sNDA 204671 / SDN 377
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Clinical and Cross-Discipline Team Leader Review

Date	March 27, 2017
From	Melisse Baylor, M.D.
Subject	Clinical Review
Supplemental NDA #	204671 / Sequence Document Number 377
Applicant	Gilead Sciences, Incorporated
Date of Submission	October 27, 2016
PDUFA Goal Date	April 27, 2017
Proprietary Name/ Established (USAN) names	Sovaldi / sofosbuvir (SOF)
Dosage forms / Strength	Oral tablets: 400 mg
Proposed indication(s)	Pediatric Patients 12 years of age and older: For treatment of genotype 2 or genotype 3 HCV infection
Recommendation on Regulatory Action	Approval

1. Introduction

This combined Clinical and Cross Discipline Team Leader (CDTL) Review provides an overview of the submitted clinical data, summarizes the findings of the FDA-multi-disciplinary team of reviewers, describes the conclusions and recommendations presented by all disciplines, and provides an overall risk-benefit assessment of sofosbuvir use in adolescent patients. The data support extension of the indication to include the pediatric population of 12 years of age and older or weighing at least 35 kg with genotype 2 and 3 without cirrhosis or with compensated cirrhosis.

The application was granted a priority review for several reasons. The current standard of care for genotype 2 and 3 infection in pediatric patients is pegylated interferon and ribavirin. SOF in combination with ribavirin offers the first interferon free regimen for genotypes 2 and 3 in pediatric patients. SOF ribavirin regimen is considered an advancement in pediatric HCV therapy both in terms of improved efficacy over interferon and ribavirin and devoid of the interferon related toxicities such as bone marrow depression, flu-like symptoms, neuropsychiatric disorders, autoimmune syndromes and effects on growth

2. Background

Sovaldi (sofosbuvir), a nucleotide inhibitor of HCV virus NS5B polymerase, was approved for use in adults with chronic HCV infection on December 6, 2013. Sofosbuvir was approved for use in combination with ribavirin (RBV) for the treatment of chronic HCV in adults with genotype 2 and 3 infection and in combination with pegylated interferon (IFN) and ribavirin for the treatment of chronic HCV in adults with genotype 1 and 4 infection. The approval was based on clinical data from five studies. Treatment-naïve subjects with genotype 2 received 12 weeks of SOF and RBV in the Phase 3 pivotal trial Study 1231. The sustained virologic response (SVR12) defined as the percentage of subjects with HCV RNA levels less than the lower level of quantification (LLOQ) 12 weeks after discontinuation of treatment was 95% compared to 78% for subjects who received IFN and RBV for 24 weeks. In Study 108, the SVR12 for treatment-

experienced subjects with genotype 2 was 82%. Subjects with genotype 3 received 24 weeks of SOF plus RBV in Study 133; the SVR12 for treatment-naïve subjects was 93% and for treatment-experienced subjects was 77%. Treatment-naïve adults with genotype 1 and 4 were studied in Study 110 and the SVR12 in these populations were 89% and 96%, respectively.

Sovaldi is indicated for use in patients without cirrhosis or with compensated cirrhosis. The efficacy of SOF in adults with and without cirrhosis was demonstrated in the pivotal studies of SOF. However, the SVR12 was typically lower in subjects with compensated cirrhosis compared to those without cirrhosis. For example, in Study 1231, the SVR12 for subjects who had genotype 2 without cirrhosis and who received SOF and RBV was 97%; while in subjects with genotype 2 who had cirrhosis and received SOF and RVB, the SVR12 was 83%. However, the SVR12 was significantly higher compared to the SVR12 observed in control subjects with genotype 2 without cirrhosis who received IFN and RBV (81%) and in those with genotype 2 and cirrhosis who received IFN and RBV (62%). Population pharmacokinetic (PK) analyses in HCV-infected subjects have demonstrated similar exposures in subjects with and without cirrhosis, and no dose adjustment is recommended for patients with mild, moderate, and severe hepatic impairment.

Up to forty-six thousand children are chronically-infected with HCV in the United States. Most of these children were infected in infancy via mother-to-child transmission. Left untreated over decades, HCV-infected patients are at high risk for cirrhosis, hepatocellular carcinoma, liver failure, and HCV-related death. The primary goal of treating HCV in children is to prevent HCV-related complications from occurring during childhood or later in adulthood. Although progression to cirrhosis typically takes place over a period of 10-30 years, four to five percent of HCV-infected children develop advanced liver fibrosis or cirrhosis during childhood, some of whom develop advanced liver disease requiring liver transplantation (Mack CL, Gonzales-Peralta RP, Gupta N, et al. NASPGAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterology; 54(6):838-855, 2012.). In addition, chronic HCV is associated with extrahepatic disorders in children including glomerulonephritis and central nervous system HCV infection, which has been associated with developmental delay, learning disorders and cognitive deficits (Mack 2012).

Currently available treatment for adolescents with chronic HCV infection is limited to pegylated interferon (IFN) and ribavirin combination therapy. Approximately 75% of patients who received IFN and RBV will experience at least one adverse event, 10-20% of patients will prematurely discontinue IFN and RBV, and 20-30% will require dose modification of one of the two drugs. IFN-related toxicities include bone marrow depression, flu-like symptoms, neuropsychiatric disorders, and autoimmune syndromes. The main toxicity associated with ribavirin is hemolytic anemia. (Manns MP, Wedemeyer H, and Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. Gut, 55(9):1350-1359, 2006.). Weight loss and reduced height growth have been observed in children receiving IFN and RBV. [Jonas MM, Balistreri W, Gonzalez-Peralta RP, et al. Pegylated interferon for chronic hepatitis C in children affects growth and body composition: results from the pediatric study of hepatitis C (PEDS-C) trial. Hepatology, 56(2):523-531, 2012.]

Although direct acting antivirals (DAA) have been FDA-approved for treatment of chronic HCV infection in adults since 2011, none have been approved for use in pediatric patients. Treatment of chronic HCV with DAAs has resulted in shorter duration of treatment than with IFN and RBV regiments, higher percentages of subjects with SVR compared to IFN and RBV, and has allowed for IFN-free treatment. The current treatment recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America for

first line treatment for all HCV genotypes, regardless of the presence or absence of cirrhosis, are DAAs. Therefore, it is important to have DAAs available for treatment of chronic HCV infection in adolescents.

