CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204671Orig1s000

SUMMARY REVIEW

ERRATA to Original CDTL Review (11/8/2013)

Page 32 (Section 8, Safety, First Paragraph)

Prior Text: 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.

Corrected Text (in bold): 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 **12** weeks.

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/s/

SARAH M CONNELLY
12/11/2013

Decisional Review for NDA 204671

Date	November 27, 2013
From	Debra Birnkrant, M.D.
Subject	Division Director's Summary Review
NDA/BLA # Supp #	NDA 204671/Original Submission
Proprietary / Established (USAN) names	SOVALDI [Sofosbuvir (SOF)]
Dosage forms / strength	400 mg tablets, once daily
Proposed Indication(s)	Indicated for the treatment of chronic hepatitis C (CHC) in adults as a component of a combination antiviral treatment regimen. Efficacy has been established in subjects with Genotype 1,2,3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation and those with HCV/HIV-1 co-infection
Action	Approval

1. Introduction to Review: This Division Director's memorandum provides a topline summary of NDA 204671 for Gilead Sciences' New Drug Application (NDA) for sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor for use as a component of a combination antiviral treatment regimen for adult subjects with Genotype 1,2,3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria awaiting liver transplantation and those with HCV/HIV-1 co-infection. This decisional review summarizes pertinent multidisciplinary findings from the original NDA submission and the additional data submitted on October 9, 2013, in addition to highlights from the Antiviral Drugs Advisory Committee meeting, post-marketing requests and labeling.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Division of Scientific Investigations (DSI) Status:
Chronic hepatitis C viral infection is a burden both globally and domestically. It is conservatively estimated that 3.2 million people in the United States are infected with the virus. It is anticipated that there will be a significant increase in cases of hepatocellular carcinoma (HCC) with a projected peak incidence in 2019 of 14,000 cases/year and decompensated cirrhosis with a projected peak incidence in 2020 of >145,000 cases/year (Davis, et al., Gastroenterology 2010) because the epidemic began decades ago with 75% of those with HCV in the United States being infected between 1945-1965 (CDC). Most are unaware that they are infected and consequently treatment is not reaching those in need. Further, treatment regimens to date have been cumbersome because of side effects and up to 30% of those diagnosed are ineligible for interferon (IFN) treatment.

Treatment allows for a chance of virologic cure. Virologic cure as measured by sustained virologic response (SVR) is associated with histologic benefit, a decrease in all cause and liver related mortality, and decreases in rates of HCC and hepatic decompensation (van der Meer, et al. JAMA 2012). Regarding treatment for CHC, current standards are outlined in 2009 and 2011 American Association for the Study of Liver Diseases (AASLD) treatment guidelines. Of note, standards-of-care have been based on genotype (GT) and previous treatment history. Patients are characterized as naïve to treatment, relapsers, partial responders and null responders by their responses to a pegylated IFN/ribavirin (PEG/RBV) regimen. As newer regimens are becoming IFN-free and perhaps RBV-free, the population of PEG/RBV failures will decrease. More recently, it has become apparent that it is the biology of the disease, taking into account host and viral factors at baseline, that impacts outcome. Factors associated with poor treatment outcome in HCV GT1 treatment-naive patients include 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 IL28B (CT and TT). Additionally, Liu, et al. in CID 2012 noted similarity between on-treatment responses following initial or subsequent treatment courses of PEG/RBV. FDA reviewers approached their review of the NDA data taking this new information into consideration.

The NDA for SOF was submitted on April 8, 2013 and reviewed under the PDUFA V program. SOF is the first drug in its class and it is recommended for use in combination with ribavirin with or without pegylated interferon depending on HCV genotype. Duration of treatment is also genotype dependent. For example, SOF 400 mg once daily is recommended for use with ribavirin for 24 weeks for patients with GT3 HCV whereas SOF plus pegylated interferon and ribavirin is recommended for 12 weeks for treatment of GT1 or GT4 HCV. See table below that is excerpted from product labeling.

	Treatment	**Duration**
Genotype 1 or 4	SOF+peg-interferon alfa+ribavirin	12 weeks
Genotype 2	SOF+ribavirin	12 weeks
Genotype 3	SOF+ribavirin	24 weeks

The safety and efficacy of SOF in pediatric patients have not been studied.

The application was granted a priority review because CHC is a serious and life-threatening disease and SOF would appear to provide improvement in safety and effectiveness. In addition, SOF was designated as a Breakthrough Therapy because preliminary clinical evidence indicated substantial improvement over

available therapies in the treatment of CHC-infected adults including the first interferon-free regimen for GT2 and GT3.

The original submission contained data from three Phase 3 trials in GT2 and GT3 (FISSION, FUSION and POSITRON), one Phase 3 trial in GT1, 4, 5 and 6 (NEUTRINO) and one ongoing Phase 2 trial in pre-transplant patients with HCC meeting Milan criteria. As we became aware of additional data that would be presented at AASLD 2013 that would impact relapse rates in GT3 and provide a treatment regimen for HCV/HIV-1 co-infected patients, we requested that the Applicant submit data from the Phase 3 trial in GT2 and GT3, VALENCE, and data from the Phase 3 HCV/HIV-1 co-infected trial, PHOTON-1.

VALENCE and PHOTON-1 data were reviewed later in the PDUFA V review cycle as part of SOF's Breakthrough Therapy designation. Dr. Rodriguez-Torres' site in Puerto Rico was already inspected as part of this NDA review so we felt we could rely on the data from PHOTON-1. VALENCE was not conducted under IND. The following five clinical investigator sites from the VALENCE trial were audited by the Applicant: Riina Salupere MD (Site 6816 Estonia), Stefan Zeuzem MD (Site 1081 Germany), Kosh Agarwal MD (Site 4472 UK), Robert Flisiak MD (Site 2188 Poland), Christophe Hezode MD (Site 1386 France). Site 6819 Alessandra Mangia was not audited.

