APPLICATION NUMBER:
204671Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW
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<td>From</td>
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<td>Subject</td>
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<td>Applicant</td>
<td>Gilead Sciences, Inc.</td>
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<td>Proprietary Name / Established (USAN) names</td>
<td>Sovaldi (pending)/Sofosbuvir</td>
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<td>Dosage forms / Strength</td>
<td>400 mg tablet</td>
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<td>Proposed Indication(s)</td>
<td>Indicated in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C in adults.</td>
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1. Introduction

Sofosbuvir (also referred to as SOF, GS-7977) is a new molecular entity, a hepatitis C virus (HCV) NS5B nucleotide analog polymerase inhibitor developed for the treatment of patients with chronic hepatitis C infection. This NDA contains the results of the nonclinical and clinical development program conducted by Gilead Sciences to support the use of sofosbuvir 400 mg once daily in combination with ribavirin (SOF+RBV) or in combination with pegylated interferon alfa and ribavirin (SOF+PEG/RBV).

The original NDA submission contained primary supportive efficacy and safety information from four Phase 3 trials: FISSION, POSITRON and FUSION in the HCV genotype (GT) 2/3 population evaluating SOF+RBV, and NEUTRINO in the HCV GT 1, 4, 5, 6 population evaluating SOF+PEG/RBV. In addition, P7977-2025 trial data were submitted to support an indication in the pre-transplant population. As will be discussed in this memo, one of the important conclusions from the initial review was that an HCV GT 3 SOF+RBV treatment duration between 12-16 weeks was not optimal due to SVR12 rates ranging 30-62% and high relapse rates ranging 38-66%. Late in the review cycle the review team became aware of data from the VALENCE trial. This trial included a SOF+RBV 24 Week arm in HCV GT 3 subjects with an overall SVR12 rate of 84% and relapse rate of 14%. In addition, new data were also available from the PHOTON-1 trial including a SOF+RBV 24 Week arm in HIV/HCV GT 1 subjects with reported overall SVR12 rates of 76%. These data supported Breakthrough Therapy designation, which was granted for SOF+RBV as an interferon-free regimen for the treatment of GT 1, 2 and 3 chronic hepatitis C infection, and led to the decision by the review team to accept these data and review these two additional trials under the current PDUFA V timeline. Specifically, the VALENCE trial data was reviewed to support a SOF+RBV 24 week duration in HCV GT 3 patients and the PHOTON-1 trial data was reviewed to support a SOF+RBV 24 week duration for HCV GT 1 patients who may be ineligible to receive an interferon-containing treatment.

Due to the timing of when data were received during this NDA review, this memo will summarize the primary efficacy, virology and safety data in the following way:

- Data provided with original NDA (FISSION, POSITRON, FUSION, NEUTRINO trials): based upon completed initial primary reviews
- VALENCE: based upon available data used for the FDA Advisory Committee Meeting
- PHOTON-1: based upon data submitted in the Applicant’s synoptic clinical study report

At this time, primary reviewers are completing their assessments of the VALENCE and PHOTON-1 trials and subsequently will be making addenda to their initial reviews. I am choosing to approach this CDTL memo in this manner for completeness; however, the preliminary nature of the VALENCE and PHOTON-1 data should be noted.
2. Background

Sofosbuvir has not been marketed outside the United States (US) to date and a marketing application is currently under consideration by the EMA. Sofosbuvir is a prodrug of a nucleotide analog inhibitor of the hepatitis C virus (HCV) NS5B RNA-dependent RNA polymerase and represents the first drug in this class submitted for review in the US.

The most common HCV 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 standard of care treatment for chronic HCV GT 1 infection is triple therapy with an NS3/4A protease inhibitor, either boceprevir or telaprevir, in combination with PEG/RBV for a total duration of 24 to 48 weeks based on on-treatment response. Sustained virologic response (SVR) rates for boceprevir and telaprevir in combination with PEG/RBV were significantly higher than those observed with PEG/RBV alone (approximately 60-70% vs. 40-45%) in HCV GT 1 treatment-naïve subjects. SVR rates were also higher in subjects treated with boceprevir or telaprevir in combination with PEG/RBV compared with PEG/RBV alone in subjects who had previously failed PEG/RBV therapy.

The approved boceprevir treatment regimen is 800 mg (four-200 mg capsules) orally three times a day with food in combination with PEG/RBV; and the currently approved telaprevir treatment regimen is 1125 mg (three-375 mg tablets) orally two times daily with food in combination with PEG/RBV. Boceprevir and telaprevir are both associated with anemia, and boceprevir has also been associated with neutropenia. Telaprevir has been associated with severe rash, including fatal and non-fatal serious skin reactions, necessitating a Black Box Warning for rash in the telaprevir prescribing information. Both drugs are associated with multiple clinically significant drug interactions. Boceprevir and telaprevir are contraindicated for coadministration with drugs highly dependent on CYP3A4/5 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events; and with potent CYP3A4/5 inducers that may lead to lower exposures and loss of efficacy.

The current standard of care treatment for chronic HCV GT 2 or 3 infection is PEG/RBV for a total duration of 24 weeks. The recommended treatment duration for chronic HCV GT 4 infection is PEG/RBV for a total duration of 48 weeks.

Priority review designation was granted for this NDA under PDUFA V because sofosbuvir may provide some advantages over currently available standard of care treatment options. Advantages of sofosbuvir in combination with pegylated interferon and ribavirin for 12 weeks include an improved safety profile, particularly due to the shorter treatment duration, and patient adherence. For the HCV GT 1 population specifically, these safety and adherence advantages are further demonstrated because of sofosbuvir’s once daily dosing in comparison to thrice daily dosing with boceprevir and twice daily dosing with telaprevir and fewer drug-drug interactions than identified for boceprevir and telaprevir. For the HCV GT 2 and 3 populations, advantages of sofosbuvir in combination with ribavirin include providing an all oral interferon-free regimen thus avoiding the tolerability issues associated with interferon-
based therapy and, for patients ineligible to receive interferon, an available treatment option addressing an unmet medical need.

This NDA was presented at the Antiviral Drug Advisory Committee Meeting on October 25, 2013. Please refer to Section 9 for summary information.

The primary endpoint for the sofosbuvir pivotal clinical trials was sustained virologic response (HCV RNA < 25 IU/mL) measured 12 weeks after the end of therapy (SVR12), and is the currently recommended primary endpoint in the revised Draft Guidance for Industry: Chronic Hepatitis C Virus Infection: Developing Direct Acting Antiviral Agents for Treatment, published in 2013. Sustained virologic response (HCV RNA < LLOQ) at the end of therapy and remaining < LLOQ through 12 or 24 weeks of follow-up) is generally considered a virologic cure for hepatitis C infection; and recent studies have shown that achievement of SVR is associated with improvements in clinical outcomes such as development of hepatocellular carcinoma, hepatic events, fibrosis, and all-cause mortality (van der Meer et al. JAMA. 2012;308(24):2584-2593; Backus, LI et al. Clin Gastroenterol Hepatol. 2011;(6):509-516; Singal, AG et al. Clin Gastroenterol Hepatol, 2010; (8):280-288; Veldt, BJ et al. Ann Intern Med. 2007; 147:677-684).

3. CMC
Please see full details regarding the chemistry, manufacturing and controls (CMC) and biopharmaceutics findings for this application in the reviews of Drs. George Lunn (drug product), Fuqiang Liu (drug substance), through Dr. Rapti D. Madurawe, Branch Chief, ONDQA DNDQA II/Branch V, and Minerva Hughes (biopharmaceutics).

Sofosbuvir is a new molecular entity. The chemical name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl) methoxy)-(phenoxy)phosphorylamino)propanoate.

Sofosbuvir for oral administration will be supplied as 400 mg strength tablets. The drug product consists of yellow film-coated capsule-shaped 400 mg tablets debossed with “GSI” on one side and “7977” on the other. There is also a tablet for the Access program.

At the time of the initial CMC review, the NDA was not recommended for approval from the CMC perspective pending resolution of the impact of and Gilead Foster City cGMP issues, including the reliability of data from these sites (see below). Despite these deficiencies, according to the ONDQA CMC and Biopharmaceutics’ reviews, the information provided for the drug substance has been reviewed and found acceptable, and this NDA provided sufficient information to assure the identity, strength, quality, purity, potency and bioavailability of the drug product. The dissolution method and acceptance criteria are acceptable. The composition, manufacturing process, and specifications for the sofosbuvir tablets are appropriate and the expiration dating period of 24 months is supported by adequate stability data.
Facilities Review/Inspections

There are a total of 12 facilities associated with this application. Three sites were identified with certain facility compliance issues that need to be resolved before the application can be approved.

Gilead Foster City: Gilead Sciences, Foster City, CA, involved in release and stability testing of drug substance and drug product, recently underwent inspection and multiple 483 observations were issued. At the time of this CDTL memo, the Gilead Foster City site has been removed from the NDA as a release testing and stability testing site for drug substance and drug product.

Gilead Ireland: FDA conducted a PAI inspection at this site in August 2013 and issued two 483 observations to the firm. This site is now acceptable following review of the corrective actions.

At the time of this CDTL memo, [redacted] has been removed from the NDA as a proposed commercial drug substance manufacturing site. On October 29, 2013 agreement was reached with Gilead on plans to remove Gilead Foster City from the NDA, and on October 31, 2013 Gilead Foster City was removed from the NDA. Additionally, all launch and future commercial batches will be tested by other facilities that have been determined to be acceptable through facility evaluation under this NDA. Finally, agreement was reached that the stability testing program for this product will be performed by a cGMP-compliant contract testing lab that is already included in the NDA. Documentation supporting these agreements is to be submitted to the NDA by November 8, 2013. Evaluation of that information will be documented in a review addendum, and Dr. Birnkrant’s Division Director memo will cover further developments of this issue.

4. Nonclinical Pharmacology/Toxicology

Please see details of the pharmacology/toxicology findings in Dr. Christopher Ellis’ review. Note, in this section the AUC exposure multiples in humans are in comparison with the recommended clinical 400 mg sofosbuvir dose.

The major target organs identified in the sofosbuvir nonclinical studies include the heart and gastrointestinal tract. GS-9851 is a 1:1 mixture of sofosbuvir and its stereoisomer. GS-331007 is the main circulating metabolite in both animals and humans, accounting for the majority of total drug-related exposure. Myocardial inflammation and degeneration occurred in rats administered oral GS-9851 doses of 2000 mg/kg/day in a 7-day toxicology study. The AUC exposures for GS-9851- and sofosbuvir-derived GS-331007 are approximately 29- and 14-fold higher, respectively, than human exposure. Cardiac toxicity was not observed in rats administered oral doses of sofosbuvir up to 500 mg/kg/day for 6 months, or in dogs and mice administered sofosbuvir at doses up to 500 and 1000 mg/kg/day, the highest doses examined in 9 and 3 month studies in dogs and mice, respectively, corresponding to AUC exposures
approximately 9 (rat), 27 (dog) and 41 (mouse)-fold higher than human exposure. No cardiac safety signals have been identified in the clinical trials to date (see Section 7: Safety).

Gastrointestinal (GI) hemorrhage occurred in male dogs administered oral sofosbuvir doses of 500 mg/kg/day, corresponding to AUC exposures at least ~29-fold that in humans. Hemorrhage occurred in the lamina propria of the pyloric stomach or jejunum in some animals. Increased frequency and incidence of emesis and diarrhea also occurred. The NOEL for GI toxicity is 100 mg/kg/day in dogs administered oral sofosbuvir doses for up to 9 months, corresponding to AUC exposure ~13-fold that in humans. GI hemorrhage has not been observed in rats or mice.

Sofosbuvir was not mutagenic or clastogenic as tested with GS-9851 in the Ames assay, the in vitro chromosomal aberration assay in human peripheral blood lymphocytes and the in vivo mouse micronucleus assay. Two-year carcinogenicity studies in mice and rats are ongoing. Because a SOF+RBV 24 week duration is recommended as a clinical treatment duration, submission of these carcinogenicity studies will be a Postmarketing Requirement.

No effects on fetal development have been observed in rats and rabbits at the highest doses tested. In the rat and rabbit, AUC exposure of GS-331007 was increased over the course of gestation from ~5 to 10-fold and 12 to 28-fold the exposure in humans, respectively. Sofosbuvir had no effects on early embryonic development or on fertility when evaluated in rats. At the highest dose tested, AUC exposure of GS-331007 was ~8-fold the exposure in humans. It is not known whether sofosbuvir and its metabolites are excreted into human breast milk. GS-331007 was the primary component observed in the milk of lactating rats at a milk:plasma concentration ratio of 0.1 at 1 hour post-dose.

Sofosbuvir is considered a pregnancy category B drug. At this time, because sofosbuvir is recommended to be used in combination with either ribavirin or ribavirin plus pegylated interferon, its use will be contraindicated in pregnant women. This rationale is based upon the fact ribavirin is embryocidal and teratogenic, and is considered a pregnancy category X drug. In addition, interferons are considered a pregnancy category C drug, and are abortifacients. The sofosbuvir package insert will include appropriate warnings and precautions about use in pregnancy, and information regarding appropriate contraception methods to avoid pregnancy. If sofosbuvir is used without the combination of ribavirin +/- pegylated interferon alfa, the potential risk of sofosbuvir on pregnancy/lactation and the developing fetus/offspring will change the risk/benefit assessment for use of sofosbuvir in this population.

**5. Clinical Pharmacology/Biopharmaceutics**

Please see details regarding clinical pharmacology in the joint review of Clinical Pharmacology, Pharmacometrics and Pharmacogenomics by Drs. Jenny Zheng, Su-Young Choi, Jeffry Florian and Sarah Dorff. In addition, please see details pertaining to Biopharmaceutics in Dr. Minerva Hughes’ review. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203). A comprehensive range of clinical studies was conducted to characterize the pharmacokinetics (PK) of sofosbuvir and its predominant circulating
metabolite, GS-331007, as GS-461203 is not measureable in plasma. Select clinical pharmacology points are summarized below.

