hepatic Neoplasm Malignant	0	4 (0.7)	0	0	0
Loss Of Consciousness	0	0	0	1 (0.3)	2 (0.8)
Vomiting	0	1 (0.2)	0	2 (0.6)	0
Arthralgia	0	1 (0.2)	0	1 (0.3)	1 (0.4)
Pyrexia	0	3 (0.5)	0	0	0
Abdominal Pain	0	2 (0.4)	0	1 (0.3)	0
Nausea	0	1 (0.2)	0	1 (0.3)	1 (0.4)
Neutrophil Count Decreased	0	0	0	1 (0.3)	2 (0.8)
Chest Pain	0	1 (0.2)	1 (1.0)	1 (0.3)	0
Depression	0	2 (0.4)	0	1 (0.3)	0
Hyperglycaemia	0	0	0	2 (0.6)	0
Suicidal Ideation	0	2 (0.4)	0	0	0
Anxiety	0	1 (0.2)	0	1 (0.3)	0
Abdominal Pain Upper	0	1 (0.2)	0	1 (0.3)	0
Back Pain	0	2 (0.4)	0	0	0
Abdominal Pain Lower	0	0	0	2 (0.6)	0
Cellulitis	0	2 (0.4)	0	0	0
Nephrolithiasis	0	1 (0.2)	1 (1.0)	0	0
Oedema Peripheral	0	2 (0.4)	0	0	0
Alanine Aminotransferase Increased	0	0	0	0	2 (0.8)
Myalgia	0	1 (0.2)	0	1 (0.3)	0
Non-Cardiac Chest Pain	0	0	0	1 (0.3)	1 (0.4)
Urinary Retention	0	1 (0.2)	0	0	1 (0.4)
Abdominal Abscess	0	1 (0.2)	0	0	1 (0.4)
Rib Fracture	0	0	0	1 (0.3)	1 (0.4)

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

Adverse Events of Special Interest

Pancytopenia

An analysis of pancytopenia was performed by the Applicant for all Gilead-sponsored Phase 2 and 3 trials. This was done as adverse events of pancytopenia have been reported in trials evaluating direct-acting antivirals when given in combination with pegylated interferon and ribavirin. Pancytopenia is also a documented adverse reaction in the Prescribing Information for approved pegylated interferon and ribavirin products. For the purposes of this analysis, pancytopenia was defined by the MedDRA preferred term.

There were no events of pancytopenia reported in the pivotal Phase 3 trials.
There was 1 event of pancytopenia reported in a subject who received treatment with 24 weeks of SOF+PEG+RBV in Study P7977-0724 (ATOMIC). The clinical summary is described below:

> Subject # 1021-7440 (Group B)
> The subject is a 57-year-old, black, non-Hispanic female with Metavir Stage 2 fibrosis and low baseline platelets (132×10^3/uL), WBC count (3.2×10^3/uL), and absolute neutrophil count (1.4×10^3/uL). The subject discontinued study drugs due to anemia on Day 78 (hemoglobin was 8.6 g/dL on Day 74, baseline hemoglobin on Day 1 was 12.0 g/dL). The SAE of pancytopenia occurred on posttreatment Day 9 when the subject was admitted with the following hematologic parameters: hemoglobin of 8.1 g/dL, platelet count of 102×10^3/uL, WBC count of $2.8\text{x}10^3$/uL, and absolute neutrophil count of 1.3×10^3/uL. She reported a 1 month history of diarrhea, and a 2-week history of dizziness, fatigue, black tarry stools, and mild epigastric pain. She was transfused with 1 unit of packed red blood cells (PRBCs), given intravenous fluids for hypovolemia and was discharged the next day. At the posttreatment Day 30 visit, her hemoglobin and WBC count increased to 10.9 g/dL and 4.1×10^3/uL, respectively, but her platelets remained low at 89×10^3/uL. The investigator assessed the event as not related to SOF, but as possibly related to PEG+RBV. The event of pancytopenia was noted as resolved on posttreatment Day 168 without additional laboratory results.

Reviewer's Comment

There is no safety concerns of pancytopenia associated with sofosbuvir use at this time.

7.3.5 Submission Specific Primary Safety Concerns

Elevated Creatine Kinase Levels

A comprehensive evaluation for elevated creatine kinase levels was done due to the findings of elevated CK levels in a subject which led to discontinuation of study drugs. The Applicant was also asked to provide their assessment of the observed finding of increased CK levels.

Data are available for SOF+RBV for 12 weeks, PEG+RBV for 24 weeks, and SOF+PEG+RBV for 12 weeks because CK was only assessed in two of the four pivotal Phase 3 trials; P7977-1231 (FISSION) and GS-US-334-0110 (NEUTRINO) trials. In response to the DAVP's query, the Applicant noted the following in their response (submission dated July 15, 2013):

> "The FISSION study employed laboratory safety assessments consistent with the Phase 2 studies which included serum creatine kinase (CK) at scheduled visits. Serum CK was not evaluated in the POSITRON and FUSION studies based on a review of the Phase 2 studies, P7977-0221, P7977-0422, P7977-0523, in which graded CK abnormalities occurred at ≤ 1% and the only 2 Grade 3 elevations were isolated and temporally associated with increased physical activity. In the NEUTRINO study, which was the last Phase 3 study initiated, serum CK was added to the safety assessments to provide additional data due to the single case of a subject in the ongoing FISSION study who discontinued sofosbuvir+RBV treatment due to elevated serum CK. Although this subject's CK elevations occurred in the setting of intensive physical activity and subsequently recurred 24 weeks posttreatment, there was recognition that additional data could be useful for a more comprehensive safety analysis of this parameter."

The overall incidence of CK elevations (all grades) in the primary safety population was 7% in subjects receiving SOF+RBV for 12 weeks, 4% in subjects receiving PEG+RBV for 24 weeks, and 3% in patients receiving SOF+PEG+RBV for 12 weeks. There were seven subjects with on-treatment Grade 3 or Grade 4 CK elevations in the SOF-containing treatment arms; all were noted to be associated with increased physical activity. Summary on these subjects was provided by the Applicant and is shown in Table 40 below.

Table 40: Summary of Subjects with Treatment-Emergent ≥ Grade 3 Creatine Kinase Elevations in the Primary Safety Population

Subject Number	Maximum CK Value	Study Day	Relevant History	Action Taken	Resolution
FISSION SOF+RBV 12 weeks					
1036-310284	2854 (G3)	8	Subject began lifting weights and undertook excessive exercise program for weight loss	Subject advised to reduce activity	No subsequent graded CK elevations
1031-310130†	8759 (G4)	21	Subject performed intensive manual labor	Study drugs discontinued	Grade 4 CK increase 24 weeks after treatment discontinuation
1232-310561	4106 (G4)	33	Subject started creatine supplements along with initiation of new exercise regimen	Subject advised to discontinue creatine	No subsequent graded CK elevations until Grade 1 CK increase 51 days after treatment completion
1005-310137	3178 (G3)	57	Subject reported being "roughed up" in a mugging	None	No subsequent graded CK elevations
1019-310007	1903 (G3)	FU 28	No information available	None	No subsequent graded CK elevations
FISSION PEG+RBV 24 weeks					
1088-310276	4034 (G4)	8	No symptoms; assessed as mild myositis due to IFN per investigator	None	No subsequent graded CK elevations
NEUTRINO SOF+PEG+RBV 12 weeks					
2130-6708	2342	29	Works as a plumber with a high level of physical activity	None	No subsequent graded CK elevations until Grade 1 elevation at Week 12 (<2-fold above baseline level)
0302-6420	3873	86	Subject had no symptoms and acknowledged exercising vigorously every day, sometimes up to 3 times per day	None	Grade 3 elevation observed at posttreatment Week 4 visit

†This subject is described in more detail in response to Comment 1.

Source: Submission to NDA received on June 28, 2013 (Table 3, Page 7)

No action was taken with respect to study drugs for CK elevations in 6 out of 7 subjects with ≥ Grade 3 CK elevations. Study drugs were discontinued in one subject (subject #1031-310130 described in Section 7.3.3). CK elevations did not appear to be related to treatment duration with respect to time of onset in these subjects.

The following observations regarding CK elevations were noted by the Applicant.

- CK elevations were mostly mild to moderate in severity and not associated with the onset of musculoskeletal symptoms, and not related to cumulative study drug exposure.
- Greater than or equal to Grade 3 CK elevations in SOF treatment groups in the primary safety population were mostly associated with increased physical activity levels.
- The frequency of CK elevations was slightly higher in IFN-free treatment groups as compared to IFN containing treatment groups (with or without SOF)
- There is no evidence of a causative relationship between SOF and CK elevations.
- There is no current evidence for SOF-related musculoskeletal toxicity

Reviewer's Comments

The number of subjects with Grade 3 or Grade 4 CK elevations is low. No cases or rhabdomyolysis were reported in the development program. Due to presence of confounding factors such as increased physical activity in subjects with Grade 3 or Grade 4 levels it is challenging to assess any causal relationship between SOF use and CK elevations. However, the contributory role of sofosbuvir cannot be fully ruled out. Additional data from ongoing/future trials evaluating sofosbuvir may be helpful in further assessment of this finding. At this time, recommend including this information in the prescribing information to ensure that health care providers are aware and can monitor CK levels as clinically indicated.

Renal Adverse Events

There were no cases of acute renal failure or renal dysfunction in the primary safety population. There were no Grade 3 or Grade 4 events of elevated creatinine levels. There was one report of increased creatinine leading to discontinuation of study drugs in a subject receiving SOF+PEG+RBV; this subject had a previously undisclosed history of renal dysfunction.

Table 41: Elevated Creatinine levels in the Primary Safety Population (Integrated Data)

Creatinine	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
Total Number of Subjects in Analysis	71 n (%)	563 n (%)	98 n (%)	327 n (%)	242 n (%)
Grade 1 (>1.5 to 2 mg/dL)	0	5 (0.9)	2 (2.0)	5 (1.5)	4 (1.7)
Grade 2 (>2 to 3 mg/dL)	0	1 (0.2)	0	1 (0.3)	1 (0.4)

Source: Submission to NDA received on June 25, 2013

Reviewer's Comments

No sofosbuvir-related renal toxicity has been identified in the sofosbuvir clinical development program to date.

Adverse Events of Completed Suicide, Suicide Attempt, and Suicidal Ideation

Based on the Safety Reports submitted to the IND 106739, Gilead was requested to conduct a comprehensive assessment of sofosbuvir clinical development program of all cases of completed suicide, suicide attempt, and suicidal ideation.

Neuropsychiatric side effects associated with alpha interferon use include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, suicide, and homicide. There is not much published data on neuropsychiatric side effect profile of ribavirin in HCV infected patients as ribavirin is indicated in combination with pegylated interferon for treatment of CHC. However, the Applicant referenced three published studies of RBV monotherapy in which neuropsychiatric events of depression, irritability, anxiety, and insomnia were reported at higher frequency in subjects receiving ribavirin as compared to those receiving placebo.

Although more subjects in the SOF+RBV 12 Week and 16 Week groups (7.2%, 41 subjects and 6.1%, 6 subjects, respectively) had depression (AEs of depression or depressed mood) compared with the subjects in the Placebo group, incidence was lower compared to the PEG+RBV group (17.3%, 43 subjects). The rate of pre-existing depression in subjects enrolled in the SOF registrational Phase 3 trials ranged from 33% (NEUTRINO) to 55% (POSITRON).

In summary, in the 3488 HCV-infected subjects treated to date with sofosbuvir, only one subject committed suicide and suicidal ideation or suicide attempt were reported in 11 subjects (< 1%). A summary of all these 11 cases was reviewed.

Subject #3317-8735 who was enrolled in Study GS-US-334-0123 (PHOTON-1) committed suicide 9 days after completing 12 weeks of treatment with SOF+RBV. No psychiatric AEs were reported while on treatment. Medical history was significant for HIV/HCV-coinfection, GERD, and insomnia, and psychiatric history was significant for ADHD. According to the investigator, the subject was acting differently towards his housemates after returning from a holiday visit with his family. Two days after his return, he left a voicemail for his girlfriend apologizing, stating he hated living in his residential program, and that he had lied to his parents about being laid off; he then jumped off the Golden Gate Bridge. The investigator considered the suicide unrelated to SOF and RBV.

Reviewer's Comments

Based on the review of data submitted to date, the incidence of adverse events of completed suicide, suicidal ideation or suicide attempt was low and were mostly observed in subjects with pre-existing psychiatric conditions and/or accompanied by major life stressors. Based on the available evidence, I agree with Applicant that sofosbuvir does not appear to contribute to the adverse events of suicide, suicidal ideation, or suicide attempt. At this time, these adverse events do not raise clinically significant safety concerns. We will continue to monitor for these adverse events in the postmarketing setting to identify any emerging safety signals.

Gastrointestinal Adverse Events

Due to observed findings of gastrointestinal hemorrhage, and increased frequency and incidence of emesis and diarrhea in male dogs, a focused safety evaluation for gastrointestinal AEs was done.

The incidence of treatment-emergent adverse events of nausea, vomiting and diarrhea in SOF+RBV containing groups (SOF+RBV 12 Weeks; SOF+RBV 16 Weeks) was similar to the placebo group and was lower than the pegylated interferon-containing regimens (PEG+SOF+RBV 12 Weeks; PEG+RBV 24 Weeks).

A high level safety summary focused on gastrointestinal adverse events was also requested by the Applicant. Response received on June 25, 2013 is summarized here.

The Applicant noted that colitis and pancreatitis, sometimes fatal, have been observed in patients treated with interferon (IFN). Therefore, the high level summary of gastrointestinal events provided by the Applicant focused on these two conditions.

There was one report of colitis in the primary safety population.

Subject #1071-1492 completed 12 weeks of SOF+RBV per protocol in Study GS-US-334-0108 (FUSION) on Day 85 and started SOF placebo + RBV placebo on Day 86 for 4 weeks. During treatment, he developed Grade 1 epigastric

discomfort and diarrhea (Day 2), Grade 1 decreased appetite (Day 5), Grade 2 diarrhea (Day 64), and Grade 2 abdominal pain (Day 80). On Day 84, the subject was reported to have cholelithiasis and portal vein thrombosis diagnosed by ultrasound. On Day 87, he was reported to have Grade 1 colitis (diagnosed by CT scan). Over the ensuing week, Grade 3 abdominal pain and pyrexia and Grade 1 ascites and hypokalemia were reported. The subject was diagnosed with poorly differentiated HCC with intrahepatic metastases and extension into the portal vein. He discontinued study drugs (placebo) on Day 87. According to the investigator, the subject's symptoms were likely related to the underlying malignancy extending into portal vein thrombosis and possibly related colitis.

There was one case of pancreatitis in the primary safety population.

Subject #5586-7268 was randomized to placebo treatment in Study GS-US-334-0107 (POSITRON). On Day 1, the subject was hospitalized for pancreatitis. He admitted to heavy alcohol use in the preceding week up to and including the day of hospitalization. The patient was also found to have choledocholithiasis on CT scan with mild dilation of the common bile duct.

There was one case of ischemic colitis reported in Study P7977-0724 (ATOMIC).

Subject #1051-7234 was a 57 year old male in Study P7977-0724 randomized to SOF+PEG+RBV for 24 weeks. Medical history included hypertension for six months and short term diarrhea with rectal bleeding approximately a year ago (with no other signs and symptoms); resolved, no work-up was done. He experienced Grade 2 focal ischemic colitis, diarrhea, and Grade 3 abdominal pain on Day 52 that was assessed as unrelated to study drugs. He was hospitalized for ischemic colitis and experienced Grade 2 lower GI hemorrhage and flatulence. Ischemic colitis resolved without sequelae on Day 71 and the patient completed treatment per protocol. A mesenteric computerized tomography angiography of the abdomen and pelvis was performed and atherosclerotic changes were noted in the descending abdominal aorta and common iliac arteries. The investigator considered focal ischemic colitis was due to atherosclerosis.

There was one case of pancreatitis in the secondary safety population (N=711).

Subject #1001-1067 was a 43 year old female in Study P7977-0221 (28-day study) with a past medical history relevant for alcohol abuse and diabetes complicated by peripheral neuropathy who was treated with SOF 400mg+PEG+RBV for 28 days followed by PEG+RBV for 44 weeks. She experienced Grade 2 acute pancreatitis requiring hospitalization 17 days after completing PEG+RBV treatment that was assessed as not related to study drugs. The event was considered resolved without sequelae on posttreatment Day 37.

There was one case of pancreatitis reported in the NIAID-sponsored Study 11-I-0258.

Subject #LDR019 had a medical history notable for a BMI of >47; he completed 24 weeks of SOF+RBV 600mg QD and 21 days posttreatment experienced transient pancreatitis, was hospitalized and was noted to have cholelithiasis. The event resolved and a planned cholecystectomy was performed. This event was assessed as not related to study drugs.

