# Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Memo

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| **Date** | August 27, 2019 |
| **From** | Samer El-Kamary, MD, MPH, Medical Officer<br>Kimberly Struble, PharmD, Cross Discipline Team Leader<br>Debra Birnkrant, MD, Division Director |
| **Subject** | Combined Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Memo |
| **NDA# and Supplement#** | 204671/Supplement 14<br>NDA 212480 |
| **Applicant** | Gilead Sciences, Incorporated. |
| **Date of Submission** | February 28, 2019 |
| **PDUFA Goal Date** | August 28, 2019 |
| **Proprietary Name** | Sovaldi |
| **Established or Proper Name** | sofosbuvir (SOF) |
| **Dosage Form(s)** | Oral tablets: 200 mg<br>Oral pellets: 150 mg and 200 mg |
| **Applicant Proposed Indication(s)/Population(s)** | Pediatric Patients 3 to < 12 years of age: For treatment of genotype 2 or genotype 3 HCV infection |
| **Applicant Proposed Dosing Regimen(s)** | Weight based dosing (see Table 3 in Labeling) |
| **Recommendation on Regulatory Action** | Approval |

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# 1 Executive Summary

## Summary of Regulatory Action

The new drug application (NDA) for SOVALDI (sofosbuvir; SOF) 150 mg and 200 mg oral pellets and the supplemental NDA for SOF 200 mg tablets are submitted by Gilead Sciences. The NDA was reviewed by the multi-disciplinary review team and each discipline recommended approval for the NDA. I, the signatory authority for this application, concur with the recommendations from the review team. SOF will be approved for the treatment of chronic hepatitis C virus (HCV), genotypes 2 or 3 infection in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis in combination with ribavirin.

The Applicant submitted a multicenter, open-label, non-comparative trial in which 54 children (41 children 6 to < 12 years old, and 13 children 3 to < 6 years old), 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 sofosbuvir dose was based on the child's weight, with tablets for those who could swallow them and pellets for the younger age groups. The SOF exposure and the exposure for its major metabolite, GS-331007, were similar to those seen in the adolescent (12 to < 18 year old) age group and in adults. 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 adolescents.

The efficacy outcome, as measured by sustained virologic response 12 weeks after treatment discontinuation (SVR12) was a 100% genotype 2 and 3 in all subjects except one, who discontinued treatment due to unplatability of the drug. All children who achieved SVR12 also normalized their ALT. None of them had virologic failure (breakthrough, rebound or nonresponse) or relapse. The drug was safe and well tolerated with no Grade 3 or higher adverse events, no serious adverse events and no deaths. The most commonly observed adverse events were similar to those seen in adults and were mild in nature. The overall Benefit-Risk is favorable as described in the Benefit-Risk Assessment below.