**Absorption and Distribution**
Following oral sofosbuvir administration, sofosbuvir was absorbed with peak plasma concentration reached within 0.5-2 hours post-dose. Peak plasma GS-331007 concentration was observed between 2 and 4 hours post-dose. Steady-state GS-331007 and sofosbuvir PK parameters after sofosbuvir once-daily administration are similar between HCV-infected subjects and healthy subjects. Sofosbuvir can be administered without regard to food (as instructed in Phase 3 trials).

Sofosbuvir is ~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 and Elimination**
The metabolic activation pathway to form the pharmacologically active triphosphate metabolite, GS-461203, is mediated by human cathepsin A (CatA) or carboxylesterase 1 (CES1) and histidine triad nucleotide-binding protein 1 (HINT1). Dephosphorylation of the active metabolite results in the formation of the nucleoside metabolite, GS-331007, which cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro. GS-331007 is the major circulating sofosbuvir metabolite and renal clearance is its major elimination pathway. Median terminal half-lives of sofosbuvir and GS-331007 are 0.4 and 27 hours, respectively.

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

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

The PK of sofosbuvir was studied in HCV-infected subjects with moderate and severe hepatic impairment (Child-Pugh Class B and C). Relative to subjects with normal hepatic function, the sofosbuvir AUC$^{0,24}$ was 126% and 143% higher in subjects with moderate and severe hepatic
impairment, while the GS-331007 AUC\(_{0-24}\) was 18% and 9% higher, respectively. Population PK analysis in HCV-infected subjects indicated that cirrhosis had no clinically relevant effect on sofosbuvir and GS-331007 exposure. No sofosbuvir dose adjustment is recommended for patients with mild, moderate and severe hepatic impairment. However, as PEG is contraindicated for use in patients with decompensated cirrhosis and sofosbuvir safety and efficacy have not been established in these patients, sofosbuvir should not be used in this patient population who would receive a PEG-based regimen.

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

Coadministration of sofosbuvir with the P-gp and BCRP inhibitor CsA (administered as a single high dose of 600 mg), resulted in a ~4.5-fold increase in sofosbuvir exposure, but GS-331007 exposure was unchanged in the presence of CsA. Safety margins for sofosbuvir and metabolites after CsA coadministration are adequate (AUC safety margins range 2.9 to 10.3), when compared with exposures obtained in rat and dog in 3 to 9-month toxicology studies. Limited safety data from an ongoing post-transplant trial (GS-US-334-0126) indicated the safety of SOF+RBV is generally similar between subjects not taking CsA and subjects taking CsA. Therefore, sofosbuvir may be coadministered with CsA.

An ongoing Phase 1 trial (GS-US-334-0146) is evaluating the effect of sofosbuvir on the PK of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol. Trial results were not available for this submission. Thus, the 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.

The effect of sofosbuvir 400 and 1200 mg on QTc interval was evaluated in a randomized, single-dose, placebo-, and active-controlled (moxifloxacin 400 mg) four period crossover thorough QT trial in 59 healthy subjects. In the trial with demonstrated ability to detect small effects, the upper bound of the two-sided 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on Fridericia correction method (QTcF) was below 10 ms, the threshold for regulatory concern, as described in the ICH E14 guidelines.

**Dose Selection**
Dose selection was evaluated and found to be appropriate based on drug exposure and antiviral activity observed in early sofosbuvir dose-finding trials. The Phase 3 sofosbuvir 400 mg once
daily dose was selected based on on-treatment virologic response data observed from P7977-0221 and P7977-0422. In 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 Emax model based on GS-331007 AUCtau fit to the virologic response data supported the sofosbuvir 400 mg once daily dose. In P7977-0422 (PROTON), a Phase 2b trial in noncirrhotic, treatment-naïve subjects with HCV GT 1, 2, or 3 infection, SVR24 rates of 90-92% in HCV GT1 subjects were observed with sofosbuvir 200 and 400 mg, in combination with PEG/RBV. In HCV GT 1 subjects, virologic breakthroughs during PEG/RBV treatment (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 the sofosbuvir 400 mg dose may provide greater suppression of viral activity.

Biopharmaceutics Considerations
Sofosbuvir is considered a highly soluble and low permeable compound based on the biopharmaceutics classification system (BCS) definition. Early Phase 2 trials used sofosbuvir tablets. The initial Phase 3 trials (P7977-1231 (FISSION) and GS-US-334-0107 (POSITRON)) used sofosbuvir tablets containing the tablet strengths was established for GS-331007 but not for sofosbuvir in P7977-1318. However, the difference in the PK characteristics of these two strengths was not considered clinically significant. Sofosbuvir 400 mg tablets containing the were used in the subsequent Phase 3 trials GS-US-334-0110 (NEUTRINO) and GS-US-334-0108 (FUSION), and will be the to-be-marketed formulation. Although PK equivalence of the was not fully established, the to-be-marketed formulation was used in all genotypes in Phase 3 trials, and the efficacy and safety results were generally similar among three genotype 2 or 3 trials, accounting for differences in prior treatment-experience.

Exposure Response
As detailed in Dr. Florian’s review, univariate analyses in HCV GT 1 and GT 3 subjects identified a trend of higher SVR12 rates in subjects with higher GS-331007 AUCtau, though no relationship was identified between sofosbuvir AUCtau and SVR12. However, GS-331007 AUCtau was not retained during multivariate analysis, suggesting other factors such as cirrhosis, IL28B, and weight-based ribavirin dose may be more important factors for predicting response. Exposure response for efficacy in HCV GT 2 was not conducted due to the high overall SVR12 rates.

For sofosbuvir and GS-331007, no relationship was observed between predicted AUCtau and common adverse events of interest. Exposure-response safety analyses for adverse events of dyspnea and system organ class cardiac disorders in the original pooled Phase 3 population identified that any grade dyspnea and any grade cardiac events were more likely in subjects with higher GS-331007 exposures. I agree with Drs. Florian and Dr. Mishra’s conclusions that the significance of these adverse events relationships should be interpreted with caution as the overall number of cardiac events in the originally submitted Phase 3 trial population administered sofosbuvir was low (19 out of 991 subjects with PK data available: 6/327 in SOF+PEG/RBV [1.8%] and 13/664 in SOF+RBV [1.9%]) and were predominantly Grade 1 with only two additional Grade 2 events. In most of the cases noted above, the subject either
had a prior history of cardiovascular disease or had cardiovascular risk factors. In addition, this event rate was lower than the cardiac event rate observed in the FISSION PEG/RBV control arm (11/243 [4.2%]). These adverse events could also be confounded by concomitant ribavirin administration, which is known to cause hemolytic anemia. Some of the symptoms of anemia include fatigue, dyspnea and tachycardia. Please refer to Section 7: Safety for further discussion of cardiac safety analysis.

Pharmacogenomics
The single nucleotide polymorphism rs12979860 near the IFNL3 (IL28B) gene encoding interferon-lambda 3 has been shown to be a strong predictor of SVR in HCV GT 1 patients receiving PEG/RBV-based therapies, with a less pronounced effect in HCV GT 2 and 3. After 12-week treatment with SOF+PEG/RBV in NEUTRINO, treatment-naïve GT 1, 4, 5 and 6 infected subjects with non-CC genotypes had modestly lower SVR12 rates compared to subjects with the CC genotype (87.1% vs. 97.9%). Among PHOTON-1 HCV GT 1 subjects receiving 24 weeks of SOF+RBV, a numerical trend toward lower SVR12 was observed in subjects with non-CC genotypes. In HCV GT 2 and 3, no consistent correlation was found between IFNL3 genotype and the rate of SVR12.

6. Clinical Virology
Sofosbuvir is a nucleotide analog inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a prodrug of 2’-deoxy-2’-fluoro-2’-C-methyluridine monophosphate that is converted by cellular enzymes to the active uridine triphosphate form (GS-461203) within the hepatocyte and inhibits HCV replication. Sofosbuvir had EC$_{50}$ values ranging from 14-110 nM in stable full-length replicon cells of genotypes 1a, 1b, 2a, 3a and 4a; chimeric GT 1b Con-1 replicons carrying NS5B coding sequences from GT 2b, 5a, or 6a; and NS5B amplified from individual patient plasma samples and cloned into the replicon-based shuttle vectors. The EC$_{50}$ values were slightly higher for GT 1b and GT 3a replicons compared to the other genotypes/subtypes replicons.

Sofosbuvir showed no antagonism when combined with other classes of direct acting antivirals for HCV, i.e. nonnucleoside palm inhibitor (GS-9190), nonnucleoside thumb-1 inhibitor (GS-9669), NS5A inhibitors (GS-5885, GS-5816), NS3/4A protease inhibitors (boceprevir, telaprevir, GS-9451), RBV, IFNα or with HIV-1 NRTIs (ABC, AZT, ddI, d4T, FTC, TDF, 3TC). Sofosbuvir did not show evidence of mitochondrial toxicity in mitochondrial assays and did not inhibit host DNA or RNA polymerases at concentrations up to 200 μM.

The NS5B S282T substitution was selected in GT 1b, 2a, 3a and 4a subgenomic replicons. The S282T substitution was associated with 4- to 24-fold decreases in susceptibility to sofosbuvir for all tested genotypes, and it is not cross-resistant with NS5A inhibitors or RBV.

The VERSANT HCV genotype assay, Version LiPA 2.0 was used for screening genotype/subtype for entry into the Phase 3 trials. Subsequently, nucleotide sequence and phylogenetic analysis of the HCV NS5B region was used to confirm genotype/subtype. In the originally submitted Phase 3 trials, nine subjects were misclassified as HCV GT 2 infection by the screening assay when they were later determined to be HCV GT 1 by the sequencing assay. The Applicant excluded these subjects from their efficacy analyses; however, DAVP
reviewers included these subjects based on the intent-to-treat (ITT) principle. As noted in Dr. Naeger’s review, in the “real world” NS5B sequencing is unlikely to be regularly performed, and genotyping/subtyping will usually be determined in the clinic by assays similar to the screening assay. Therefore, the efficacy should reflect what can be expected in the clinic with a screening assay. Further evaluation of the HCV samples derived from these subjects by the Applicant led to the conclusion these subjects were infected with intergenotypic recombinant HCV viruses. Based on these analyses and further discussion with the Division, the Applicant agreed to include these subjects as HCV GT 2 in the ITT analyses.

For subjects with HCV GT 2 infection across the FISSION, POSITRON and FUSION trials, the most common HCV GT 2 subtype when assessed by NS5B nucleotide sequence analysis was subtype 2b in 79% of subjects followed by subtype 2a in 19.5% of subjects. There were no obvious differences in response rates to SOF+RBV across the GT 2 subtypes. For subjects with HCV GT 3 infection, 99% of subjects were infected with subtype 3a by NS5B sequencing and only 6 subjects had another subtype. Therefore, no conclusions could be made about the response rates for other HCV GT 3 subtypes. In NEUTRINO, 77% of the subjects were infected with HCV GT 1a and 23% were infected with HCV GT 1b. There were only 28 subjects with HCV GT 4 infection most of which were GT 4a, six subjects with HCV GT 6 infection (a, e, j or q) and a single subject with HCV GT 5a infection.

In the originally submitted Phase 3 trials, there were no significant differences between baseline sequences of viruses from subjects who achieved SVR12 and those who relapsed. Notably, S282T was not present in any of the baseline samples or at the time of relapse. However, six HCV GT 1b subjects whose virus had C316N (N=4) or C316H (N=2) substitutions in NS5B at baseline had SVR12 rates of 50% compared to SVR12 rates of 83% (52/63) for HCV GT 1b subjects viruses with C316 at baseline.

An independent assessment of the next generation sequence (NGS) data by the Division from the originally submitted four Phase 3 trials included a total of 224 subjects in the sofosbuvir-containing arms and 676 raw data files. The L159F substitution emerged in six HCV GT 3a relapsers and the V321A substitution emerged in five HCV GT 3a relapsers. L159F is a previously identified NS5B substitution shown, along with L320F, to confer reduced susceptibility to HCV nucleotide inhibitors (Tong X et al., AASLD 2012). Phenotypic data for the L159F substitution and the V321A substitution alone did not show detectable decreased susceptibility to sofosbuvir. However, these substitutions emerged at highly conserved amino acid positions and occurred in multiple subjects and trials. Additionally, one HCV GT 1a relapse subject’s virus had emergent C316F detected at Week 4 follow-up. Phenotypic data for C316N or F substitutions have not yet been submitted by the Applicant.

An S282T substitution was detected by NGS analysis in one HCV GT 2b infected subject’s virus from the Phase 2 trial P7977-0523 (ELECTRON) who received sofosbuvir monotherapy for 12 weeks and relapsed at Week 4 post-treatment. The sample from this subject with detectable S282T had a mean 13.5-fold reduced susceptibility to sofosbuvir. The S282T substitution was no longer detectable at Week 12 post-treatment by NGS analysis with an assay cut off of 1%.
The available pre-transplant trial P7977-2025 population and deep sequencing resistance data of SOF+RBV treated subjects who had on-treatment failure (N=5) or who relapsed (N=20) provided supportive information for the FDA resistance findings in the sofosbuvir Phase 2 and 3 trials. The L159F substitution emerged on-treatment in the virus from two subjects infected with HCV GT 1a (one breakthrough and one relapse) and one subject infected with HCV GT 2b (breakthrough). The presence of an L159F substitution at baseline was also associated with sofosbuvir breakthrough and relapse post-transplant in four subjects infected with HCV GT 1b. These four subjects’ virus also had the C316N substitution along with the L159F substitution at baseline. A total of six subjects’ virus had the C316N substitution in their HCV GT 1b at baseline in this trial and all were post-transplant relapsers. The S282R and L320F substitutions were detected in the on-treatment sample from a subject infected with HCV GT 1a who did not respond to sofosbuvir.