There was one case of colitis in the AI444040 study.

Colitis was reported 11.5 weeks after starting study drugs in a 49-year-old female subject receiving SOF+DCV (daclatasvir). Colitis resolved without treatment interruption, and was assessed as unrelated to study drugs.

Reviewer's Comment

There is no obvious safety concern of gastrointestinal toxicity associated with sofosbuvir use (as assessed by gastrointestinal symptoms of nausea, vomiting and diarrhea and adverse events of colitis and pancreatitis).

Elevated Lipase Levels

Treatment-emergent lipase elevations were reported in 9-31% of subjects in the primary safety population (Table 42). None of these isolated, sporadic elevations, with the exception of the pancreatitis case reported in the placebo group, was associated with clinical signs or symptoms of pancreatitis.

Table 42: Lipase Elevations in the Primary Safety Population (Integrated Data)

Lipase (U/L)	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
Total Number of Subjects in Analysis	N=71 n (%)	N=563 n (%)	N=98 n (%)	N=327 n (%)	N=242 n (%)
Total	12 (17)	92 (17)	12 (12)	30 (9)	76 (31)
Grade 1 (>1 to 1.5xULN)	7 (10)	51 (9)	6 (6)	18 (6)	40 (17)
Grade 2 (>1.5 to 3xULN)	4 (6)	32 (6)	6 (6)	11 (3)	31 (13)
Grade 3 (>3 to 5xULN)	1 (1)	7 (1)	0	0	3 (1)
Grade 4 (>5xULN)	0	2 (<1)	0	1 (<1)	2 (<1)

Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

Reviewer's Comments

No clinically meaningful conclusions can be drawn from this observation of abnormal laboratory lipase values. The mechanism of these lipase elevations remains unclear. Recommend to convey this information in the Prescribing Information so that health

care providers are fully informed when discussing treatment and management decisions with their patients.

Elevated Bilirubin Levels

No Grade 4 elevations (>5 x ULN) in total or direct bilirubin levels were noted in pivotal trials. The incidence of Grade 3 total bilirubin laboratory abnormalities was low in subjects in the SOF+RBV 12 Week (2.3%, 13 subjects) and SOF+RBV 16 Week group (2.0%, 2 subjects). No subjects in the SOF+PEG+RBV group had a Grade 3 or 4 total bilirubin laboratory abnormality (Table 43). However, the SOF+PEG+RBV group had a higher overall incidence of graded total bilirubin abnormalities compared with the PEG+RBV group. This difference was likely due to the lower RBV dose (800 mg) in the PEG+RBV regimen compared with the weight-based RBV dosing (1000 or 1200 mg) in the SOF+PEG+RBV regimen.

Table 43: Bilirubin Values Abnormalities in the Primary Safety Population (Integrated Data)

Laboratory Parameter Maximum Toxicity Grade	**Placebo (N=71)**	**SOF+RBV 12 Weeks (N=566)**	**SOF+RBV 16 Weeks (N=98)**	**SOF+PEG+RBV 12 Weeks (N=327)**	**PEG+RBV 24 Weeks (N=243)**
Total Number of Subjects in Analysis	71 n (%)	563 n (%)	98 n (%)	327 n (%)	242 n (%)
Total Bilirubin (mg/dL)					
Grade 1 (>1 to 1.5 x ULN)	2 (2.8)	102 (18.1)	28 (28.6)	37 (11.3)	18 (7.4)
Grade 2 (>1.5 to 2.5 x ULN)	2 (2.8)	52 (9.2)	7 (7.1)	22 (6.7)	7 (2.9)
Grade 3 (>2.5 to 5 x ULN)	0	13 (2.3)	2 (2.0)	0	2 (0.8)
Direct Bilirubin (mg/dL)					
Number of Subjects*	6	172	39	62	29
Grade 1	3 (50.0)	44 (25.6)	6 (15.4)	18 (29.0)	13 (44.8)
Grade 2	1 (16.7)	9 (5.2)	1 (2.6)	2 (3.2)	2 (6.9)
Grade 3	0	0	0	1 (1.6)	1 (3.4)

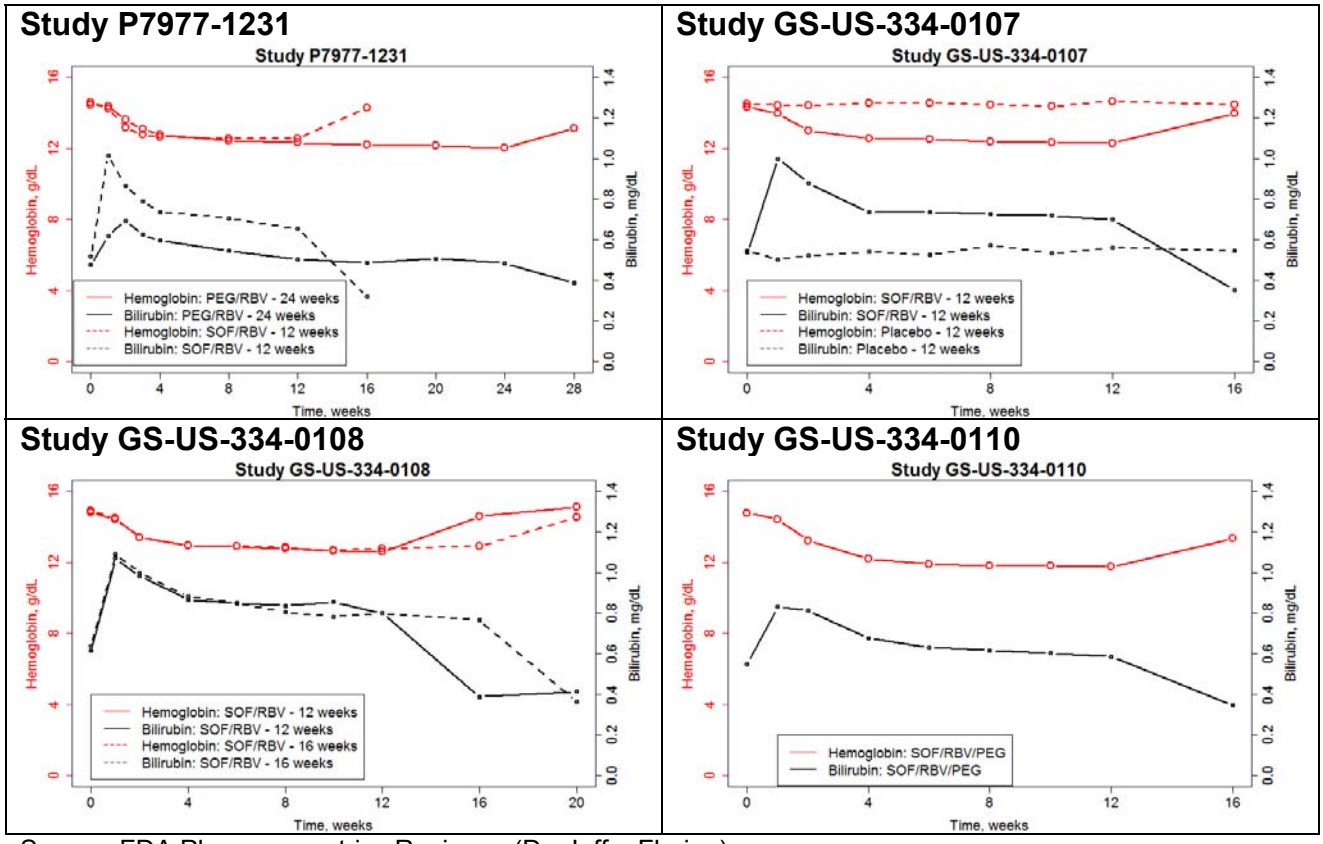
* Direct Bilirubin assessment was measured only if total bilirubin greater than the upper limit of normal.
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

Increases from baseline in median total bilirubin values were observed in both the SOF+RBV groups, which peaked at Week 1 for the SOF+RBV 12 Week group and peaked at Week 2 for the SOF+RBV 16 Week group. Subsequently, median total bilirubin values decreased and were returning towards baseline levels by the end of study treatment.

Transient elevations of bilirubin (hyperbilirubinemia) are consistent with RBV-induced hemolysis. This is illustrated in Figure 3, which shows that the elevations in bilirubin

corresponded with the decrease in hemoglobin parameter and this was evident in all four pivotal trials.

Figure 3: Relationship between Total Bilirubin Elevations and Decline in Hemoglobin Values (Pivotal Phase 3 Trials)



Source: FDA Pharmacometrics Reviewer (Dr. Jeffry Florian)

Reviewer's Comments

Elevated bilirubin levels seen in clinical trials of sofosbuvir seem to be driven by ribavirin-induced hemolytic anemia. Moreover, the levels peeked in the first 1-2 weeks and then returned to baseline values after completion of ribavirin-containing regimen. These isolated elevations in bilirubin values do not raise safety concerns.

7.4 Supportive Safety Results

The supportive safety results have been integrated in the different sections of this review.

7.4.1 Common Adverse Events

Treatment-Emergent Adverse Events

Treatment-emergent adverse events were defined by the Applicant as the events that meet one of the following criteria:

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study regimen from each specified study phase, and continuing adverse events diagnosed prior to the start of treatment with worsening severity grade after the start of treatment

- Continuing adverse events that are serious or result in any study drug discontinuation

For Study GS-US-334-0108, AEs that occurred up to 30 days after the last dose of active study drugs (i.e., SOF and RBV) were included in the integrated safety analysis.

The AE tables in this section are derived from FDA analyses of the pooled data from Phase 3 pivotal trials. The AEs represented in the tables are without regard to drug causality, which in this reviewer's opinion is an appropriate way to present AE data for this application, as frequently reported adverse events are those observed with pegylated interferon and ribavirin therapy.

A summary of AEs reported in ≥ 10% subjects in any group in the Primary Safety Population is provided in Table 46.

The most frequently reported AEs in subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups were (Table 46):

- Fatigue (SOF+RBV 12 Week: 40%; SOF+RBV 16 Week: 47%)
- Headache (SOF+RBV 12 Week: 23%; SOF+RBV 16 Week: 33%)
- Insomnia (SOF+RBV 12 Week: 16%; SOF+RBV 16 Week: 29%)
- Nausea (SOF+RBV 12 Week: 20%; SOF+RBV 16 Week: 20%)

As noted by the Applicant, the higher incidences of headache and insomnia in the SOF+RBV 16 Week group were unlikely due to the longer treatment duration because beginning on or after Day 84 (Week 12), there were only three AEs of headache and no AEs of insomnia in this group.

For most of the AEs that occurred in ≥ 10% of subjects, similar percentages of SOF+RBV 12 Week and SOF+RBV 16 Week subjects experienced these AEs (Table 44). A higher incidence of cough was reported in the SOF+RBV 16 Week group compared with the SOF+RBV 12 Week group (13.3%, 13 subjects and 6.9%, 39 subjects, respectively). The higher incidence of cough in the SOF+RBV 16 Week group was unlikely due to longer treatment duration because only two AEs of cough began on or after Day 84 (Week 12). Nausea, rash, pruritus, diarrhea, dizziness, and vomiting were reported at comparable incidence rates in the placebo, SOF+RBV 12 Week, and SOF+RBV 16 Week groups.

Table 44: Treatment-Emergent Adverse Events by Preferred Term (>10% of subjects in any treatment group) in the Primary Safety Population (Integrated Data)

MedDRA Preferred Term	Placebo 12 weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	PEG+SOF+RBV 12 Weeks	PEG+RBV 24 Weeks
	N=71	N=566	N=98	N=327	N=243
Number of subjects with any AE (%)					
Fatigue	17 (24)	229 (40)	46 (47)	192 (59)	134 (55)
Headache	14 (20)	132 (23)	32 (33)	118 (36)	108 (44)
Nausea	13 (18)	114 (20)	20 (20)	112 (34)	70 (29)
Insomnia	3 (4)	91 (16)	28 (29)	81 (25)	70 (29)
Rash	6 (8)	48 (8)	12 (12)	59 (18)	43 (18)
Pruritus	6 (8)	53 (9)	7 (7)	54 (17)	42 (17)
Anaemia	0	58 (10)	4 (4)	68 (21)	28 (12)
Irritability	1 (1)	58 (10)	11 (11)	42 (13)	40 (16)
Diarrhoea	4 (6)	57 (10)	6 (6)	38 (12)	42 (17)
Decreased Appetite	7 (10)	33 (6)	5 (5)	58 (18)	44 (18)
Dizziness	5 (7)	52 (9)	5 (5)	41 (13)	33 (14)
Arthralgia	1 (1)	42 (7)	9 (9)	47 (14)	35 (14)
Myalgia	0	35 (6)	9 (9)	45 (14)	40 (16)
Influenza like Illness	2 (3)	16 (3)	3 (3)	51 (16)	44 (18)
Chills	1 (1)	16 (3)	0	54 (17)	43 (18)
Pyrexia	0	19 (3)	3 (3)	58 (18)	33 (14)
Dyspnoea	1 (1)	45 (8)	5 (5)	39 (12)	20 (8)
Cough	2 (3)	39 (7)	13 (13)	34 (10)	21 (9)
Depression	1 (1)	34 (6)	6 (6)	31 (9)	34 (14)
Vomiting	5 (7)	33 (6)	4 (4)	39 (12)	23 (9)
Pain	2 (3)	17 (3)	5 (5)	33 (10)	30 (12)
Neutropenia	0	0	0	54 (17)	30 (12)

SOF=sofosbuvir; PEG=peginterferon alfa-2a; RBV=ribavirin;
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

As shown in Table 44, the three most common AEs in subjects in the SOF+PEG+RBV group were fatigue (59%), headache (36%), and nausea (34%). These common AEs were consistent with the expected safety profile of PEG+RBV treatment.

7.4.2 Laboratory Findings

This section summarizes the reported laboratory findings for each of the four pivotal Phase 4 trials.

Hematology Test Abnormalities

Anemia is the most common cause of RBV dose reduction. Guidance on the management of RBV dose reductions was provided in the protocol for each of the trials, based upon the RBV labeling. The number of subjects with hemoglobin < 10 g/dL (the level that recommended RBV dose reduction per protocol) and < 8.5 g/dL (the level that recommended RBV dose discontinuation per protocol) at any post baseline visits is summarized in Table 45. Hemoglobin values of < 10 g/dL and < 8.5 g/dL are those recommended in the approved ribavirin package inserts for ribavirin dose-reduction and discontinuation, respectively.

Table 45: Hemoglobin Nadir Values in the Primary Safety Population (Integrated Data)

Lowest Hemoglobin Value	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+PEG+RBV 12 Weeks	PEG+RBV 24 Weeks
Subjects in Analysis*	N=71	N=563	N=98	N=327	N=242
Hemoglobin (g/dL)					
< 10 g/dL	0	48 (9%)	5 (5%)	74 (23%)	35 (14%)
< 8.5 g/dL	0	5 (1%)	0	8 (2%)	4 (2%)

*N was based on number of subjects with post-baseline hemoglobin measurement
Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

A higher percentage of subjects in the SOF+PEG+RBV group (23%) had lowest hemoglobin value < 10 g/dL compared to PEG+RBV alone group (14%). This difference could be attributed to the lower dose of RBV (800 mg daily) used in PEG+RBV control group compared to weight-based RBV dosing in SOF+PEG+RBV group.

A higher proportion of subjects in PEG+RBV containing arms experienced hemoglobin nadirs of ≤10 g/dL and ≤ 8.5 g/dL than subjects who received SOF+RBV alone. This could be attributed to longer duration of treatment in the PEG+RBV group as compared with the SOF+RBV groups.

Three subjects in the SOF+RBV 12 Week group received blood transfusions for anemia during the trial (Subject #1073-310378, P7977-1231; Subject #2074-7350, GS-US-334-0107; Subject #5586-1449, GS-US-334-0108). Subject #0452-7426 received a blood transfusion on posttreatment Day 31 for a Grade 2 AE of anemia that started on Day 57 (GS-US-334-0107). Erythropoiesis-stimulating agents such as epoetin alfa (EPO) used to treat anemia were prohibited medications from 28 days prior to the Day 1 (baseline) visit through the end of treatment in all Phase 3 studies.

Decreased hemoglobin was the most commonly reported Grade 3 or 4 laboratory abnormality across the SOF+RBV 12 Week and 16 Week groups in the Primary Safety

Population (Table 46). Grade 3 abnormalities of decreased hemoglobin were observed in 51 of 563 subjects (9.1%) in the SOF+RBV 12 Week group and 11 of 98 subjects (11.2%) in the SOF+RBV 16 Week group. No Grade 4 decreases in hemoglobin occurred in either of the SOF+RBV treatment groups.