# II Benefit-Risk Assessment

Benefit-Risk Dimensions

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | • Chronic HCV (CHC) infection remains a significant global health cause of chronic liver disease, cirrhosis, hepatocellular carcinoma and death.<br>• Hepatitis C virus (HCV) is easily transmissible through percutaneous and parenteral exposure, and the majority of pediatric HCV infections in the US are the result of vertical transmission.<br>• Children with active CHC inflammation tend to have a mild clinical course but in some cases can result in serious liver inflammation and even liver failure. The long-term complications of liver fibrosis and cirrhosis can occur over many years, and when HCV infection starts in early childhood, the likelihood of developing these complications by early adulthood is very high.<br>• There is no vaccine and no post-exposure immunoprophylaxis available for HCV. | Chronic HCV infection (CHC) remains a major cause of morbidity and mortality worldwide. While it has a mild prognosis in most children, it can become serious in some cases. Furthermore, when acquired early in childhood can lead to the development of serious or fatal complications by early adulthood. This can result in a debilitating disease at the prime productive years of an individual, with significant limitations in a person's professional and personal activities, disability, reduced healthy life expectancy, and potential years of life lost. |
| Current Treatment Options | • Pegylated interferon alfa with ribavirin (PEG-IFN/RBV) is approved for children ≥ 3 year. However it has a poor tolerability and safety profile, and are curative in only a small fraction. Furthermore, PEG-IFN is an injectable medication.<br>• Although the proportion of children 3 to <12 years or older who will be recommended for treatment are relatively few, safer all-oral treatment options are needed. | There is only one other treatment option for children infected with CHC, pegylated interferon/ribavirin which is only effective in about half the cases, is injectable (pegylated interferon), and has many serious side-effects.<br><br>The availability of another therapy, particularly one that is all-oral, with a much higher efficacy and safety is highly desirable. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Benefit | • To support an efficacy claim for the use of SOF (Sovaldi) for the treatment of children with chronic hepatitis C (CHC) infection in children 3 to < 12 years old, the applicant submitted the 24 Week efficacy and safety results from a single study (Study Trial GS-US-334-1112), which is a Phase 3, open-label, non-comparator trial.<br>• In this study, 54 subjects aged 3 years to less than 12 years of age with chronic HCV infection genotype 2 (n=18) were treated with SOF + RBV once daily for 12 weeks; and those with genotype 3 (n=36) were treated with SOF + RBV once daily for 24 weeks.<br>• The study demonstrated that 100% of patients who received the treatment achieved a sustained virolocal response at week 12 (SVR12) which is an indication of complete viral clearence and cure. Also, all subjects who completed the treatment also achieved ALT normalization. | SOF was highly efficacious in clearing HCV in children 3 to < 12 years old. This viral clearance led to a ALT normalization in all the children who took the treatment, which is reflective of reduced hepatic inflammation.<br><br>Given long-term studies in children adults, clearance of HCV (spontaneosly or by treatment) stops resultant liver inflammation and prevents or reduces long-term complications such as fibrosis, cirrhosis, liver failure and hepatocellular complications. It is reasonable to assume that long-term viral suppression in children 3 to < 12 years old would also prevent or lead to fewer complications later in their life.<br><br>SVR12 rates were comparable between age cohorts and similar to adolescents and adults. |
| Risk and Risk Management | SOF had a few mild side-effects, the most common of which were vomiting, headache, fatigue, cough, nasopharyngitis, decreased appetite, and diarrhea. All of them were categorized as mild (Grade 1 or 2 Adverse Events). There were no drug-related Serious Adverse Events, and no deaths. Only one child discontinued the drug due to inability to take the drug due to the sensation of an abnormal taste.<br><br>There were no notable effects of treatment on development or growth (baseline to posttreatment Week 24) in Tanner stage, bone age, height, weight and Body Mass Index (BMI) percentiles, and vital signs. | The frequency of side-effects observed in this study were all mild and similar to those noted in adolescents and adults.<br><br>Based on the available safety profile for SOF, no Risk Evaluation and Mitigation Strategy (REMS) is recommended at this time. |

## Conclusions Regarding Benefit and Risk

CHC remains a major cause of morbidity and mortality worldwide. While CHC has a mild prognosis in most children, CHC can become serious in some cases. Currently, pegylated interferon/ribavirin is the only treatment option for children less than 12 years of age who are infected with CHC. Pegylated interferon/ribavirin is only effective in about half the cases, is injectable (pegylated interferon), and has many serious side-effects. The overall benefit-risk assessment for SOF/RBV in children 3 years to less than 12 years of age with CHC genotype 2 and 3 is favorable as demonstrated by the high SVR12 rates. SVR12 rate was a 100% genotype 2 and 3 in all subjects except one, who discontinued treatment due to unplatability of the drug Also, all subjects who completed the treatment also achieved ALT normalization. SOF/RBV was safe and well tolerated with no serious adverse events and no deaths. The most commonly observed adverse events were similar to those seen in adults and were mild in nature. The availability of LDV/SOF for children less than 12 years of age is a major public health benefit and offers these children with HCV genotype 2 and 3 infection a safe and effective all-oral treatment option.

# 1. Patient Experience Data

Patient Experience Data for Harvoni in children 3 to < 12 years old with HCV infection were collected within the clinical trials. The table below presents where Patient Experience Data Relevant to this Application is described in Study GS-US-334-1112. *See Appendix 1 for a summary of the data collected in this study.*