In this supplemental NDA, Sofosbuvir was evaluated in a single open-label, uncontrolled, pharmacokinetic (PK), safety, and efficacy trial in 50 adolescent subjects in 28 centers in seven countries. An open-label, uncontrolled design was acceptable because of the high SVR12 rates reported in adult subjects treated with SOF and RBV regimens compared to IFN- and RBV-containing regimens without SOF and in order to avoid the toxicity associated with use of IFN-containing regimens. Electronic materials submitted included, interim Clinical Study Report (CSR) for post-treatment Week 12 data and datasets as SAS transport files.

This pediatric supplement partially fulfills the single outstanding post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA):

> PMR # 2110-1:
> The study is a deferred pediatric study under PREA for the treatment of chronic hepatitis C virus (HCV) infection in pediatric subjects 3 through 17 years of age. The trial will collect long-term safety data for subjects enrolled in the pediatric SOVALDI (sofosbuvir) pharmacokinetic, 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 sofosbuvir in pediatric subjects, including growth assessment, sexual maturation and characterization of sofosbuvir resistance-associated substitutions in viral isolates from subjects failing therapy.

The applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the applicant, the pivotal trial was conducted in conformance with Good Clinical Practice standards and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The Division did not consult the Office of Scientific Investigations for inspection of the trial sites.

The applicant also submitted financial information pertinent to the application. There were 29 principal investigators and 104 subinvestigators; none were employees of Gilead Sciences. None of the investigators received compensation where the value could have influenced the outcome of the study, none received payments greater than $25,000, none held proprietary interested in the study drug, and none held significant equity interest in Gilead Sciences. Therefore, the conduct of this trial complied with the regulations as defined in 21 CFR 54.4(a)(3)(i), 54.2(a). Please see the Clinical Investigator Financial Disclosure Review Template in Section 15 of this review.

3. CMC

A new formulation was not developed for use in adolescents. As a result, no new product information regarding drug substance or manufacturing was submitted. Please refer to the original review of NDA 204671 for additional information on chemistry and manufacturing.

4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original review of NDA 204671 for details. However, Sections 8.1 Pregnancy, 8.2 Lactation, and 8.3

Females and Males of Reproductive Potential were revised in accordance with FDA's Pregnancy and Lactation Labeling Rule (PLLR).

5. Clinical Microbiology

Please see both the original NDA review and Dr. Naeger's review of this supplemental NDA for a detailed assessment of the clinical microbiology data.

Of the 50 adolescent subjects in Trial GS-US-334-1112, the only trial in this sNDA, 49 achieved a sustained virologic response. The remaining subject did not return for the Week 12 post-treatment visit. No subjects experienced viral breakthrough or viral relapse; therefore, resistance to SOF could not be assessed.

6. Clinical Pharmacology / Biopharmaceutics

Trial GS-US-334-1112

Refer to the USPI and reviews from the original NDA for details of adult pharmacokinetics. Please see Dr. Zheng's Clinical Pharmacology review of this application for additional information.

As stated previously, sofosbuvir administered in combination with interferon alpha and ribavirin for 12 weeks, is indicated for the treatment of adults infected with chronic HCV due to genotypes 1, or 4. Sofosbuvir in combination with ribavirin for 12 weeks is indicated for treatment of patients with HCV genotype 2, and sofosbuvir plus ribavirin for 24 weeks is indicated for treatment of HCV due to genotype 3. The recommended dose for adults of 400 mg daily is used in the treatment of all four genotypes. The dose evaluated in adolescents in Trial GS-US-334-1112 was 400 mg. SOF was administered as a single 400 mg tablet in 44 of 50 subjects, as four 100 mg tablets in 5 subjects, and as granules in water in one subject. Only five adolescents received 100 mg tablets in this study; however, the PK of 100 mg tablets is expected to be the same as that with 400 mg tablets because all ingredients are dose proportional between the two tablet strengths and the manufacturing processes are the same for the two tablet strengths. Only a single adolescent subject received SOF as granules, so the sample size was too small to evaluate the pharmacokinetics of the granule formulation in the adolescent study. However, the granule formulation has been compared to the tablet formulation in a relative bioavailability study in healthy adults. While the results of this study have not been reviewed by FDA, the applicant stated that the GS-331007 exposures were bioequivalent between the granule and 400 mg tablet formulations. Although there was insufficient PK data to evaluate differences in PK by formulation in adolescent subjects in Trial GS-US-3334-112, data from adult PK studies support bioequivalence of the 400 mg tablet, the 100 mg tablet, and the granule formulation. The SVR12 results (see efficacy section) provide further supportive data to demonstrate efficacy. Any differences in the pharmacokinetics for the formulations did not appear to impact efficacy, albeit only 50 pediatric patients were evaluated. The 400 mg tablet is the marketed formulation to date.

All subjects were started on 400 mg daily of SOF with RBV dosed by weight. During the PK lead-in phase of the study, serial blood samples for PK were collected on Day 7 from 10 adolescent subjects with chronic HCV to determine the PK of SOF and its metabolite, GS-331007. Blood samples were also obtained for PK analysis at each study visit for all 50 subjects. The primary PK endpoint was AUC_{tau} of SOF and its main metabolite, GS-331007, which was compared to the exposures observed in Phase 2 and Phase 3 studies in adults. The mean SOF AUC_{tau} in adolescents was 1157 h·ng/mL compared to a mean AUC_{tau} in adults (N=28) from Phase 2 and 3 studies of 1027 h·ng/mL. The mean GS-331007 AUC_{tau} in

adolescents was 7969 h·ng/mL compared to a mean GS-331007 AUC_{tau} in adults of 7123 h·ng/mL.

Population PK modeling in adults identified baseline clearance to be the major statistically significant covariate for the PK of GS-331007. The effect of clearance on the PK of SOF was minimal. Therefore, the exposures of SOF and GS-331007 were compared across baseline eGFR quartiles. The mean AUC_{tau} for GS-331007 ranged from 10136 h·ng/mL in subjects with the lowest eGFR to 6623 h·ng/mL in subjects in the highest quartile eGFR. The difference in mean AUC_{tau} for SOF exposures from the lowest to the highest eGFR quartile was lower and ranged from 1241 h·ng/mL to 903 h·ng/mL. Although differences in exposures for GS-331007 and SOF were higher in subjects with lower eGFRs, the differences in exposure were not considered clinically significant.