Per Dr. El-Hage, Office of Scientific Investigations (OSI), review of the Applicant's audit of the five clinical investigators (Drs. Salupere, Zeuzem, Agarwal, Flisiak, Hezode) revealed minor regulatory deviations that are not expected to impact the study outcome or affect the quality of the data reviewed; therefore, the data submitted from these five sites are considered reliable and may be considered in support of the pending application.

In addition, four domestic and two international Phase 3 clinical trial sites were selected for inspection by OSI. Overall, the data submitted from these six sites are considered acceptable in support of the pending application.

The application was presented before the Antiviral Drugs Advisory Committee on October 25, 2013. The Committee voted unanimously to approve SOF for the treatment of GT1, GT2, GT3 and GT4 CHC as a component of a combination treatment regimen in adults with compensated liver disease including cirrhosis as well as for a subpopulation of the pretransplant population with HCC meeting Milan criteria.

3. Chemistry/Manufacturing/Controls (CMC): The CMC reviewers of the SOF NDA are: Drs. George Lunn, Fuqiang Liu and Minerva Hughes and Steven Donaldson. Dr. Rapti Madurawe supervised the CMC review with Dr. Stephen Miller serving as CMC-Lead. The CMC team reviewed data to assure the identity, strength, purity and quality of SOF 400 mg tablets.

The CMC reviewers concluded that the stability data contained in the NDA support an expiry date of 24 months.

The CMC reviewers, however, could not recommend approval because review of facilities inspections revealed significant issues with this application that were identified by the Office of Compliance. Specifically, three sites had issues that needed to be resolved before the application could be approved: (b) (4) Gilead Foster City and Gilead Ireland. (b) (4) is an active pharmaceutical ingredient (API) manufacturing site that was inspected in (b) (4) by the European Directorate for the Quality of Medicines (EDQM). EDQM found major data integrity issues at the time they were inspecting the site for manufacture of (b) (4) API. Gilead has since removed the (b) (4) facility from the NDA as a proposed commercial API manufacturing site. Gilead Foster City is involved in release and stability testing of drug substance and drug product. They recently underwent inspection and multiple 483 observations were issued. Gilead has removed this facility from the NDA as a release and testing site for drug substance and drug product. An agreement was reached between the Office of Compliance and Gilead Sciences that all launch and future commercial batches will be tested by other facilities that have been determined to be acceptable by the Office of Compliance. Additionally,the stability testing program for this product will be performed by a current good manufacturing practice (cGMP)-compliant contract testing lab that is already included in the NDA.

FDA conducted a product active ingredient (PAI) inspection at the Gilead Ireland site in August 2013 and issued two 483 observations to the firm. Corrective actions were taken and this site is now acceptable. In their addenda to their original reviews, CMC reviewers and the Office of Compliance support the approval of this NDA.

4. Pharmacology/Toxicology: Please see review of submitted nonclinical toxicology studies by Dr. Christopher Ellis, supervised by Dr. Hanan Ghantous.

The nonclinical safety profile of SOF has been adequately evaluated in safety pharmacology studies in two species, rats and dogs, and in single- and repeat-dose toxicology studies in mice, rats and dogs for up to 3, 6 and 9 months duration. Additionally, repeat-dose studies up to 1 month with SOF were conducted to qualify impurities; fertility and pre- and post-natal developmental studies were performed in rats, and embryo-fetal developmental studies were conducted in rats and rabbits with SOF. Ames, *in vitro* chromosomal aberration and *in vivo* mouse micronucleus assays were conducted to assess genotoxicity. In addition, numerous *in vitro* and *in vivo* nonclinical pharmacokinetic studies, evaluating the absorption, distribution, metabolism and excretion of SOF have been conducted.

Myocardial inflammation and degeneration occurred in rats administered oral GS-9851 doses, a 1:1 mixture of SOF and its diasteriomer, of 2000 mg/kg/day in a 7-day toxicology study. Cardiac toxicity was not observed in rats administered oral doses of SOF up to 500 mg/kg/day for 6 months, or in dogs and mice administered SOF up to 500 and 1,000 mg/kg/day with corresponding exposures approximately 9-fold (rat), 27-fold (dog) and 41-fold (mouse) that in humans at the recommended SOF dose of 400 mg once daily. Nonetheless, cardiac effects seen in nonclinical studies were examined in clinical trials and will be summarized later in this memorandum; also see Dr. Poonam Mishra's Clinical Review.

Gastrointestinal (GI) hemorrhage occurred in male dogs administered oral SOF doses of 500 mg/kg/day at 3 and 6 months, corresponding to AUC exposures ~39 to 29-fold that in humans at the recommended SOF 400 mg once daily dose. Per Dr. Ellis' review, GI-related toxicities appear to be dose-dependent, however they could also be consistent with idiopathic hemorrhagic gastroenteritis of spontaneous origin. Notably, GI hemorrhage has not been observed in rats, mice or in clinical trials.

The conclusions of the Pharmacology/Toxicology review team are reflected in sections 8 and 13 of product labeling. SOF is a Pregnancy Category B drug as there are no adequate and well-controlled studies in pregnant women and no effects on fetal development have been observed in reproductive toxicology studies in two species. SOF was not genotoxic and carcinogenicity studies are ongoing. Since SOF will be administered with RBV with or without IFN, SOF labeling contains clinically important references to those labels.

5. Clinical Pharmacology: The Office of Clinical Pharmacology reviewers were Drs. Jenny H. Zheng, Su-Young Choi, Shirley Seo (Team Leader, Clinical Pharmacology), Jeffry Florian and Yaning Wang (Team Leader, Pharmacometrics), and Sarah Dorff and Mike Pacanowski (Team Leader, Pharmacogenomics).