Table 46: Selected Hematology Test Abnormalities in the Primary Safety Population (Integrated Data)

Laboratory Parameter Maximum Toxicity Grade	**Placebo (N=71)**	**SOF+RBV 12 Weeks (N=566)**	**SOF+RBV 16 Weeks (N=98)**	**SOF+PEG+RBV 12 Weeks (N=327)**	**PEG+RBV 24 Weeks (N=243)**
Total Number of Subjects in Analysis	71 n (%)	563 n (%)	98 n (%)	327 n (%)	242 n (%)
Hemoglobin (g/dL)					
Grade 1 (10.0 to 10.9 g/dL OR any decrease from Baseline 2.5 to <3.5 g/dL)	2 (2.8)	169 (30.0)	31 (31.6)	91 (27.8)	69 (28.5)
Grade 2 (9.0 to <10.0 g/dL OR any decrease from Baseline 3.5 to <4.5 g/dL)	0	105 (18.7)	15 (15.3)	94 (28.7)	61 (25.2)
Grade 3 (7.0 to <9.0 g/dL OR any decrease from Baseline ≥4.5 g/dL)	0	51 (9.1)	11 (11.2)	88 (26.9)	24 (9.9)
Grade 4 (<7.0 g/dL)	0	0	0	1 (0.3)	0
Leukocytes ($x10^3$/uL)					
Grade 1 (2000 to 2500/mm^3)	1 (1.4)	10 (1.8)	1 (1.0)	77 (23.5)	67 (27.7)
Grade 2 (1500 to <2000/mm^3)	0	3 (0.5)	0	61 (18.7)	39 (16.1)
Grade 3 (1000 to <1500/mm^3)	0	0	0	18 (5.5)	10 (4.1)
Grade 4 (<1000/mm^3)	0	1 (0.2)	0	0	1 (0.4)
Lymphocytes ($x10^3$/uL)					
Grade 1 (600 to 650/mm^3)	1 (1.4)	8 (1.4)	2 (2.0)	13 (4.0)	22 (9.1)
Grade 2 (500 to <600/mm^3)	0	10 (1.8)	4 (4.1)	19 (5.8)	25 (10.3)
Grade 3 (350 to <500/mm^3)	0	5 (0.9)	0	17 (5.2)	15 (6.2)
Grade 4 (<350/mm^3)	0	2 (0.4)	0	0	12 (5.0)
Neutrophils ($x10^3$/uL)					
Grade 1 (1000 to 1300/mm^3)	2 (2.8)	9 (1.6)	0	69 (21.1)	65 (26.9)
Grade 2 (750 to <1000/mm^3)	2 (2.8)	7 (1.2)	1 (1.0)	69 (21.1)	49 (20.2)
Grade 3 (500 to <750/mm^3)	1 (1.4)	0	0	49 (15.0)	30 (12.4)
Grade 4 (<500/mm^3)	0	1 (0.2)	0	17 (5.2)	6 (2.5)
Platelets ($x10^3$/uL)					
Grade 1 (100,000 to <125,000/mm^3)	8 (11.3)	16 (2.8)	2 (2.0)	69 (21.1)	51 (21.1)
Grade 2 (50,000 to <100,000/mm^3)	2 (2.8)	7 (1.2)	3 (3.1)	60 (18.3)	67 (27.7)
Grade 3 (25,000 to <50,000/mm^3)	2 (2.8)	2 (0.4)	0	1 (0.3)	18 (7.4)
Grade 4 (<25,000/mm^3)	0	0	0	0	0

Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

Although the RBV dose of 800 mg in the PEG+RBV group was lower than the weight-based RBV dose of 1000 or 1200 mg in the SOF+RBV groups, the frequency of hemoglobin reductions (all grades) was similar across groups. These reductions could be due to the additive effect of PEG-related bone marrow suppression. When weight-based RBV dosing was administered with PEG (as in the SOF+PEG+RBV regimen), the rates of hemoglobin reduction were higher than with either SOF+RBV or PEG+RBV (800 mg), and the reticulocytosis observed at the same dose of RBV was lower in the SOF+PEG+RBV group compared with SOF+RBV groups. Similarly, the incidence of hyperbilirubinemia appeared to be directly related to the amount of hemolysis and degree of reticulocytosis; this was highest in the SOF+RBV group even though the rate of anemia was higher in the SOF+PEG+RBV group

Decreased neutrophil counts (20.2%, 66 subjects) and decreased hemoglobin (27.2%, 89 subjects) were the most commonly reported Grade 3 or 4 laboratory abnormalities in the SOF+PEG+RBV group in the Primary Safety Population (Table 46). This finding was consistent with the expected bone marrow suppressive effects of PEG and the hemolytic anemia observed with RBV treatment in this subject population.

Overall, few subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups had any grade of decreased neutrophils (3.0%, 17 subjects and 1.0%, 1 subject, respectively). One subject (0.2%) in the SOF+RBV 12 Week group and no subjects in the SOF+RBV 16 Week group had Grade 4 decreased neutrophils (Table 46). No subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups had Grade 3 decreased neutrophils.

In the SOF+PEG+RBV group, Grade 3 decreased neutrophils were reported in 49 subjects (15.0%). Seventeen subjects (5.2%) had a Grade 4 decreased neutrophil laboratory abnormalities. Neutrophil levels returned to near-baseline values at the posttreatment Week 4 visit. The incidence of Grade 3 or 4 decreased neutrophils was slightly higher frequency in the SOF+PEG+RBV group compared with the PEG+RBV group (20.2%, 66 subjects and 14.9%, 36 subjects, respectively). This decrease may be due to the difference in baseline neutrophil counts in the 2 treatment groups: the SOF+PEG+RBV group had overall lower baseline neutrophil counts as compared with the PEG+RBV group. A higher percentage of black subjects in the SOF+PEG+RBV group compared with the PEG+RBV group may account for these differences in baseline neutrophil values (16.5% and 2.1%, respectively).

The incidences of platelet laboratory abnormalities (all grades) were low in the SOF+RBV 12 Week (4.4%, 25 subjects) and SOF+RBV 16 Week groups (5.1%, 5 subjects) No subjects in the SOF+RBV 12 Week or SOF+RBV 16 Week groups had a Grade 4 laboratory abnormality for platelet counts (Table 46). Two subjects (0.4%) in

the SOF+RBV 12 Week group and no subjects in the SOF+PEG+RBV 16 Week group had a Grade 3 laboratory abnormality for platelets counts.

On-Treatment Liver Related Abnormalities

An analysis of subjects meeting 1 or more of 3 criteria for liver-related abnormalities as defined below was performed by the Applicant for all Gilead-sponsored Phase 2 and Phase 3 trials.

- Criterion 1: AST or ALT > 3 × ULN and total bilirubin > 2 × ULN
- Criterion 2: ALT > 5 × ULN
- Criterion 3: Total bilirubin > 2 × ULN

In both SOF+ RBV 12 Week group and 16 Week group, within the Primary Safety Population, the majority of on-treatment liver abnormalities were Criterion 3 (total bilirubin > 2 × ULN). These analyses are summarized in Table 47. In most cases, these total bilirubin elevations were isolated and transient and occurred for 1 or 2 visits. These events appeared consistent with RBV-associated hemolysis. These have been discussed earlier in Section 7.3.5. The subjects meeting criterion 1 and 2 are further discussed in this section.

Table 47: Summary of Subjects with Liver-related Abnormalities

		Criterion 1: AST/ALT> 3 × ULN and Total Bilirubin > 2 × ULN	Criterion 2: ALT > 5 × ULN	Criterion 3: Total Bilirubin > 2 × ULN
Primary Safety Population	Placebo (N = 71)	0/71	9/71 (12.7%)	0/71
	SOF+RBV[a] (N = 664)	1/659 (0.2%)	1/659 (0.2%)	35/659 (5.3%)
	PEG+RBV (N = 243)	0/242	15/242 (6.2%)	3/242 (1.2%)
	SOF+PEG+RBV (N = 327)	0/327	9/327 (2.8%)	3/327 (0.9%)
Secondary Safety Population	P7977-0523 (N = 120)	0/120	1/120 (0.8%)	2/120 (1.7%)
	P2938-0721 (N = 50)	0/50	0/50	1/50 (2.0%)
	P7977-0221 (N = 63)	0/63	2/63 (3.2%)	0/63
	P7977-0422 (N = 146)	0/146	0/146	4/146 (2.7%)
	P7977-0724 (N = 332)[b]	2/332 (0.6%)	6/332 (1.8%)	7/332 (2.1%)
Special HCV Population	GS-US-334-0123 (N = 31)	0/31	1/31 (3.2%)	1/31 (3.2%)
	P7977-2025 (N = 61)	0/61	0/61	7/61 (11.5%)

[a] 12 and 16 week groups combined
[b] Subject 1004-7085 experienced Criteria 1–3 concurrently and Subject 1019-7006 experienced Criteria 1and 3 concurrently
Source: Applicant's Summary of Clinical Safety (Table 21, page 108)

Liver enzyme elevations (all grades) observed in primary safety population is shown in Table 48.

Table 48: Selected Liver Test Abnormalities in the Primary Safety Population (Integrated Data)

Laboratory Parameter Maximum Toxicity Grade	**Placebo (N=71)**	**SOF+RBV 12 Weeks (N=566)**	**SOF+RBV 16 Weeks (N=98)**	**SOF+PEG+RBV 12 Weeks (N=327)**	**PEG+RBV 24 Weeks (N=243)**
Total Number of Subjects in Analysis	71 n (%)	563 n (%)	98 n (%)	327 n (%)	242 n (%)
Alanine Aminotransferase (U/L)					
Grade 1 (1.25 to 2.5 x ULN)	6 (8.5)	6 (1.1)	1 (1.0)	7 (2.1)	8 (3.3)
Grade 2 (>2.5 to 5x ULN)	12 (16.9)	9 (1.6)	0	7 (2.1)	9 (3.7)
Grade 3 (>5 to 10x ULN)	6 (8.5)	1 (0.2)	2 (2.0)	7 (2.1)	9 (3.7)
Grade 4 (>10 x ULN)	0	0	0	0	0
Aspartate Aminotransferase (U/L)					
Grade 1 (1.25 to 2.5 x ULN)	10 (14.1)	9 (1.6)	0	30 (9.2)	10 (4.1)
Grade 2 (>2.5 to 5x ULN)	6 (8.5)	5 (0.9)	0	11 (3.4)	17 (7.0)
Grade 3 (>5 to 10x ULN)	9 (12.7)	0	0	9 (2.8)	3 (1.2)
Grade 4 (>10x ULN)	1 (1.4)	0	0	1 (0.3)	1 (0.4)
Alkaline Phosphatase (U/L)					
Grade 1 (1.25 to 2.5 x ULN)	4 (5.6)	8 (1.4)	2 (2.0)	6 (1.8)	5 (2.1)
Grade 2 (>2.5 to 5x ULN)	0	1 (0.2)	0	0	0
Grade 3 (>5 to 10x ULN)	0	0	0	0	1 (0.4)
Grade 4 (>10x ULN)	0	0	0	0	0

Source: Integrated Datasets (P7977-1231, GS-US-334-0107, GS-US-334-0108, GS-US-334-0110)

Liver-related abnormalities, SOF+RBV (Primary Safety Population)

- One subject (0.2%) in the SOF+RBV 12 Week group had an on-treatment liver abnormality of Criterion 1 on Day 57.
    - Subject #2493-1426 had baseline ALT value ranging from 99-114 U/L, AST values were 122-138 U/L, total bilirubin was 0.6 mg/dl. On Day 57, values increased to AST of 110 U/L (3.1 × ULN) and total bilirubin 2.6 mg/dL (> 2.2 × ULN). ALT and alkaline phosphatase values were elevated to < 2 × ULN and direct bilirubin was modestly elevated to 1.5 × ULN. After Day 57, AST remained elevated until the end of treatment (range: 3.1−3.3 × ULN) and total bilirubin remained elevated until Day 86 (range: 2.0−2.6 mg/dL), albeit to a lesser extent (i.e., < 2 × ULN). No other signs

or symptoms of liver disease, including jaundice, were reported. No additional diagnostic testing was performed to evaluate the laboratory abnormalities.

- Only one subject had Criterion 2 on-treatment liver abnormality (ALT > 5 × ULN). Subject #0530-1419 had an ALT value of 328 U/L (7.6 × ULN) on Day 10; however, baseline ALT values were also > 5 × ULN (308 U/L). AST was also elevated to 4.6 × ULN (164 U/L) and alkaline phosphatase and total bilirubin were within normal range. ALT and AST continued to decline over time and both were within normal range by Day 58.

Liver-related abnormalities, SOF+PEG+RBV (Primary Safety Population)

All of the on-treatment liver abnormalities occurring in SOF+PEG+RBV subjects in Study GS-US-334-0110 were either Criterion 2 (ALT > 5 × ULN) or Criterion 3 (total bilirubin > 2 × ULN). Nine subjects in had ALT ≥ 5 × ULN (Criterion 2): A total of six subjects had ALT > 5 × ULN for 1 or 2 visits occurring between Days 9 and 69. In these subjects, elevations in AST occurred in parallel (range: 3.9−6.1 × ULN) and generally other liver chemistry parameters remained within normal range. Three subjects had ALT > 5 × ULN for longer periods:

- Subject #2760-6606 had intermittent ALT values > 5 × ULN (range: 5.1−6 × ULN) throughout treatment (maximum value 257 U/L); at baseline ALT was 133 U/L. AST was elevated to > 5× ULN from Day 29 through the end of treatment (peak 10 × ULN at the Week 6 visit on Day 36). Alkaline phosphatase remained within normal range and total bilirubin was mostly within normal range (except for Days 36 and 43 [1.3 mg/dL and 1.4 mg/dL, respectively]). The increase in transaminases was reported as a Grade 3 AE. AEs ongoing at the time of the laboratory abnormalities included Grade 2 tinea pedis, Grade 1 influenza-like illness, Grade 1 laryngitis, and Grade 1 arthralgia. New concomitant medications at the time of the laboratory abnormalities included ibuprofen and paracetamol (flu-like symptoms).The final ALT value was 20 U/L at the follow-up Week 12 visit on posttreatment Day 84.
- Subject #2760-6641 experienced an ALT value > 5 × ULN on Day 85 (235 U/L); AST was also elevated to > 5× ULN (179 U/L) and alkaline phosphatase and total bilirubin were within normal range. Baseline ALT was 196 U/L and AST was 98 U/L. AEs ongoing at the time of the laboratory abnormalities included Grade 1 headache, nausea, and rash. New concomitant medications at the time of the laboratory abnormalities included paracetamol. The study drugs were discontinued on Day 85 after completing 12 weeks of treatment per protocol. The final ALT value was 30 U/L at the follow-up Week 12 visit on posttreatment Day 84.
- Subject #3995-6478 had ALT 6.9 × ULN (235 U/L) at Day 54 which remained > 5 × ULN to end of treatment (range 235 U/L–281 U/L); at baseline ALT was 93 U/L. AST was also elevated to > 5× ULN (range 207 U/L–278 U/L). Alkaline

phosphatase and total bilirubin remained within normal range. AEs ongoing at the time of the laboratory abnormalities included Grade 1 fatigue, myalgia, and decreased appetite. New concomitant medications at the time of the laboratory abnormalities included paracetamol (headache). The study drugs were discontinued on Day 82 after completing 12 weeks of treatment per protocol. The final ALT value was 57 U/L at the follow-up Week 12 visit on posttreatment Day 83.

All 9 subjects with on-treatment ALT >5x ULN completed 12 weeks of treatment per protocol.

Three subjects also had total bilirubin > 2 × ULN (Criterion 3). In all three subjects, total bilirubin elevations > 2 × ULN (range: 2.1−2.4 × ULN) were isolated and transient and occurred during Weeks 1 and 2 only. Other liver chemistry parameters (ALT, AST, and alkaline phosphatase) were within normal range and these events appeared consistent with RBV-associated hemolysis.

Liver-related abnormalities (Secondary Safety Population)

The majority of liver abnormalities identified in trials P7977-0523 and P2938-0721 were Criterion 3 (total bilirubin > 2 × ULN) consistent with RBV-associated hemolysis.

- One subject in trial P7977-0523 who met Criterion 2 had elevated ALT at baseline, which then transiently increased to ALT ≥ 5 × ULN at Day 2; after which, ALT continued to decline and was at baseline at Week 1 and within the normal range at Week 2.