**Patient Experience Data Relevant to this Application (check all that apply)**

| | | | | |
|---|---|---|---|---|
| ☒ | The patient experience data that was submitted as part of the application include: | | | Section where discussed, if applicable |
| | ☒ | Clinical outcome assessment (COA) data, such as | | - |
| | | ☒ | Patient reported outcome (PRO) | Clinical study report CSR for Study GS-US-334-1112 Synopsis, Section 12.1 |
| | | ☒ | Observer reported outcome (ObsRO) | Clinical study report CSR for Study GS-US-334-1112 Synopsis, Section 12.1 |
| | | □ | Clinician reported outcome (ClinRO) | - |
| | | □ | Performance outcome (PerfO) | - |
| | □ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) | | - |
| | □ | Patient-focused drug development or other stakeholder meeting summary reports | | - |
| | □ | Observational survey studies designed to capture patient experience data | | - |
| | □ | Natural history studies | | - |
| | □ | Patient preference studies (e.g., submitted studies or scientific publications) | | - |
| | ☒ | Other: (Please specify) Swallowability of oral tablets and palatability of oral pellet formulation were assessed in Study GS-US-334-1112. | | Module 2.5, Section 2.5; GS-US-334-1112 CSR Synopsis, Sections 8.1.4, 8.2.4, 8.3.4. |
| □ | Patient experience data that were not submitted in the application, but were considered in this review: | | | |
| | | □ | Input informed from participation in meetings with patient stakeholders | - |
| | | □ | Patient-focused drug development or other stakeholder meeting summary reports | - |
| | | □ | Observational survey studies designed to capture patient experience data | - |
| | | □ | Other: (Please specify) | - |

| | |
|---|---|
| □ | Patient experience data was not submitted as part of this application. - |

## 2. Background

Hepatitis C virus (HCV) is the main cause of chronic liver disease worldwide, and the global prevalence of chronic HCV was estimated to average 1% in 2015, for a total of 71 million individuals {The Polaris Observatory HCV Collaborators 2017, World Health Organization (WHO) 2018b}. Globally, there are an estimated 2.1 to 3.5 million children 15 years of age or younger with chronic HCV {Nwaohiri 2018, European Association for the Study of the Liver (EASL) 2018a}. The prevalence varies by geographic location, with an estimated prevalence of 0.4% in Europe and the United States (US), for a total of forty-six thousand children in the US; and up to 6% in resource-limited countries {El-Shabrawi 2013, Khaderi 2014}.

Most children chronically infected with HCV are asymptomatic or have mild nonspecific symptoms. In approximately 20%, clinical symptoms are present in the first 4 years of life, with hepatomegaly being the most frequent sign (10%); and in some cases severe liver disease is encountered {Mohan 2010}. Many, but not all, perinatally infected children will have intermittently or persistently abnormal alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, particularly in the first 2 years of life. Despite the more favorable prognosis compared to adults, approximately 4% to 6% of children with chronic HCV infection have evidence of advanced fibrosis or cirrhosis, and some children will eventually require liver transplantation for end-stage liver disease {Hu 2010}.

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 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 children younger than 12 years of age 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 2006}. Weight loss and reduced height growth have been observed in children receiving IFN and RBV {Jonas 2012, Wirth 2012}.

Although direct acting antivirals (DAA) have been FDA-approved for treatment of chronic HCV infection in adults since 2011, and in adolescents older than 12 years of age since 2017, none have been approved for use in pediatric patients younger than 12 years. Treatment of chronic HCV with DAAs has resulted in a 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. As such, the current international guidelines recommend that in subjects younger than 12 years, treatment should be deferred until direct antiviral agents are available {American Association for the Study of Liver Diseases (AASLD) 2017, European Association for the Study of the Liver (EASL) 2018b, Indolfi 2018, World Health Organization (WHO) 2018a}. Therefore, it is important to have DAAs available for treatment of chronic HCV infection in younger children.

Sofosbuvir was first approved for commercial marketing in the United States (US) on 06 December 2013 and in the European Union (EU) on 16 January 2014, for use in combination with ribavirin (RBV) for the treatment of chronic HCV with genotype 2 and 3 infection in adults. The marketing application for SOF was updated on 07 April 2017 in the US and on 14 September 2017 in the EU to expand the indication for the treatment of patients 12 years of age and older, or weighing at least 35 kg (in the US only), with genotype 2 or 3 HCV infection.

In this supplemental NDA, sofosbuvir was evaluated in a single open-label, uncontrolled, pharmacokinetic (PK), safety, and efficacy trial in 104 children 3 to less than 18 years old in eight countries (US, UK, Australia, New Zealand, Belgium, Germany, Italy and the Russian Federation). regimens. The goal of pediatric development in HCV was to determine whether the PK and safety in children was similar to that of adults, given that the HCV disease process is similar to adults. An open-label, uncontrolled design was considered acceptable because of the high SVR12 rates reported in adolescent and adult subjects treated with SOF and RBV regimens, and the ethical concerns associated with the poor response rate and toxicity associated with use of IFN-containing regimens.