Multiple clinical studies were conducted to characterize the pharmacokinetics (PK) of SOF and its predominant circulating metabolite GS-331007. This submission includes 22 studies with biopharmaceutic or clinical pharmacology data. Important findings from the review team are described thoroughly in their combined reviews and product labeling. Highlights include the following information:

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

- The administration of a single dose of SOF with a standardized high fat meal slowed the rate of absorption of SOF but did not substantially affect the extent of absorption. Therefore, SOF can be administered without regard to food.

- SOF is extensively metabolized in the liver to form the pharmacologically active, intracellular nucleoside triphosphate analog GS-461203. Dephosphorylation of the active metabolite results in the formation of the major circulating metabolite GS-331007, which cannot be efficiently rephosphorylated and lacks anti-HCV activity in vitro.

- The majority of the SOF dose recovered in urine was GS-331007 (78%) while 3.5% was recovered as SOF. These data indicate that renal clearance is the major elimination pathway for GS-331007.

- The median terminal half-lives of SOF and GS-331007 were 0.4 and 27 hours, respectively.

In addition to the data described above, an ongoing Phase 1 trial (GS-US-334-0146) is evaluating the effect of SOF on the PK of a representative hormonal contraceptive medication, norgestimate/ethinyl estradiol. Results from this study were not available for this submission. Therefore, labeling recommends that two effective non-hormonal methods of contraception be used during treatment with SOF and RBV. To collect data on pregnancy outcomes based on exposures to a SOF-based regimen, health care providers are requested to submit data to the Antiretroviral Pregnancy Registry as outlined in product labeling for HCV/HIV-1 coinfected subjects and to the Ribavirin Pregnancy Registry for other subjects receiving SOF in combination with RBV with or without PEG.

Regarding the potential for other interactions, SOF is a substrate of drug transporter P-gp and breast cancer resistance protein (BCRP) while GS-331007 is not. Drugs that are potent P-gp inducers in the intestine (e.g., rifampin or St. John's wort) should not be used with SOF because decreased SOF plasma concentrations are expected to lead to a reduced therapeutic effect. Coadministration of SOF with drugs that inhibit P-gp and/or BCRP may increase SOF plasma concentrations without increasing GS-331007 plasma concentrations such that SOF may be coadministered with P-gp and/or BCRP inhibitors. See Table 5 in product labeling for potentially significant drug interactions. Of note, no dose adjustment is needed for either SOF or the following drugs: cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

Use of SOF in specific populations is also described in labeling. No dose adjustment of SOF is required for patients with mild or moderate renal impairment. Recommendations can not be made for dosing in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end stage renal disease

(ESRD) requiring hemodialysis because these populations have not been fully studied. No dose adjustment of SOF is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C); however safety and efficacy of a SOF-based regimen have not been established in patients with decompensated cirrhosis.

The Applicant conducted a thorough QT study with SOF. The effect of SOF 400 and 1200 mg on the 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. This study was reviewed by the FDA's Interdisciplinary Review Team for QT Studies (IRT). The IRT concluded SOF's effect on QTc prolongation was below the threshold for regulatory concern and there appeared to be no clinically relevant effects on PR and QRS intervals.

6. Clinical Virology: Please see extensive reviews by Drs. Lisa Naeger and Eric Donaldson who conducted the review of virology and resistance data, including next generation sequencing (NGS) data with supervisory concurrence by Dr. Jules O'Rear. Resistance and cross-resistance wording appears in product labeling. In cell culture, HCV replicons with reduced susceptibility to SOF have been selected for multiple genotypes. Reduced susceptibility to SOF was associated with the primary NS5B substitution, S282T, in all replicon genotypes examined. Site-directed mutagenesis of the S282T substitution in replicons of 8 genotypes conferred 2- to 18-fold reduced susceptibility to SOF.

In Phase 3 clinical trials, 224 subjects had post-baseline NS5B genotypic data from NGS. The SOF-associated treatment-emergent resistance substitution S282T was not detected at baseline or in the failure isolates from Phase 3 trials. However, an S282T substitution with a mean 13.5-fold reduced susceptibility was detected in one GT2b subject enrolled in a Phase 2 trial who relapsed at Week 4 post-treatment after 12 weeks of SOF monotherapy. For this subject, the S282T substitution was no longer detectable at Week 12 post-treatment by NGS with an assay cut off of 1%. Treatment-emergent substitutions L159F (n= 6) and V321A (n= 5) were detected in GT3a-infected subjects in Phase 3 clinical trials, however no detectable shift in the phenotypic susceptibility to SOF was seen.

Product labeling contains the following wording related to resistance seen in the pre-transplant trial, P7977-2025, where subjects received up to 48 weeks of SOF and RBV: the L159F substitution emerged in multiple subjects with GT1a or GT2b HCV who experienced virologic failure (breakthrough and relapse). Furthermore, the presence of substitutions L159F and/or C316N at baseline was associated with sofosbuvir breakthrough and relapse post-transplant in multiple subjects infected with GT1b HCV. In addition, S282R and L320F substitutions were detected on-treatment by next generation sequencing in a subject infected with GT1a HCV with a partial treatment response.

The clinical significance of these substitutions is not known.

Addressing cross-resistance, HCV replicons expressing S282T were susceptible to NS5A inhibitors and RBV. HCV replicons expressing the RBV-associated substitutions T390I and F415Y were susceptible to SOF. Furthermore, SOF was active against HCV replicons with NS3/4A protease inhibitor, NS5B non-nucleoside inhibitor and NS5A inhibitor resistant variants.