Most of the on-treatment liver abnormalities occurring in subjects in trials P7977-0221, P7977-0422, and P7977-0724 were either Criterion 2 (ALT > 5 × ULN) or Criterion 3 (total bilirubin > 2 × ULN). Two subjects in Study P7977-0724 had AST or ALT > 3 × ULN and total bilirubin > 2 × ULN at the same time point (Criterion 1) and are summarized below:

- Subject #1019-7006 (Group C2) experienced an increase in ALT to > 3 × ULN, in AST to > 6.0 × ULN and in total bilirubin to > 2 × ULN at Day 8. Total bilirubin normalized by Week 3 (Day 22), and ALT and AST normalized at Week 20 (last subject visit). No jaundice was reported and no additional diagnostic testing was performed to evaluate liver disease.
- Subject #1004-7085 (Group C2) completed 12 weeks of dosing with SOF+PEG+RBV and was re-randomized, per protocol, to receive an additional 12 weeks of sofosbuvir 400 mg/day monotherapy before liver tests increased to Grade 2 (ALT) and Grade 3 (AST) at Day 85. At Day 98, ALT and AST increased to 9.1 and 19.0 × ULN, respectively; total bilirubin increased to 1.4 × ULN; and direct bilirubin increased to 5.0 × ULN. On Day 104, the subject returned to the site and reported abdominal discomfort and was jaundiced. Sofosbuvir was

permanently discontinued due to elevated liver abnormalities at this visit. The next day, the subject was admitted to a local hospital and the event was reported as an SAE of autoimmune hepatitis. A liver biopsy revealed severe inflammatory activity and areas of multiacinar collapse, and a differential diagnosis of concurrent autoimmune hepatitis versus drug-induced liver injury was reported. Although the subject underwent preparation for a liver transplant, her laboratory tests significantly improved and by posttreatment Day 20, all liver parameters had decreased but remained abnormal. Her physical examination on Day 20 was unremarkable except for mild jaundice and right upper quadrant mild discomfort but with no hepatosplenomegaly. The subject was advised to complete Week 4 of steroid therapy during the next week. The autoimmune process was considered stable with prednisone 10 mg once daily treatment. *Detailed past medical history revealed a diagnosis of Hashimoto's thyroiditis (an autoimmune disease).*

Reviewer's Comments

A consultation by Senior Hepatologists at FDA was also requested and can be accessed under IND 106739 (signed 10/04/2011) for details.

Two subjects in trial P7977-0221 and five subjects in trial P7977-0724 had ALT ≥ 5 × ULN (Criterion 2). In P7977-0221, both subjects had transient ALT > 5 × ULN and also AST > 5 × ULN elevations for one visit (either Week 24 or 28); these two subjects received treatment with PEG+RBV after discontinuing SOF on Day 28. Both subjects completed treatment with PEG+RBV.

In P7977-0724, five subjects had ALT ≥ 5 × ULN that began between Days 8 and 64. Increases in AST ≥ 5 × ULN occurred in parallel, although other liver chemistry parameters (total bilirubin, direct bilirubin, and alkaline phosphatase) generally remained within normal range throughout the trial. Four subjects completed their assigned study treatment. One subject (Subject #1015-7064) had elevated ALT > 5 × ULN and AST > 5 × ULN on Day 29 that was reported as a clinical Grade 3 AE of hepatic enzyme increased, although other liver chemistry parameters remained within normal range (Day 29 to posttreatment Day 28). Study drugs were discontinued on Day 32 because of this AE. Final ALT and AST values at posttreatment Day 28 were within normal range.

Liver-related abnormalities (Special HCV Population)

In the Special HCV Population, the majority (8 of 9 subjects) of liver abnormalities identified in trials GS-US-334-0123 and P7977-2025 were Criterion 3. All eight occurrences appeared consistent with RBV-associated hemolysis. In trial P7977-2025, all seven occurrences of hyperbilirubinemia was also considered consistent with underlying cirrhosis and/or advanced liver disease.

- One subject in GS-US-334-0123 who met Criterion 2 (Subject #0994-8731) had elevated ALT at baseline (74 U/L) and an ALT nadir at Week 1 (53 U/L), but subsequently did not achieve any value within normal range. ALT steadily increased to 5.7 × ULN (193 U/L) at Day 70 (Week 10). AST also increased to a peak at 114 U/L on Day 70 as well. Mild increases in total bilirubin were noted from Week 4 onward but remained < 2 × ULN. There were no concurrent AEs observed during the study period. Both ALT and AST values decreased by posttreatment Week 4 to 98 U/L and 70 U/L, respectively.

Reviewer's Comments

Marked elevations in ALT levels (5- to 10-fold above the upper limit of normal) have been reported in one percent of subjects during treatment and follow-up in hepatitis C trials for Pegasys. Transient elevations in ALT (2- to 5-fold above baseline) were observed in 10% of subjects treated with PegIntron, and were not associated with deterioration of other liver functions (Re: USPI for Pegasys and PegIntron). No specific safety concern related to hepatotoxicity associated with sofosbuvir use has been identified to date.

7.4.3 Vital Signs

The mean and median systolic and diastolic blood pressures remained stable during treatment. Slight increases from baseline in mean heart rate were observed that returned towards or near baseline by posttreatment Week 4 in most treatment groups. No clinically significant changes in vital signs were reported.

7.4.4 Electrocardiograms (ECGs)

In nonclinical studies, in a range-finding, 7-day, repeat-dose dog study, an increase in QT/QTc interval was observed in male but not female dogs at the high dose of GS-9851 1500 mg/kg/day. Systemic exposure (C_{max}) to GS-331007 at 1500 mg/kg/day in the study was approximately 90-fold greater than the exposure in HCV-infected subjects at the recommended dose of 400 mg. No QT, electrocardiogram, or waveform changes were observed in a cardiovascular safety pharmacology study in dogs with oral GS-9851 at up to 1000 mg/kg, doses of SOF at 500 mg/kg/day for up to 9 months, or GS-9851 at 500 mg/kg/day for 28 days.

A formal ECG study (thorough QT study, TQT) was performed in healthy volunteers; Protocol P7977-0613 entitled "A Single Dose, Randomized, Blinded, Placebo and Positive Controlled, Four Period Cross Over Study to Investigate the Effect of PSI 7977 at a Projected Therapeutic and Supratherapeutic Dose on the QT/QTc Interval in Healthy Volunteers". The data was reviewed by the FDA Interdisciplinary Review Team (IRT) for QT Studies. The IRT Review Team concluded the following:

No significant QT prolongation effect of sofosbuvir (400 mg and 1200 mg) was detected in this TQT trial. The largest upper bounds of the 2-sided 90% CI for the mean differences between sofosbuvir (400 mg and 1200 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated *(shown in Figure 5 of the IRT review, not included in this review),* indicating that assay sensitivity was established.

This was a randomized, blinded, placebo and positive controlled, four period cross over trial, 60 subjects received sofosbuvir 400 mg, sofosbuvir 1200 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 49.

Table 49: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Sofosbuvir (400 mg and 1200 mg) and the Largest Lower Bound For Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Sofosbuvir 400 mg	8	2.6	(0.6, 4.7)
Sofosbuvir 1200 mg	22.5	2.6	(0.8, 4.5)
Moxifloxacin 400 mg*	3	11.1	(9.3, 12.9)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 8.6 ms
Source: IRT Consult Review in DARRTS (signed November 26, 2012)

The supratherapeutic dose (1200 mg) produces C_{max} and AUC values ~3.6-fold and 4-fold that of the therapeutic dose (400 mg). These concentrations are similar to those for the predicted high exposure scenario (drug interaction with cyclosporine). At these concentrations there is no detectable prolongation of the QT interval.

For detailed assessment please refer to the full IRT Review.

Twelve-lead ECG data were collected at protocol-prespecified intervals in the Phase 2 trials and select Phase 3 trials (GS-US-334-0110 and P7977-1231).

In Study P7977-0724, one subject (Group C2) had a change from baseline in QTcF interval of > 60 msec during the treatment period of the trial that was considered an abnormal clinically significant ECG result. An AE of increased heart rate was reported during the abnormal ECG; though the elevated rate (101 bpm) was higher than baseline (77 bpm), it was lower than the screening value (108 bpm). All other ECG parameters were considered normal at the time of the event.

7.4.5 Special Safety Studies/Clinical Trials

Trials in Special HCV Populations

Interim data are included from two ongoing trials in special HCV populations:

P7977-2025: An Open-Label Study to Explore the Clinical Efficacy of GS-7977 with Ribavirin Administered Pre-Transplant in Preventing Hepatitis C Virus (HCV) Recurrence Post-Transplant

GS-US-334-0123 (PHOTON-1): A Phase 3 open-label study evaluating the efficacy and safety of SOF+RBV in HCV/HIV-coinfected subjects with chronic genotype 1, 2, or 3 HCV infection.

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 10-30% developing cirrhosis within 5 years of transplant. Moreover, 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 (Fontana et al. *Liver Transplantation* 2012). There are currently no approved therapies to prevent recurrence of HCV infection post liver transplant. Hence, therapies administered pretransplant to prevent HCV recurrence posttransplant are much needed.

P7977-2025

Study P7977-2025 is an ongoing Phase 2, open-label trial evaluating the efficacy of SOF+RBV administered pretransplant in preventing HCV recurrence post liver transplant in subjects with genotype 1 through 6 HCV infection and HCC meeting the Milan criteria[*] prior to undergoing liver transplantation with an anticipated time until transplantation within 1 year.

The updated efficacy, safety, and virology information for ongoing Study P7977-2025 was submitted by the Applicant on July 30, 2013 and has been summarized here. The primary objective of this trial is as follows:

- To determine if the administration of a combination of SOF and RBV to HCV-infected subjects with HCC meeting the Milan criteria prior to undergoing liver transplantation can prevent posttransplant reinfection as determined by a sustained posttransplant virological response (HCV RNA < lower limit of quantitation [LLOQ]) at 12 weeks posttransplant.

[*] Milan criteria: solitary tumor = 5 cm or up to three nodules = 3 cm

Some of the secondary objectives of this trial are as follows:

- To determine if the administration of a combination of SOF and RBV to HCV-infected subjects with HCC meeting the Milan criteria prior to undergoing liver transplantation can elicit a sustained viral response as determined by HCV RNA < LLOQ 12 weeks after the discontinuation of therapy (SVR12).
- To evaluate the safety and tolerability of a combination of SOF+RBV in HCV-infected subjects prior to undergoing liver transplantation.

This trial is being conducted at 14 centers in the US, 1 center in New Zealand, and 1 center in Spain. Subjects must have been listed for liver transplantation for HCC (meeting the Milan criteria) secondary to HCV-related cirrhosis with a MELD score of < 22 and an HCC-weighted MELD score of ≥ 22 and a Child-Pugh Turcotte (CPT) score ≤ 7.

Enrolled subjects will receive oral SOF 400 mg once daily and RBV 1000 or 1200 mg (administered as a divided dose, BID) for a maximum of 24 weeks (before Protocol Amendment 4) or a maximum of 48 weeks (after Protocol Amendment 4) or until time of transplant, whichever comes first. Treatment will be discontinued within 24 hours prior to the liver transplant if it occurs before the subject has completed their 24- or 48-week treatment course, as appropriate.

Subjects who experience post-treatment viral relapse and have no resistance mutations (before Protocol Amendment 4); subjects who stopped treatment at Week 24 and are currently in post-treatment follow-up; and subjects who reach Week 24 and have not yet been transplanted (after Protocol Amendment 4) may receive up to 24 additional weeks of treatment in the retreatment substudy. For purposes of analysis, only those subjects who completed Week 24 of study treatment, relapsed in post-treatment follow-up, and then restarted on SOF+RBV study treatment will be included in the “Relapsers Retreated with SOF+RBV” analysis set. Subject #7585-7709 had HCV RNA < LLOQ (16 weeks post-treatment) when Protocol Amendment 4 was approved and did not consent to restarting study drug. All other subjects who were in posttreatment follow-up and waiting for transplant at the time of Amendment 4 approval had HCV RNA ≥ LLOQ. For purposes of analysis, subjects who continued on treatment (without interruption) at the Week 24 visit will be analyzed with the “main part” of the pre-transplant phase of the trial.

Once a subject received a cadaveric organ, they entered the posttransplant follow-up phase for up to 48 weeks and were followed closely for evidence of recurrent HCV infection as determined by HCV RNA ≥ LLOQ.
The planned posttransplantation immunosuppressive regimen during the first 12 weeks posttransplant is as follows:

- Solumedrol/Prednisone (tapered over approximately 7 days)

- Tacrolimus (maintained a serum level of 5−12 ng/mL)
- Mycophenolate mofetil (up to 2 g/day)

Of the 61 subjects who received at least one dose of study drugs (safety analysis set), 9 subjects (14.8%) were on treatment in the pretransplant phase at the time of the data cutoff for updated response, 29 subjects (47.5%) have undergone liver transplantation while on treatment, 8 subjects (13.1%) completed 24 weeks of treatment and subsequently have undergone a liver transplantation, 2 subjects (3.3%) completed 24 weeks of treatment and were prematurely terminated from the trial due to disease progression, 7 subjects (11.5%) relapsed during posttreatment follow-up and were retreated with SOF+RBV in the retreatment substudy, and 6 subjects (9.8%) prematurely discontinued treatment (Table 50).

Table 50: Subject Disposition in Study P7977-2025

Subject Disposition	SOF+ RBV
Subjects in Safety Analysis Set	61
FAS with Any Treatment and HCV RNA < LLOQ at Last Measurement Prior to Transplant	37
FAS with ≥ 12 Weeks of Treatment and HCV RNA < LLOQ at Last Measurement Prior to Transplant	27
Study Treatment Status	
On Study Treatment (Pretransplant)	9 (14.8%)
Transplanted While on Treatment	29 (47.5%)
Completed 24 Weeks of Study Treatment and Subsequently Transplanted	8 (13.1%)
Completed 24 Weeks of Study Treatment and Prematurely Terminated From Study Due to Progressive Disease and Subject was no Longer a Transplantation Candidate	2 (3.3%)
Relapsers in Off-Treatment Follow Up who were Retreated with SOF+RBV	7 (11.5%)
Prematurely Discontinued Study Treatment	6 (9.8%)
Reasons for Study Treatment Discontinuation	
Adverse Event(s)	2 (3.3%)
Efficacy Failure	4 (6.6%)

Source: Adapted from Applicant's Submission dated July 30, 2013 (Table 4-1, Page 14)

Of the 6 subjects who prematurely discontinued treatment, 4 subjects (6.6%) had efficacy failure (2 breakthrough and 2 nonresponse) and 2 subjects (3.3%) discontinued due to an AE.
Of the subjects who prematurely discontinued the trial, 5 subjects (8.2%) died, 3 subjects (4.9%) had efficacy failure, and 3 (4.9%) subjects had progressive disease and were no longer transplant candidates.

Demographic and Baseline Characteristics

The mean age was 59 years (range, 46 to 73 years). The majority of subjects were male (80.3%), and white (90.2%). The majority of the subjects had genotype 1 HCV infection (73.8%, genotype 1; 39.3%, genotype 1a and 34.4%, genotype 1b) while 13.1%, 11.5%, and 1.6% of the subjects had genotype 2, 3, and 4 HCV infection, respectively. The majority of subjects had a baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL (67.2%) and had an IL28B non-CC allele (78.3%). The baseline Child-Pugh-Turcotte (CPT) scores ranged from 5 to 8, with scores of 5, 6, 7, and 8 in 42.6%, 29.5%, 23.0%, and 4.9% of the subjects, respectively. The baseline MELD score ranged from 6 to 14, with approximately half of subjects (49.2%) with a score of 7 or 8. The majority of subjects (75.4%) had prior HCV treatment experience.

Interim Efficacy Results

After starting treatment with SOF+RBV, a mean decrease of 3.87 $\log_{10}$ IU/mL in HCV RNA was observed after 1 week of treatment and HCV RNA < LLOQ in 93.1% of subjects by Week 4 of SOF+RBV treatment. After 12 weeks of SOF+RBV treatment, 45 of 48 subjects (93.8%) had HCV RNA < LLOQ.

Five subjects (one with HCV RNA ≥ LLOQ on the day of transplantation was not discontinued from the trial) had on-treatment virologic failure (3 breakthroughs and 2 non-response).

Reviewer's Comments

Additional data on the above noted five subjects has been requested from the Applicant.

A total of 11 of 15 subjects, who completed 24 weeks of treatment and had an observed or imputed Week 4 posttreatment follow-up HCV RNA value, relapsed during posttreatment follow-up. Of these 11 subjects, two subjects underwent a liver transplantation before they were able to receive an additional 24 weeks of retreatment, two subjects had progressive disease and were no longer transplant candidates, and seven subjects were retreated with SOF+RBV. Of the seven retreated subjects, three subjects continue on retreatment and four have undergone a liver transplantation at the time of the data cutoff for this response. Of the four retreatment subjects who underwent a liver transplantation, two subjects died (Subjects #1028-7706 and #1028-7724); one subject had a graft loss 2 days posttransplant (Subject #7585-7710), was retransplanted 3 days later and has achieved pTVR12; and one subject had recurrent HCV infection at posttransplant Week 4 (Subject #7585-7731).
Reviewer's Comments

The outcome in three out of the four retreatment subjects who underwent a liver transplantation was not favorable.