Because the exposures in adolescents receiving sofosbuvir 400 mg daily were similar to the exposures observed in adults who received 400 mg daily and because there was no clinically relevant differences in SOF exposure across a range of renal function, the dose identified for use in adolescents was 400 mg daily. The data from adult PK trials demonstrate that differences in the pharmacokinetics of SOF in subjects with cirrhosis are not clinically relevant and the same dose is used in adults with or without cirrhosis. In addition, the PK of SOF was similar in adults and adolescents. Therefore, the 400 mg daily dose is acceptable for use in adolescents with and without evidence of cirrhosis.

7. Clinical / Statistical – Efficacy

As stated previously, the sNDA was submitted to partially fulfill the outstanding PREA PMR which required efficacy data through post-treatment Week 12. The data for adolescent subjects were submitted in an interim Clinical Study Report. The final study report will include safety and efficacy data for subjects from 3 years to <18 years of age and will address the entire pediatric population requested in the PREA PMR. When the study is complete, efficacy will be followed for 24 Weeks post-treatment for all age groups, and safety of the study subjects will be followed for 5 years.

Overview of Trial Design

Trial GS-US-334-1112 is an ongoing two-phase, pharmacokinetic, safety, and efficacy study of sofosbuvir and ribavirin for the treatment of pediatric subjects with genotype 2 or 3 chronic HCV infection. The trial is designed to enroll pediatric subjects from 3 to <18 years of age sequentially by descending age cohort. The first cohort enrolled adolescent subjects, 12 to <18 years of age. Collection of safety and efficacy through week 12 after the completion of treatment for this age cohort was completed in June 2016 and was submitted as an interim Clinical Study Report to support the safety and efficacy of sofosbuvir in adolescents.

The trial was conducted in two phases. The first phase was a pharmacokinetic (PK) lead-in phase, and the second was a treatment phase. The primary objective of the pharmacokinetic lead-in phase was to evaluate the steady state PK and confirm the dose of SOF in HCV-infected pediatric patients. See the Clinical Pharmacology section of this review and the Clinical Pharmacology/Biopharmaceutics review for a discussion of the pharmacokinetic results of the study. The second part of the study was the treatment phase; the primary objective of the treatment phase was to evaluate the safety and tolerability of treatment with SOF and ribavirin (RBV) for 12 weeks in HCV-infected pediatric subjects infected with genotype 2 and for 24 weeks in subjects with genotype 3.

The trial enrolled adolescents from 12 to <18 years of age who had one of the following in the previous six months: positive anti-HCV antibody test, positive HCV RNA, or positive HCV genotyping. Subjects had an HCV RNA level ≥ 1,000 IU/mL. Subjects had to have a screening absolute neutrophil count ≥ 1500/mm^3; male subjects also had to have a hemoglobin ≥ 12 g/L while females had to have a hemoglobin ≥ 11 g/dL. In the PK lead-in phase, subjects had to weigh 45 kilograms or more and be treatment naïve. Treatment-experienced subjects who had failed a regimen that included interferon (with or without RBV) and had completed their treatment regimen eight weeks or more prior to Day 1 were allowed to enroll in the treatment phase. Subjects co-infected with HIV, acute hepatitis A, or hepatitis B were excluded from trial participation. Subjects with decompensated liver disease, defined as INR > 1.2 times the upper limit of normal, platelets <50,000 mm^3, albumin < 3.5 g/dL, or history of clinical hepatic decompensation (ascites, jaundice, encephalopathy, or variceal hemorrhage) were also excluded. Subjects with alpha-fetoprotein > 50 ng/mL, serum creatinine > 1.5 mg/dL or eGFR < 90 mL/min/1.73 m^2 were excluded from the trial.

In the PK lead-in phase, subjects received SOF 400 mg orally once daily in combination with ribavirin. RBV was administered by tablet or oral solution and was dosed by weight as shown in the following table.

Table 1: Dosage of Ribavirin by Weight

Weight	Ribavirin Dose
< 50 kg	15 mg/kg twice daily
50 kg - < 65 Kg	40 mg twice daily
65 kg - < 75 kg	400 mg in the morning and 600 mg in evening
≥ 75 kg	600 mg twice daily

Source: Clinical Study Protocol GS-US-334-1112: Text. Page 32.

On day 7 of the PK lead-in phase, blood for intensive pharmacokinetic analysis was obtained and safety was assessed.

Subjects in the PK lead-in phase immediately rolled over into the treatment phase without interruption in study treatment. After analysis of the PK data from the PK lead-in phase and identification of the appropriate SOF dose in adolescents (400 mg daily), additional subjects were enrolled directly into the treatment phase.

Blood was obtained for analysis of HCV RNA levels at screening and on Days 1, 3, and 7 of the PK lead-in phase. In subjects with genotype 2, who received 12 weeks of treatment, blood for HCV RNA levels was also obtained at weeks 2, 4, 8, and 12 during treatment, and at post-treatment weeks 16, 20 and 24. In subjects with genotype 3, who received 24 weeks of treatment, blood for HCV RNA levels was also obtained at weeks 2, 4, 8, 12, 16, 20, and 24 during treatment, and at post-treatment weeks 16, 20 and 24.

The primary efficacy endpoint was sustained virologic response (SVR12), defined as HCV RNA less than the lower limit of quantification (LLOQ), 12 weeks after discontinuation of study drug. The primary population for evaluation of the primary efficacy endpoint was the Full Analysis Set. Secondary efficacy endpoints included sustained SVR 4 weeks after discontinuation of study treatment, SVR 24 weeks after discontinuation of study treatment, proportion of subjects with HCV RNA less than LLOQ by study visit, change in HCV RNA from baseline, and percentage of subjects with virologic failure. The interim Clinical Study Report includes efficacy and safety results through 12 weeks after discontinuation of the study treatment and is sufficient to

determine approvability; results for SVR 24 weeks after study treatment discontinuation will be submitted at a later date.

The primary statistical analysis of efficacy was descriptive. However, the results for SVR12 were also compared to historical data in which the SVR12 for children and adolescent patients receiving an interferon-containing regimen for chronic HCV was 80% (Wirth S. Current treatment options and response rates in children with hepatitis C. World J Gastroentero. 14; 18(2):99-104). With 50 total adolescents enrolled in this age cohort and an estimated SVR12 rate of 80%, the two-sided 95% confidence interval would extend to 11.1% at most in both directions.

Safety was monitored by assessment of adverse events, clinical safety laboratory tests, Tanner staging, and growth. Safety was analyzed using descriptive statistics.