Lastly, SVR rates in the SOF Phase 3 trials of GT1 subjects differed between subtype 1a and 1b with GT1a having an SVR rate of 92% and GT1b having an overall response rate of 82% in the NEUTRINO trial. In other development programs, it appeared that GT1b subjects had better SVR response rates. Our Clinical Virology team performed sequence and structural bioinformatics analyses to determine if amino acid differences between these two subtypes in the NS5B polymerase could account for the differences in efficacy. Per Dr. Donaldson, structural analysis showed that amino acid substitutions that add larger side chains at amino acid position 316 are predicted to interfere with SOF's ability to enter the active site and inhibit HCV RNA replication, by blocking the space required to accommodate the additional 2'Me and 2'F groups of SOF; whereas sequence analysis showed that C316N is the only difference in the active site between the HCV GT 1a and GT 1b NS5B polymerases, where C316 is highly conserved in GT 1a (99.89%) but polymorphic in GT 1b (81.83%). Dr. Donaldson concludes that substitutions at position C316 may contribute to reduced efficacy among subjects infected with HCV GT 1b.

7. Efficacy and Safety: Clinical reviews were conducted by Dr. Poonam Mishra with secondary review provided by Dr. Sarah Connelly. The Biometrics review was conducted by Dr. Karen Qi with secondary review provided by Dr. Wen Zeng and supervisory review provided by Dr. Dionne Price. The Phase 3 program encompasses multiple patient populations within GT1, 2, 3, 4, 5, and 6 who enrolled in six clinical trials.

Please refer to the Primary Clinical Review archived in DARRTS on September 06, 2013, and Dr. Connelly's cross-discipline team leader (CDTL) memorandum for detailed efficacy and safety analyses of these trials, including the pre-transplant trial and the addendum (archived November 20, 2013) to the original NDA review that contained review of VALENCE and PHOTON-1 trials. VALENCE provided data to support a 24-week treatment duration for GT3 subjects to improve relapse rates and PHOTON-1 provided data to support regimens for HCV/HIV-1 co-infected subjects along with an interferon-free regimen for GT1 subjects.

Genotypes 2 and 3

At the time of the original NDA submission, the primary clinical data supporting the use of SOF in combination with RBV for the treatment of GT2 and GT3 CHC viral infection came from three registrational Phase 3 trials:

- FISSION (P7977-1231) evaluating SOF/RBV treatment for 12 weeks in treatment-naïve subjects
- POSITRON (GS-US-334-0107) evaluating SOF/RBV for 12 weeks in subjects who were interferon intolerant, ineligible, or unwilling to take interferon
- FUSION (GS-US-334-0108) evaluating SOF/RBV for 12 or 16 weeks in treatment-experienced subjects

The primary efficacy endpoint, SVR12 and relapse rates for these trials are summarized in Table 1 below from Dr. Mishra's addendum to her primary review.

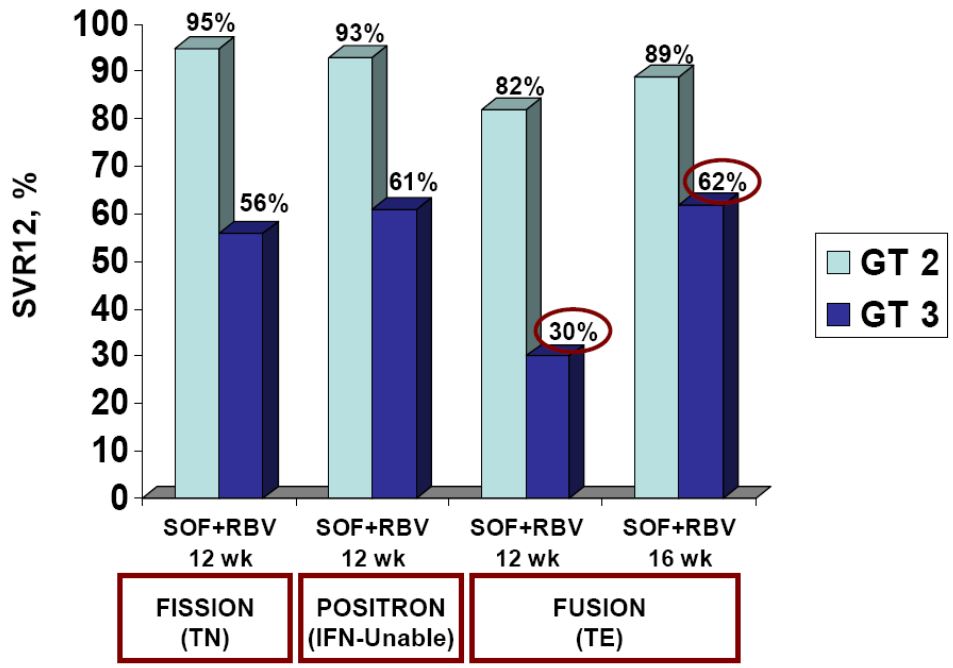
Table 1: Efficacy Data for Genotypes 2 and 3 (Phase 3 Trials - Original NDA Submission)

Trial	Treatment Regimens	n/N	SVR12
Trials in Subjects with Genotype 2 or 3 HCV Infection			
FISSION (P7977-1231) (Treatment-naive)	**SOF+RBV 12 weeks**		
	Genotype 2	69/73	95%
	Genotype 3	102/183	56%
	Relapse Rates GT2	**4/73**	**5%**
	Relapse Rates GT3	**72/179**	**40%**
POSITRON (GS-US-334-0107) (Intolerant, ineligible, or unwilling to take interferon)	**SOF+RBV 12 weeks**		
	Genotype 2	101/109	93%
	Genotype 3	60/98	61%
	Relapse Rates GT2	**5/107**	**5%**
	Relapse Rates GT3	**37/98**	**38%**
FUSION (GS-US-334-0108) (Treatment-experienced)	**SOF+RBV 12 weeks**		
	Genotype 2	32/39	82%
	Genotype 3	19/64	30%
	Relapse Rates GT2	**7/39**	**18%**
	Relapse Rates GT3	**42/64**	**66%**
	SOF+RBV 16 weeks		
	Genotype 2	31/35	89%
	Genotype 3	39/63	62%
	Relapse Rates GT2	**4/35**	**11%**
	Relapse Rates GT3	**24/63**	**38%**