A total of 41 subjects who had any duration of treatment with SOF+RBV have undergone liver transplantation to date. Of the 41 subjects, 38 (92.7%) had HCV RNA < LLOQ at the time of liver transplantation. One subject was transplanted with a HCV infected liver and is not part of the posttransplant analysis.

At the time of this updated report submission, 35 of 37 subjects have been followed to posttransplant Week 12 and 23 subjects (65.7%) had HCV RNA < LLOQ. Of the 24 subjects who have reached 24 weeks posttransplantation, 17 (70.8%) had HCV RNA < LLOQ (Table 51).

Table 51: Posttransplantation Virologic Response by Visit (FAS with Any Treatment Duration and HCV RNA <LLOQ at Last Measurement Prior to Transplant)

	SOF+RBV (N=37)
Posttransplant Week 12	
<LLOQ	23/35 (65.7%)
90% CI	50.4% to 78.9%
Posttransplant Week 24	
<LLOQ	17/24 (70.8%)
90% CI	52.1% to 85.4%

Source: Applicant's Submission Dated July 30, 2013

There were no identifiable differences in the nine subjects with observed recurrent HCV infection, with the exception of genotype. Of the nine subjects with observed recurrence, six subjects had genotype 1b, two subjects had genotype 1a, and one subject had genotype 3a HCV infection. No S282T mutations were observed in any posttransplant subjects with recurrent HCV infection.

Since, a total of 11 of 15 subjects (73%) who completed 24 weeks of treatment relapsed in the pretransplant phase. The protocol was amended (Amendment 4) to extend the treatment duration from 24 weeks to 48 weeks or the time of transplant. The rate of virologic relapse after 24 weeks of treatment in this patient population and the need for HCV RNA to be < LLOQ at the time of transplant suggests that subjects should continue on SOF+RBV treatment until the time of transplant.

Reviewer's Comments
As noted by the Applicant, a total of 11 of 15 subjects who completed 24 weeks of treatment and had a Week 4 posttreatment follow-up visit relapsed in the pretransplant phase. Based on this observation, treatment with SOF+RBV therapy for 24 weeks pretransplant does not appear to be the optimum treatment regimen and duration.

Addition of another DAA might potentially improve the response rates in hard-to-treat pretransplant population.

Interim Safety Results

The mean exposure to SOF+RBV prior to transplantation was 17.7 weeks for subjects in the FAS with any treatment duration and HCV RNA < LLOQ before transplantation. The mean exposure to retreatment SOF+RBV for subjects who had relapsed and were being retreated with SOF+RBV in the retreatment substudy was 13.2 weeks.

The majority of subjects (52/61, 85.2%) experienced at least one AE. The most frequently reported AEs were fatigue (36.1%), anemia (23.0%), and headache (21.3%). One subject (Subject #6927-7713) had a Grade 4 AE of malignant hepatic neoplasm (significant and rapid progression of the HCC tumor) and tumor thrombosis; and one subject (Subject #0585-7758) had a fatal AE of pneumonitis. A total of 46 subjects (75.4%) had AEs that were considered by the investigator to be related to study drug (fatigue, anemia, and headache were observed in >15% of subjects).

Eight subjects (13.1%) had at least 1 Grade 3 AE. Hepatocellular carcinoma, anemia, and obstructive umbilical hernia (two subjects each) were the only Grade 3 AEs reported in > one subject. Anemia (two subjects) was the only Grade 3 AE considered related to study drug by the investigator.

One death from sepsis occurred 15 days after the last dose of study drug.

- Subject #0522-7739 had AEs of sepsis, spontaneous bacterial peritonitis, acute renal failure (Grade 3) and anemia (Grade 3) at the time of death. The anemia was considered related to study drug and led to the interruption of RBV on Day 163 and discontinuation on Day 165. The events of acute renal failure and sepsis (which were not considered related to study drug) led to the discontinuation of sofosbuvir on Day 165.

Four additional deaths, that were not considered treatment-emergent, were reported and are described below:

- Subject #0585-7758 died of pneumonitis. This 67-year-old male subject of African descent with medical history significant for cirrhosis, hypertension, peripheral neuropathy, diabetes, hepatocellular carcinoma (HCC), s/p transcatheter arterial chemoembolization (TACE), depression, coronary artery disease and history of heart surgery including 3 stents and 3 valve replacements, drug allergies to epinephrine and lidocaine, allergy to citrus, stopped smoking in 1993, was hospitalized on Day 54 of SOF+RBV treatment for new onset of dyspnea, cough and fever with prominent right sided pulmonary infiltrates thought to be secondary to community acquired pneumonia (CAP). Both study drugs were discontinued on same day. A high

resolution computed tomography (HRCT) was done which showed diffuse interstitial infiltrate throughout the right lung with patchy consolidative opacities in the right lung base. The diagnosis was changed to pneumonitis, not yet determined (NYD). Rheumatology work-up for immune-mediated lung injury was negative. The patient required intubation. Due to concern for interstitial lung disease (ILD), the patient was started on high dose intravenous solumedrol. Lung biopsies showed: "right lung, middle lobe: organizing acute lung injury with organizing pneumonia and right lung, upper lobe: organizing acute lung injury with organizing pneumonia". The investigator's overall assessment was that the most likely sequence of events was: 1) viral URI --> 2) bacterial superinfection (pneumonia) --> 3) partial control of infection via antibiotics preventing florid sepsis --> 4) progression of infection vs infection related ARDS to involve bilateral lung fields --> 5) hypoxemic respiratory failure requiring intubation --> 6) infection/inflammation related necrosis leading to pulmonary hemorrhage- improvement in right sided disease with residual LLL consolidation, persistent interstitial fibrosis and new bronchopleural fistula. After a prolonged clinical course, the subject died 38 days after the last dose of study drugs.

- Subject #1028-7705 died 6 days after the first liver transplantation, which resulted in primary graft non-function (Grade 4 acute hepatic failure, hepatic necrosis starting on Day 1 after transplant). The subject underwent a second liver transplantation 3 days after the first transplantation (Grade 5 acute renal failure started on Day 1 after the second transplantation), which also resulted in graft failure and renal failure. The subject died 3 days after the second liver transplantation. Study drugs were stopped on the day of the first transplant (6 days prior to death). These events were considered not related to study drug.
- Subject #1028-7706, who relapsed and was retreated with SOF+RBV, received a liver transplantation that resulted in graft failure. The subject had cardiogenic shock resulting in a low-flow state on the day of transplant, and developed hepatic artery thrombosis on the day after transplantation (Grade 4 hepatic artery thrombosis and renal failure). Despite aggressive management and surgical removal of the hepatic artery thrombosis, the subject died of cardiogenic shock 3 days after the transplant. Study drugs were stopped on the day before the transplant (4 days prior to death). These events were considered not related to study drug.
- Subject #1028-7724, who relapsed and was retreated with SOF+RBV, had a Grade 4 AE of hepatic artery thrombosis on the day of liver transplantation leading to graft dysfunction. The subject developed renal failure the day after transplantation. The subject underwent a second liver transplantation 5 days after the first transplantation. The subject developed sepsis after the second transplantation, which led to death 14 days after the first transplant, and 9 days after the second transplant. All study drugs were stopped on the day prior to the first transplant. These events were considered not related to study drug.

A total of 11 subjects (18.0%) had at least one SAE during SOF+RBV treatment during the pretransplant phase of the trial, none of which were considered related to study drug by the investigator. An SAE of acute renal failure led to the discontinuation of SOF. One subject in the pretransplant retreatment phase had a treatment-emergent SAE of hepatic encephalopathy that was considered unrelated to study drug.

Three subjects in the safety analysis set had graft loss. Subject #1028-7705 and Subject #1028-7724 are described above.

- Subject #7585-7710 had an SAE of graft dysfunction on the same day as the first liver transplantation. This event was Grade 4, considered not related to study drug. The subject received a second liver transplant 4 days later with good graft function and is now in post-treatment follow up and has met the primary efficacy endpoint (pTVR12).

Six subjects (9.8%) had a Grade 4 laboratory abnormality: decreased lymphocyte count (4 subjects, 6.6%) and increased aspartate aminotransferase (AST) and total bilirubin (1 subject, 1.6% each). A total of 21 subjects (34.4%) had at least one Grade 3 laboratory abnormality. Decreased hemoglobin (14.8%, 9 subjects), increased non-fasting glucose (11.5%, 7 subjects), and increased total bilirubin (8.2%, 5 subjects) were the most frequent Grade 3 laboratory abnormalities.

Reviewer's Comments

The demonstrated efficacy (as measured by pTVR12 of 66%) coupled with a well-tolerated safety profile in pretransplant population addresses an unmet medical need. Moreover, the sustained virologic response posttransplantation was maintained through Week 24 (pTVR24 of 71%). However, it should be noted that the number of subjects evaluated so far is limited and the population studied was subpopulation of pretransplant patients (those with HCC). These patients were eligible to undergo liver transplants due to upgrade in their MELD scores due to HCC and not necessarily due to higher MELD scores because of advanced liver disease.

Safety data from Study GS-US-334-0125 and compassionate use program is discussed briefly in Section 7.7.

HCV/HIV Coinfection

An estimated 4 to 5 million people worldwide are coinfected with HCV/HIV. About 25% of individuals infected with HIV in the US are also infected with HCV (http://www.cdc.gov/hiv/resources/factsheets/hepatitis.htm accessed May 14, 2013).HCV/HIV coinfection leads to increased rates of liver fibrosis progression and hepatic decompensation. As HIV-related morbidity and mortality has decreased due to use of highly active antiretroviral therapy (HAART), liver-related complications associated with HCV infection have become a leading cause of non-AIDS-related deaths in the HIV/HCV-coinfected population. Hence, development and availability of effective and safe drugs with better tolerated side effect profile for this patient population remains a priority for the Division.

GS-US-334-0123 (PHOTON-1)

Study GS-US-334-0123 (PHOTON-1) is an ongoing trial to evaluate the efficacy and safety of SOF+RBV for 12 or 24 weeks in subjects with genotype 1, 2, or 3 HCV infection who are coinfected with HIV. In this NDA submission, Applicant has provided interim data for this trial. The safety data from Study GS-US-334-0123 provided in the Safety Update has also been included in this section.

This submission includes interim data from treatment-naive subjects with genotype 2 or 3 HCV infection. Subjects included in this submission were males and nonpregnant, nonlactating females, naive to HCV antiviral treatment, at least 18 years old, and had a BMI ≥ 18 kg/m^2. Subjects had HCV RNA levels ≥ 10^4 IU/mL at screening. Subjects were either ARV untreated for ≥ 8 weeks before screening with a CD4 count > 500 cells/mm^3 or on a protocol-approved ARV for > 8 weeks before screening with a CD4 count > 200 cells/mm^3 and undetectable plasma HIV-1 RNA levels for ≥ 8 weeks preceding screening. Approximately 20% of the enrolled subjects were to have evidence of compensated cirrhosis at screening. There was no randomization stratification because

this was a single-group trial. Twenty-seven subjects (87.1%) completed treatment and 4 (12.9%) prematurely discontinued treatment.

Demographics and Baseline characteristics

The majority of subjects had HCV genotype 3 infection (61.3%), were noncirrhotic (90.3%), and had a baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL (74.2%). Twelve subjects (38.7%) had the IL28B CC allele. A total of 23 subjects (74.2%) were IFN eligible. Each of the 8 IFN-ineligible subjects (25.8%) had significant psychiatric disease as the reason for ineligibility, 1 of whom also had autoimmune disorder and 1 of whom also had seizure disorder. More than half of subjects (61.3%) had CD4 T-lymphocyte counts ≥ 500 cells/mm^3. The mean baseline CD4 T-lymphocyte count in the safety analysis set was 601 cells/mm^3. Most subjects were on ARV treatment at study enrollment (87.1%). Of the 27 subjects on ARVs during the treatment period, all took an emtricitabine/tenofovir-based regimen that was combined with a non-nucleoside reverse transcriptase inhibitor (n = 13), a boosted PI (n = 9), or an integrase inhibitor (n = 5).

Interim Efficacy Results

SVR4 was observed in 21 subjects (67.7%) with a 95% CI of 48.6% to 83.3%. Regarding virologic outcome rate by HCV genotype, SVR4 was observed in 9 of 12 subjects (75.0%) with genotype 2 HCV infection and 12 of 19 subjects (63.2%) with genotype 3 HCV infection.

A total of ten subjects (32.3%) did not achieve SVR4, seven of whom had virologic failure and three of whom could not be assessed for SVR4 (one was lost to follow-up, one died, and one withdrew consent). Of the seven subjects with virologic failure, six subjects relapsed, all of whom had genotype 3 HCV infection and an IL28B non-CC genotype, and one subject had on-treatment virologic failure at Week 10. The reasons subjects with HCV genotype 2 infection did not achieve SVR4 were lost to follow-up, withdrawal of consent, and on-treatment virologic failure likely due to study drug nonadherence.

Two of the four subjects who prematurely discontinued treatment had posttreatment Week 4 HCV RNA assessments; one subject relapsed after receiving approximately 6 weeks of treatment (discontinued due to investigator decision) and one subject had SVR4 after receiving approximately 10 weeks of treatment (discontinued due to AEs).

Two subjects who were receiving ARV treatment had HIV-1 virologic rebound during the SOF+RBV treatment:

- Subject #4262-8725 (Group 1; treatment-naive with genotype 2 or 3 HCV infection) was receiving ARV treatment with RAL and FTC/TDF. HIV-1 RNA was not detected from baseline through Week 8 in the subject, but was detected at

Week 12. As per the investigator, this subject had poor adherence to HIV medications at the time of HIV virologic rebound. In addition, this subject had HCV virologic relapse and may not have adhered to study drug.

- Subject #0843-8852 (Group 3; treatment-naive subject with genotype 1 HCV infection) was receiving ARV treatment with ATV, ritonavir (RTV), and FTC/TDF. HIV-1 RNA was < 20 copies/mL at baseline and ranged between < 20 and 75 copies/mL during SOF+RBV treatment (through the last available observation at Week 20). The subject had HCV RNA < lower limit of quantitation (LLOQ) from Weeks 8 through 20 of SOF+RBV treatment (Week 20 was last available observation).

Interim Safety Results

One death from suicide was reported in this trial. Subject #3317-8735 (Group 1; SOF+RBV 12 Weeks) committed suicide 9 days after the last dose of study drug. The event was considered not related to study procedures, study drug, or ARV treatment. This case was described earlier in Section 7.3.5.

Subject #0843-8722 had SAEs of acute myocardial infarction, drug abuse, encephalopathy, pneumonia, acute renal failure, respiratory failure, septic shock, and staphylococcal bacteremia related to relapse of drug abuse (intravenous methamphetamine). This case was described earlier in Section 7.3.5.

Subject #0994-8788 had SAEs of acute renal failure and anemia in the setting of colitis and enteritis, which led to severe volume depletion. The AEs were reported as resolved.

Subject #1603-8855 had SAE of salmonella gastroenteritis which was considered related to study drug (RBV). The AE resolved.

One Grade 3 ALT laboratory abnormality was observed in Group 1. Subject # 0994-8731 had a baseline Grade 1 ALT level of 74 U/L and Grade 3 ALT levels of 193 and 194 U/L at Weeks 10 and 12, respectively. The ALT levels returned towards baseline after cessation of study drugs, with ALT levels of 73 and 98 U/L at 15 and 27 days after the last dose of study drug, respectively.

Reviewer's Comments

Available efficacy and safety data in HIV/HCV coinfected subjects is limited at this time and precludes a full indication in this patient population. The DDI information will be available in the Prescribing Information to guide health care providers make treatment decisions for patients in emergent need of therapy and in which benefit outweighs the potential risk.

Post-Liver Transplant Population

At the time of this NDA submission, there are no recommended therapies for treatment of chronic hepatitis C in post-liver transplant patients thus there still exists an unmet need for this population. (b) (4)

Reviewer's Comments

(b) (4)

7.4.6 Immunogenicity

Sofosbuvir is a small molecule, not a peptide; therefore, development of immunogenicity directed against sofosbuvir was not specifically evaluated.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Only the sofosbuvir 400 mg QD dose was used in all four pivotal Phase 3 trials and sofosbuvir 400 mg QD is the proposed dose for use if the marketing application is approved.

7.5.2 Time Dependency for Adverse Events

Two different treatment durations were explored in Phase 3 trials. No notable difference in side effect profile was identified between 12 Week vs. 16 Week treatment duration. There is supportive safety data available for use of SOF+RBV for 24 weeks. No safety issues or concerns have been notified by the Applicant with the extended use up to 24 weeks.

7.5.3 Drug-Demographic Interactions

- Population pharmacokinetics analysis in HCV-infected subjects indicated that race had no clinically relevant effect on the exposures of SOF or GS-331007.
- No clinically relevant pharmacokinetic differences have been observed between men and women for SOF and GS-331007.