Overall, these results suggest that in cases where sofosbuvir is not used in an optimal regimen or duration, genotypic resistance may emerge. The impact of these substitutions in future treatment options, including SOF-based retreatment, is not known at the present time. In addition, the significance of baseline C316N on the efficacy of sofosbuvir in subjects with HCV GT 1b infection remains under review.

### 7. Clinical/Statistical- Efficacy

Details on trial design, inclusion and exclusion criteria, demographics, subject disposition, and statistical analysis are included in the Clinical Review by Dr. Poonam Mishra and the Statistical Review by Dr. Karen Qi. Data on virologic resistance are included in Dr. Naeger’s and Dr. Donaldson’s virology reviews. I will approach this CDTL memo by highlighting the original trials, and integrating VALENCE and PHOTON-1 data where pertinent. Note the VALENCE and PHOTON-1 reviews remain ongoing at the time of this CDTL memo with details to be provided in an amendment to the primary reviews.

Data from five Phase 3 trials form the principal basis for characterizing the safety and efficacy of sofosbuvir in patients with chronic HCV infection. PHOTON-1 is under review to support use in HCV GT 1 patients who are ineligible to receive an interferon-based treatment. In addition, P7977-2025 provides safety and efficacy data in pre-transplant HCV-infected subjects with hepatocellular carcinoma awaiting liver transplantation.

Four trials were conducted in subjects with HCV genotype 2 or 3:

- **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
- **GS-US-334-0133 (VALENCE)** evaluated SOF+RBV for 12 weeks in HCV GT 2 subjects and for 24 weeks in HCV GT3 subjects

An additional trial, **GS-US-334-0110 (NEUTRINO)**, evaluated SOF+PEG/RBV for 12 weeks in HCV GT 1, 4, 5 or 6 treatment-naïve subjects.
Finally, GS-US-334-0123 (PHOTON-1) evaluated SOF+RBV for 12 weeks in HIV/HCV GT 2 or 3 treatment-naïve subjects and for 24 weeks in HIV/HCV GT 1 treatment-naïve or GT 2 or 3 treatment-experienced subjects.

The primary endpoint in all six Phase 3 trials is sustained virologic response defined as HCV RNA < lower limit of quantification (LLOQ) 12 weeks after the discontinuation of active treatment (SVR12). P7977-2025 determined prevention of post-transplant reinfection by a sustained post-transplant virological response (HCV RNA < LLOQ) at 12 weeks post-transplant (pTVR12).

All sofosbuvir-containing arms used sofosbuvir 400 mg once daily and weight-based RBV (1000 or 1200 mg daily doses). Weight-based RBV was used in the HCV GT 2/3 trials since interferon was being removed from the regimen and the Applicant wanted to maximize the potential efficacy of the SOF+RBV regimen by using weight-based rather than fixed dose RBV. These trials included a subset of subjects with compensated cirrhosis which represents a harder to treat subgroup.

Although the HCV GT 2/3 trials combined these genotypes, after data became available the SVR12 and relapse differences between the HCV GT 2 and GT 3 populations were apparent. Therefore, throughout this memo the HCV GT 2 and GT 3 SVR12 and relapse rates will be highlighted.

**Major Efficacy Findings**

*HCV Genotypes 2 and 3*

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

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

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

Subjects were stratified by HCV GT (2 or 3), screening HCV RNA levels (< 6 log10 IU/mL or ≥ 6 log10 IU/mL), and cirrhosis (present or absent). It should be noted higher RBV doses (1000 or 1200 mg) were used in the sofosbuvir-containing arm compared with the control arm (800 mg). A 15% noninferiority margin was prespecified. Based on literature review, the Applicant assumed the SVR rate for the 24-week PEG/weight-based RBV was approximately 70% in HCV GT2/3 subjects and that the monotherapy RBV treatment effect was small, and therefore proposed a non-inferiority margin of 15%. As noted in the IND 106739 SDN 100 submission “(b)ased on the historical monotherapy RBV data, the estimated RBV treatment effect reported from the meta-analysis by Jesper Brok (Brok J, Gluud LL, Gluud C. Ribavirin monotherapy for chronic hepatitis C (Review). *Cochrane Database of Systematic Review* 2009; Issue 4) is 0% with 95% CI (~3%, 3%). Many of subjects were of GT 1 in the meta-analysis, but overall only one out of 199 patients on Ribavirin had a sustained virological
response (SVR).” The review team agreed with the margin based on clinical judgment for an interferon-free regimen believed to offer a clinical benefit to patients with respect to tolerability and ease of administration.

A total of 499 randomized subjects received treatment (256 subjects in the SOF+RBV group; 243 subjects in the PEG/RBV group), including 20% with compensated cirrhosis. The mean age was approximately 48 years. The majority of subjects were male (66%), white (87%), non-Hispanic (86%) and enrolled in US sites (63%). Approximately 5% subjects enrolled in the EU. Most (72%) had HCV GT 3 infection. Approximately 57% of subjects had non-CC IL28B alleles and 57% of subjects had baseline HCV RNA ≥ 6log10IU/mL. Three subjects in the SOF+RBV group were classified as HCV GT 2 by the screening assay and later determined to have intergenotypic recombinant HCV viruses. These subjects are included in the FDA analyses based on the ITT principle.

As noted in Dr. Qi’s review, 22% discontinued study drug in the PEG/RBV 24 Week group, approximately 5 times higher than the 4% discontinuation rate in the SOF+RBV 12 Week group. This difference was predominately driven by the lower rate of discontinuations due to AEs or efficacy failure in the SOF+RBV 12 Week group. Specifically, 1% and 0.4% of SOF+RBV-treated subjects discontinued study drug due to AE and efficacy failure, respectively; while 11% and 7% of PEG/RBV-treated subjects discontinued study drug due to AE and efficacy failure, respectively.

The overall SVR12 rate was 67% in both groups (Table 1). The difference in proportions (95% confidence interval, CI) was 0.1% (-8% to 8%). The lower bound of the 2-sided 95% CI for the difference between groups (i.e., [SOF+RBV] − [PEG/RBV]) was within the prespecified noninferiority margin of -15%. There was a significant interaction between treatment and HCV genotype for SVR12 rate: the SOF+RBV group had a significantly higher SVR12 rate in the HCV GT 2 subjects, but numerically lower SVR12 rate in the HCV GT 3 subjects than in the PEG+RBV group.

In the SOF+RBV group, HCV GT 2 subjects had significantly higher SVR12 rates compared with HCV GT 3 subjects, 95% versus 56%, respectively (p-value <0.0001 based on Chi-Square test). Within each genotype, relapse accounted for most treatment failures with HCV GT 3 having a relapse rate of 40% compared with a 5% relapse rate in HCV GT 2.

HCV GT 2 subjects with cirrhosis in the SOF+RBV group had an SVR12 rate of 83% (10/12) compared with 97% (59/61) in subjects without cirrhosis. HCV GT 3 subjects with cirrhosis in the SOF+RBV group had an SVR12 rate of 34% (13/38) compared with 61% (89/145) in subjects without cirrhosis.

These collective results support a 12 week SOF+RBV duration for the studied HCV GT 2 population and suggest a longer duration or an additional antiviral agent is needed to optimize response rates in the HCV GT 3 treatment-naive population.

SVR24 data were available for the SOF+RBV arm, and the positive predictive value between SVR12 and SVR24 was 98.8% (161/163).
Table 1: FISSION Primary Efficacy Results and Relapse Rates (All Treated)\(^1\)

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

\(^1\) All Treated defined as all randomized subjects who received at least one dose of study medication, based on ITT. The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits.

Source: FDA Statistical Reviewer and NDA 204671 FDA Advisory Committee Backgrounder

During the trial, one subject experienced virologic breakthrough at Week 8. This subject was infected with HCV GT 3a genotype/subtype, had IL28B CT genotype and a baseline viral load of 7 log10 IU/mL. This subject had evidence of poor compliance with low plasma GS-331007 concentrations. There was only population sequence available from the Week 8 sample. The substitutions T84S, A150T and E202D emerged in NS5B on-treatment and were not associated with detectable reduced susceptibility to sofosbuvir.

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

This Phase 3, randomized, double-blind, placebo-controlled, multicenter trial enrolled subjects with chronic HCV GT 2 or 3 infection who were interferon (IFN) intolerant, interferon ineligible, or unwilling to take interferon. Subjects must have been intolerant to IFN as demonstrated during a prior course of treatment, ineligible to receive IFN due to medical history or unwilling to receive IFN (documented more than three months prior to signing of the informed consent). There is no current treatment available for chronic HCV patients of any GT who are IFN intolerant, or are medically ineligible or unwilling to receive IFN treatment.

Eligible subjects were randomized in a 3:1 ratio to one of two treatment arms:
- SOF+RBV for 12 weeks
- Placebo for 12 weeks

Randomization was stratified by presence/absence of cirrhosis at screening. A total of 278 subjects received treatment (207 subjects in the SOF+RBV group and 71 subjects in the placebo group), including 16% with compensated cirrhosis. Subjects were classified as IFN
ineligible (44%), intolerant (9%) or unwilling to take IFN (47%). The mean age was 52 years. The majority of subjects were male (54%), white (91%), and non-Hispanic (89%). Most subjects were enrolled in US sites (82%). Approximately equal percentages of HCV GT 2 (51%) and GT 3 (49%) subjects were enrolled. Approximately 55% of subjects had non-CC IL28B alleles and most subjects had baseline HCV RNA ≥ 6 log10IU/mL (70%).

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

The primary efficacy hypothesis was 12-week SOF+RBV was superior to placebo as measured by the SVR12 rate. The SOF+RBV 12 Week regimen was superior to placebo with SVR12 rates of 78% and 0%, respectively (Table 2). The difference (95% CI) in proportions was 78% (72% to 83%). No sofosbuvir-treated subject had on-treatment virologic failure.

In the SOF+RBV group, HCV GT 2 subjects had significantly higher SVR12 rates compared with HCV GT 3 subjects, 93% versus 61%, respectively (p-value < 0.0001). Within each genotype, relapse accounted for most treatment failures with HCV GT 3 having a relapse rate of 38% compared with a 5% relapse rate in HCV GT 2.

HCV GT 2 subjects with cirrhosis in the SOF+RBV group had an SVR12 rate of 94% (16/17), similar to the 92% (85/92) rate in subjects without cirrhosis. HCV GT 3 subjects with cirrhosis in the SOF+RBV group had a lower SVR12 rate of 21% (3/14) compared with 68% (57/84) in subjects without cirrhosis.

Interferon classification yielded different trends in the HCV GT 2 and 3 populations treated with SOF+RBV, and the differences are not clearly explained due to the small subgroups. Among HCV GT 2 subjects, SVR12 rates were 88% (36/41), 100% (9/9) and 95% (56/59) in the IFN-ineligible, intolerant and unwilling groups, respectively. Among HCV GT 3 subjects, SVR12 rates were highest in the IFN-ineligible group, 70% (33/47), with similar rates in the intolerant and unwilling groups, 50% (4/8) and 53% (23/43), respectively.

The SOF+RBV group had 100% concordance between SVR12 and SVR24 in subjects with data available for both time points.
Table 2: POSITRON Primary Efficacy Results and Relapse Rates (All Treated\(^1\))

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

\(^1\)All Treated was defined as all randomized subjects who received at least one dose of study medication. The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits.

Source: FDA Statistical Reviewer and NDA 204671 FDA Advisory Committee Backgrounder

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

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

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

Randomization was stratified by the presence or absence of cirrhosis and HCV GT (2 or 3) at screening. A historical response rate of 25% was set based on considering historical data from the EPIC trial where HCV GT 2/3 treatment-experienced subjects treated with PEG/RBV for 48 weeks achieved SVR rates of 57% and 36% in prior relapser and nonresponders, respectively, and based on clinical judgment for an IFN-free regimen believed to offer a clinical benefit to patients with respect to tolerability and ease of administration (Poynard T et al. Gastroenterology 2009; 136(5):1618-28).

A total of 201 subjects received treatment (103 subjects in the SOF+RBV 12 Week group and 98 subjects in the SOF+RBV 16 Week group), including 34% with compensated cirrhosis, a higher percentage than enrolled in the other Phase 3 trials. Approximately 25% subjects had prior nonresponse to an IFN-based regimen, and 75% had prior relapse/breakthrough. The mean age was 54 years. The majority of subjects were male (70%), white (87%), non-Hispanic (91%), and from US sites (76%). Approximately two-thirds of subjects (63%) had HCV GT 3 infection. Most subjects (70%) had non-CC IL28B alleles (73%) and the majority of subjects had baseline HCV RNA ≥ 6 log10IU/mL. Six subjects were classified as HCV GT 2 by the
screening assay and later determined to have intergenotypic recombinant HCV viruses. These subjects are included in the FDA analyses based on the ITT principle.

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

The SVR12 rate in the SOF+RBV 12 Week group was 50% and in the SOF+RBV 16 Week group was 71%, each statistically significantly higher (p < 0.001) compared to the historical rate of 25% (Table 3). In addition, treatment with SOF+RBV for 16 weeks resulted in statistically significant higher SVR12 rates compared with the shorter treatment duration of 12 weeks. No subject in either treatment group had on-treatment virologic failure.

In both the SOF+RBV 12 Week and 16 Week groups, HCV GT 2 subjects had significantly higher SVR12 rates compared with HCV GT3 subjects.