Source: Clinical Review (Archived September 06, 2013)

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

Figure 1: SVR12 Rates for Genotypes 2 and 3



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

Notably, for the treatment-naïve GT2 population including those who are IFN-unwilling or ineligible, SVR rates were greater than 90%. For GT2 subjects who were treatment-experienced, SVR rates were 82% in subjects receiving 12 weeks of SOF/RBV. Relapse rates were 5-18% for these populations, respectively. GT3 subjects were more difficult to treat. SVR rates for GT3 naïve and experienced subjects were 56% for naïve subjects and 30% for treatment-experienced subjects also receiving 12 weeks of SOF/RBV. Extending treatment to 16 weeks in the treatment-experienced population of GT3 subjects yielded SVR rates of 62% with relapse rates of 38%.

Additional data were submitted during the initial NDA review from the ongoing non-IND Phase 3 VALENCE trial (GS-US-334-0133). FDA accepted these data because preliminary results that were to be presented at AASLD showed improved SVR rates and decreased relapse rates with longer treatment in the GT3 population. VALENCE evaluated SOF/RBV for the treatment of HCV genotypes 2 or 3 infection in treatment-naïve or treatment-experienced subjects, including subjects with compensated cirrhosis, with treatment durations of 12 or 24 weeks, depending on HCV genotype.

The following table is taken from Dr. Mishra's addendum to her original review.

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

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

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

SVR rates for the GT2 population enrolled in this trial were 97% and 90% for treatment-naïve and treatment-experienced subjects, respectively. The overall relapse rate in GT2 subjects was 7%. SVR rates for the GT3 population receiving 24 weeks of SOF/RBV were 93% and 77%, respectively for treatment-naïve and treatment-experienced subjects, respectively. GT3 relapse rates in subjects receiving 24 weeks of SOF/RBV were markedly decreased compared to rates based on 16 weeks of treatment. Overall, relapse rates were 14%.

Most treatment failures were attributed to relapse.

HCV Genotypes 1, 4, 5 and 6
NEUTRINO is a Phase 3, multicenter, open-label trial that enrolled treatment-naive subjects with CHC GT1, 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. Per Dr. Connelly's CDTL memorandum, the rationale for a single arm trial design with an historical comparison included the following: shorter duration treatment regimen compared to standard of care, no requirement for response-guided therapy compared with an HCV protease inhibitor (PI)-based regimen, the approximately 90% SVR12 rate from the Phase 2 ATOMIC trial, and the inclusion of non-GT1 subjects who are not part of any direct acting antiviral (DAA) labeled indication. For all of these reasons, it would be difficult to conduct a controlled trial. 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 the NEUTRINO regimen was believed to offer a clinical benefit to patients with respect to tolerability and ease of administration with a shorter treatment duration. Results are shown in the Table 8 from product labeling below:

Table 8 Response Rates in Study NEUTRINO

	SOVALDI + Peg-IFN alfa + RBV 12 weeks
	N=327[a]
Overall SVR	90% (295/327)
Genotype 1[b]	89% (261/292)
Genotype 1a	92% (206/225)
Genotype 1b	82% (54/66)
Genotype 4	96% (27/28)
Outcome for subjects without SVR	
On-treatment virologic failure	0/327
Relapse[c]	9% (28/326)
Other[d]	1% (4/327)

a. Seven subjects with genotype 5 or 6 infection are not included in the table.

b. One subject had genotype 1a/1b mixed infection.

c. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment.

d. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria (e.g., lost to follow-up).

Although the SVR rate for GT1 subjects was 89%, subjects with multiple baseline factors traditionally associated with a lower response rates to interferon-based treatment may approximate the response rate expected in patients who previously failed PEG/RBV therapy (a patient group not included in this NDA). The SVR rate in the NEUTRINO trial in GT1 subjects with IL28B non-C/C allele, HCV RNA >800,000 IU/mL and Metavir F3/F4 fibrosis was 71% (37/52).

According to the Draft Guidance for Industry on the Development of Direct-acting Antivirals for treatment of CHC infection, some DAA regimens may provide different efficacy for different genotypes. Clinical trial data should be sufficient to inform differences in responses between each of the most common genotypes and subtypes. Further, it is understood that enrollment of enough subjects with genotypes 4, 5, or 6 into trials to fully characterize responses may not be feasible, especially for trials conducted only in the United States. NEUTRINO enrolled only one subject with GT5 and six subjects with GT6. The numbers are too small to inform differences between various genotypes and therefore, product labeling will not contain an indication for this population.

In addition, Drs. Florian, Mishra and Qi's reviews contain modeling and simulation analyses to support use of the NEUTRINO regimen in GT1 subjects who previously failed PEG/RBV therapy.

GT 1, 2, and 3 HCV/HIV-1 Co-infection

GS-US-334-0123 (PHOTON-1) is an ongoing Phase 3, open-label, multicenter trial to evaluate the efficacy and safety of SOF/RBV in subjects with GT1, GT2, or GT3 HCV/HIV-1 coinfection that was submitted on October 9, 2013. It not only provides data in an important subgroup of patients co-infected with CHC and HIV-1, but review of the data will also allow for use of an IFN-free regimen for 24 weeks in subjects with CHC GT1 who are ineligible for an IFN-containing regimen.

Table 10 from Dr. Mishra's addendum shows the overall SVR12 rate for the three treatment groups and the SVR12 rate by HCV genotype in each group in PHOTON-1.