- Population pharmacokinetic analysis in HCV-infected subjects showed that within the age range (19 to 75 years) analyzed, age did not have a clinically relevant effect on the exposures of SOF or GS-331007.

Safety data in the primary safety population based on demographic characteristics such as age and gender is briefly discussed here.

Age

None of the sofosbuvir Phase 3 trials imposed an upper age limit as part of the trial entry criteria. An age cutoff of < 65 and ≥ 65 years was chosen to evaluate elderly subjects. Across the 5 treatment groups in the Primary Safety Population, 66 subjects (5.1%) were ≥ 65 years of age. The mean (SD) age across the groups was 51 (10.3) years.

In the SOF+RBV 12 Week group, anemia was reported at a higher frequency in subjects aged ≥ 65 years compared with < 65 years (anemia: 18.5%, 5 subjects vs 9.8%, 53 subjects). In the SOF+RBV 16 Week group, only 4 subjects (4.1%) reported AEs of anemia, with 1 subject aged ≥ 65 years. However, a higher frequency of anemia was also reported in the PEG+RBV group, in subjects aged ≥ 65 years compared with < 65 years (anemia: 45.5%, 5 subjects vs 9.9%, 23 subjects). Hence, any effects on anemia noted in older subjects may not be associated with sofosbuvir use.

In the SOF+PEG+RBV group, anemia was the only AE reported at a 2-fold higher incidence in subjects aged ≥ 65 years compared with < 65 years. As noted by the Applicant, no other differences indicative of a sofosbuvir-containing regimen treatment effect were apparent for any other AEs or Grade 3 or 4 AEs.

Gender

In the SOF+RBV 12 and 16 Week groups , the incidence of overall AEs was slightly higher for female subjects compared with male subjects (approximately 93% vs 85%); however, the incidence of Grade 3 or 4 AEs was similar between male and female subjects.

Female subjects had a higher incidence of AEs leading to dose modification or interruption of study drug compared with male subjects in the SOF+RBV 12 Week group (22.0%, 45 subjects vs 5.0%, 18 subjects) and SOF+RBV 16 Week group (19.4%, 6 subjects vs 1.5%, 1 subject). Dose modification or interruption was allowed per study protocol for RBV or RBV placebo only; no dose modification of SOF was permitted. Female subjects had a higher incidence of AEs leading to modification or interruption of study drug compared with male subjects in the SOF+PEG+RBV group (47% and 26% respectively). In the PEG+RBV group, female subjects had a higher incidence of dose

modifications or interruptions compared with male subjects (33% and 23% respectively). Dose modification or interruption was allowed per study protocol for PEG and/or RBV.

Anemia was reported at a higher incidence in female subjects compared with male subjects in the SOF+RBV 12 Week group (19.0%, 39 subjects and 5.3%, 19 subjects, respectively) as well as the SOF+RBV 16 Week group (12.9%, 4 subjects and no subjects, respectively). Overall, this difference in part could be explained by the trend of generally lower pretreatment hemoglobin levels in female subjects. In addition, based on lower median BMIs, female subjects may have had higher overall exposures to RBV from the weight-based RBV dosing in Phase 3 trials.

In the SOF+PEG+RBV, anemia was the only AE reported at a 2-fold higher incidence in female subjects (32%) compared with male subjects (14%). As noted by the Applicant, no other differences indicative of a sofosbuvir-containing regimen treatment effect were apparent for any other AEs or Grade 3 or 4 AEs.

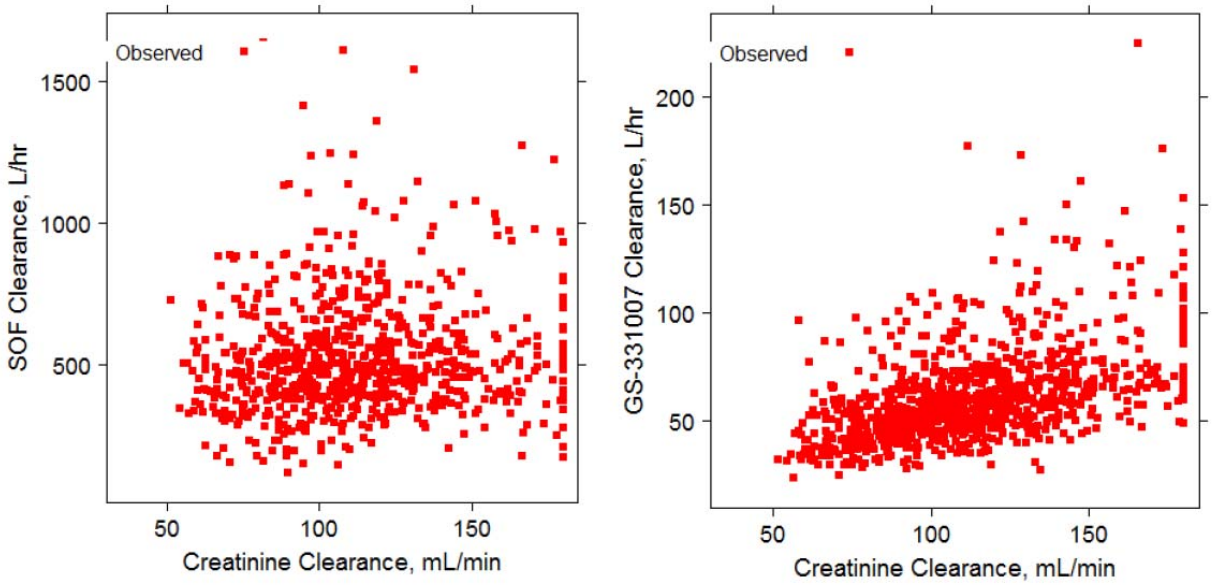
7.5.4 Drug-Disease Interactions

Phase 1 Renal Impairment Trial

> The pharmacokinetics of SOF were studied in HCV negative subjects with mild (eGFR ≥ 50 and < 80 mL/min/1.73m^2), moderate (eGFR ≥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 SOF. Relative to subjects with normal renal function (eGFR > 80 mL/min/1.73m^2), the SOF $AUC_{0\text{-inf}}$ 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), SOF and GS-331007 $AUC_{0\text{-inf}}$ was 28% and 1280% higher when SOF was dosed 1 hour before hemodialysis compared with 60% and 2070% higher when SOF was dosed 1 hour after hemodialysis.

Elimination of GS-331007, but not SOF, is dependant on CrCL as shown in Figure 4 below. It should be noted that Phase 3 clinical trials did not enroll any subjects with CrCL < 50 mL/min.

Figure 4: Apparent Clearance of GS-331007, but not Sofosbuvir, is associated with Creatinine Clearance



Source: Clinical Pharmacology Reviewer (Dr. J Zheng)

No dose adjustment is required for patients with mild or moderate renal impairment. The safety of SOF has not been assessed in patients with severe renal impairment or ESRD and dose recommendation cannot be made in these populations at this time.

Phase 1 Hepatic Impairment Trial (Study P2938-0515)

Twenty-five subjects were enrolled: 9 subjects with moderate hepatic impairment and 8 subjects with severe hepatic impairment received SOF 400 mg.

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

Sofosbuvir was generally well tolerated when administered to subjects with moderate or severe hepatic impairment, with no clinically significant AEs or laboratory abnormalities. No deaths, SAEs, or AEs that led to discontinuation of study drug were reported.

Subjects with Cirrhosis

Subjects with cirrhosis were enrolled in pivotal trials; however, cirrhotic subjects with decompensation were excluded. In the SOF+RBV 12 Week and SOF+RBV 16 Week groups, overall no differences indicative of a SOF-containing regimen treatment effect were noted on the incidence of any AE, or any Grade 3 or 4 AE, when cirrhotic subjects were compared with noncirrhotic subjects. There was no apparent difference in the incidence of AEs that led to dose modification or interruptions in cirrhotic compared with noncirrhotic subjects in the SOF+RBV 12 Week and SOF+RBV 16 Week groups.

In the SOF+PEG+RBV group, anemia and neutropenia were reported at a higher incidence in cirrhotics (32% and 22% respectively) compared with noncirrhotic subjects (19% and 15% respectively). There was a higher incidence of AEs leading to modification or interruption of study drug (PEG and/or RBV) in cirrhotic subjects as compared with non-cirrhotic subjects in the SOF+PEG+RBV group (44%, 24 subjects vs. 31%, 85 subjects).

The overall incidence of total bilirubin abnormalities (all grades) was higher in cirrhotic compared with noncirrhotic subjects in the SOF+RBV 12 Week (39.7%, 46 subjects vs. 27.1%, 121 subjects) and SOF+RBV 16 Week groups (50.0%, 16 subjects vs. 31.8%, 21 subjects). In the SOF+PEG+RBV group, the only difference in overall graded laboratory abnormalities between cirrhotics and non-cirrhotics was total bilirubin (35.2%, 19 subjects, vs. 14.7%, 40 subjects). A similar trend was observed for the PEG+RBV group (20.0%, 10 subjects vs. 8.9%, 17 subjects), which indicates that cirrhotic subjects are more likely to develop hyperbilirubinemia in response to RBV-associated hemolytic anemia due to the decreased hepatic function.

Reviewer's Comments

The available clinical data across the development program supports the use of sofosbuvir 400 mg without dose modification in subjects with mild, moderate, or severe hepatic impairment.

7.5.5 Drug-Drug Interactions

Please refer to Clinical Pharmacology Review for detailed assessment of the Phase 1 drug-drug interaction trials. The key findings are noted below:

- 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 SOF plasma concentration leading to reduced therapeutic effect of SOF and thus should not be used with SOF. Coadministration of SOF with drugs that inhibit P-gp and/or BCRP would likely increase SOF 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 significant effects of coadministered drugs on the exposure of SOF and GS-331007 have been observed except cyclosporine (CsA).

- Coadministration of SOF with the potent P-gp and BCRP inhibitor CsA (administered as single dose at a high dose of 600 mg), resulted in an increase (approximately 4-fold) in SOF exposure, but the exposure of GS-331007 was unchanged in the presence of CsA. Limited safety data from an ongoing post-transplant study (GS-US-334-0126) indicate that the safety of SOF+RBV is similar between subjects not taking CsA (n=30) and subjects taking CsA (n=10). Furthermore, the safety margins for SOF (and metabolites), after coadministration with cyclosporine, are adequate (AUC safety margin ranges from 1.9 to 16.0) compared with exposures obtained in toxicology studies. Therefore, dose modification of SOF is not warranted when coadministered with CsA.

- No drug interaction study has been formally conducted for SOF and PEG/RBV or RBV. However, Study P7977-0523 shows that GS-331007 exposures were higher in monotherapy as compared to when SOF is coadministered with PEG/RBV or RBV alone. GS-331007 exposure is similar when SOF is coadministered with PEG/RBV or RBV alone. An interaction between GS-331007 and RBV is plausible since both compounds are mainly renal eliminated.

- The effects of SOF on the exposure of coadministered drugs were studied for cyclosporine, darunavir/ritonavir, emtricitabine, efavirenz, methadone, raltegravir, rilpivirine, tacrolimus, and tenofovir disoproxil fumarate. No clinically significant effect of SOF has been observed on these drugs.

- An ongoing Phase 1 trial (GS-US-334-0146) is evaluating the effect of SOF on the PK of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol. Results from this trial were not available for this submission. Thus, the Applicant's proposed recommendation for pregnancy prevention is two non-hormonal methods of contraception during treatment with concomitant ribavirin due to the known teratogenic effects of ribavirin.

In addition, interim data from ongoing non-Gilead sponsored trials (Janssen-sponsored Study HPC2002 and BMS-sponsored Study AI444040) evaluating the efficacy and

safety of sofosbuvir in combination with other direct-acting antivirals (DAAs) with or without RBV was discussed previously in Section 5.3.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The maximum study duration of sofosbuvir trials (approximately 48 weeks) limits the assessment for oncologic events. Most of the reported malignancies are those consistent with the patient population and no clustering of any particular events was noted.

7.6.2 Human Reproduction and Pregnancy Data

Because ribavirin is genotoxic and teratogenic, pregnancy was one of the exclusion criterion during the clinical development program of sofosbuvir. Breastfeeding women were excluded as well. Women of childbearing potential included in trials were required to use two effective methods of birth control. In addition, urine pregnancy testing was performed at regular intervals during the trial as defined in each protocol. Pregnancy, once determined, was a condition for required withdrawal of the subject from the trial.

In total, there have been three pregnancies reported in clinical trials in the SOF clinical development program. These are briefly described below:

- Two of the pregnancies were reported in the female partners of male study subjects. Both female partners were pregnant at the start of the trial.
    - In the first case, the female partner was pregnant while the male subject was taking SOF for approximately 6 months. At 39 gestational weeks, the mother delivered a full-term healthy male infant via cesarean delivery with no labor/delivery complications.
    - In the second case, contraception use and other details are not available; the outcome was reported as spontaneous abortion.
- A placebo subject (Placebo+PEG+RBV) had a confirmed pregnancy during the off-treatment follow-up period of the trial. The pregnancy was ongoing at time of CSR reporting.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Proposed Pediatric Study Request (PPSR) was previously submitted to IND 106,739 in Serial No. 0243, dated December 12, 2012 and was also included with the original NDA. An updated PPSR was received on August 12, 2013, and is under review.

The Applicant has requested a waiver of pediatric studies in children < 3 years of age and a deferral for submission of pediatric data in children aged 3 to 18 years. This will

be discussed at the FDA Pediatric Review Committee meeting scheduled on September 11, 2013.

Sofosbuvir has only been administered in adults, and therefore no clinical assessment of effects on growth has been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is limited experience with overdosage of sofosbuvir. Doses of SOF above the therapeutic dose (400 mg) have been administered in two Phase 1 trials. The highest dose of SOF administered in clinical trials to date was a single supratherapeutic dose of SOF 1200 mg to 59 healthy subjects in Study P7977-0613. As reported by the Applicant, the observed AEs were similar in frequency and severity to those reported in the placebo and SOF 400 mg treatment groups.

There is no specific antidote for sofosbuvir. The Applicant has noted that hemodialysis can remove the predominant circulating metabolite GS-331007 with an extraction ratio of 53%.

Sofosbuvir is not expected to have abuse or dependence potential. Elevations in liver enzymes and HCV RNA levels can be observed with virologic relapse.

7.7 Additional Submissions / Safety Issues

The Applicant provided responses to FDA's Information Requests throughout the review cycle. Pertinent information provided through these responses is incorporated throughout this review in relevant sections.

The Applicant submitted the Safety Update Report on July 08, 2013 (90 days after the submission of the original NDA as was previously agreed). The report provides the available updated safety data from ongoing sofosbuvir-containing trials. The Applicant presented sofosbuvir safety data from 20 Gilead-sponsored clinical trials, 2 individual investigator compassionate-use protocols, and 3 non-Gilead-sponsored trials. The data submitted in the safety report by the Applicant has been summarized in this section and has also been integrated into other sections of this review as relevant. No independent analyses have been done for the data provided in the safety update.

This section summarizes the data included in safety update on Phase 2 and 3 trials that was not included with the original NDA submission. These trials are: P2938-0721 (QUANTUM), Re-treatment group; P7977-0523 (ELECTRON), Groups 10 and 11 (Part 4); GS-US-334-0109; GS-US-334-0114; GS-US-334-0125; GS-US-334-0126; and GS-US-334-0133 (VALENCE). The data presented by the Applicant is cumulative from the initiation of the clinical trials to the safety update data cutoff dates.

Study P2938-0721 (QUANTUM; Re-Treatment Group)

This Phase 2 multicenter, randomized, blinded, placebo-controlled trial evaluated efficacy, PK, PD, safety, and tolerability of SOF in combination with GS-0938 (guanidine nucleotide analog, an NS5B inhibitor) and/or RBV for 12 or 24 weeks in subjects with genotype 1 through 6 HCV infection. Due to ALT elevations associated with GS-0938 treatment, on December 16, 2011 Pharmasset, Inc. (subsequently acquired by Gilead) notified sites to immediately discontinue all study drugs in all subjects who were receiving GS-0938. Discontinued study drugs included GS-0938 monotherapy or GS-0938 in combination with SOF, with or without RBV. These subjects were monitored weekly for the first 4 weeks after discontinuing therapy and then biweekly during a safety follow-up period (12 weeks after the last dose of GS-0938). Following the safety follow-up period, subjects who were eligible based on ALT and HCV RNA values received SOF 400 mg once daily + RBV 1000 or 1200 mg daily (divided dose) for 24 weeks.