- **SOF+RBV for 12 weeks**: SVR12 rates were 82% and 30% for HCV GT 2 and 3 subjects, respectively (p-value < 0.0001).
- **SOF+RBV for 16 weeks**: SVR12 rates were 89% and 62% for HCV GT 2 and 3 subjects, respectively (p-value = 0.0052).

Extending the treatment duration by 4 weeks increased SVR12 rates in HCV GT 2 subjects from 82% to 89%, and in HCV GT 3 subjects from 30% to 62%. Within each genotype, relapse accounted for most treatment failures, and notably the HCV GT 3 relapse rate in the 16 Week arm was still as high as 38%.

HCV GT 2 subjects with cirrhosis in the SOF+RBV Week 12 and 16 groups had SVR12 rates of 60% (6/10) and 78% (7/9), respectively. In HCV GT 2 subjects without cirrhosis, similar SVR12 rates were observed in the HCV GT 2 Week 12 (90%, 26/29) and Week 16 (92%, 24/26) groups. HCV GT 3 subjects with cirrhosis in the SOF+RBV 12 Week group had an SVR12 rate of 19% (5/26), compared with 61% (14/23) in the SOF+RBV 16 Week group. In addition, HCV GT 3 subjects without cirrhosis in the SOF+RBV 12 Week group had an SVR12 rate of 37% (14/38), compared with 63% (25/40) in the SOF+RBV 16 Week group.

HCV GT 2 prior relapser/breakthrough subjects experienced similar SVR12 rates in the SOF+RBV Week 12 and Week 16 groups, 86% (25/29) and 89% (24/27), respectively. HCV GT 2 prior nonresponder subjects had higher SVR12 rates in the SOF+RBV Week 16 group compared with the Week 12 group, 88% (7/8) versus 70% (7/10); however, the subgroups are small. HCV GT 3 prior relapser/breakthrough and nonresponder subjects in the SOF+RBV Week 12 group had SVR12 rates of 31% (15/49) and 27% (4/15), respectively, compared with the Week 16 group with rates of 65% (30/46) and 53% (9/17), respectively.

These observations suggest the efficacy in the HCV GT 3 population could potentially be further improved with longer treatment duration or an additional antiviral agent (e.g., PEG or another DAA), and contributed to the Division’s decision to review the VALENCE data.
Table 3: FUSION Primary Efficacy Results and Relapse Rates (All Treated)\(^1\)

<table>
<thead>
<tr>
<th>Efficacy Parameter</th>
<th>SOF+RBV 12 Weeks N=103</th>
<th>SOF+RBV 16 Weeks N=98</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained Virologic Response</td>
<td></td>
</tr>
<tr>
<td>Overall SVR12 Rate</td>
<td>50% (51/103)</td>
<td>71% (70/98)</td>
</tr>
<tr>
<td>Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]</td>
<td>-22% [-35%, -9%]</td>
<td></td>
</tr>
<tr>
<td>SVR12 in Genotype 2</td>
<td>82% (32/39)</td>
<td>89% (31/35)</td>
</tr>
<tr>
<td>Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]</td>
<td>-7% [-23%, 9%]</td>
<td></td>
</tr>
<tr>
<td>SVR12 in Genotype 3</td>
<td>30% (19/64)</td>
<td>62% (39/63)</td>
</tr>
<tr>
<td>Proportion Difference SOF+RBV 12 Weeks vs. SOF+RBV 16 Weeks [95% CI]</td>
<td>-32% [-49%, -16%]</td>
<td></td>
</tr>
</tbody>
</table>

Relapse Rates at Posttreatment Week 12

<table>
<thead>
<tr>
<th></th>
<th>Overall Relapse Rate</th>
<th>Relapse Rate in Genotype 2</th>
<th>Relapse Rate in Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48% (49/103)</td>
<td>18% (7/39)</td>
<td>66% (42/64)</td>
</tr>
<tr>
<td></td>
<td>29% (28/98)</td>
<td>11% (4/35)</td>
<td>38% (24/63)</td>
</tr>
</tbody>
</table>

\(^1\) All Treated defined as all randomized subjects who received at least one dose of study medication, based on ITT. The 95% confidence interval (CI) was calculated using the Wald asymptotic confidence limits. Source: FDA Statistical Reviewer and NDA 204671 FDA Advisory Committee Backgrounder.

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

Prior to VALENCE trial results, Dr. Qi performed bridging analyses to explore SOF+RBV 16 week treatment duration in HCV GT 3 treatment-naive subjects. Due to the subsequent VALENCE data review and support for the longer SOF+RBV 24 duration in HCV GT 3 subjects, this memo will not address the former bridging analyses.

Efficacy in HCV Genotype 2 and 3 population (VALENCE)

This Phase 3 non-IND European trial was initially a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of the SOF+RBV for 12 weeks compared with placebo in treatment-naive or treatment-experienced HCV GT 2 and 3 subjects. Subjects were randomized in a 4:1 ratio to receive either 12 weeks of SOF+RBV regimen or placebo.

During the treatment phase of trial, emerging Phase 3 data demonstrated 12 weeks of SOF+RBV was not optimal for the HCV GT 3 subjects, primarily due to the high relapse rates. Therefore, changes were made to the trial as follows (Amendment 2):

- HCV GT 2 subjects in the SOF+RBV group completed 12 weeks of treatment and follow-up visits as originally planned.
- SOF+RBV treatment duration for HCV GT 3 subjects was extended to 24 weeks for those who had not completed 12 weeks of treatment. Subjects who had already completed 12 weeks of SOF+RBV treatment or who had prematurely discontinued treatment continued to complete the follow-up visits as originally planned.
- Subjects initially randomized into the placebo group were discontinued from the study and offered the SOF+RBV treatment under GS-US-334-0109.
The trial was no longer to be blinded or placebo-controlled after the changes.

A total of 419 subjects received treatment (85 subjects in the placebo group, 84 subjects in the SOF+RBV 12 Week group and 250 subjects in the SOF+RBV 24 Week group), including 21% with compensated cirrhosis. A total of 42% of subjects were treatment-naive, including 5% classified as IFN-ineligible. Approximately 58% subjects were treatment-experienced, including 17% with a prior nonresponse to an IFN-based regimen, 38% with prior relapse/breakthrough and 3% classified as IFN-intolerant. The mean age was 50 years. The majority of subjects were male (60%), white (94%) and non-Hispanic (83%). Approximately three-fourths of subjects (78%) had HCV GT 3. Most subjects (68%) had non-CC IL28B alleles and the majority of subjects (73%) had baseline HCV RNA ≥ 6 log10IU/mL.

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

Among the 73 HCV GT 2 subjects in the SOF+RBV 12 Week group, the overall SVR12 rate was 93%: treatment-naive subjects achieved an SVR12 rate of 97% and treatment-experienced subjects an SVR12 rate of 90% (Table 4). Of the 11 HCV GT 3 subjects in the SOF+RBV 12 Week group, only 27% achieved SVR12 (data not shown). In the extended SOF+RBV 24 Week group for HCV GT 3 subjects, the overall SVR12 rate was 84%: treatment-naive subjects achieved an SVR12 rate of 93% and treatment-experienced subjects achieved an SVR12 rate of 77%.

The overall relapse rate in HCV GT 2 subjects was 7%. Among HCV GT 3 subjects in the SOF+RBV 24 Week group, the overall relapse rate was 14%, a rate lower than observed in prior trials of 12-16 week durations.

HCV GT 2 treatment-naive SVR12 rates were similar in cirrhotic (100%, 2/2) and non-cirrhotic subjects (97%, 29/30), though the comparison is based on only two cirrhotic subjects. HCV GT 2 treatment-experienced cirrhotic (88%, 7/8) and non-cirrhotic (91%, 30/33) subjects also had comparable SVR12 rates. Similar SVR12 rates were observed in HCV GT 3 treatment-naive subjects with cirrhosis (92%, 12/13) and without cirrhosis (94%, 86/92). In HCV GT 3 treatment-experienced subjects, however, subjects with cirrhosis had lower SVR12 (60%, 27/45) compared with subjects without cirrhosis (85%, 85/100). Recognizing limitations of cross-trial comparisons, this SVR12 rate in HCV GT 3 treatment-experienced cirrhotic subjects receiving SOF+RBV for 24 weeks is similar to the SVR12 rate observed in the FUSION SOF+RBV Week 16 group (61%), and potential explanations for this observation such as differences in baseline factors between the trial populations are undergoing review at the time of this CDTL memo.
Table 4: VALENCE Primary Efficacy Results and Relapse Rates in the HCV GT 2 SOF+RBV 12 Week and HCV GT 3 SOF+RBV 24 Week Arms

<table>
<thead>
<tr>
<th></th>
<th>GT 2 SOF+RBV 12 Weeks N=73</th>
<th>GT 3 SOF+RBV 24 Weeks N=250</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall SVR12</td>
<td>93%</td>
<td>84%</td>
</tr>
<tr>
<td>Treatment-Naive</td>
<td>97% (31/32)</td>
<td>93% (98/105)</td>
</tr>
<tr>
<td>Treatment- Experienced</td>
<td>90% (37/41)</td>
<td>77% (112/145)</td>
</tr>
<tr>
<td>Overall Relapse Rate</td>
<td>7% (5/73)</td>
<td>14% (34/249)</td>
</tr>
<tr>
<td>Treatment-Naive</td>
<td>3% (1/32)</td>
<td>5% (5/105)</td>
</tr>
<tr>
<td>Treatment- Experienced</td>
<td>10% (4/41)</td>
<td>20% (29/144)</td>
</tr>
</tbody>
</table>

Source: NDA 204671 FDA Advisory Committee Presentation, 10/25/13

We learned from the originally submitted Phase 3 trials that the HCV GT 3 SOF+RBV 12-16 week treatment duration was not optimal as evidenced by relapse rates ~40%. The VALENCE data demonstrated extending SOF+RBV treatment duration to 24 weeks in the HCV GT 3 population both increased SVR12 and decreased relapse rates (Figure 1). Therefore, collectively I believe the HCV GT 3 data across the four Phase 3 trials supports a SOF+RBV 24 week duration in this population.

Figure 1: SVR12 and Relapse Rates for HCV Genotype 3 Across Phase 3 Trials FISSION, FUSION, VALENCE

Source: NDA 204671 FDA Advisory Committee Presentation, 10/25/13
Subgroup analyses in FUSION and VALENCE showed similar SVR12 rates in HCV GT 3 treatment-experienced cirrhotic subjects despite extending SOF+RBV treatment duration from 16 to 24 weeks. Possible explanations for this observation include differences in baseline factors between the trials in this cirrhotic subgroup, a lack of benefit from further extending SOF+RBV duration, or a need for another antiviral agent in the regimen to further improve treatment response. The ongoing Phase 3 randomized, multinational trial, GS-US-334-0153, is currently evaluating SOF+RBV 16 Weeks, SOF+RBV 24 Weeks and SOF+PEG/RBV 12 weeks in HCV GT 2 treatment-experienced subjects with cirrhosis and GT 3 treatment-naïve/experienced subjects with and without cirrhosis. I recommend these trial data are requested postmarketing to advance further understanding of treatment for the HCV GT 3 population.

Applicability of VALENCE data to the US Population
The FISSION trial included a total of 24 HCV GT 3 subjects from the European Union (EU, 5% trial population): 15 subjects in the SOF+RBV 12 Week group and 9 subjects in the PEG/RBV group. HCV GT 3 EU-subjects receiving SOF+RBV for 12 weeks had lower SVR12 rates compared to US subjects, 27% versus 60%, respectively. Although the numbers are small, these data suggest the observed HCV GT 3 SVR12 rates from VALENCE should not be an overestimation of what may be observed in the US population with other similar baseline factors. The PHOTON-1 trial, conducted at sites in the US and Puerto Rico, includes a SOF+RBV 24 Week arm with HCV GT 3 treatment-experienced subjects. These data remain under review at the time of this CDTL memo; however, these data may support the observed VALENCE SVR12 and relapse rate results.

The ongoing Phase 3 trial, GS-US-334-0153, has sites planned in European, North American, Australian and New Zealand, and will allow data comparison between the different geographic regions.