Table 10: Primary Efficacy Results (PHOTON-1 GS-US-334-0123)

	Group 1 GT2/3 TN SOF+RBV 12 Week (N=68)	**Group 2 GT2/3 TE SOF+RBV 24 Week (N=28)**	**Group 3 GT1 TN SOF+RBV 24 Week (N=114)**
Overall SVR12 95% CI	75% (51) (63%, 85%)	93% (26) (77%, 99%)	76% (87) (67%, 84%)
Genotype 1a SVR12 95% CI	n/a	n/a	82% (74/90) (73%, 89%)
Genotype 1b SVR12 95% CI	n/a	n/a	54% (13/24) (33%, 74%)
Genotype 2 SVR12 95% CI	88% (23/26) (70%, 98%)	93% (14/15) (68%, 99.8%)	n/a
Genotype 3 SVR12 95% CI	67% (28/42) (50%, 80%)	92% (12/13) (64%, 99.8%)	n/a

GT1 = genotype 1, GT2/3 = genotype 2/3, TN = treatment-naïve, TE = treatment-experienced
CI based on the Clopper-Pearson method
Source: FDA Statistical Reviewer

Findings in Group 1 (SOF/RBV 12 Weeks) for HCV GT 2 or GT3 treatment-naïve subjects were consistent with what had been observed in mono-infected trials, FISSION, POSITRON and VALENCE. Sample sizes in Group 2 were small and it may be difficult to draw definitive conclusions, however the SVR12 rate in the GT2 subjects was comparable to the rate seen in VALENCE in which GT2 treatment-experienced subjects received 12 weeks of SOF/RBV.

Treatment-naïve GT1 participants in Group 3 who received SOF/RBV for 24 Weeks had an overall SVR12 rate of 76%. A total of 90 (79%) subjects in Group 3 had HCV genotype 1a HCV and 24 (21%) subjects had HCV genotype 1b infection and the respective SVR12 rates were 82% in HCV genotype 1a subjects and 54% in HCV genotype 1b subjects. The relapse rate in this group was 22%. This regimen appears to have a lower SVR rate than the NEUTRINO triple regimen for 12 weeks in GT1 subjects, but could be used as an alternative in patients unable to take interferon. The regimen also provides evidence of safety and efficacy of SOF in co-infected subjects.

Relapse accounted for the majority of HCV virologic failures across the groups. Importantly, the majority of the subjects did not experience the protocol-specified HIV virologic rebound; only two subjects met the rebound criteria.

Safety

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Overall a total of 1548 HCV infected subjects received SOF in Phase 3 trials, of which 1221 received SOF in combination with RBV for 12, 16 and 24 weeks and 327 received the triple combination for 12 weeks.

I am in agreement with Drs. Mishra and Connelly that adverse reactions observed in SOF/RBV regimens are consistent with the known safety profile of RBV. I am also in agreement with the clinical team that adverse reactions observed in SOF/RBV/PEG regimens are consistent with the known safety profile of PEG/RBV.

A detailed safety evaluation was undertaken to assess cardiac toxicity in light of the fact that another investigational drug in the NS5B class had significant cardiac issues, although they were structurally dissimilar in that the other investigational agent is a guanosine analog whereas SOF is a uridine analog with a 2' fluorine in the α position. At this time, no specific safety concerns were identified in the safety data base related to cardiac toxicity. Exposure-response safety analyses by Dr. Jeffrey Florian for adverse events of dyspnea and cardiac disorders from the Phase 3 trials were conducted. This analysis revealed that

any grade dyspnea and any grade cardiac event were more likely in subjects with higher GS-331007 exposures. However, the significance of this relationship should be interpreted with caution because the overall cardiac event rate was small and lower than the PEG/RBV control arm. In addition, the adverse event listings under this system organ class were predominantly grade 1; only two events were grade 2. No events were related to cardiomyopathy. These adverse events were also confounded by concomitant administration of RBV which is known to cause hemolytic anemia. The Office of Safety and Evaluation (OSE) will assess post marketing safety reports related to cardiac issues.

In GT 2 and 3 subjects, the most frequently reported AEs in subjects in the SOF/RBV 12 Week and SOF/RBV 16 Week groups were: fatigue, headache, insomnia and nausea. Also, no notable differences in the safety profile were observed by extending treatment duration to 16 weeks in GT 2 and 3 subjects evaluated in FUSION. In VALENCE the most common AEs were fatigue, HA and nausea, occurring at a similar or decreased frequency in the SOF/RBV 24 Week group compared with the SOF/RBV 12 Week group.

Safety data for the SOF/PEG/RBV regimen in subjects with GT 1, 4, 5, and 6 HCV infection were evaluated in NEUTRINO. The three most common adverse events in this single-arm trial were: fatigue(59%), headache(36%), and nausea (34%).

Overall, an improved safety profile for the all-oral SOF/RBV regimens was noted as compared to PEG-based treatment regimens. The observed incidences of adverse events (any grade), Grade 3 or higher adverse events, and adverse events leading to permanent discontinuation, interruption or dose modification of the study drugs was lower in SOF- containing treatment regimens. The incidence of treatment emergent adverse events reported as related to study drug (by investigator's causality assessment) was low. No renal adverse events of concern have been identified to date. Mild elevations of serum creatine kinase values were noted without associated clinical symptoms. Asymptomatic elevations of lipase values were also noted. Gastrointestinal toxicity was seen in nonclinical studies and diarrhea (Grades 1 or 2) occurred approximately twice as frequent in the SOF/RBV 24 week treatment group compared with the SOF/RBV 12 Week treatment group in VALENCE.

Elevated bilirubin levels without transaminase elevations were consistent with hemolytic anemia associated with RBV use and no safety signals related to hepatotoxicity were identified. Further, no acute hypersensitivity reactions were seen and there were not any cases of Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN).