A total of 132 subjects were enrolled in the re-treatment group and received at least one dose of study drug, out of which 123 subjects (93.2%) completed study drug treatment. A total of 9 subjects (6.8%) did not complete study drug treatment: 5 subjects (3.8%) discontinued for other reasons, 2 subjects (1.5%) discontinued due to an AE, 1 subject (0.8%) was lost to follow-up, and 1 subject (0.8%) withdrew consent.

The mean age was 52 years (range, 19 to 74 years). The majority of subjects were male (56%), white (86%), and non-Hispanic/Latino (90%). Black or African American subjects and subjects of other race comprised 9.8% and 4.5% of subjects, respectively. The mean baseline body mass index (BMI) was 27.7 kg/m^2, and most subjects (68.2%) had a baseline BMI < 30 kg/m2. The majority of subjects had genotype 1a HCV infection (60.6%) while 18.9%, 9.8%, 8.3%, and 2.3% of subjects had genotype 1b, 2, 3, and 4 HCV infection, respectively. The majority of subjects (58%) had a baseline HCV RNA ≥ 6 $\log_{10}$ IU/mL, and 9.8% of subjects had cirrhosis. The majority of subjects had an IL28B gene (IL28B) non-CC allele (67%).

The mean exposure to study drug for the SOF+RBV re-treatment group was 23.4 weeks. A total of 107 subjects (81.1%) received SOF+RBV for 24 weeks.

Four subjects experienced SAEs (preferred terms: aneurysm (carotid artery aneurysm), cerebral hemorrhage, bipolar disorder, cellulitis, and myocardial infarction). Subject #1005-20017 had a Grade 4 AE of myocardial infarction on Day 34 of the re-treatment period (history of previous MI only one month after start of study drug and strong family history of heart disease). SOF+RBV treatment was interrupted. The AE was considered unlikely to be related to SOF or RBV and resolved with sequelae on Day 36.

Two subjects discontinued SOF due to an AE:

- Subject #1005-20064 discontinued SOF and RBV on Day 90 due to the Grade 2 AE of gingival inflammation and the Grade 3 AEs of mouth ulceration and increased upper airway secretion. All events were considered possibly related to SOF+RBV treatment, and resolved with sequelae on posttreatment Day 10.
- Subject #1085-20216 discontinued SOF+RBV treatment on Day 142 due to a Grade 3 AE of depression. This event was considered unlikely to be related to SOF, possibly related to RBV, and was ongoing at the time of the data cutoff date.

Reviewer's Comment

Due to the above noted adverse events of gingival inflammation, mouth ulceration and increased upper airway secretion (Subject #1005-20064) which were considered possibly related to SOF+RBV treatment and led to discontinuation of therapy, the Applicant was asked to provide an assessment of adverse events of hypersensitivity in sofosbuvir clinical development plan to further guide labeling recommendations. The response received on September 03, 2013 is summarized below.

> An analysis of hypersensitivity AEs was performed by the Applicant for all clinical trials submitted to the NDA 204671 and/or the 90-day safety update. As per the Applicant, no subject experienced any acute type 1 hypersensitivity AE in any sofosbuvir-containing treatment arm. Hypersensitivity occurred in none or less than 1% of active treatment arms. There were no Grade 3 or 4 hypersensitivity events reported in any subject receiving sofosbuvir. No subjects had any dose reduction, treatment interruption or discontinuation of study drugs due to hypersensitivity. No cases of angioedema were reported in any sofosbuvir-treated subject across the sofosbuvir clinical program, and no subject with hypersensitivity experienced any increase in eosinophil count. As per the Applicant, "There is no current evidence for SOF-related hypersensitivity as assessed by the AEs of hypersensitivity in the SOF clinical development program".

No deaths were reported during the re-treatment period.

Decreased hemoglobin (18 subjects, 13.7%) was the most frequently observed Grade 3 or 4 laboratory abnormality; decreased lymphocytes and increased lipase (5 subjects each, 3.8%) and hyperglycemia and hyperbilirubinemia (2 subjects each, 1.5%) also occurred in more than one subject. Hemolysis-related increases in total bilirubin were not associated with increases in ALT levels. No Grade 3 or 4 ALT laboratory abnormalities were observed.

Reviewer's Comment

Subjects enrolled in Re-treatment Group of Study P2938-0721 (Quantum) received 24 weeks of SOF+RBV regimen. 24 week treatment duration was not evaluated in pivotal Phase 3 trials submitted in the NDA. Thus data from Re-Treatment Group provides insight into safety of sofosbuvir and ribavirin combination regimen beyond 16 weeks of duration.

No unusual pattern of AEs or laboratory abnormalities was observed in the presented data for SOF+RBV 24 Week regimen. Adverse event profile was similar to that described with 12 or 16 week SOF-containing regimens.

Study GS-US-334-0133 (VALENCE)

This Phase 3, multicenter, randomized, double-blind, placebo-controlled trial is evaluating the efficacy and safety of SOF and RBV treatment for 12 or 24 weeks in treatment-naive and treatment-experienced subjects with genotype 2 or 3 HCV infection. Subjects were randomized in a 4:1 ratio to receive SOF 400 mg once daily + RBV 1000 or 1200 mg daily (divided dose) or SOF placebo once daily + RBV placebo twice daily, and the planned treatment duration was 12 weeks. Based on emerging clinical data suggesting that subjects with HCV genotype 3 could benefit from extending the SOF+RBV treatment duration from 12 to 24 weeks, the protocol was amended. Subjects with genotype 2 HCV infection randomized to SOF+RBV treatment continued to received SOF+RBV for 12 weeks and subjects with genotype 3 HCV infection randomized to SOF+RBV treatment who had not completed treatment received SOF+RBV for 24 weeks. Subjects who had completed treatment at the time of the amendment completed follow-up visits as planned. Subjects randomized to the placebo group were terminated from the trial and offered open-label treatment through Study GS-US-334-0109 if they were eligible. Randomization was stratified by prior treatment experience (treatment-naive or treatment-experienced) and cirrhosis (presence or absence).

In total, 419 subjects received at least one dose of study drugs: 85 subjects in Group 1 (SOF+RBV 12 Weeks), 85 subjects in Group 2 (placebo) and 249 subjects in Group 3 (SOF+RBV 24 Weeks). At the time of safety update data cutoff date, 68.2% of subjects in Group 1 had completed study treatment. In Group 3, no subjects have completed study treatment or discontinued study treatment at the time of the safety update data cutoff date.

The mean exposure to study drug was 11.9 weeks for Group 1 (SOF+RBV 12 Weeks), 7.3 weeks for Group 2 (placebo), and 17.2 weeks for Group 3 (SOF+RBV 24 Weeks). There were no Grade 4 AEs reported in this trial up to the data cutoff date. Adverse events of anemia (3 subjects), fatigue (2 subjects), and hyperglycemia (2 subjects) were the only Grade 3 AEs reported in more than one subject in the trial. The Grade 3 AEs of arrhythmia, gastroenteritis, hyperglycemia, malignant hepatic neoplasm, road traffic accident, amylase increased, lipase increased, breast cancer, and colon cancer were

also SAEs. No SAE was reported in more than one subject in any group. All SAEs were considered not related to SOF+RBV, except for the SAEs of increased amylase and increased lipase in Subject #4021-2103, which were considered related to SOF+RBV treatment. The SAEs of increased amylase and increased lipase both started on Day 18, were ongoing at the time of safety update data cutoff date, and led to no action taken with SOF or RBV. It was noted that this subject had no clinical signs or symptoms of pancreatitis.

Nine subjects had Grade 3 AEs that were considered related to SOF+RBV: one subject in Group 1 (anemia), one subject in Group 2 (liver function test abnormal), and seven subjects in Group 3 (amylase increased, anemia [n = 2], asthenia, fatigue [n = 2], headache, and lipase increased). For most treatment-related Grade 3 AEs, no action on study drugs was taken. For all 3 Grade 3 AEs of anemia, RBV dose was either interrupted (Subject #2716-2419) or reduced (Subjects #3912-2188 and 6830-2373). In Subject #4472-2038 who had abnormal liver function tests, placebo treatment was discontinued;

> Subject #1065-2244 had an SAE of Grade 3 cardiac arrhythmia on Day 37, which resolved on Day 38 with beta blocker (metoprolol) treatment. The subject reported the symptoms of “lump in throat, awareness of heart beat and that it was out of rhythm,” breathlessness, cough, and inability to sleep. These symptoms were similar to those experienced during previous episodes prior to trial participation. “Ventricular ectopics” were noted on ECG during hospitalization. The subject was discharged on bisoprolol and zopiclone (sleep aid) the following day and the event was considered resolved with sequelae.
>
> Subject #1081-2327 in Group 1 (SOF+RBV 12 Weeks) discontinued SOF+RBV due to AEs of malaise and headache. Both of these Grade 2 events started on Day 31 and resolved on posttreatment Day 10, and were considered related to SOF and RBV.

Grade 3 or 4 ALT elevations reported in this trial are listed below:

- In Group 1, Subject #5528-2236 (Grade 2 ALT at baseline) had normal ALT values Weeks 1 through 12. In the setting of virologic relapse, had Grade 4 ALT level of 401 U/L at posttreatment Week 4.
- In Group 3, Subject #1088-2273 and Subject #1386-2171 had baseline ALT of Grade 2 (175 and 176 U/L, respectively) which increased to Grade 3 ALT at Week 1 (247 and 223 U/L, respectively) before normalizing on treatment.
- In Group 3, Subject #4021-2103 (Grade 2 ALT at baseline) and Subject #0487-2357 (Grade 1 ALT at baseline) had isolated occurrences of Grade 4 ALT at Week 16 and 6, respectively.

Two subjects in Group 3 had Grade 4 lipase abnormalities.

Study GS-US-334-0125

This Phase 2, ongoing, open-label trial is evaluating the efficacy and safety of SOF and RBV for 48 weeks in HCV-infected subjects with cirrhosis and portal hypertension with or without liver decompensation. Patients with Child-Turcotte-Pugh scores up to 10 (Child-Turcotte-Pugh class A and B) and the presence of esophageal or gastric varices with hepatic venous pressure gradient (HVPG) > 6 were included. At the time of the 90-day safety update, 20 subjects had been enrolled with mean treatment duration of 9.5 weeks for the 9 patients randomized to SOF+RBV treatment. The mean age was 57 years (range 44 to 69 years), mean BMI 30, baseline Model for End-Stage Liver Disease (MELD) scores ranged from 6 to 19. The Applicant notes that the safety of SOF+RBV in these patients has been similar to what was observed in the pre-transplant patients. There have been no Grade 3 or 4 AEs, and only a single SAE of ascites reported to date. No patients discontinued treatment due to AEs. Laboratory abnormalities were consistent with RBV-associated hemolysis with a mean reduction in hemoglobin of -2.8 g/dL at Week 12. No additional safety issues have been identified in these patients as per the Applicant.

Updates on Phase 2 and 3 Trials Included in Original NDA Submission

In Study GS-US-334-0107, Subject #5498-7435 died of a suspected overdose of bipolar medications approximately 24 weeks after the last dose of study dose. The death was not considered related to SOF+RBV. No other deaths were reported during the posttreatment follow-up periods in the Phase 2 and 3 trials included in the original NDA submission.

Three partner pregnancies were reported: 1 each in Studies P7977-0523, GS-US-334-0108, and GS-US-334-0110 during the posttreatment follow-up periods in the Phase 2 and 3 trials included in the original NDA submission.

In Study GS-US-334-0139, an access trial in posttransplant subjects with aggressive, recurrent HCV, two subjects had SAEs:

- Subject #0380-2805 died from a fatal variceal bleed.
- Subject #4447-2804 had SAEs of anemia and exacerbation of elevated creatinine. At the Week 1 visit, the subject underwent paracentesis at which time the subject's hemoglobin level was 7.9 g/dL and creatinine was 2.4 mg/dL. The subject received 2 units of PRBCs and hemoglobin levels subsequently increased. As reported, creatinine also decreased somewhat and both events were considered resolved.

SOF Compassionate-Use Studies

The SOF Compassionate Use Program provides access to SOF (dosed with RBV with or without PEG) to HCV patients post liver transplantation with rapid fibrosis progression and limited life expectancy without treatment. Protocol numbers were assigned to

enable Gilead to track the regimen each patient received (SOF+RBV: IN-US-334-0141; SOF+PEG+RBV: IN-US-334-0143).

Of the 55 subjects in the SOF compassionate use program as of April 1, 2013, five deaths were reported: four subjects receiving SOF+RBV under protocol IN-US-334-0141 (gastrointestinal hemorrhage and pruritus, death [due to disease progression], autoimmune hepatitis [SAE of severe allo-immune hepatitis; liver biopsy showed a severe autoimmune hepatitis and an acute rejection; auto antibodies were negative], acute respiratory failure), and one subject receiving SOF+PEG+RBV under protocol IN-US-334-0143 (pneumonia with respiratory failure).

Reviewer's Comments

As per Applicant, the incidence of SAEs was higher in the SOF-compassionate-use protocols (43.6%) than across the rest of the sofosbuvir clinical development program.

Non-Gilead Sponsored Trials

The Applicant has provided safety data for 3 non-Gilead sponsored trials to support the safety of SOF in combination with other agents. These include: Study CO-US-334-0137, Study CO-US-334-0136, and Study CO-US-334-0112 from the interim abbreviated CSR provided by the NIAID (11-I-0258 CSR).

Of the 168 subjects in the Study CO-US-334-0137 (Janssen Study HPC2002) as of 01 April 2013, two subjects (1.2%) had died. One subject had a fatal trauma (accidental fall down stairs) and the other subject had a fatal ischemic stroke (The event occurred over one month after the last dose of study drugs in a 58 year old male subject. Polycythemia rubra vera was noted as a possible alternative explanation for the ischemic stroke in this case). Six subjects (3.6%) reported SAEs. No pregnancies were reported.

Of the 211 subjects in Study CO-US-334-0136 (BMS Study AI444040), 20 subjects (9.5%) reported SAEs through April 1, 2013. Only one SAE of accidental drug overdose was considered related to study treatment by the investigator. A mild headache was reported as being associated with the overdose. Two female subjects (0.9%) reported pregnancies. One 29-year-old subject was estimated to have conceived around the time of discontinuation of SOF, DCV, and RBV and delivered a healthy full-term infant. A 44-year-old subject became pregnant approximately 6 months after discontinuing study drug but spontaneously aborted early in the pregnancy.

Of the 60 subjects in Study CO-US-334-0112 (NIAID Study 11-I-0258) as of April 1, 2013, one subject (1.7%) reported an SAE of acute pancreatitis. This event occurred more than four months after study treatment had been discontinued. One partner

pregnancy was reported. This pregnancy was not medically confirmed and the partner was lost to follow-up.

Other Notable Adverse Events in the Safety Update

- Subject #1543-9011 (Study GS-US-334-0109) in Group 1 (SOF+RBV 12 Weeks group) discontinued SOF and RBV on Day 16 due to the Grade 1 AE of dyspnea and Grade 2 AE of tinnitus. Subject is a 69-year-old white, Hispanic male with past medical history significant for GERD, benign prostate hypertrophy, diverticulosis, and a history of seizure related to a traumatic brain injury and jaw fracture. The subject experienced mild dyspnea on Day 12 and moderate pulsatile tinnitus of the right ear on Day 15. Both were considered unrelated to study drug by the investigator. Study drugs were discontinued on Day 12 – at the onset of dyspnea. The dyspnea resolved and the tinnitus remained ongoing at the week 4 follow-up visit (Day 27).

- Subject #0532-9082 (Study GS-US-334-0109) in Group 1 (SOF+RBV 12 Weeks group) had a Grade 4 increased lipase. The subject had normal lipase at baseline and through Week 2 visit, and then had a single occurrence of an asymptomatic Grade 4 increased lipase at Week 4. Lipase levels returned to normal from Week 6 through posttreatment Week 4.

- Three subjects in the SOF+RBV 24 Week group (Study GS-US-334-0114, a Phase 2 trial in HCV GT4 infected Egyptian adults) had SAEs (all were Grade 3, considered not related to SOF+RBV, and did not result in treatment discontinuation):
    - Subject #0407-8494 had abdominal pain, which started on Day 91 and was ongoing at the time of the data cutoff date;
    - Subject #0407-8488 had chest pain (subject is a 65-year-old Caucasian female with past medical history significant for hypokalemia, hypertension, left ventricular hypertrophy, diabetes mellitus, shortness of breath and heart burn presented with complaints of non-radiating left sided chest pain associated with shortness of breath on study Day 53. Pain improved with Motrin. Stress test was negative for ischemia. Ejection fraction was noted as 43% with mild diffuse global hypokinesia. Hemoglobin was 11.6 g/dl and Troponin I was <0.01 ng/ml (RR:0-0.10). ECG revealed sinus tachycardia. Chest pain resolved on Day 54. No actions were taken with the study drugs. The investigator assessed the event not related to the study medications. Alternative causality was provided as pre-existing condition.
    - Subject #0407-8441 had loss of consciousness. Subject is a 57 year old Caucasian male with past medical history significant for cerebrovascular accident, hypertension, diabetes mellitus and mild mitral valve regurgitation. Concomitant medications included Cardio Aspirin (acetylsalicylic acid), Perindopril EG, and metformin. The subject discontinued study medications (reason not specified) 5.5 months after initiating therapy. Two days later, the

subject travelled from US to Italy. Per subject report, he had a brief attack of shortness of breath, sweating, body aches, cold sensation and chills, then lost consciousness for 45 minutes. Doppler ultrasound of neck vessels revealed atherosclerosis. Echo was normal (ejection fraction of 65%). ECG revealed normal sinus rhythm with "eleven extra systoles and three ventricular with no significant breaks." The investigator reported causality as not related to study medications or procedures, but related to an unspecified pre-existing condition.