Subgroup Analyses of Selected Baseline Factors in HCV Genotype 2 Subjects
Subgroup analyses were performed by Dr. Qi to determine if particular HCV GT 2 subpopulations may benefit from a longer treatment duration (Table 5). Acknowledging the small subgroup size, prior treatment-experience and cirrhosis were not consistent factors in determining SVR12 response. IL28B non-CC genotype had numerically lower SVR12 rates in the 12 week arms; however, the pharmacometrics review across trials found no consistent correlation between IL28B genotype and SVR12 rates in HCV GT 2 and 3. At the time of this CDTL memo, the implications of these observations and any translation to labeling remain under review.
Table 5: FDA Selected Subgroup Analysis in HCV Genotype 2 Subjects

<table>
<thead>
<tr>
<th>Genotype 2 TN 12-Week SOF+RBV</th>
<th>FISSION (N=73)</th>
<th>VALENCE (N=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>97% (59/61)</td>
<td>97% (29/30)</td>
</tr>
<tr>
<td>Yes</td>
<td>83% (10/12)</td>
<td>100% (2/2)</td>
</tr>
<tr>
<td><strong>IL28 B</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>97% (32/33)</td>
<td>100% (14/14)</td>
</tr>
<tr>
<td>CT or TT</td>
<td>93% (37/40)</td>
<td>94% (17/18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype 2 TE</th>
<th>FUSION</th>
<th>VALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-Week SOF+RBV (N=39)</td>
<td>16-Week SOF+RBV (N=35)</td>
</tr>
<tr>
<td>Treatment experience classification</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IFN tolerant</td>
<td>86% (25/29)</td>
<td>89% (24/27)</td>
</tr>
<tr>
<td>Relapse/breakthrough</td>
<td>70% (7/10)</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Null response</td>
<td>90% (26/29)</td>
<td>92% (24/26)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>60% (6/10)</td>
<td>78% (7/9)</td>
</tr>
<tr>
<td></td>
<td>88% (7/8)</td>
<td>71% (10/14)</td>
</tr>
<tr>
<td>IL28 B</td>
<td>81% (25/31)</td>
<td>100% (21/21)</td>
</tr>
</tbody>
</table>

Based on ITT
Source: FDA Statistical Reviewer

HCV Genotypes 1, 4, 5 and 6

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

This Phase 3, multicenter, open-label trial enrolled treatment-naïve subjects with chronic HCV GT 1, 4, 5, or 6 infection. Subjects received SOF+PEG (180 μg/week)/RBV (1000 or 1200 mg/day) for 12 weeks. A total of 327 subjects received study drugs, including 17% with compensated cirrhosis. The rationale for a single arm trial design considered the factors of shorter duration and no requirement for response-guided therapy compared with a PI-based control arm, the approximately 90% SVR12 rate from the Phase 2 ATOMIC trial, and the inclusion of non-GT 1 subjects, all of which would make a controlled trial difficult to conduct. A historical response rate of 60% was determined by our statistical colleagues based upon the upper limit of the 95% CI for the highest SVR rate for PEG/RBV treatment observed in historical trials. The historical control was not based upon PI-based treatment responses because, at the time of protocol review, a regimen with a shorter treatment duration, simpler dosing regimen and anticipated improved safety profile would allow consideration of a regimen not necessarily superior to or even non-inferior to a PI-based regimen. In summary, these general factors contributed to the selection of the 60% historical rate for a regimen believed to offer a clinical benefit to patients with respect to tolerability and ease of administration.
The mean age was 52 years and the majority of subjects were male (64%), white (79%) and non-Hispanic (86%). Most subjects (89%) had HCV GT 1. There were 28 subjects with HCV GT 4, only one subject with HCV GT 5 and six subjects with HCV GT 6. More than two-thirds of the subjects had non-CC IL28B allele and the majority of subjects had a baseline HCV RNA $\geq 6$ log$_{10}$ IU/mL (78%).

Few sofosbuvir-treated subjects discontinued treatment (2%), with AE the most common reason (~2%).

Overall, a statistically significant proportion of subjects achieved SVR12 (90%, p < 0.0001) compared with a historical SVR12 rate of 60% (Table 6). Relapse accounted for most treatment failures, with an overall rate of 9%. No subject had on-treatment virologic failure. Subjects with HCV GT 1 (N=292) had an SVR12 rate of 89%, with a GT 1a and GT 1b subtype difference noted (SVR12 92% and 82%, respectively). Subjects with GT 4 (N=28) had an SVR12 rate of 96%. It should be noted that few subjects with GT 5 (N=1) and GT 6 (N=6) were included in the clinical trial and the available data are believed to be insufficient to make definitive dosing recommendations for patients with HCV GT 5 or 6 infection.

### Table 6: NEUTRINO Primary Efficacy Results (FAS)$^1$

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

$^1$FAS= full analysis set, defined as all randomized subjects who received at least one dose of study medication; Source: FDA Statistical Reviewer and NDA 204671 FDA Advisory Committee Back grounder

### Response Rates in HCV Genotype 1a and 1b Subjects

HCV GT 1a treatment-naive subjects had 10% higher SVR12 rates than GT 1b subjects. Post-hoc analyses between the two genotype subtypes across demographics and baseline characteristic subgroups found HCV GT 1a subjects had numerically higher SVR12 rates than HCV GT 1b subjects in almost all subgroups. Thus, the HCV GT 1 subtype SVR12 rate differences are not clearly explained by such factors. Cell culture replicon data with sofosbuvir demonstrate EC$_{50}$ values are slightly higher for GT1b (110 nM) and GT3a (50 nM) replicons compared to GT1a (40 nM) and GT2b (15 nM) replicons, which may offer some supportive
Cross Discipline Team Leader Review
NDA 204671 (sofosbuvir)
Sarah M. Connelly, MD

evidence for why subjects infected with HCV GT 1b and GT 3a had lower overall clinical
efficacy compared to subjects infected with HCV GT 1a and GT 2. In addition, presence of
baseline substitutions at C316, which is a polymorphic site in the GT 1b NS5B polymerase,
may be a contributing factor for the reduced efficacy among these subjects.

HCV Genotype 1 Infection, Prior Pegylated Interferon Nonresponders: Exploratory Analyses
Clinical HCV trials have generally categorized patients as treatment-naïve or treatment-
experienced based upon their prior virologic response to a PEG/RBV regimen. During an End-
of-Phase 2 meeting (June 5, 2012), when asked about sofosbuvir development plans in prior
PEG/RBV treatment-experienced patients, the Applicant stated they intended to identify the
best regimen in HCV GT 1 treatment-naïve patients, then would proceed in trials in the more
difficult to treat patients including those who failed prior PEG/RBV treatment. Therefore,
HCV GT 1 patients who failed prior treatment with PEG/RBV were not specifically studied in
the sofosbuvir development program supporting this NDA. During the review we recognized
this population was in need of new therapies and, particularly due to the high overall SVR12
rate observed in NEUTRINO, attempted to estimate response rates in prior PEG/RBV
nonresponders using existing data. Analyses conducted by the sofosbuvir review team to
address this issue are summarized below, with details to be included in addendums to the
initial review. In addition, this issue was presented at the Advisory Committee meeting in a
collaborative presentation from Drs. Karen Qi and Jeffry Florian; please refer to Section 9 for
a summary of the discussion.

Predicting SVR rate in HCV Genotype 1 PEG/RBV treatment-experienced subjects based on
the historical SVR rates on PEG/RBV treatment
The historical SVR rate for PEG/RBV in treatment-naïve subjects ranged from 40% to 50%.
As a conservative assessment, the review team assumed that approximately 50% of treatment-
naïve subjects in NEUTRINO could be PEG/RBV treatment failure subjects and that all 11%
SOF+PEG/RBV failure subjects observed in NEUTRINO were PEG/RBV treatment failure
subjects. Based on these assumptions, then 39% (50%-11% = 39%) of the historical PEG/RBV
treatment failure subjects will respond to SOF+PEG/RBV. Using this approach results in a
predicted 78% SVR rate (39/50) for SOF+PEG/RBV 12 week treatment in the overall HCV
GT 1 prior PEG/RBV treatment-experienced population.

This analysis assumes that the 50% of PEG/RBV treatment failures in the above analysis
would not have their SOF+PEG/RBV treatment response impacted by first failing a treatment
course of PEG/RBV. This assumption is supported by a lack of identified resistance to PEG
treatment, similarity between on-treatment responses following initial or subsequent course of
PEG/RBV treatment (Liu et al. CID 2012), and previous FDA analyses bridging observations
between treatment-naïve and prior PEG/RBV treatment failures (Liu et al. Hepatology 2013,
Florian et al. Hepatology 2013). In addition, the analysis assumes baseline characteristics were
similar between subjects in the historical PEG/RBV studies and in NEUTRINO. The review
team identified that NEUTRINO consisted of an older demographic that was more likely to
have HCV GT 1a, cirrhosis and higher baseline HCV RNA compared to the historical
PEG/RBV studies. Finally, the 11% SOF+PEG/RBV treatment failure subjects are all assumed
to be PEG/RBV treatment failure subjects.
Subset of more difficult-to-treat HCV Genotype 1 subjects from NEUTRINO and other HCV submissions using baseline characteristics

Review of published literature and HCV treatment guidelines identified baseline factors which are more likely to result in PEG/RBV treatment failure in HCV GT 1 treatment-naïve patients: high baseline viral load, fibrosis score of F3 or F4, presence of steatosis, pretreatment fasting glucose ≥ 5.6 mmol/L, high baseline ALT levels, age over 40 years and African American race. More recent published analyses have also identified that IL28B is associated with response to PEG/RBV treatment, and may partly explain the impact of race.

An analysis was performed selecting treatment-naïve subjects from NEUTRINO with the following three baseline factors which are representative of lower SVR response to PEG/RBV treatment: IL28B non-CC genotype, baseline HCV RNA viral load >800,000 IU/mL and METAVIR score of F3-F4. Within NEUTRINO, subjects with all three of these baseline factors had an observed SVR12 rate of 71%, with a 95% confidence interval of 57-83% (Figure 2). Other identified baseline factors associated with lower response to SOF+PEG/RBV (e.g., HCV GT 1b) were not included in this analysis, as additional combinations resulted in very small denominators and genotype subtype is not commonly associated as a predictive factor in PEG/RBV treatment; however, it should be noted that the HCV GT 1b subtype was an identified treatment factor associated with lower response to SOF+PEG/RBV and that the subset of subjects with HCV GT 1b with IL28B TT and cirrhosis had an SVR12 of 57% (4/7 subjects).

Figure 2: NEUTRINO: SVR12 Rates in Harder-to-Treat HCV Genotype 1 Treatment-Naïve Subjects

Source: NDA 204671 FDA Advisory Committee Presentation, 10/25/13
An analysis combining the same baseline factors of IL28B non-CC, high baseline HCV RNA viral load and F3-F4 fibrosis were applied to other recent HCV development programs (Table 7). This analysis identified that the SVR rate observed in this more difficult to treat subset of treatment-naïve subjects was between the response rates observed in documented prior PEG/RBV null and partial responders. Therefore, it may be assumed the SVR rate for prior PEG/RBV partial and null responders treated with SOF+PEG/RBV for 12 weeks may be similar to 71%.

Table 7: Comparison of SVR12 Rates From Various Direct-Acting Antiviral Treatment-Naïve and Prior PEG/RBV Treatment Failure Trials. SVR12 Rates Shown for the Treatment-Naïve Trials are Based on the Subject of Subjects with Multiple Poor Baseline Predictive Factors (IL28B non-CC, Baseline HCV RNA viral load >800,000 IU/mL, F3 or F4 Fibrosis)

<table>
<thead>
<tr>
<th>Drug</th>
<th>DAA+PEG/RBV</th>
<th>Treatment-naïve</th>
<th>Prior Null</th>
<th>Prior Partial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir</td>
<td></td>
<td>44% (61/138)</td>
<td>32% (47/147)</td>
<td>59% (57/97)</td>
</tr>
<tr>
<td>Boceprevir</td>
<td></td>
<td>45% (32/71)</td>
<td>38% (20/52)</td>
<td>46% (53/115)</td>
</tr>
<tr>
<td>Simeprevir</td>
<td></td>
<td>51% (36/73)</td>
<td>49% (49/101)</td>
<td>66% (91/137)</td>
</tr>
</tbody>
</table>

Source: Adapted from Dr. Florian’s Pharmacometrics Review

Calculation of SVR rates for HCV Genotype 1 prior null responders based on an assumption of equivalent odds ratios and relative risk between SOF+PEG/RBV regimen and previous HCV programs

This analysis calculated the SVR rate for HCV GT 1 prior PEG/RBV null responders based on the assumption of equivalent odds ratios and relative risk between HCV GT 1 treatment-naïve subjects and prior PEG/RBV treatment-experienced subjects in SOF+PEG/RBV treatment and previous HCV programs including telaprevir, simeprevir, and boceprevir. The review team selected prior null responders for this analysis as they represent the most difficult to treat subset of prior PEG/RBV treatment failures. The results from the more conservative odds ratio calculation will be discussed here. Using this methodology, the review team predicted that prior PEG/RBV null responders administered SOF+PEG/RBV for 12 weeks may have an SVR rate ranging between 52-73% based on the previously mentioned HCV development programs. A limitation of this analysis is that response-guided therapy was used in the treatment-naïve trials but not in the prior PEG/RBV null responder studies in the comparator drugs, so the treatment durations within the comparator drugs may inflate the predicted SVR rate.

Together, these analyses provide supportive evidence that SOF+PEG/RBV for 12 weeks may be an effective treatment option in prior PEG/RBV treatment failures, with predicted SVR12 rates ranging 52-78%. An ongoing trial offering sofosbuvir-based treatment to prior Gilead trial participants, GS-US-334-0109, has enrolled 59 HCV GT 1 subjects who did not achieve an SVR following treatment with PEG/RBV in combination with other DAAs. These subjects have received retreatment with SOF+PEG/RBV for 12 weeks and the Applicant states final SVR12 results will be available for submission mid-April 2014 (NDA 204671 SDN 39 communication).
It is recognized that the prior PEG/RBV treatment classification will be less applicable as PEG/RBV is no longer the standard of care for HCV GT 1 patients and that alternative definitions of these populations based on baseline characteristics may become more common in the future. However, it should be noted that other factors could be important in predicting a patient’s treatment outcome on PEG/RBV and that there may be other baseline factors (e.g., HCV genotype subtype) or combinations of factors that are predictive of patient response among DAA+PEG/RBV regimens as well as emerging IFN-free regimens.

How best to communicate this information in labeling remains under review. We have agreed with the Applicant that the dosing and administration section should convey assumed SVR12 rates with SOF+PEG/RBV for 12 weeks in prior PEG/RBV nonresponders, I favor including the NEUTRINO SVR12 rates as presented in Figure 2 to demonstrate that some patients, due to underlying biologic and virologic factors, are anticipated to have lower response rates to SOF+PEG/RBV treatment than the overall trial’s response rate.

**Efficacy in HCV Genotype 1, 2 and 3 HIV/HCV population (PHOTON-I)**

This Phase 3, open-label ongoing trial evaluates SOF+RBV in subjects with HCV GT 1, 2 or 3 infection who are coinfected with HIV. The trial is being conducted in the US and Puerto Rico. Treatment durations were 12 or 24 weeks, depending on HCV GT and treatment history. HCV GT 2 or 3 treatment-naïve subjects (N=68) received SOF+RBV 12 Weeks, HCV GT 2 or 3 treatment-experienced subjects (N=41) received SOF+RBV 24 Weeks and HCV GT 1 treatment-naïve subjects (N=114) received SOF+RBV 24 Weeks. Enrolled subjects were coinfected with HIV-1, either untreated with antiretroviral therapy (ART) with a CD4+ T-cell count >500 cells/mm³ or treated with ART with a CD4+ T-cell count >200 cells/mm³.