Changes in hematological parameters are outlined in Table 4 in product labeling. Total white blood cell counts to less than 1,500/mm^3 were observed infrequently. Among all subjects receiving treatment with SOF/RBV for 12 weeks or 24 weeks, a single subject experienced a decrease in white blood cells counts to less than

1,500/mm^3. Similarly, decreases in lymphocyte counts to less than 500/mm^3 were also infrequently observed. One percent of subjects in the SOF/RBV 12 week group and 2% of subjects in the SOF/RBV 24 week group had lymphocyte decreases to less than 500/mm^3. Changes in hematologic parameters will be monitored by OSE post-marketing.

Subjects with cirrhosis were enrolled in pivotal trials, however, decompensated cirrhotic subjects were excluded. According to Dr. Mishra's review, there was no apparent difference in the incidence of AEs that led to dose modification or interruptions in cirrhotic subjects compared with noncirrhotic subjects in the SOF/RBV 12 Week and SOF/RBV 16 Week groups. In the SOF/PEG/RBV group, anemia and neutropenia were reported at a higher rate in cirrhotics (32% and 22% respectively) compared with noncirrhotic subjects (19% and 15% respectively). There was a higher incidence of AEs leading to modification or interruption of study drug (PEG and/or RBV) in cirrhotic subjects as compared with non-cirrhotic subjects in the SOF/PEG/RBV group (44%, 24 subjects vs. 31%, 85 subjects). The overall incidence of total bilirubin abnormalities (all grades) was also higher in cirrhotic compared with noncirrhotic subjects. In the SOF/PEG/RBV group, the only difference in overall graded laboratory abnormalities between cirrhotics and non-cirrhotics was total bilirubin (35.2%, 19 subjects, vs. 14.7%, 40 subjects). A similar trend was observed for the PEG/RBV group (20.0%, 10 subjects vs. 8.9%, 17 subjects), which indicates that cirrhotic subjects appear to be more likely to develop hyperbilirubinemia in response to RBV-associated hemolytic anemia due to decreased hepatic function. Despite these findings, the benefits of using a SOF-containing regimen is supported in subjects with compensated cirrhosis.

The safety profile of SOF/RBV in other populations was similar to populations in FISSION, POSITRON, FUSION and NEUTRINO. The safety profile in HCV-infected subjects with HCC prior to liver transplantation in the ongoing Phase 2 trial was comparable to that observed in subjects treated with SOF/RBV in Phase 3 clinical trials, taking into account the more advanced stage of liver disease and/or the underlying disease progression in these subjects. Thus, the safety data in this population supports SOF/RBV up to 48 weeks or until liver transplantation. Similarly, the observed safety profile of SOF/RBV from VALENCE and PHOTON-1 is consistent with the previously noted adverse event profile in the Primary Clinical Review. In sum, the safety profile of SOF appears acceptable in multiple HCV-infected adult populations.

Deaths

In the completed and ongoing Phase 3 trials, there were two deaths within 30 days of the last treatment. One death was due to cocaine and heroin intoxication and one death was due to suicide that occurred 9 days after the last dose of study drug. Deaths beyond 30 days of treatment included 4 subjects with the following diagnoses: brain neoplasm, cardiogenic shock secondary to aortic stenosis, metastatic lung cancer and suspected overdose of medications used in the treatment of bipolar disorder.

In the pre-transplant trial, there were 5 deaths reported that appeared to be related to their underlying liver disease. Other deaths in the data base included one death in an access trial (a fatal variceal bleed) and 5 deaths reported in a Compassionate Use study. In addition, there were 2 deaths consisting of fatal trauma and fatal ischemic stroke in a Janssen-sponsored trial where SOF was used in as part of an antiviral combination. For a complete description of all deaths, please see Dr. Mishra's review.

8. Postmarketing Requirements (PMR):

Recommended Postmarketing Requirements include:

1. Evaluate the pharmacokinetics, safety and treatment response using SVR of SOF as a component of an antiviral treatment regimen in pediatric subjects 3 through 17 years of age with CHC. Dose selection and treatment duration for proposed pediatric subgroups must be agreed upon with the FDA prior to initiation of the trial(s).

2. Collect and analyze long-term safety data for subjects enrolled in the pediatric SOF PK, safety and efficacy trial(s). Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of SOF in pediatric subjects, including growth assessment, sexual maturation and characterization of SOF resistance-associated substitutions in viral isolates from subjects failing therapy.

3. Submit the final study report and datasets including next generation sequencing for the ongoing pre-transplant trial P7977-2025 in order to identify treatment-emergent substitutions and to obtain additional safety and efficacy data in this population with HCC meeting Milan criteria and awaiting liver transplantation.

4. Submit the final study report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg SOF/RBV for 24 Weeks in GT 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for CHC patients with severely impaired renal function.

5. Submit the final study report and datasets for the ongoing trial GS-US-334-0154, entitled, "A Phase 2b, Open-Label Study of 200 mg or 400 mg SOF/RBV for 24 Weeks in GT 1 or 3 HCV-Infected Subjects with Renal Insufficiency", in order to provide dosing recommendations for CHC patients with ESRD.

6. Submit the final study reports for the 2 year carcinogenicity studies.

7. Determine the phenotypic susceptibility of sofosbuvir against:

Genotype 1a
L159F
L159F + L320F
LI59F + C316N
C316N, H, and F
L320F, S282R, and L320F + S282R
D61G
D61G + N62H, D and N
Genotype 1b
L159F
L159F+L320F
L159F+C316N
C316N, H, and F
E440G
Genotype 2b
L159F
L159F+L320F
L159F+C316N
Genotype 3a
L159F
L159F+L320F
L159F+C316N
K211R
V321A
P540L
T542A

Recommended Postmarketing Commitments
8. Submit the final study report and datasets for the ongoing trial GS-US-334-0133 (VALENCE), entitled, “A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Efficacy and Safety of SOF/RBV for 12 Weeks in Treatment Naïve and Treatment Experienced Subjects with Chronic GT2 or 3 HCV Infection”.