Electronic materials submitted included the final Clinical Study Report (CSR) and the accompanying datasets as required. This pediatric supplement fulfills the single outstanding post-marketing requirement (PMR) under the Pediatric Research Equity Act (PREA):

- PMR 2110-1 under PREA to provide PK, safety and treatment response data for 3 to <18 year HCV-infected children. Here they provide data for 3 to < 12 year olds.

The efficacy supplement also supports a new 200 mg tablet and is a response to the pediatric written request.

This supplement provides the data for evaluating the proposed indication for SOF in the treatment of chronic HCV infection in pediatric patients 3 to < 18 years old with genotype 2 or 3 HCV infection. Only data for pediatric subjects 3 to < 12 years old are presented in this clinical review. The proposed treatment regimens are SOF+RBV for 12 weeks in patients with genotype 2 HCV infection, and SOF+RBV for 24 weeks in patients with genotype 3 HCV infection.

The proposed recommendation for the use of SOF in pediatric patients aged 3 to < 12 years old is supported by PK, efficacy, and safety data from the Phase 2 Study GS-US-334-1112. Data for adolescent subjects 12 to < 18 years old were previously presented in the GS-US-334-1112 Interim Clinical Study Report (CSR), and final data through post-treatment Week 24 are presented in the GS-US-334-1112 Final CSR. *For a full clinical review of the data for adolescent subjects 12 to < 18 years old, please refer to Dr. Melisse Baylor's review in the original NDA 204671*.

## 2.1. Product Information

Tablets
SOVALDI is the brand name for sofosbuvir, a nucleotide analog inhibitor of HCV NS5B polymerase. Each Sovaldi tablet contains 200 mg or 400 mg of sofosbuvir. The tablets include the following inactive ingredients.

Pellets
SOVALDI pellets, 150 mg or 200 mg, are for oral administration, supplied as white to off-white pellets in unit-dose packets. Each unit-dose packet contains 150 mg or 200 mg of sofosbuvir. The pellets include the following inactive ingredients.

## 2.2. Summary of Regulatory Activity Related to Submission

In the US, Study GS-US-334-1112 was conducted in accordance with postmarketing requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

- The agreed pediatric plan for SOF in the treatment of HCV infection was submitted to the FDA as a Proposed Pediatric Study Request to Investigational New Drug (IND) 106739 on 12 December 2012 (Serial No. 0243) and to New Drug Application (NDA) 204671 on 05 April 2013 (Seq No. 0000).
- An updated version of the pediatric plan was submitted to NDA 204671 on 09 August 2013 (Seq No. 0015).
- A Written Request (WR) for studies of SOF in pediatric patients with HCV infection aged 3 to < 18 years was received by Gilead on 02 September 2016.
- The terms of the WR were further negotiated and Gilead agreed to the terms of the pediatric WR dated 10 February 2017 (Amendment 2), which included changing the age groups being studied to pediatric subjects 3 to < 12 years of age (Seq No. 0195).

As per this review, 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. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312).

## 2.3. Summary of Study Protocol

Trial GS-US-334-1112, entitled, *A Phase 2, Open-Label, Multicenter, Multi-cohort, Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir + Ribavirin in Adolescents and Children with Genotype 2 or 3 Chronic HCV Infection*; is a 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 was designed to enroll 100 pediatric subjects from 3 to <18 years of age sequentially by descending age cohort (50 adolescents subjects 12 to < 18 years of age; and 50 children 3 to < 12 years of age). Subjects of 3 age groups were enrolled

in a sequential fashion: 12 to < 18 years old, followed by 6 to < 12 years old, and 3 to < 6 years old.

The first cohort enrolling adolescent subjects, 12 to <18 years of age, and collecting safety and efficacy through week 12 after the completion of treatment 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 data was reviewed and the drug approved for this adolescent age group in 2017. ***This report only presents the clinical review of the data for the next two cohorts: 6 to < 12 years of age, and 3 to < 6 years of age.***

Subjects received the following regimen based on HCV genotype:

- Subjects with genotype 2 HCV infection: SOF+RBV for 12 weeks
- Subjects with genotype 3 HCV infection: SOF+RBV for 24 weeks

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. 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. Subjects who participated in the PK lead-in phase were immediately rolled over into the treatment phase with no interruption of study drug administration. The first visit in the treatment phase for these subjects was the Week 2 visit.