Trial GS-US-334-1112 was reviewed for efficacy, safety and tolerability, and pharmacokinetics. Subject demographics and baseline characteristics, clinical and laboratory adverse events, as well as safety and efficacy results were reviewed using JMP Statistical software.

Disposition
Sixty-six subjects were screened; 50 of these were enrolled and received study drug. This included 10 subjects who were enrolled in the PK lead-in phase and continued into the treatment phase and an additional 40 subjects who were enrolled directly into the treatment phase. All 50 subjects completed treatment. Two of the 50 subjects did not attend their week 12 post-treatment visit but continued in the study. Data for HCV RNA levels are missing for these two subjects at the week 12 post-treatment visit; however, the HCV RNA levels for weeks 8 and 24 are available for one of the two subjects allowing for imputation of the results at Week 12.

Demographics and Baseline Characteristics
The Full Analysis Set included all 50 subjects. Of the 50 subjects, 13 were infected with genotype 2 HCV and 37 with genotype 3. Demographics and baseline characteristics are shown in the following table.

Table 2: Demographics and Baseline Characteristics

	Genotype 2	**Genotype 3**	**Total**
Number of Subjects	13	37	50
Mean Age (years)	15	15	15
Sex: Number (Percentage)			
Male	8 (6.5%)	21 (57%)	29 (58%)
Female	5 (38.5%)	16 (43.2%)	21 (42.0%)
Race: Number (Percentage)			
White	11 (85%)	34 (91%)	45 (90%)
African American or Black	2 (15.4%	0	2 (4.0%)
Asian	0	1 (2.7%)	1 (2.0%)
Hawaiian or Pacific Islander	0	1 (2.7%)	1 (2.0%)
Other	0	1 (2.7%)	1 (2.0%)
Ethnicity: Number (Percentage)			
Hispanic or Latino	0	2 (5.4%)	2 (4.0%)
Not Hispanic or Latino	13 (100%)	35 (94.6%)	48 (96.0%)

Source: Clinical Study Report GS-US-334-1112: Table 9-4. Page 78.

The demographics and baseline characteristics were similar between the subjects with genotype 2 and genotype 3.

In the PK lead-in phase, subjects had to weigh ≥45 kilograms; however, there was no entry criterion regarding weight for the treatment phase. All subjects received 400 mg daily regardless of weight; therefore, subjects who weigh less may have had higher SOF exposures and more safety concerns. An analysis of subject weight is shown in the following table.

Table 3: Baseline Weights

	Genotype 2	Genotype 3	Total
Number of Subjects	13	37	50
Median Weight (kgs) **(IQR)**	57.3 47.5, 62.25	62.3 51.0, 68.35	67.5 49.8, 67.47
Number with weight ≥ 45 kg	11 (85%)	36 (97%)	47 (94%)
Number with weight < 45 kg	2 (15%)	1 (3%)	3 (6%)

Source: Clinical Study Report GS-US-334-1112: Vital Signs Dataset.

The overwhelming majority of subjects weighed 45 kilograms or more. Two subjects with genotype 2 and one with genotype 3 weighed less than 45 kg; the subjects with genotype 2 who were <45 kg weighed 29.6 kilograms and 38 kilograms and the subject with genotype 3 weighed 42 kilograms. See the safety section of this review for a description of adverse events in these subjects.

Baseline HCV disease characteristics are shown in the following table.

Table 4: Baseline HCV Disease Characteristics

	Genotype 2	Genotype 3	Total
Number of Subjects	13	37	50
HCV Genotype			
2	6 (46%)	0	6 (12%)
2b	5 (38.5%)	0	5 (10%)
2a/c	2 (15.4%)	0	2 (4%)
3	0	1 (2.7%)	1 (2%)
3a	0	36 (97.3%)	36 (72%)
Mode of Infection*: Number (Percentage)			
Vertical	8 (51%)	28 (73.7%)	36 (69.2%)
Blood product transfusion	0	5 (13.2%)	5 (9.6%%)
Past IV drug abuse or contaminated needle	1 (7.1%)	0	1 (1.9%)
Surgery/operation	0	1 (2.6%)	1 (1.9%)
Unknown	5 (35.7%)	4 (10.5%)	9 (17.3%)
Cirrhosis			
No	4 (30.8%)	16 (43.2%)	20 (40%)
Unknown	9 (69.2%)	21 (56.8%)	30 (60%)
IL28B Gene: Number (Percentage)			
CC	3 (23.1%)	16 (43.2%)	19 (38%)
CT	9 (69.2%)	19 (51.4%)	28 (56%)
TT	1 (7.7%)	2 (5.4%)	3 (6%)
Prior HCV Treatment			
Treatment naïve	13 (100%)	28 (75.7%)	41 (82%)
Treatment experienced	0	9 (24.3%)	9 (18%)
Response to Treatment in Treatment Experienced Subjects			
Non-responder	0	6 (66.7%)	6 (12%)
Relapse/breakthrough	0	2 (22.2%)	2 (4%)
IFN intolerant	0	1 (11.1%)	1 (2%)
Mean HCV Baseline RNA (log10 IU/mL)	5.9	6.2	6.1
HCV Baseline RNA Range (log_{10} IU/mL)	3.6-6.9	4.5-7.3	3.6-7.3
Mean Baseline ALT (U/L)	37	61	55
Baseline ALT Range (U/L)	10-108	12-296	10-296

*Two subjects were infected by more than one mode of transmission
Source: Clinical Study Report GS-US-334-1112: Table 9-5. Pages 79-80.

Subjects with genotype 2 were primarily infected with genotype 2 or 2b, and the majority of subjects with genotype 3 were infected 3a. Most subjects (69%) with a known method of transmission were infected through vertical transmission. The majority of subjects (69% with genotype 2 and 51% with genotype 3) had the CT IL28B allele; 23% of subjects with genotype 2 and 43% with genotype 3 had the CC allele, and less than 8% of subjects had the TT allele. Mean baseline HCV RNA and ALT levels were slightly higher in subjects with genotype 3 (6.2 log_{10} IU/mL and 61 IU/L, respectively) compared to in subjects with genotype 2 (5.9 log_{10} IU/mL and 37 IU/L respectively). This could have been related to the enrollment of treatment-

experienced subjects with genotype 3 (24.3%) but not with genotype 2; all subjects with genotype 2 were treatment-naïve. There were no subjects with documented cirrhosis in the study.