At the time of the interim clinical study report, all subjects are included in the safety analyses. A total of 68% (28/41 subjects) in the HCV GT 2/3 treatment-experienced SOF+RBV 24 Week group have available SVR12 data. Mean CD4+ T-cell count was 625 cells/mm³ and approximately 95% of subjects were receiving antiretroviral therapy. HIV subjects on ART received tenofovir/emtricitabine plus efavirenz (37%), atazanavir/ritonavir (18%), darunavir/ritonavir (16%), raltegravir (17%) or another antiretroviral agent (12%). Overall 10% subjects had compensated cirrhosis: 10% in the GT 2/3 12 week arm, 24% in the GT 2/3 24 week arm, and 4% in the GT 1 24 week arm. Black/African American subjects comprised approximately 15% of the GT 2/3 subjects and 33% of the GT 1 subjects.

Two subjects had on-treatment failure, one subject each in the HCV GT 2/3 SOF+RBV 12 Week and HCV GT 1 SOF+RBV 24 Week groups. Nonadherence was suspected as the explanation for both subjects based upon factors such as serum sofosbuvir levels and hematologic parameters.

Table 8 displays SVR12 and relapse rates. Overall SVR12 rates were 76% in the HCV GT 1 treatment-naïve SOF+RBV 24 Week group, with 22% relapse. Overall SVR12 rates in the
HCV GT 2/3 treatment-naïve and treatment-experienced populations were 75% and 93%, respectively.

### Table 8: PHOTON-1 Primary Efficacy Results and Relapse Rates

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF+RBV 12 Weeks TN (N = 68)</td>
<td>SOF+RBV 24 Weeks GT 2/3 TE (N = 28)</td>
<td>SOF+RBV 24 Weeks GTI TN (N = 114)</td>
</tr>
<tr>
<td>SVR12</td>
<td>51/68 (75.0%)</td>
<td>26/28 (92.9%)</td>
<td>87/114 (76.3%)</td>
</tr>
<tr>
<td>Overall Virologic Failure</td>
<td>13/68 (19.1%)</td>
<td>2/28 (7.1%)</td>
<td>26/114 (22.8%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>12/67 (17.9%)</td>
<td>2/28 (7.1%)</td>
<td>25/113 (22.1%)</td>
</tr>
</tbody>
</table>

Source: Applicant GS-US-334-0123 Interim Clinical Study Report, Table 4

Based on the available data, SVR12 rates were generally similar between the HCV GT 2 treatment-naïve 12 week and treatment-experienced 24 week arms. For HCV GT 3 subjects, SVR12 rates were consistent with observed prior Phase 3 treatment-naïve 12 week trial data. Extending the SOF+RBV treatment duration to 24 weeks in the HCV GT 3 treatment-experienced population led to a higher SVR12 rate of 92% which supports observations from the VALENCE trial. Few HCV GT 2 cirrhotic subjects enrolled (N=3), though all achieved SVR12. HCV GT 3 treatment-naïve subjects treated with SOF+RBV 12 Weeks achieved 67% SVR12 in both cirrhotic and non-cirrhotic subgroups. All HCV GT 3 treatment-experienced non-cirrhotic subjects treated with SOF+RBV 24 Weeks achieved SVR12, compared with 80% SVR12 in cirrhotic subjects. The subgroups are small; however, the numerical SVR12 trend for the SOF+RBV 24 Week arm in HCV GT 3 treatment-experienced cirrhotics is higher than observed in VALENCE.

These interim efficacy data in HIV/HCV GT 2 and 3 subjects suggest that treatment regimens for these genotypes result in similar HCV virologic outcomes to those observed in mono-infected patients (Table 9).

### Table 9: PHOTON-1 SVR12 by HCV Genotype (2/3), Prior Treatment History, and Cirrhosis Status

<table>
<thead>
<tr>
<th></th>
<th>HCV Genotype 2</th>
<th>HCV Genotype 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOF+RBV 12 Weeks TN (N = 26)</td>
<td>SOF+RBV 24 Weeks TE (N = 42)</td>
</tr>
<tr>
<td>Overall</td>
<td>23/26 (88.5%)</td>
<td>14/15 (93.3%)</td>
</tr>
<tr>
<td>No cirrhosis</td>
<td>22/25 (88.0%)</td>
<td>12/13 (92.3%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1/1 (100%)</td>
<td>2/2 (100%)</td>
</tr>
</tbody>
</table>

Source: Applicant GS-US-334-0123 Interim Clinical Study Report, Table 5
For the HCV GT 1 treatment-naïve SOF+RBV 24 Week group, subjects without cirrhosis had higher SVR12 than subjects with cirrhosis (77%, 84/109 subjects versus 60%, 3/5 subjects); however it should be noted that the only five subjects in this group had compensated cirrhosis. SVR12 rates were higher in HCV GT 1a versus GT 1b subjects, 82% versus 54%, consistent with observations from NEUTRINO.

Labeling for this trial remains under review. At this time, the review team recommends including language in the dosage and administration section for SOF+RBV 24 week duration as a considered treatment option for HCV GT 1 patients ineligible to receive interferon, and to include the PHOTON-1 trial results in the specific populations section under a HIV/HCV coinfection heading.

**On-Treatment Viral Kinetics from Phase 3 Trials**

On-treatment viral kinetics have commonly been used to guide treatment duration decisions in HCV treatment. The review team evaluated whether viral kinetics from the four Phase 3 trials, FISSION, POSITRON, FUSION and NEUTRINO, could be used to identify patients who were unlikely to respond to sofosbuvir-based treatment. In the IFN-free trials with SOF+RBV in HCV GT 2 subjects, no trend between on-treatment response and SVR was observed. For HCV GT 3, subjects with HCV RNA target not detected by Week 1 were more likely to achieve SVR, though an analysis of whether a similar trend remains for 24-weeks of treatment using the VALENCE data remains to be determined. For HCV GT 1, subjects with HCV RNA >25 IU/mL at Week 2 were less likely to achieve SVR (80%, 20/25), compared to subjects with HCV RNA <25 IU/mL but detectable (87%, 108/124) or HCV RNA not detected (94%, 131/140). However, this observation was not used to provide any response-guided therapy recommendations as: i) the SVR rate remained high in all three groups; and ii) there were no data to support whether a longer treatment duration would further improve SVR.

**Efficacy in Pre-Transplant Population, P7977-2025**

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

P7977-2025 is an ongoing Phase 2, open-label trial evaluating the efficacy of SOF+RBV administered pre-transplant in preventing HCV recurrence post liver transplant in subjects with HCV GT 1 through 6 infection and hepatocellular carcinoma (HCC) specifically meeting the Milan criteria\(^1\) prior to undergoing liver transplantation with an anticipated time until

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\(^1\) Milan criteria were defined as the presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinomas and no more than three tumor nodules, each 3 cm or less in diameter, in subjects with multiple tumors. There should be no extrahepatic manifestations of the cancer and no evidence of vascular invasion of the tumor.
transplantation within one year. 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. The original protocol-specified treatment duration was for a maximum of 24 weeks and later extended via protocol amendment to 48 weeks, or until transplant, whichever comes first. Treatment is discontinued within 24 hours prior to liver transplant if it occurs before the subject has completed their treatment course, as appropriate. Prevention of post-transplant reinfec tion is determined by a sustained post-transplant virological response (HCV RNA < LLOQ) at 12 weeks post-transplant (pTVR12).

A total of 61 subjects received at least one study drug dose at the submission data cutoff. The majority of subjects had HCV GT 1 (73.8%, GT 1; 39.3%, GT 1a and 34.4%, GT 1b) while 13.1%, 11.5%, and 1.6% had HCV GT 2, 3, or 4, respectively. Most subjects had a baseline HCV RNA ≥ 6 log_{10} IU/mL (67.2%) and an IL28B non-CC allele (78.3%). Baseline CPT scores ranged 5 to 8. Baseline MELD score ranged 6 to 14, with approximately half of subjects (49.2%) having a score of 7 or 8. About 75% of subjects had prior HCV treatment experience.

Pre Liver Transplant Phase
A total of 11 of 15 subjects (73%) who completed 24 weeks of SOF+RBV treatment relapsed in the pre-transplant phase. Ten of these subjects had HCV GT 1 infection (7 GT 1a, 3 GT 1b) and one subject had GT 2b infection. The virologic relapse rate after 24 weeks of treatment in this patient population suggested a longer treatment duration may be indicated to achieve HCV RNA < LLOQ at the time of transplant. This finding led to a protocol amendment to extend the treatment duration from 24 weeks to 48 weeks or to the time of transplant. Five subjects had on-treatment virologic failure: 3 breakthroughs (1 GT 1a, 1 GT 1b and 1 GT 2b) and 2 non-responders (both GT 1a) (see Virology Summary for resistance information).

Post Liver Transplant Phase
A total of 41 subjects with any SOF+RBV treatment duration have undergone liver transplantation at the time of the updated submission. Median time to transplant was 21 weeks (range: 2-42 weeks). Thirty-seven subjects had HCV RNA <LLOQ at the time of liver transplantation and 36 have been followed to post-transplant Week 12. Of those subjects, 64% achieved sustained pTVR12 (Table 10). Of the approximately two-thirds of subjects (N=24) reaching post-transplant Week 24, 71% (17/24) achieved sustained pTVR24. A total of 28% subjects (10/36) experienced recurrent HCV infection post-transplant. By genotype, HCV GT 1b had the highest recurrence rates (54%, 7/13) followed by GT 1a (15%, 2/13). A single HCV GT 3a subject had recurrence as well.

HCV GT 2 and GT 3 infected subjects had improved virologic outcomes (75-100%) compared with HCV GT 1 subjects (54%). Among HCV GT 1 subjects, those with HCV GT 1a had improved pTVR12 rates compared with HCV GT 1b subjects, 62% versus 46%, respectively.
Table 10: Post-Transplant Virologic Response At Week 12, by Genotype

<table>
<thead>
<tr>
<th>HCV Genotype</th>
<th>SOF+RBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall pTVR12, % (n/N)</td>
<td>64% (23/36)</td>
</tr>
<tr>
<td>GT 1a</td>
<td>62% (8/13)</td>
</tr>
<tr>
<td>GT 1b</td>
<td>46% (6/13)</td>
</tr>
<tr>
<td>GT 2</td>
<td>100% (5/5)</td>
</tr>
<tr>
<td>GT 3</td>
<td>75% (3/4)</td>
</tr>
<tr>
<td>GT 4</td>
<td>100% (1/1)</td>
</tr>
</tbody>
</table>

Source: NDA 204671 FDA Advisory Committee Presentation, 10/25/13

This trial in the pre-transplant population included subjects who were eligible to undergo liver transplant due to an upgrade in their MELD scores due to HCC and not necessarily because of worsening liver disease. An overall response rate of 64% is encouraging and provides a therapeutic option for these subgroups of patients undergoing liver transplantation for HCC.

8. Safety

The safety database for sofosbuvir 400 mg daily in combination with RBV for 12-24 weeks or PEG/RBV for 12 weeks is adequate. The primary safety pool with the Phase 3 trials, FISSION, POSITRON, FUSION, VALENCE, PHOTON-1 and NEUTRINO, included approximately 1220 subjects treated with SOF+RBV ≥ 12 weeks, 405 subjects treated with SOF+RBV ≥ 24 weeks and 327 subjects treated with SOF+PEG/RBV for 24 weeks. In addition, safety data from Phase 2 trials, including ATOMIC, QUANTUM and P7977-2025, were considered supportive for the 24 week duration.

Please refer to Dr. Poonam Mishra’s clinical review for detailed safety assessment. No major safety issues related to sofosbuvir use have been identified in the sofosbuvir clinical development program to date that would support language in the warnings and precautions section of the label. The following is a brief summary of sofosbuvir safety from clinical trial data submitted to the NDA. The primary safety analyses evaluated treatment-emergent adverse events (AEs), serious AEs (SAEs), severe and life-threatening AEs, AEs leading to discontinuation, deaths and laboratory abnormalities in the Phase 3 trials FISSION, POSITRON, FUSION and NEUTRINO. Safety review from non-pivotal trials provides supportive data. Please note that the VALENCE and PHOTON-1 trials remain under review at the time of this CDTL memo and their assessments will be provided as an addendum to Dr. Mishra’s clinical review, though selected safety information is incorporated below.

In the originally submitted Phase 3 trials to the NDA, one death due to cocaine and heroin intoxication occurred in FISSION in the SOF+RBV 12 Week arm on Study Day 1, with uncertainty if study drugs were taken. Non-treatment-emergent deaths occurred in two subjects in the POSITRON SOF+RBV 12 Week arm (metastatic lung cancer 63 days after last study
drug dose, cardiogenic shock secondary to aortic stenosis 47 days after last study drug dose in a subject with a history of aortic stenosis), and in one subject in the FISSION PEG/RBV arm (brain neoplasm). Please refer to Dr. Mishra’s review for further details, and I agree with her assessment that these events are considered to be unlikely related to study drugs. No treatment-emergent deaths were reported in VALENCE, and in the PHOTON-1 trial one subject with HIV/HCV and a history of attention deficit hyperactivity disorder committed suicide nine days after completing SOF+RBV 12 Week treatment.