9. Submit the final study report and datasets for the ongoing trial GS-US-334-0123 (PHOTON-1), entitled, “A Phase 3, Open-label Study to Investigate the Efficacy and Safety of SOF/RBV in Chronic GT1, 2 and 3 HCV and Human Immunodeficiency Virus (HIV) Co-infected Subjects”.

10. Submit the final study report and datasets for the ongoing trial GS-US-334-0109, entitled, “An Open-Label Study of SOF/RBV with or without Peginterferon Alfa-2a in Subjects with Chronic HCV Infection who Participated in Prior Gilead HCV Studies”.

11. Submit the final study report and datasets for the ongoing trial GS-US-334-0153, entitled, “A Phase 3B Randomized, Open-Label, Multi-Center Trial Assessing SOF/RBV for 16 or 24 Weeks and SOF/PEG/RBV for 12 Weeks in Subjects with GT2 or 3 Chronic HCV Infection”.

12. Submit the final study report and datasets for the ongoing trial GS-US-334-0126, entitled, “A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of SOF/RBV for 24 weeks in Subjects with Recurrent Chronic HCV Post Liver Transplant”.

13. Submit the final study report and datasets for the ongoing trial GS-US-334-0125, entitled, “A Phase 2, Multicenter, Open-Label, Randomized Study to Investigate the Safety and Efficacy of SOF/RBV Administered for 48 weeks in Patients Infected with Chronic HCV with Cirrhosis and Portal Hypertension with or without Liver Decompensation”.

14. Submit an interim study report from the ongoing trial GS-US-248-0122, entitled, “A Long Term Follow-up Registry for Subjects Who Achieve a SVR to Treatment in Gilead-Sponsored Trials in Subjects with CHC Infection”, with the three year follow-up data from: P7977-1231 (FISSION), GS-US-334-0107 (POSITRON), GS-US-334-0108 (FUSION), GS-US-334-0110 (NEUTRINO), GSUS-334-0133 (VALENCE), GS-US-334-0123 (PHOTON-1).

9. Advisory Committee: This NDA was presented before the Antiviral Products Advisory Committee on October 25, 2013. Transcripts are available.

The following questions were posed to the Committee:

1. 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: The committee voted 15 yes/0 no/0 abstentions on this question. The discussion centered on the favorable benefit-risk profile of SOF as part of an all-oral regimen.

2. 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: The committee voted 15 yes/0 no/0 abstentions on this question. The discussion centered on the favorable benefit-risk profile of SOF including the shortened treatment duration.

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

Two exploratory analyses were presented to explain FDA's approach. One analysis assumed that the overall increase in SVR from 50% in GT1 subjects receiving PEG/RBV to 89% SVR rates in responders to 12 weeks of SOF/PEG/RBV resulted from observed response rates in patients who were otherwise expected to be PEG/RBV treatment failures. The predicted SVR rate in the GT1 PEG/RBV treatment-experienced population was 78% (39/50). A second analysis examined selective baseline predictive factors. Some members accepted the extrapolation from the HCV GT1 treatment-naïve population with baseline factors predictive of lower PEG/RBV response in GT1 (e.g. high baseline HCV RNA, Metavir fibrosis score F3 or F4 and IL28B non-CC genotype) to the prior PEG/RBV nonresponder population to support use of SOF plus PEG/RBV in the latter population, given the high NEUTRINO SVR rates and general tolerability of the regimen. Other committee members stated more data are needed in the prior PEG/RBV nonresponder population. One member made a point that the currently available data suggest the SOF/PEG/RBV regimen is not expected to be less effective than currently approved therapy in the prior PEG/RBV nonresponder population.

4. 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?

The committee generally supported use of the P7977-2025 data for dosing recommendations in HCC patients meeting Milan criteria awaiting liver transplantation, but requested more data in the population with higher MELD scores.

Conclusions and Recommendations: This comprehensive NDA contained multiple clinical trials examining use of SOF plus RBV with or without PEG for different treatment durations in multiple patient populations of varying genotypes, including subjects with HCV/HIV-1 co-infection. SOF is an efficacious and well-tolerated drug that provides some of the highest SVR rates in certain populations, e.g. 92% SVR in GT1a subjects treated with SOF plus PEG/RBV for

12 weeks. It also provides, in combination with RBV, the first all-oral regimen for GT2 and GT3. There were adequate data from PHOTON-1 to support an interferon-free regimen for 24 weeks as a therapeutic option for subjects with CHC GT1 infection who are ineligible to receive an interferon-based regimen. Data were also reviewed that supported use of SOF in a pre-transplant population with HCC meeting Milan criteria awaiting liver transplantation. It is important to note that modeling and simulation data were used to support use of the NEUTRINO regimen in treatment-experienced GT1 subjects.

SVR represents a virologic cure and attainment of SVR depends on many factors including potency of an antiviral regimen, viral characteristics such as presence of baseline or emergent resistance substitutions, host factors such as IL28B genotype along with patient adherence and tolerability of a regimen. SOF in combination with other antiviral agents addresses many of these issues. SOF is dosed once daily and is also well tolerated. Of note, drug-drug interactions were limited.

I am in agreement with the conclusions of the multidisciplinary review team that the risk-benefit assessment favors approval of SOF as part of a combination regimen in adult patients with CHC. The review team was in agreement with a broad indication after supplemental information was reviewed from VALENCE and PHOTON-1 trials and after reconsidering the fact that treatment response varies and greatly depends on baseline host and viral factors. Although SOF will be indicated for multiple patient populations, there remains an unmet medical need for certain subpopulations such as those with recurrence of HCV infection post- liver transplant and those with decompensated cirrhosis.

In sum, I am confident that with the use of this drug in combination with an antiviral regimen, we will be able to positively address the burden of chronic hepatitis C.

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/s/

DEBRA B BIRNKRANT
11/27/2013