Efficacy Results at Week 12 after Discontinuation of Treatment
The primary efficacy endpoint was the SVR12, defined as the HCV RNA<LLOQ 12 weeks after discontinuation of the study drug. The SVR12 for the 13 subjects with genotype 2 was 100% (95% CI:75.3%, 110%) and for the 37 subjects with genotype 3 was 94.6% (95% CI:81.8%, 99.3%). One subject with genotype 3, who did not attend the post-treatment week 12 visit, had HCV RNA levels <LLOQ at the last treatment visit (Week 24) and at post-treatment week 16, allowing for imputing the post-treatment week 12 results to <LLOQ. Therefore, the SVR12 rate for subjects with genotype 3 is 97%. Although the primary statistical analysis of SVR12 was descriptive, the SVR12 for genotype 2 and 3 were higher than the historical control of 80% in children and adolescents who received 24 weeks of RBV and IFN to treat chronic HCV.

Further analysis of the primary endpoint by subgroup (race, ethinicity, gender, etc) is not possible because all subjects who returned for the post-treatment week 12 visit had a sustained virologic response.

The SVR at different endpoints was a secondary efficacy endpoint. SVR at each on treatment study visit is shown in the following table. As demonstrated in this table, there were no treatment breakthroughs and no treatment failures.

Table 5: Number and Percentage of Subjects with Sustained Virologic (SVR) by On Treatment Visit and by Genotype

	Genotype 2	**Genotype 3**
Number of Subjects		
Week 2	13 (100%)	28 (75.7%)
Week 4	13 (100%)	35 (94.6%)
Week 8	13 (100%)	37 (100%)
Week 12	13 (100%)	37 (100%)
Week 16	NA	37 (100%)
Week 20	NA	37 (100%)
Week 24	NA	37 (100%)

Source: Clinical Study Report GS-US-334-1112: Table 9-6. Pages 81-82.

Response to treatment with SOF plus ribavirin occurred soon after the start of treatment in all subjects with genotype 2 and in the majority of subjects with genotype 3. This is further supported by the mean change from baseline in HCV RNA levels from baseline to one week after starting treatment: -4.25 $\log_{10}$ IU/mL for subjects with genotype 2 and -4.13 $\log_{10}$ IU/mL for subjects with genotype 3. The mean decrease in HCV RNA from baseline to the end of treatment for subjects with genotype 2 was -5.03 $\log_{10}$ IU/mL and for subjects with genotype 3 was -4.74 $\log_{10}$ IU/mL.

Efficacy Summary and Conclusions
The efficacy of sofosbuvir in combination with ribavirin in adolescents with chronic HCV due to genotype 2 or 3 was demonstrated in this single arm, uncontrolled trial. At 12 weeks after discontinuation of study treatment, a sustained virologic response was demonstrated in 100% of subjects with HCV due to genotype 2 and in 97% of subjects with HCV due to genotype 3; the

response rate is consistent with the antiviral response observed in studies of treatment-naive adults.

In summary the exposure data from the PK analyses support the 400 mg daily dose in pediatric patients 12 years of age and older with and without cirrhosis, and the efficacy outcome as measured in Trial GS-US-334-1112 by sustained virologic response 12 weeks after discontinuation of treatment are consistent with results observed during trials of treatment-experienced adults. Therefore, these results support the antiviral activity of sofosbuvir in combination with ribavirin in treatment of adolescents with chronic HCV genotype 2 or genotype 3 infection.

8. Safety

The data submitted support the safety and tolerability of sofosbuvir in combination with ribavirin in adolescents with chronic HCV infection. The applicant has submitted safety data from 50 adolescent subjects who received at least one dose of SOF in Trial GS-US-331-1112. The duration of follow-up was 12 weeks after discontinuation of treatment for all 50 subjects. The types of adverse events observed were similar to the types of AEs observed in adults with chronic HCV infection who received SOF and RBV in Phase 3 studies. The study was not powered or designed to have an active comparator arm, nor was there a pre-specified number of subjects required for testing statistical differences in AE incidences. Descriptive statistics were therefore applied to describe the observed findings.

Duration of Treatment

Subjects enrolled in Trial GS-US-334-1112 are to be followed for safety for five years. The interim Clinical Study Report summarized the safety data for the 12 or 24 week on treatment period along with safety data for 12 weeks after the end of treatment. Safety data for 24 weeks and 36 week are available for subjects with genotype 2 and genotype 3, respectively. All subjects completed the study and 12 week post-treatment period and thereforeall 50 subjects were included in the safety evaluation.

Deaths and Other SAEs

There were no deaths up to week 12 post-treatment. There were no serious adverse events.

Discontinuations due to Adverse Events

There were no discontinuations due to adverse events.

There were no adverse events due to sofosbuvir that lead to treatment interruption. One subject had temporary interruption of ribavirin due to an adverse event that was judged as ribavirin-related.

Adverse Events with Severe or Life-threatening Intensity

All AEs were Grade 1 or 2 in severity except for one Grade 3 adverse event, which was due to shoulder trauma (joint injury) that was not considered related to study treatment.

Common Adverse Events

A total of 46 adverse drug reactions (ADRs), e.g., adverse events considered sofosbuvir-related, as assessed by the investigator, were reported in 22 (28.1%) subjects through 12 weeks post-treatment. There were no ADRs reported in more than one subject with genotype 2. ADRs reported in at least 2 subjects with genotype 3 are shown in the following table. Even though ADRs for genotype 2 subjects did not meet the criteria for inclusion in this table, the ADRs for this group are included for completeness. Because the period of safety follow-up

differed for genotype 2 and genotype 3, pooling results for the two groups is not appropriate and results for the total group are not included in the table.

Table 6: Adverse Drug Reactions (ADRs) Reported in at Least 2 Subjects through Week 12 Post-Treatment

	Genotype 2	Genotype 3
Total Number of Subjects	13	37
Number (Percentage) of Subjects with ADR	3 (21%)	19 (51.5%)
Nausea	0	7 (18.9%)
Headache	0	5 (13.5%)
Asthenia	1 (7.7%)	4 (10.8%)
Fatigue	0	3 (8.1%)
Upper abdominal pain	0	2 (5.4%)
Alopecia	0	2 (5.4%)
Decreased appetite	0	2 (5.4%)
Dizziness	0	2 (5.4%)
Vomiting	1 (7.7%)	1 (2.7%)
Diarrhea	1 (7.7%)	0

Source: Clinical Study Report GS-US-334-1112: Table 11-4. Page 92 and AE Dataset.