As noted in Dr. Mishra’s initial review, the overall SAE incidence was comparable between the pooled Phase 3 trial SOF+RBV 12 Week group (4%) and SOF+RBV 16 Week group (3%), and was low in the SOF+PEG/RBV group (1%). There was no apparent clustering of SAEs observed within system organ classes. The incidence of SAEs considered related to study drug by the investigators was low (four subjects): anemia; peripheral edema and eczema; anemia and cryoglobulinemia; leukopenia and pyrexia. Malignant hepatic neoplasm (0.5%, 3 subjects) was the only SAEs reported in > 2 subjects in the SOF+RBV 12 Week group. All three subjects with malignant hepatic neoplasm had documented evidence of baseline cirrhosis either on histology or imaging study.

A total of 13 sofosbuvir-treated subjects discontinued study treatment due to AEs, with anemia (3 subjects) the only event occurring in > 2 subjects. AEs classified as ≥ Grade 3 occurred in 7% subjects in the SOF+RBV 12 Week group and 15% in the SOF+PEG/RBV group. These ≥ Grade 3 AEs observed in >2 subjects include fatigue, anemia, hepatic neoplasm malignant and pyrexia in the SOF+RBV groups and include neutropenia, fatigue, anemia and headache in the SOF+PEG/RBV group. The most common treatment-emergent AEs in both the SOF+RBV and SOF+PEG/RBV groups were fatigue, headache, nausea and insomnia.

**SOF+RBV 24 Week duration**
Overall safety data from the VALENCE SOF+RBV 24 Week arm are similar to data observed in the prior Phase 3 trials (Figure 3). No deaths occurred in VALENCE and the incidence of SAEs was comparable between the SOF+RBV 12 Week group (3.9%) and SOF+RBV 24 Week group (4%), as was the general incidence of Grade 3 or 4 AEs (7% in both groups). Dr. Mishra’s primary review addendum will contain further 24 week safety assessment.
Figure 3: Overall Summary of Adverse Events comparing SOF+RBV 12 and 24 Week Durations

Overall Summary of Adverse Events (Integrated Data)

<table>
<thead>
<tr>
<th></th>
<th>Placebo 12 Weeks POSITRON</th>
<th>SOF+RBV 12 Weeks FISSION, POSITRON, FUSION</th>
<th>SOF+RBV 24 Weeks VALENCE</th>
<th>SOF+PEG/RBV 12 Weeks NEUTRINO</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=71 n (%)</td>
<td>N=566 n (%)</td>
<td>N=250 n (%)</td>
<td>N=327 n (%)</td>
<td></td>
</tr>
<tr>
<td>Any Adverse Event (AE)</td>
<td>55 (78)</td>
<td>496 (88)</td>
<td>226 (91)</td>
<td>310 (95)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>2 (2.8)</td>
<td>22 (3.9)</td>
<td>10 (4.0)</td>
<td>4 (1.2)</td>
</tr>
<tr>
<td>Grade 3 or 4 AE</td>
<td>1 (1.4)</td>
<td>41 (7.2)</td>
<td>17 (6.8)</td>
<td>48 (14.7)</td>
</tr>
<tr>
<td>AE Leading to Permanent Discontinuation from Any of the Study Drugs</td>
<td>3 (4.2)</td>
<td>9 (1.6)</td>
<td>1 (0.4)</td>
<td>8 (2.4)</td>
</tr>
</tbody>
</table>

Source: NDA 204671 FDA Advisory Committee Presentation, 10/25/13

Specific Safety Assessments
Specific safety assessments were performed for elevated creatine kinase levels; elevated lipase levels; anemia; elevated bilirubin levels; completed suicide, suicide attempt and suicidal ideation; hypersensitivity; gastrointestinal and cardiac events. This memo contains summary information for these safety assessments. Please refer to Dr. Mishra’s clinical review for complete details.

Creatine Kinase
Creatine kinase laboratory data are available for the FISSION and NEUTRINO trials only. 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. Study drugs were discontinued in one subject who developed Grade 4 CK at the Week 3 visit (note, baseline CK was 2x ULN) preceded by reported heavy manual labor and Grade 1 arthralgia, myalgia and Grade 2 upper extremity muscle twitching. Study drugs were stopped at Week 4 with symptomatic improvement. By post-treatment Day 28, CK has returned to baseline; however, at the post-treatment Week 24 visit, Grade 4 CK recurred. Rheumatologic evaluation, including electromyography (EMG) and a muscle biopsy, concluded the subject probably had a metabolic myopathy with elevated CK and negative autoimmune profile. No cases of rhabdomyolysis have been reported in the sofosbuvir development program to date. I agree with Dr. Mishra’s assessment that due to presence of confounding factors such as increased physical activity in subjects with ≥Grade 3 levels it is challenging to assess any causal relationship between sofosbuvir use and CK elevations; however, the contributory role of
sofosbuvir cannot be fully excluded. Additional data from ongoing/future trials evaluating sofosbuvir may be helpful in further assessment of this finding, and these trials have been requested to include CK laboratory testing. At this time, the review team recommends including this information in the prescribing information to ensure that health care providers are aware and can monitor CK levels as clinically indicated.

**Lipase**

Treatment-emergent lipase elevations were reported in 9-17% of sofosbuvir-treated subjects from the FISSION, POSITRON, FUSION and NEUTRINO trials. None of these isolated, sporadic elevations were associated with clinical signs or symptoms of pancreatitis. At this time, the review team recommends including this information in the prescribing information to ensure that health care providers are aware and can monitor lipase levels as clinically indicated.

**Hemoglobin**

Hemoglobin values < 10 g/dL occurred in 0%, 9%, 23% and 14% of the placebo, SOF+RBV 12 Week, SOF+PEG/RBV 12 Week and PEG/RBV 24 Week groups, respectively. The observed difference between the SOF+PEG/RBV and PEG/RBV groups may be explained by the higher (weight based) RBV dose used in the SOF+PEG/RBV group. A total of three subjects in the SOF+RBV 12 Week group received blood transfusions for anemia. In VALENCE, hemoglobin values < 10 g/dL were similar in the SOF+RBV 12 Week (7%) and 24 Week (6%) groups. Across these five Phase 3 trials, hemoglobin values < 8.5 g/dL occurred in < 2% SOF+RBV and ≤ 2% SOF+PEG/RBV groups.

**Bilirubin**

No Grade 4 elevations (>5 x ULN) in total or direct bilirubin levels were noted in FISSION, POSITRON, FUSION or NEUTRINO. The incidence of Grade 3 total bilirubin was low in subjects in the SOF+RBV 12 Week group (2.3%, 13 subjects). No subjects in the SOF+PEG/RBV group had ≥Grade 3 total bilirubin. However, the SOF+PEG/RBV group had a higher overall incidence of graded total bilirubin abnormalities (18%) compared with the PEG/RBV group (11%). This difference is believed to be 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 and resulting RBV-induced hemolysis. The bilirubin levels generally peaked in the first 1-2 weeks and then returned to baseline values after completion of ribavirin-containing regimen. In addition, no safety signals related to hepatotoxicity were identified in the sofosbuvir-treated groups.

**Suicidal-Related Events**

As described above, one subject in PHOTON-1 completed suicide and in the sofosbuvir clinical development program, 11 subjects (<1%) reported suicidal ideation or suicide attempt. More subjects in the SOF+RBV 12 Week and 16 Week groups (7.2% and 6.1%, respectively) had depression compared with the subjects in the Placebo group; however, the incidence was lower compared to the PEG/RBV group (17.3%) and the rate of pre-existing depression in subjects enrolled in the original registrational Phase 3 trials ranged from 33% (NEUTRINO) to 55% (POSITRON). I agree with Dr. Mishra’s assessment that based on the review of data submitted to date, the AE incidence of completed suicide, suicidal ideation or suicide attempt
was low and mostly observed in subjects with pre-existing psychiatric conditions and/or accompanied by major life stressors; however, due to the seriousness of these events, the currently proposed label includes language in the Less Common Adverse Reactions section. Emerging safety signals for these AEs will be monitored in the post-marketing setting.

**Hypersensitivity**
The Safety Update Report included one subject from the Phase 2 QUANTUM SOF+RBV 24 Week retreatment group who experienced AEs of gingival inflammation, mouth ulceration and increased upper airway secretion considered possibly related to SOF+RBV treatment and led to discontinuation of therapy on Study Day 90. In the sofosbuvir clinical development program, hypersensitivity occurred in <1% of active treatment arms. No acute hypersensitivity reactions such as Stevens-Johnson Syndrome or toxic epidermal necrolysis were reported, and there were no ≥ Grade 3 hypersensitivity events reported in any subject receiving sofosbuvir. No cases of angioedema were reported in any sofosbuvir-treated subject across the sofosbuvir clinical program, and no subject with an AE of hypersensitivity experienced any increase in eosinophil count. Therefore, a definite causal relationship between sofosbuvir use and hypersensitivity has not been identified as this time.

**Gastrointestinal 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 performed. I agree with Dr. Mishra’s assessment 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).

**Cardiac Events**
The development of an investigational agent in the same class for the treatment of hepatitis C was halted in 2012 after nine patients in a clinical trial were hospitalized and one of them died of heart failure (http://news.bms.com/press-release/financial-news/bristol-myers-squibb-discontinues-development-bms-986094-investigationa). Although sofosbuvir is structurally different (GS-7977 is a 2'-F, 2'-Me uridine monophosphate analogue prodrug and the other compound is a 2'-Me guanosine monophosphate analogue prodrug), the review team conducted a detailed safety evaluation focused on cardiac disorders to identify any potential safety signal.

As noted in Section 4, myocardial inflammation and degeneration occurred in rats in a 7-day toxicology study at AUC exposures of GS-9851- and sofosbuvir-derived GS-331007 approximately 29- and 14-fold higher, respectively, than human exposure at the recommended sofosbuvir dose. Cardiac toxicity was not observed in rats administered oral doses of sofosbuvir up to 500 mg/kg/day for 6 months, or in dogs and mice administered sofosbuvir at doses up to 500 and 1000 mg/kg/day, the highest doses examined in 9 and 3 month studies in dogs and mice, respectively, corresponding to AUC exposures approximately 9 (rat), 27 (dog) and 41 (mouse)-fold higher than human exposure at the recommended sofosbuvir dose.

As outlined in Dr. Mishra’s review, clinically there have been no cases of cardiomyopathy reported in sofosbuvir-containing trials and no obvious safety issues related to cardiac toxicity.
have been noted in clinical development program of sofosbuvir to date. Emerging safety signals for cardiac events will be monitored in the post-marketing setting.

**Pre-Transplant Trial, P7977-2025**

One death from sepsis/spontaneous bacterial peritonitis occurred 15 days after the last dose of study drug. Four additional deaths, that were not considered treatment-emergent, were reported: pneumonitis, graft failure/renal failure, hepatic artery thrombosis/cardiogenic shock, sepsis. The latter three deaths occurred within 2 weeks following transplantation. The rates of SAEs (18%) and deaths reported in this pre-transplant population are higher compared to the general AE profile in the Phase 3 trials, and this difference in safety profile can be attributed to the more advanced stage of liver disease and/or due to underlying disease progression (cirrhosis with HCC) in these subjects. In addition, some of the AEs noted were associated with liver transplantation. After accounting for these factors, the safety profile in this subpopulation does not appear to differ from the overall SOF+RBV safety profile in subjects not undergoing transplantation.

**PHOTON-1 HIV/HCV Coinfection Trial: Effects of SOF+RBV on HIV and CD4+ T-cells**

In PHOTON-1, two subjects on ART experienced HIV-1 virologic rebound. One subject in the HCV GT 2/3 treatment-naive SOF+RBV 12 Week group on raltegravir plus tenofovir/emtricitabine had detectable HIV 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 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.

Median CD4+ T-cell counts decreased during SOF+RBV treatment, ranging -73 to 87 cells/mm3 at the end of treatment; however, CD4+ T-cell percentage remained stable between approximately 31-37%.

**9. Advisory Committee Meeting**

An Advisory Committee (AC) meeting was held on October 25, 2013. The following questions were discussed at the AC meeting. The reviewer comments are based upon my notes from the AC meeting: please refer to the official transcript for details of the committee discussion.

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

   **VOTE**: Yes/No/Abstain

   **Reviewer Comment**: The committee voted 15 yes/0 no/0 abstentions on this question. The discussion centered on the positive benefit-risk profile of sofosbuvir including the potential first all oral HCV regimens.
2. **VOTE:** Considering potential risks and benefits does 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 genotypes 1 and 4 infection?

**VOTE:** Yes/No/Abstain

**Reviewer Comment:** The committee voted 15 yes/0 no/0 abstentions on this question. The discussion centered on the positive benefit-risk profile of sofosbuvir including the shortened treatment duration. One committee member commented having a second trial in this population would have been preferred.

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

**Reviewer Comment:** The committee expressed a spectrum of responses, with some members accepting the extrapolation from the HCV GT 1 treatment-naïve to the prior PEG/RBV nonresponder population using baseline factors to support use of sofosbuvir plus PEG/RBV in the latter population, particularly given the high SVR rates observed in NEUTRINO and general tolerability of the regimen. Other committee members stated more data are needed in the prior PEG/RBV nonresponder population, including data combining additional baseline factors such as low platelets, though individual providers could chose to use this regimen “off-label” for their patients. A point was made that the currently available data suggest sofosbuvir plus PEG/RBV is not expected to be less effective than currently approved therapy in the prior PEG/RBV nonresponder population. Options to obtain additional data include use of a registry and submission of data from the GS-US-334-0109 open-label trial in subjects who participated in prior Gilead HCV trials.

4. **DISCUSSION:** 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? (*Milan criteria were defined as the presence of a tumor 5 cm or less in diameter in subjects with single hepatocellular carcinoma 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.)

**Reviewer Comment:** The committee generally supported use of the P7977-2025 data for dosing recommendations in HCC patients meeting Milan criteria awaiting liver transplantation. Regarding use in a broader pre-transplant population, committee members expressed the opinion that more data were needed in the population with higher MELD scores.
5. **DISCUSSION**: Please comment on postmarketing studies/trials that are needed to further define the optimal use of sofosbuvir.