**The PK lead-in phase** evaluated and/or confirmed the dose of SOF by analyzing PK and safety of SOF administered in combination with RBV through 7 days of dosing for each cohort. Three cohorts, each with at least 10 treatment-naive subjects with genotype 2 or genotype 3 HCV infection, were sequentially enrolled:

- Cohort 1: 12 to < 18 years old weighing ≥ 45kg *(completed in 2016)*
- Cohort 2: 6 to < 12 years old weighing ≥ 17kg and < 45 kg
- Cohort 3: 3 to < 6 years old

Weight limits were defined for the subjects enrolled in the PK lead-in phase cohorts only. Weight limits for Cohort 1 and Cohort 2 did not apply to additional subjects of each age group enrolled in the treatment phase.

Intensive PK and safety results through Day 7 of treatment for each cohort were reviewed to confirm the appropriateness of the evaluated SOF dose prior to initiating the treatment phase of that age group and determining the age-appropriate dose to be evaluated in the PK lead-in phase of the next age group.

**Treatment Phase.** Subjects who participated in the PK lead-in phase were immediately rolled over into the treatment phase with no interruption of study drug administration. The first visit in the treatment phase for these subjects was the Week 2 visit. Additional treatment-naive or treatment-experienced subjects with genotype 2 or genotype 3 HCV infection were enrolled into

the treatment phase upon confirmation of the age-appropriate SOF dose from the PK lead-in phase. Weight limits for Cohort 1 and Cohort 2 did not apply to additional subjects of each age group enrolled in the treatment phase. The treatment phase was initiated sequentially by age group as defined in Cohort 1, 2, and 3 of the PK lead-in phase.

In this submission, the trial enrolled children from 3 to <12 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 (positive genotype 2 or 3). 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 6 to < 12 years of age had to weigh ≥ 17kg and < 45 kg 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.

Subjects were administered SOF orally once daily as oral tablets or pellets in combination with RBV (Table 1). RBV was administered by tablet or oral solution as shown in Table 2:

**Table 1: Dosage of Sofosbuvir by Weight**

| Body Weight (kg) | Dosing of SOVALDI Tablets or Oral Pellets | SOVALDI Daily Dose |
|---|---|---|
| at least 45 | one 400 mg tablet once daily<br>or<br>four 100 mg tablets once daily<br>or<br>eight 50 mg packets of pellets once daily | 400 mg per day |
| 17 to less than 45 | two 100 mg tablet once daily<br>or<br>four 50 mg packet of pellets once daily | 200 mg per day |
| less than 17 | three 50 mg packet of pellets once daily | 150 mg per day |

Source: Summarized from Clinical Study Report GS-US-334-1112: Pages 42, 45, 46.

SOF dosage in Table 1 reflects the actual weight bands used to administer LDV/SOF in the protocol. The final approved dosage weight bands are in the label, and in section 12 Labeling below.

**Table 2: Recommended Dosing for Ribavirin in Combination Therapy with HARVONI for Pediatric Patients 3 Years and Older**

| Body Weight (kg) | Ribavirin Daily Dosage[a] |
|---|---|
| less than 47 | 15 mg per kg per day (divided dose AM and PM) |
| 47–49 | 600 mg per day (1 x 200 mg AM, 2 x 200 mg PM) |
| 50–65 | 800 mg per day (2 x 200 mg AM, 2 x 200 mg PM) |
| 66–80 | 1000 mg per day (2 x 200 mg AM, 3 x 200 mg PM) |
| greater than 80 | 1200 mg perday (a x 200 mg AM, 3 x 200 mg PM) |

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

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 posttreatment 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 and SVR 24 weeks after discontinuation of study treatment, to evaluate the kinetics of circulating HCV RNA during and after completion of treatment, and to evaluate the emergence of viral resistance to SOF during and after completion of treatment.

The primary statistical analysis was descriptive. It was estimated that with approximately 50 subjects enrolled into the 12 to < 18 years old group and approximately 50 subjects enrolled into the 3 to < 12 years old group of the treatment phase, a 2-sided 95% CI of the SVR12 rate would extend at most 11.1% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 80%. In addition, a sample size of 100 subjects would provide over 80% power to detect an 11% improvement in SVR12 rate from 80% to 91% using 2-sided one-sample binomial test at significance level of 0.05.

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.