The Applicant concluded that “The overall safety profile for SOF in combination with other antiviral agents is consistent with the profile observed in the original NDA submission and, therefore, there are no new safety concerns for SOF based on the data presented in this safety update.”

Reviewer’s Comment

No new safety concerns associated with sofosbuvir use have been identified based on the review of the data provided in the 90 Day Safety Update Report.

8 Postmarket Experience

This product has not yet been approved for marketing in any country and therefore there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

Links to the referenced websites are provided throughout the review and additional references are noted below.

Backus, LI, D Boothroyd, B Phillips, P Belperio, J Halloran, L Mole, 2011, A Sustained Virologic Response Reduces Risk of All-Cause Mortality in Patients With Hepatitis C, Clin Gastroenterol Hepatol, June;9(6):509-516

Ghany, MG, DB Strader, DL Thomas, LB Seeff, 2009, Diagnosis, Management, and Treatment of Hepatitis C: An Update, HEPATOLOGY, 49:1335-1374.

Ghany MG et al, 2011. An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases, Hepatology 2011

Kim, WR, 2002, The Burden of Hepatitis C in the United States, Hepatology, 36(Suppl):S30-S34.

Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012 Feb 21;156(4):271-8.

Manos, MM, WK Zhao, VA Shvachko, N Volkova, CP Quesenberry, Viral Hepatitis Registry, Kaiser Permanente Division of Research, Oakland, CA, 2009, Long Term Outcomes in Patients Treated With Peg-Interferon/Ribavirin Therapy for Hepatitis C: The Substantial Effect of Sustained Viral Response (SVR) on Liver Disease, Mortality and Diabetes, 13th International Symposium on Viral Hepatitis and Liver Disease, Abstract PL-3.

Shiratori, Y, Y Ito, O Yokosuka, F Imazeki, R Nakata, N Tanaka, Y Arakawa, E Hashimoto, K Hirota, H Yoshida, Y Ohashi, M Omata; Tokyo-Chiba Hepatitis Research Group, 2005, Antiviral Therapy for Cirrhotic Hepatitis C: Association With Reduced Hepatocellular Carcinoma Development and Improved Survival, Ann Intern Med, Jan 18;142(2):105-14, PMID: 15657158.

Singal AG, M Volk, D Jensen, et al. 2010, A sustained viral response is associated with reduced liver related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 8:280–288.

van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL 2012. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA,308(24):2584-2593

Veldt, BJ, EJ Heathcote, H Wedemeyer, J Reichen, WP Hofmann, S Zeuzem, MP Manns, BE Hansen, SW Schalm, HL Janssen, 2007, Sustained Virologic Response and Clinical Outcomes in Patients With Chronic Hepatitis C and Advanced Fibrosis, Ann Intern Med, 147:677-684.

Yoshida, H, Y Shiratori, M Moriyama, et al., 1999, Interferon Therapy Reduces the Risk for Hepatocellular Carcinoma: National Surveillance Program of Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C in Japan, IHIT Study Group, Inhibition of Hepatocarcinogenesis by Interferon Therapy, Ann Intern Med, Aug 3;131(3):174-81.

9.2 Labeling Recommendations

The proposed Package Insert (PI or label) is being reviewed by all disciplines. Labeling discussions are ongoing and the recommendations have not been finalized at the time of this review. Please refer to Cross Discipline Team Leader Memo by Dr. Sarah Connelly for detailed labeling recommendations. Some of the key recommendations under consideration by the clinical review team are outlined below:

- After in-depth discussions about the regulatory implications of proposed indication (for sofosbuvir use) - “in combination with other agents”, the review team has decided to propose the use of sofosbuvir in combination with ribavirin in subjects with genotype 2 or 3 HCV infection and sofosbuvir in combination with pegylated interferon and ribavirin in treatment-naïve subjects with genotype 1 or 4 HCV infection.

- Few subjects with genotype 5 (N=1) and genotype 6 (N=6) were included in the clinical trials. Discussions are ongoing whether available data on genotypes 5 and 6 is sufficient for dosing recommendations.
  - *Propose to include a statement in the Prescribing Information - Data on genotypes 5 and 6 are insufficient for dosing recommendations*

- [redacted] (b) (4) we believe an indication should specify the subpopulation studied which was patients with HCC meeting Milan criteria and awaiting liver transplantation.
  - *Discussions regarding how best to communicate the available information are ongoing.*

- Available efficacy and safety data in HIV/HCV coinfected subjects (N=31) is limited and precludes an indication in this special population at this time.

- Proposed 16 weeks treatment duration for GT 3 treatment-naïve was not evaluated in trials
  - *recommendations are based on bridging analyses*

- Discussions to recommend 16 weeks of sofosbuvir and ribavirin in harder-to-treat subgroups of genotype 2 patient population which might potentially benefit from extended treatment duration are ongoing.
  - *Small numbers in these subgroups are acknowledged but improved SVR trends in GT2 treatment-experienced (mainly prior non responders) and GT 2 patients with cirrhosis and non-CC IL28B genotype look promising*

- Overall SVR lower in Genotype 1b compared to 1a
  - *Discussions are ongoing whether this information needs to be conveyed in the Prescribing Information*

- Ongoing discussions regarding best approach to present data on subgroup analyses (treatment response predictors such as cirrhosis, and non-CC IL28B) are ongoing

- Ongoing discussions regarding the available evidence to support potential treatment recommendations in treatment-experienced genotype 1 patients

- Recommend including all grades in the treatment-emergent adverse event table in the PI (b) (4)

- Information on adverse events of special interest may be added to the PI based on clinical significance.

The final PI will be available at the time of approval.

9.3 Advisory Committee Meeting

The Antiviral Drugs Advisory Committee (AC) Meeting is being convened by the FDA on October 25, 2013 to solicit the committee's comments and recommendations regarding this NDA. Preliminary questions/issues for discussion at the upcoming AC are listed below:

1. Considering potential risk 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?
   a. If no, what additional studies are recommended?
   b. If yes, proceed with the remaining questions.

2. Considering potential risk 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?
   a. If no, what additional studies are recommended?
   b. If yes, proceed with the remaining questions.

3. 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.

4. Please comment on the strength of evidence for use of sofosbuvir and ribavirin for 16 weeks duration in the following groups of genotype 2 patients:
   a. Should genotype 2 patients with cirrhosis receive 16 weeks of sofosbuvir and ribavirin therapy?
   b. Should genotype 2 treatment-experienced patients with poor baseline predictors such as non-CC IL28B genotype receive 16 weeks of sofosbuvir and ribavirin therapy?
   c. Should genotype 2 treatment-experienced patients who are prior null and partial responders receive 16 weeks of sofosbuvir and ribavirin therapy?

5. 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?

6. Are there any other postmarketing studies/trials needed to further define the optimal use of sofosbuvir?

Please refer to the FDA background package for in depth discussion of these issues. Detailed information on the AC discussions and recommendations will be accessible via the official transcripts of the meeting.

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

/s/

POONAM MISHRA
09/06/2013

SARAH M CONNELLY
09/06/2013
I concur with Dr. Mishra's assessments and conclusions in this review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204671 **Applicant:** Gilead Sciences, Inc. **Stamp Date:** Received April 08, 2013

Drug Name: Sofosbuvir (GS-7977) **NDA/BLA Type:** Original NDA Submission/NME

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			ISS in Module 5.3.5.3.28 has a reference link to Summary of Clinical Safety (Module 2.7.4)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			ISE in Module 5.3.5.3.27 has a reference link to Summary of Clinical Efficacy (Module 2.7.3)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2 Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Dose, duration and regimen were explored in the following Phase 2 studies:	X			

	Content Parameter	Yes	No	NA	Comment
	Study Number: P7977-0221 Study Title: Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, multicenter study of the efficacy, PK, PD, safety, and tolerability of SOF+PEG+RBV for 28 days in treatment-naïve subjects with chronic genotype 1 HCV infection Sample Size: 64 Treatment and Duration: SOF 100 mg+PEG+RBV group: SOF 100 mg QD PO on Days 0–27 and PEG+RBV Weeks 1–48 SOF 200 mg+PEG+RBV group: SOF 200 mg QD PO on Days 0–27 and PEG+RBV Weeks 1–48 SOF 400 mg+PEG+RBV group: SOF 400 mg QD PO on Days 0–27 and PEG+RBV Weeks 1–48 Placebo+PEG+RBV group: SOF-matching placebo QD PO on Days 0−27 and PEG+RBV Weeks 1−48 For all groups, PEG dose was 180 µg/week SC and RBV dose was 1000 or 1200 mg/day (divided daily dose) PO. Treatment duration was 48 weeks (SOF+PEG+RBV for 4 weeks followed by 44 weeks of PEG+RBV). Location in submission: Module 5.3.4.2 Study Number: P7977-0422 (PROTON) Study Title: Phase 2b, placebo-controlled, dose-ranging, multicenter study in treatment-naïve subjects with chronic genotype 1 HCV infection and an open-label assessment in subjects with genotype 2 or 3 HCV infection of the efficacy, PK, PD, safety and tolerability of SOF administered with PEG+RBV for 12 weeks Sample Size: 147 Treatment and Duration: **Randomized, Double-Blind Groups (Genotype 1):** SOF 200 mg+PEG+RBV group: SOF 200 mg QD PO+PEG 180 µg/week SC+RBV 1000 or 1200 mg (divided daily dose) PO for 12 weeks followed by PEG+RBV for up to 36 weeks SOF 400 mg+PEG+RBV group: SOF 400 mg QD PO+PEG 180 µg/week SC+RBV 1000 or 1200 mg (divided daily dose) PO for 12 weeks followed by PEG+RBV for up to 36 weeks Placebo+PEG+RBV group: SOF-matching placebo QD PO+PEG 180 µg/week SC+RBV 1000 or 1200 mg (divided daily dose) PO for 12 weeks followed by PEG+RBV for up to 36 weeks **Open-Label Group (Genotype 2/3):** SOF 400 mg+PEG+RBV group: SOF 400 mg QD PO+PEG 180 µg/week SC+RBV 800 mg/day (divided daily dose) for 12 weeks Location in submission: Section 5.3.5.1 Study Number: P7977-0724 (ATOMIC) Study Title: Phase 2b, randomized, open-label, treatment duration-finding, multicenter study of the efficacy, PK, PD, safety, and tolerability of treatment with SOF+PEG+RBV for 12 or 24 weeks in treatment-naive subjects with				

	Content Parameter	Yes	No	NA	Comment
	genotype 1, 4, 5, 6, or genotype indeterminate HCV infection Sample Size: 332 Treatment and Duration: Group A: SOF 400 mg QD PO+PEG+RBV for 12 weeks Group B: SOF 400 mg QD PO+PEG+RBV for 24 weeks Group C: SOF 400 mg QD PO+PEG+RBV for 12 weeks Subjects in Group C were then rerandomized to 1 of 2 groups to receive another 12 weeks of treatment: Group C1: SOF 400 mg QD PO for 12 weeks Group C2: SOF 400 mg QD PO+RBV for 12 weeks For all groups, PEG dose was 180 µg/week SC and RBV dose was 1000 or 1200 mg/day (divided daily dose) PO. Location in submission: Section 5.3.5.1 Study Number: P7977-0523 (ELECTRON) Study Title: Phase 2a, open-label, multicenter study of the efficacy, PK, PD, safety, and tolerability of SOF 400 mg for 8 or 12 weeks administered with and without RBV and/or PEG in subjects with genotype 1, 2, or 3 HCV infection Treatment and Duration: Part 1 (Treatment-Naive Subjects with Genotype 2/3 HCV): Group 1: SOF+RBV 12 weeks Group 2: SOF+PEG+RBV for 4 weeks then SOF+RBV for 8 weeks Group 3: SOF+PEG+RBV for 8 weeks then SOF+RBV for 4 weeks Group 4: SOF+PEG+RBV for 12 weeks Part 2 (Treatment-Naive Subjects with Genotype 2/3 HCV in Groups 5 and 6 and Null Responders with Genotype 1 HCV in Group 7): Group 5: SOF for 12 weeks Group 6: SOF+PEG+RBV for 8 weeks Group 7: SOF+RBV 12 weeks Part 3 (Treatment-Naive Subjects with Genotype 1 HCV in Group 8 and Treatment-Experienced Subjects with Genotype 2/3 in Group 9): Groups 8 and 9: SOF+RBV 12 weeks For all groups, SOF dose was 400 mg QD PO, PEG dose was 180 µg/week SC, and RBV dose was 1000 or 1200 mg/day (divided daily dose) PO This study was not designed to evaluate formal statistical hypotheses. Location in submission: Section 5.3.5.1 Study Number: P2938-0721 (QUANTUM) Study Title: Phase 2, randomized, double-blind, multicenter study of the efficacy, PK, PD, safety, and tolerability of regimens containing SOF and RBV in treatment-naïve subjects with chronic genotype 1−6 HCV infection. For this submission, only data for the SOF 400 mg + RBV treatment regimens (Groups C and G) are included. Sample Size (Groups C and G): 50 Treatment and Duration:				

	Content Parameter	Yes	No	NA	Comment
	Group C: SOF 400 mg QD PO+RBV PO for 12 weeks Group G: SOF 400 mg QD PO+RBV PO for 24 weeks For all subjects, RBV dose was 1000 or 1200 mg/day (divided daily dose) Location in submission: Section 5.3.5.1 Study Number: 11-I-0258 (NIAID sponsored) Study Title: Phase 1/2a, randomized, open-label, prospective, multicenter study to assess the efficacy, safety, and tolerability of SOF administered in combination with full- or low-dose RBV for 24 weeks in treatment-naïve, subjects monoinfected with genotype 1 HCV Sample Size: 60 Treatment and Duration: Part 1: SOF 400 mg QD PO+RBV 1000 or 1200 mg/day (divided daily dose) PO for 24 weeks Part 2: Group A: SOF 400 mg QD PO+RBV 1000 or 1200 mg/day (divided daily dose) PO for 24 weeks Group B: SOF 400 mg QD PO+RBV 600 mg QD PO for 24 weeks Location in submission: Section 5.3.5.4				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? The application includes data from four pivotal Phase 3 studies: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), and GS-US-334-0110 (NEUTRINO). Pivotal Study #1 P7977-1231: Phase 3, randomized, open-label study of the efficacy and safety of 12 weeks of SOF+RBV or 24 weeks of PEG+RBV in treatment-naïve subjects with genotype 2 or 3 HCV infection (enrolled in approximately a 1:3 ratio of genotype 2 to genotype 3). Pivotal Study #2 GS-US-334-0107: Phase 3, randomized, double-blind, placebo-controlled study of the efficacy and safety of 12 weeks of SOF+RBV in subjects with genotype 2 or 3 HCV infection who are IFN-intolerant, IFN-ineligible, or unwilling to take IFN Pivotal Study #3 GS-US-334-0108: Phase 3, randomized, double-blind study of the efficacy and safety of 12 or 16 weeks of SOF+RBV treatment in subjects with chronic genotype 2 or 3 HCV infection who had failed prior treatment with an IFN-based regimen.	X			

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #4 GS-US-334-0110: Phase 3, open-label study of the efficacy and safety of 12 weeks SOF+PEG+RBV in treatment-naive subjects with chronic genotype 1, 4, 5, or 6 HCV infection Proposed Indication [TRADENAME] is indicated in combination with other agents for the treatment of chronic hepatitis C (CHC) in adults				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			A QT study has been completed and reviewed by IRT.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	Drug is first-in-class
25.	Have narrative summaries been submitted for all deaths and	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?				
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Sponsor provided a request for waiver of pediatric studies for children < 3 years of age (Module 1.9.1) and a request for deferral of pediatric studies for children 3 to < 18 years of age (Module 1.9.2).
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

N/A

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None from clinical perspective at this time.

Poonam Mishra, MD	May 08, 2013
Reviewing Medical Officer	Date
Sarah Connelly, MD	May 08, 2013
Clinical Team Leader	Date

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

/s/

POONAM MISHRA
05/08/2013

SARAH M CONNELLY
05/08/2013