**Reviewer Comment:** The committee noted that more data is needed in a number of patient populations, including HIV-HCV coinfected patients, patients with advanced MELD scores, prior sofosbuvir treatment failures, prior protease inhibitor treatment failures, HCV GT1 patients unwilling/unable to take interferon, pediatric patients, older patients and patients from underserved communities. Some committee members recommended trials with sofosbuvir combined with other DAAs as the field moves to interferon-free regimens. Other members recommended longer term surveillance after treatment to follow resistance mutations and quality of life parameters.

10. **Pediatrics**

Under the Pediatric Research Equity Act (PREA), the Applicant is required to conduct pediatric study(ies) for the indication for which the Applicant is seeking approval. The Applicant requested a waiver of pediatric studies in patients less than 3 years old, and a deferral in patients ≥3 to < 18 years of age. The Division agreed with the request for waiver in pediatric patients under the age of 3 because:

- No systematic surveillance of chronic HCV infection among pediatric patients is available, making an accurate assessment of prevalence and severity in this age group difficult.
- The primary mode of HCV transmission to children is via vertical transmission.
- Rate of vertical transmission is estimated to be about 5%, but may be increased in the presence of HIV infection.
- Infants infected by vertical transmission have a high rate of spontaneous resolution approaching 25% to 40%. Most have spontaneous resolution by 24 months of age, but some may have spontaneous resolution as late as 7 years after vertical infection.
- Severe manifestations or complications of infection are unusual in infants and young children, and pediatric hepatologists acknowledge a lack of consensus regarding when to begin treatment in pediatric patients.

Based on these data and current practice guidelines, a waiver for children less than 3 years of age is deemed appropriate. The Division also agreed with the request for deferral in pediatric patients ≥3 to < 18 years old because adult studies are ready for approval.

The review team met with the Pediatric Review Committee (PeRC) on September 11, 2013. The PeRC agreed with the Division to grant a partial waiver in pediatric patients aged birth to less than 3 years because studies are impossible or highly impractical. In addition, the PeRC agreed with the Division to grant a deferral for pediatric patients aged 3 to 18 years because the product is ready for approval in adults.

The Applicant plans to conduct the following clinical trials to fulfill the PREA requirements:

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Reference ID: 3404743
The Division is in general agreement with the Applicant’s overall pediatric plans to evaluate sofosbuvir as a component of a combination antiviral treatment regimen in pediatric subjects ≥ 3 to < 18 years old with chronic hepatitis C.

The current standard of care for treatment of chronic hepatitis C in pediatric patients remains PEG/RBV. Although the NDA supports a regimen of sofosbuvir in combination with PEG/RBV in adult patients, the overall field of development of DAAs in interferon-free regimens is rapidly moving forward. Because of these rapid changes in the field and the significant risks associated with PEG/RBV, the Division believes that the path forward for pediatric HCV development should avoid study of PEG-based regimens. Therefore, at this time, the Division will not request a pediatric study evaluating sofosbuvir in combination with pegylated interferon and ribavirin. The proposed pediatric postmarketing study requirements (PMR) will be to evaluate sofosbuvir as a component of a combination antiviral treatment regimen in pediatric subjects ≥ 3 to < 18 years old with chronic hepatitis C. Final language remains to be negotiated with the Applicant at the time of this CDTL memo.

11. Other Relevant Regulatory Issues

Office of Scientific Investigation Inspections
Four domestic and two international Phase 3 clinical trial sites (one in Canada and one in Italy) were selected for inspection. These inspections revealed no regulatory violations and the final classifications are No Action Indicated (NAI). Overall, the data submitted from these six sites are considered acceptable in support of the pending application. See review by Dr. Antoine El-Hage for full details.

As previously mentioned, VALENCE and PHOTON-1 data were reviewed later in the PDUFA V review cycle as part of sofosbuvir’s Breakthrough Therapy designation. PHOTON-1 contains one site (Puerto Rico, Dr. Rodriguez-Torres) which was investigated as part of this NDA review. VALENCE was not conducted under IND and contains non-US sites. The Applicant has had two sites audited, Dr. Riina Salupere (site #6816) and Professor Stefan Zeuzem (site #1081). To further support the reliability of the data submitted to the NDA for VALENCE, the review team requested that the Applicant conduct audits of three additional randomly selected sites. Dr. El-Hage will provide an addendum to determine if these data are considered acceptable in support of the VALENCE trial.
Good Clinical Practice
The clinical trials were conducted in accordance with ICH Good Clinical Practice (GCP) Guidelines. No GCP issues were identified in the primary reviews.

Financial Disclosures
The Applicant examined financial disclosure information from all clinical investigators for the covered clinical trials. Please see Dr. Poonam Mishra’s review for full details. Dr. Mishra concluded that based on the information provided, the likelihood that the trial results were biased based on financial interests is minimal.

Other discipline consults
No other disciplines were consulted for this review. All review disciplines agreed that sofosbuvir labeling will include a Patient Package Insert and neither a Medication Guide nor a REMS is warranted.

Any other outstanding regulatory issues
There are no other outstanding regulatory issues.

12. Labeling

Proprietary Name: Initial review of the proposed proprietary name, Sovaldi, was considered unacceptable because it could result in medication errors due to confusion with another product also under review; and therefore the ultimate acceptability of the proposed name, Sovaldi, was dependent on which application was approved first. The Applicant subsequently resubmitted Sovaldi as the proposed proprietary name in addition to an alternate name, DMEPA has determined that the proposed proprietary name, is acceptable, and is currently awaiting comment from the review team before finalizing their review and notifying the Applicant.

Prescribing Information: Sofosbuvir prescribing information is currently under negotiation with the Applicant. The substantially completed labeling is not yet under review by the Office of Prescription Drug Promotion. The following information addresses ongoing or otherwise major issues discussed during this review cycle. At the time of this memo, the VALENCE and PHOTON-1 data are under review. Importantly, how to incorporate the PHOTON-1 information has not yet been determined.

1. Indications and Usage:
DAVP proposed the indication, as follows, which has been accepted by the Applicant: “TRADENAME is a hepatitis C virus (HCV) NS5B nucleotide analog polymerase inhibitor indicated in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of chronic hepatitis C (CHC) in adults.”

I agree with the above proposed indication and, at this time, do not believe there are sufficient data to support a broader indication for sofosbuvir in combination with other agents for the treatment of CHC, as the Applicant originally proposed. Specifically, only the regimens of SOF+RBV and SOF+PEG/RBV were used in the Phase 3 and supportive Phase 2 trials for this
application with clinical study reports and reviewable analysis datasets. The recommendation for the currently proposed indication, however, does not preclude re-evaluation in the future as more experience is gained with sofosbuvir used with other agents, particularly as part of an interferon and/or ribavirin-free regimen.

2. Dosage and Administration
The recommended dosage and administration is categorized by genotype. The current version of how this information is displayed in the label is as follows:

<table>
<thead>
<tr>
<th>Table X</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with genotype 1 or 4 CHC</td>
<td>[TRADE NAME]+peginterferon alfa (^a)+ribavirin (^b)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with genotype 2 CHC</td>
<td>[TRADE NAME]+ribavirin (^b)</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patients with genotype 3 CHC</td>
<td>[TRADE NAME]+ribavirin (^b)</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

a. See peginterferon alfa prescribing information for dosing recommendation for patients with genotype 1 or 4 CHC.

b. Dose of ribavirin is weight-based (<75 kg = 1000 mg and ≥ 75 kg = 1200 mg). The daily dose of ribavirin is administered orally in two divided doses with food. Patients with renal impairment (CrCl ≤ 50 mL/min) require ribavirin dose reduction; refer to ribavirin prescribing information.

6. Adverse Reactions
The Applicant proposes a single table to display treatment-emergent adverse events. A proposed hematologic laboratory table displays information similarly. DAVP discussions are ongoing regarding the preferred approach to display safety information. Information pertaining to creatine kinase and lipase laboratories is included. The current version of the label’s Less Common Adverse Reactions section lists Psychiatric Disorders: severe depression (particularly in subjects with pre-existing history of psychiatric illness), including suicidal ideation and suicide.
8. Use in Specific Populations
Information pertaining to the pre-transplant population with hepatocellular carcinoma and CHC patients with Genotype 5 or 6 HCV Infection is included.

8.8 Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation
This section was updated to include the number of subjects with a virologic response post-transplant who had HCV RNA <LLOQ at the time of liver transplantation.

8.10 CHC Patients with Genotype 5 and 6 HCV Infection
DAVP proposed this section with the language:
“Available data on subjects with genotype 5 or 6 HCV infection are insufficient for dosing recommendations.”

12.4 Microbiology
Resistance data pertaining to clinical trials are included in this section. Details regarding specific language to convey this information remain under discussion.

13.2 Animal Toxicology and/or Pharmacology
DAVP recommended inclusion of the preclinical cardiac findings. At this time, displaying AUC exposures by GS-9851 and/or GS-331007 requires resolution with the Applicant.

14. Clinical Studies
The Applicant accepted DAVP’s recommendation to include all subjects in the FISSION and FUSTION trials for efficacy analyses based upon the ITT principle. The following general issues are not resolved at the time of this memo:

14.1 Clinical Trials in Subjects with Genotype 1, 4, 5 or 6 CHC
Language to communicate that subjects in NEUTRINO with multiple baseline factors traditionally associated with lower response to PEG/RBV is proposed in this section; however, details on the exact wording remain under discussion.
14.2 Clinical Trials in Subjects with Genotype 2 or 3 CHC

Confirmation of VALENCE efficacy results has not been completed at the time of this memo.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**: *APPROVAL* is recommended for sofosbuvir 400 mg once daily in combination with ribavirin or in combination with pegylated interferon alfa and ribavirin for treatment of patients with chronic hepatitis C. This recommendation for approval is contingent on successful completion of all pending facility inspections and resolution of any cGMP issues.

- **Risk Benefit Assessment**: Efficacy of sofosbuvir for treatment of chronic HCV infection in combination with ribavirin (genotypes 2 and 3) and in combination with PEG/RBV (genotypes 1 and 4) was demonstrated in five Phase 3 trials. In addition, efficacy of sofosbuvir in combination with ribavirin was demonstrated in the pre-transplant population in patients with HCC awaiting liver transplantation. Furthermore, efficacy of sofosbuvir in combination with ribavirin was also demonstrated in the HIV/HCV GT 1 population providing an oral treatment option for HCV GT 1 patients who are ineligible to receive interferon-based treatment. The available data are believed to be insufficient to make definite dosing recommendations for patients with HCV GT 5 or 6.

No major clinically significant safety issues associated with sofosbuvir use have been identified to date. The observed safety profile between the SOF+RBV 12 and 24 week durations is similar. Additional risks of sofosbuvir in combination with ribavirin or in combination with PEG/RBV include those associated with pegylated interferon and ribavirin. These risks are addressed in the prescribing and patient information for the approved pegylated interferon and ribavirin products.

Sofosbuvir appears to provide a number of advantages in the treatment of HCV infection including improved tolerability, once daily dosing, limited drug-drug interactions and ease of administration. In combination with pegylated interferon and ribavirin for the treatment of HCV GT 1 or 4 infection, sofosbuvir also offers a shortened treatment duration in comparison to the currently approved standards of care, and this shorter 12 week duration translates into a better tolerated side effect profile with observed treatment discontinuations due to AEs of less than 2%. In combination with RBV, sofosbuvir offers an all-oral, interferon free treatment regimen for HCV GT 1, 2 or 3 patients. For patients ineligible to receive interferon, this treatment option addresses an unmet medical need. Furthermore, sofosbuvir plus ribavirin treatment in HCV infected patients with HCC awaiting liver transplantation addresses an unmet medical need for a population with almost universal HCV reinfection rates post-transplantation.

Overall the risk-benefit assessment for sofosbuvir is favorable.
Recommendation for Postmarketing Risk Evaluation and Management Strategies: Based on the safety profile of sofosbuvir, DAVP does not recommend a Risk Evaluation and Management Strategy (REMS) for sofosbuvir.

Recommendation for other Postmarketing Requirements and Commitments: Postmarketing Requirements/Commitments are currently under discussion and final agreements have not been reached with the Applicant. The lists that follow provide preliminary items at this time.

Recommended Postmarketing Requirements include:
1. Pediatric studies required under PREA as discussed in Section 10 of this review (Pediatrics).
2. Submit the complete study report and datasets for GS-US-334-0154, currently entitled, “A Phase 2b, Open-Label Study of 200 mg or 400 mg Sofosbuvir + RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency”, in order to provide dosing recommendations for chronic hepatitis C patients with severely impaired renal function and ESRD.
3. Submit the complete study report for the 2 year carcinogenicity studies.

Recommended Postmarketing Commitments include:
- Submission of a complete study report and datasets for VALENCE
- Submission of a complete study report and datasets for P7977-2025
- Submission of a complete study report and datasets for PHOTON-1
- Submission of a complete study report and datasets for GS-US-334-0153, entitled, A Phase 3B Randomized, Open-Label, Multi-Center Trial Assessing Sofosbuvir + Ribavirin for 16 or 24 Weeks and Sofosbuvir + Pegylated Interferon + Ribavirin for 12 Weeks in Subjects with Genotype 2 or 3 Chronic HCV Infection

Other Postmarketing Commitments discussed: Discussions are ongoing regarding the need for submission of the following data as postmarketing commitments: (1) SVR24 data from the ongoing and completed Phase 3 trials to determine SVR12/SVR24 concordance and (2) three year follow up data from these trials.

Recommended Comments to Applicant: No additional comments need to be communicated to the Applicant at this time.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SARAH M CONNELLY
11/08/2013