The ADRs reported were all Grade 1 or 2 in intensity; there were no Grade 3 or 4 AEs or SAEs that were judged as sofosbuvir–related.

In adult studies of subjects who received SOF and RBV for the treatment of chronic HCV, the most commonly reported ADRs were fatigue, headache, and nausea. (See Sovaldi package insert). The ADRs reported in Trial GS-US-334-1112 were consistent with those reported in adults.

Adverse events of any causality

Most subjects [12/13 (92.3%) with genotype 2 and 28/37 (75.7%) with genotype 3] experienced at least one adverse event through Week 12 post-treatment. The most common AEs (by preferred term, all grades, regardless of causality) with incidence reported in at least 10% of subjects are shown in the following table.

Table 7: Adverse Events (AEs) Reported in ≥10% of Subjects through Week 12 Post-Treatment

	Genotype 2	Genotype 3
Total Number of Subjects	13	37
Number (Percentage) of Subjects with ADR	12 (92.3%)	28 (75.7%)
Headache	3 (23.1%)	9 (24.3%)
Nausea	3 (23.1%)	9 (24.3%)
Asthenia	1 (7.7%)	5 (13.5%)
Upper abdominal pain	2 (15.4%)	3 (8.1%)
Dizziness	0	4 (10.8%)
Diarrhea	2 (15.4%)	1 (2.7%)

Source: Clinical Study Report GS-US-334-1112: Table 11-3. Page 91.

The types of commonly reported adverse events were similar to those that were reported as adverse drug reactions in this trial and with those that were reported in Phase 3 trials of adults. The percentage of subjects with each adverse event was typically higher in subjects with

genotype 3, which was likely due to the longer treatment phase (24 weeks compared to 12 weeks) in subjects with genotype 3. This is supported by the later mean study onset day for AEs in subjects with genotype 3 (Day 71) compared to genotype 2 (Day 29).

Three subjects in Trial GS-US-334-1112 weighed less than 45 kilograms. There was no increase in the number of adverse events or adverse drug reactions or in the types of AEs or ADRs in these subjects. Subject 7805-51123 with genotype 2 who weighed 29.6 kg had one ADR (vomiting). Subject 8719-51128 with genotype 2 who weighed 38 kg had AEs of pruritus and scratch marks on the upper extremities. Subject 9330-51131 with genotype 3 who weighed 42 kg had one ADR (asthenia) and one AE (diarrhea).

Laboratory Abnormalities

Laboratory abnormalities were reported in 9 (69%) subjects with genotype 2 and in 31 (84%) subjects with genotype 3. Grade 3 or 4 laboratory abnormalities were not observed in subjects with genotype 2 but were reported in 6 (16%) of subjects with genotype 3. Ribavirin is associated with a dose dependent hematologic toxicity, including hemolytic anemia, and the increase the laboratory abnormalities observed in subjects with genotype 3 is likely due in part to the longer exposure to RBV in that group of subjects compared to the genotype 2 group.

The Grade 3 laboratory abnormalities reported were decreased hemoglobin (N=3), increased total bilirubin (N=2), decreased white blood cell count (N=1), and increased INR (N=1). One subject had a Grade 4 increase in INR. All abnormalities were isolated, e.g. were observed at a single visit only, except for one subject with a Grade 3 increase in total bilirubin at several visits. This subject had a history of Gilbert's disease, was jaundiced at baseline, and had a Grade 2 total bilirubin at baseline. The Grade 3 increase in total bilirubin was observed at Weeks 1 and 2 and at Weeks 8 through 20. The AE of increased bilirubin was judged by the investigator as related to the underlying Gilbert's disease and not to treatment with SOF. Because this subject has underlying liver disease, other than chronic HCV, this subject did not meet entry criteria and his enrollment was a protocol violation.

Assessments of Growth

There was no clinically significant change in height, weight, body mass index (BMI), or Tanner Pubertal Stage during the study. The changes from baseline to Week 12 post-treatment in height, weight, and BMI are shown in the following table.

Table 8: Mean Change in Growth Parameters from Baseline to Week 12 Post-Treatment

	Genotype 2	Genotype 3
Height (cm)	1.4	1.1
Weight (kg)	0.9	1.9
Body Mass Index (kg/m^2)	0.09	0.47

Source: Clinical Study Report GS-US-334-1112: Text. Pages 102-103.

All subjects were Tanner Pubertal Stage 4 or 5 for pubic hair, breasts (female), and genitalia (males) at baseline. At the 12 week post-treatment visit, all subjects were either the same Tanner Pubertal Stage or had increased from Stage 4 to Stage 5. In conclusion, notable effects of SOF and RBV treatment on adolescent growth or development were not apparent in this small trial of short duration. Analysis of long-term data from trial GS-US-334-1112, when available, will be more meaningful.

Safety Summary
In summary, no new safety signal or changes in the frequency of previously described AEs were identified for sofosbuvir. Although Trial GS-US-334-1112 was not powered to detect differences between individual populations, race, ethnicity, and gender did not appear to influence the frequency or severity of adverse events or laboratory abnormalities. Overall, the findings in this pediatric clinical trial are consistent with previously described adverse events observed with the use of sofosbuvir in treatment-experienced adults. The Clinical Adverse Events (Section 6) will be updated to include ADRs as identified by the applicant.

9. Advisory Committee Meeting
Not applicable.

10. Pediatrics
This application contains pediatric data for subjects from 12 to <18 years of age. The pediatric trial design, clinical outcome, and proposed labeling for pediatric patients from 12 to <18 years of age was presented to the PeRC. The PeRC agreed with the Division's proposed plans for labeling.

The submission of the interim Clinical Study Report for GS-US-334-112 is a partial response to a PREA PMR for the study of sofosbuvir in patients 3 to <18 years of age. The requirement to study sofosbuvir in subjects <3 years of age was waived in 2013.

Data included in this submission represents a partial response to the Pediatric Written Request for sofosbuvir. Additional data to satisfy the outstanding elements of the Written Request must be submitted by February 28, 2019.

11. Other Relevant Regulatory Issues
No additional regulatory issues have been identified.

12. Labeling
The labeling has been updated to reflect changes in the indication, extending the population to chronic HCV genotype 2 or 3 infected pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis. The rationale for including "or weighing at least 35 kg" is based on the following. The Harvoni approval in pediatric patients includes dosing for 12 years of age and older or weighing at least 35 kg. SOF is a component of Harvoni; therefore the SOF dosing from Harvoni applies to SOF as a single agent. The treatment phase for the Harvoni trial GS-US-337-1116 had no weight restrictions and 16 subjects weighed less than 45 kg (including three who weighed less than or equal to 35 kg). The sparse PK data from 15 subjects with body weight greater than 35 kg to less than or equal to 45 kg showed that the exposures were similar to those observed in pediatric subjects greater than 45 kg and in adults. No safety concerns were identified in the Harvoni trial for subjects weighing less than 45 kg compared to those weighing at least 45 kg or greater. Additionally, the treatment phase of the SOF Trial GS-US-334-1112 did not have any weight restrictions. Two subjects weighed between 35 and 45 kg and one weighed less than 35 kg. Population PK analysis showed median C_{max} values for both SOF and GS-331007 were generally similar between subjects with body weight of 45 kg or less and those with body weight greater than 45 kg, while GS-331007 AUC was higher for subjects weighing 45 kg or less as compared to greater than 45 kg. Exposure at steady state was also similar between the two weight groups. There was no increase in SOF toxicity observed in subjects weighing less than 45 kg in Trial GS-US-334-1112. The differences in PK parameters by weight in both the Harvoni trial and in the SOF trial are not considered clinically relevant. Collectively the data from Harvoni and SOF

support the dosing for pediatric patients weighing at least 35 kg. Please see Dr. Sheikh's review of this study in the clinical review of sNDA 205834/SDN 017

Although the labeling changes have not yet been finalized at the time of this review, the changes with this efficacy supplement primarily affected the following sections. The majority of these changes were accepted by Gilead and only minor edits are accepted before approval action.

1 INDICATIONS AND USAGE

The following section was added:

Pediatric Patients:

SOVALDI is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin [see Dosage and Administration (2.3) and Clinical Studies (14.5)].

2.3 Recommended Dosage in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

This section was added to Section 2. Dosage and Administration. Tables describing recommended treatment regimens and duration of treatment and recommended ribavirin dosing for pediatrics were added.

The recommended dosage of SOVALDI in pediatric patients 12 years of age and older or weighing at least 35 kg is one 400 mg tablet taken orally once daily with or without food in combination with ribavirin *[see Clinical Pharmacology (12.3) and Clinical Studies (14.5)]*.
The recommended treatment regimen and duration for SOVALDI combination therapy is provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination with SOVALDI for pediatric patients. For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 2 and Table 3. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 2 Recommended Treatment Regimen and Duration in Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

	Patient Population	**Treatment Regimen and Duration**
Genotype 2	Treatment-naïve and treatment-Experienced[a] without cirrhosis or With compensated cirrhosis (Child-Pugh A)	SOVALDI + ribavirin[b] 12 weeks
Genotype 3	Treatment-naïve and treatment-Experienced[a] without cirrhosis or With compensated cirrhosis (Child-Pugh A)	SOVALDI + ribavirin[b] 24 weeks

a. Treatment-experienced patients have failed an interferon based regimen with or without ribavirin.

b. See Table 3 for weight-based ribavirin dosing recommendations.

Table 3 Recommended Dosing for Ribavirin in Combination Therapy with SOVALDI for Pediatric Patients 12 Years of Age and Older or Weighing at Least 35 kg

Body Weight kg	Ribavirin Daily Dosage[a]
less than 47	15 mg/kg/day
47–49	600 mg/day
50–65	800 mg/day
66–80	1000 mg/day
greater than 80	1200 mg/day

a. The daily dosage of ribavirin is weight-based and is administered orally in two divided doses with food

5.2 Serious Symptomatic Bradycardia When Coadministered with Amiodarone

Changes to Section 5.2 , and Section 7.1 were revised to state coadministration of amiodarone with a SOF-containing regimen may result in serious symptomatic bradycardia. Originally the label stated coadministration of amiodarone with Sovaldi in combination with another DAA may result in serious symptomatic bradycardia. In response to PMR 2993-1 (see below) Gilead conducted several in vitro studies. Please refer to reviews by Wendy Wu (entered into DAARTs by Renmeet Grewal), Jenny Zheng and Sarah Connelly for details. Collectively the results from the in vitro studies show a pharmacodynamic interaction can occur with SOF and amiodarone alone without additional DAAs; hence the revision to the SOF label as noted above to remove reference to “in combination with another DAA”.

Postmarketing Requirement 2993-1:
Using appropriate in vitro approaches (including, but not limited to, patch clamp studies of L-type and T-type calcium channels and transporter phenotyping),evaluate the potential mechanism of both pharmacodynamic and pharmacokinetic interactions between sofosbuvir and amiodarone, with and without other hepatitis C virus (HCV) direct acting antiviral drugs (DAA).

6.1 Clinical Trials Experience

The following section was added:

Adverse Reactions in Pediatric Subjects 12 Years of Age and Older
The safety assessment of SOVALDI in pediatric subjects 12 years of age and older is based on data from 50 subjects who were treated with SOVALDI plus ribavirin for 12 weeks (genotype 2 subjects) or 24 weeks (genotype 3 subjects) in a Phase 2, open-label clinical trial. The adverse reactions observed were consistent with those observed in clinical studies of SOVALDI plus ribavirin in adults [see *Clinical Studies* 14.5)].

Sections 8.1 Pregnancy, 8.2 Lactation, and 8.3 Females and Males of Reproductive Potential

These three sections were revised in accordance with FDA’s Pregnancy and Lactation Labeling Rule (PLLR).

8.4 Pediatric Use

This section was updated to provide the rationale for and limitations of the pediatric indication and includes the following:

The safety, pharmacokinetics, and efficacy of SOVALDI in pediatric patients 12 years of age and older or weighing at least 35 kg with genotype 2 and 3 infection have been established. SOVALDI was evaluated in an open-label clinical trial (Study 1112), which included 50 subjects (13 genotype 2, 37 genotype 3) 12 years of age and older. The safety, pharmacokinetics, and efficacy were comparable to that observed in adults *[see Dosage and Administration (2.3), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.5)]*.

The safety and efficacy of SOVALDI in pediatric patients 12 years of age and older or weighing at least 35 kg with compensated cirrhosis is supported by comparable sofosbuvir and GS-331007-exposures between: 1) adults and adolescents without cirrhosis and 2) adults without cirrhosis and adults with compensated cirrhosis. Thus, similar efficacy would be expected for adolescent patients with compensated cirrhosis as adults with compensated cirrhosis.

The safety and efficacy of SOVALDI have not been established in pediatric patients less than 12 years of age and weighing less than 35 kg with HCV genotype 2 or 3. The safety and efficacy of SOVALDI have not been established in pediatric patients with HCV genotype 1 or 4.

12.3 Pharmacokinetics

This section was revised to include a subsection, entitled Pediatric Patients, which contains the following text:

The pharmacokinetics of sofosbuvir and GS-331007 were determined in 50 pediatric subjects 12 years of age and older, infected with HCV genotype 2 or 3, receiving a daily dose of SOVALDI (400 mg sofosbuvir). The pharmacokinetic properties of sofosbuvir and GS 331007 in pediatric subjects 12 years of age and older are provided in Table 7. Exposures in pediatric subjects were similar to those observed in adults.

Table 7 Pharmacokinetic Properties of SOVALDI in HCV-infected Pediatric Subjects 12 Years of Age and Older[a]

Geometric Mean	**Sofosbuvir[b]**	**GS-331007[b]**
AUC_{tau} (ng•hr/mL)	1060	7570
C_{max} (ng/mL)	472	572

a. Population PK derived parameters
b. Sofosbuvir N=28; GS-331007 N=50

The pharmacokinetics of sofosbuvir have not been established in pediatric subjects less than 12 years of age *[see Use in Specific Populations (8.4)]*.

14.5 Clinical Studies in Pediatric Subjects

This section has been added to include demographic and efficacy data from Trial GS-US-334-1112 as follows:

The efficacy of SOVALDI in HCV-infected pediatric subjects 12 years of age and older was evaluated in 50 subjects with HCV genotype 2 (N = 13) or genotype 3 (N = 37) in a Phase 2, open label clinical trial. Subjects with HCV genotype 2 or 3 infection in the trial were treated with SOVALDI and weight-based ribavirin for 12 or 24 weeks, respectively [*see Dosage and Administration (2. 3)*].

Of the 50 treated subjects, the median age was 15 years (range: 12 to 17); 42% of the subjects were female; 90% were White, 4% were Black, and 2% were Asian; 4% were Hispanic/Latino;

mean weight was 61 kg (range 30 to 101 kg); 18% were treatment experienced; 66% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 74% of subjects had non-CC IL28B alleles (CT or TT); and no subjects had known cirrhosis. The majority of subjects (69%) had been infected through vertical transmission.

The SVR12 rate was 100% (13/13) in genotype 2 subjects and 97% (36/37) in genotype 3 subjects. No subject experienced on-treatment virologic failure or relapse.

13. Outstanding Issues

None. However labeling negotiations are currently ongoing.

14. Recommendations / Risk Benefit Assessment

Based on the totality of the data presented and input from each of the review disciplines, the clinical review team recommends approval of SOF in combination with ribavirin for the treatment of pediatric patients 12 years of age and older or weighting at least 35 kg with HCV genotype 2 and 3 infection without cirrhosis or with compensated cirrhosis.

Throughout the review of this sNDA, no deficiencies that would preclude the approval were identified. Sofosbuvir was studied in a multicenter, open-label, non-comparative trial in which 50 adolescent subjects were enrolled and followed for 12 weeks after discontinuation of study treatment. The trial design comprised two phases: a PK lead-in phase and a treatment phase in which the safety and efficacy of the sofosbuvir were evaluated.

The adult sofosbuvir dose of 400 mg daily was administered in combination with RBV in the PK-lead in phase and extensive PK evaluation was conducted on Day 7. The SOF exposure and the exposure for its major metabolite, GS-331007, were similar in adolescents to those observed in Phase 2 and 3 studies in adults. Therefore, the SOF dose of 400 mg daily was also administered in the treatment phase. There is no clinically relevant difference in PK in adults with cirrhosis compared to those without cirrhosis. Since the PK of SOF is similar in adults and adolescents, the adolescent dose of 400 mg daily is recommended for both patients with and without cirrhosis.

This trial was not powered for true statistical analysis of safety or efficacy. However, the results were compared to the efficacy results of Phase 3 trials of SOF in adults and to historical controls of INF and RBV use in children and adolescents. The efficacy outcome, as measured by sustained virologic response 12 weeks after treatment discontinuation was 100% for genotype 2 and 97% for genotype 3. No subjects experienced on-treatment virologic failure or relapse. The efficacy outcome was similar to that observed in treatment-naive adults with chronic HCV due genotype 2 and 3. The SVR12 for genotype 2 and 3 was greater than the SVR12 of 80% that has been observed in studies of IFN and RBV in children and adolescents.

The applicant demonstrated an acceptable safety profile for sofosbuvir in combination RBV. Sofosbuvir was generally safe and well tolerated in adolescents subjects enrolled in this trial. No deaths or serious adverse events were reported, and no subjects discontinued the study prematurely due to an adverse event. No new safety concerns were identified. The observed risks of sofosbuvir use have been described previously, and the rate and nature of adverse events were similar to those in adults with chronic HCV infection.

Of note, the size of the safety database in pediatric patients is limited and this trial will continue to follow subjects beyond the post-treatment Week 12 cutoff.

Recommendation for Postmarketing Risk Evaluation and Management Strategies
The current submission partially fulfills the Pediatric Written Request, and no additional pediatric post-marketing study commitments will be sought. The current submission also partially fulfills the only Post-Marketing Requirement under Pediatric Research Equity Act (PREA) (see Section 2.5).

Recommendation for Other Postmarketing Requirements and Commitments
None. The applicant will continue to submit PAERS and annual reports (DSURs) for review.

15. Clinical Investigator Disclosure Review Template for sNDA 204617/377

Submission Date(s): October 27, 2016
Applicant: Gilead Sciences, Incorporated
Product: Sovaldi (sofosbuvir)

Reviewer: Melisse Baylor, MD
Date of Review: 03/20/2017
Covered Clinical Trial (Name and/or Number): GS-US-334-1112

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **133**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0** Significant payments of other sorts: **0** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	**Yes** ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	**Yes** ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) **0**		
Is an attachment provided with the reason: N/A	**Yes** ☐	No ☐ (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the Guidance for Industry: *Financial Disclosure by Clinical Investigators*.

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/s/

MELISSE S BAYLOR
04/03/2017

KIMBERLY A STRUBLE
04/03/2017