## 2.4. Protocol Amendments

The original study protocol (20 December 2013) was amended 6 times. Key changes to the protocol for each amendment were as follows:

- The protocol was amended for the first time on 10 February 2014; key changes in this amendment specified that subjects must be treatment naive for the PK lead-in phase and that subjects would be administered a dosing diary with instructions for the PK lead-in phase. Additional changes included administrative updates and clarification of study procedures, additional laboratory assessments, and added information regarding the SOF swallowability assessment.
- The protocol was amended for the second time on 14 March 2014. Key changes in Amendment 2 included updates to the design and conduct of the PK lead-in phase; specified the RBV study drug as Rebetol, as well as some changes to the study procedures and assessments intended to improve patient safety.
    - Amendment 2.1 (specific to Russia only): The protocol was next amended on 15 August 2014 to reflect the following key change: Removed all references to the enrollment of subjects under 12 years of age from the protocol based on guidance from the Russian Ministry of Health. In Russia, the study only enrolled subjects aged 12 to < 18 years of age.
- The protocol was amended for the third time on 10 October 2014. Key changes in this amendment included a clarification of breakthrough futility assessment to specify that enrollment would be suspended if 3 or more of the first 10 subjects had viral breakthrough by Week 8. Additional changes included revisions to the RBV dose administration and information about bioavailablity of SOF oral pellets,
- The protocol was amended for the fourth time on 12 November 2014. This amendment included an update for the RBV dosing chart, and an update to the statistical analysis section
- The protocol was amended for the fifth time on 29 May 2015. Changes made in this amendment included modifications for Cohort 2 (6 to < 12 year old children) based on Cohort 1 (12 to < 18 year old adolescents) data analysis after completion of Cohort 1.
- The protocol was amended for the sixth time on 26 February 2016. Changes were made to update the dose for Cohort 3 (3 to < 6 year old children) based on the Cohort 2 data analysis; and an update to the PK and safety results.

# 3. Product Quality

A 400 mg oral tablet is already approved for use in adolescents and adults. New formulations in the form of a 200 mg tablet, and oral pellets (150 mg and 200 mg), were developed for use in children. *Please refer to the original review of Chemistry, Manufacturing and Control (CMC) in NDA 204671 for additional information.*

# 4. Nonclinical Pharmacology/Toxicology

*No new Pharmacology/Toxicology information was submitted. See original NDA 204671 for full details.*

# 5. Clinical Pharmacology

Exposures in pediatric subjects were similar to those observed in adults.
*Please refer to Dr. Hazem Hassan's Clinical Pharmacology Review for full details.*

# 6. Clinical Microbiology

There was no evidence that sofosbuvir resistance had emerged during the study period. *Please refer to Dr. Llaji Mishra's Clinical Microbiology Review for full details.*

# 7. Clinical/Statistical-Efficacy

The primary statistical analysis was descriptive. It was estimated that with approximately 50 subjects enrolled into the 3 to < 12 years old group of the treatment phase, a 2-sided 95% CI of the SVR12 rate would extend at most 11.1% in both directions from the observed SVR12 rate, assuming the expected SVR12 rate is 80%.

A total of 54 pediatric subjects 3 to < 12 years old were enrolled and received study drug (13 enrolled in the 3 to < 6 year old group; and 41 in the 6 to < 12 year old group)This exceeded the planned enrollment of 50 subjects needed for statistical analysis.

The following is a summary of the disposition and demographics of study subjects and the assessment of efficacy for each of the remaining two cohorts separately.

## 7.1. Cohort 2: 6 to < 12 years old

### 7.1.1. Disposition of Subjects

Fifty five subjects were screened; 41 of these were enrolled and received study drug. This included 13 subjects with Genotype 2 who were enrolled to receive SOF (200mg) + RBV for 12 weeks; and 28 subjects who were enrolled to receive SOF (200 mg) + RBV for 24 weeks. All 41 subjects completed treatment. All but one clinical site enrolled patients, with no more than 1-5 patients per site. A total of of 9 important protocol deviations occurred in 7 subjects during the

study. Of the 7 subjects, 6 subjects had a single important deviation and 1 subject had 3 important deviations. The majority of important protocol deviations were for deviations of informed consent (5 of 9 deviations) and incorrect dose (2 of 9 deviations). Relevant protocol deviations were proportionally distributed among study sites. None of these protocol deviations affected the overall quality or interpretation of the study data.

#### 7.1.2. Demographic and Baseline Characteristics

The Full Analysis Set included 41 subjects. Demographics and baseline characteristics are shown in the following table.

**Table 3. Demographics and Baseline Characteristics**

| Number of Subjects | Genotype 2 (n=13) | Genotype 3 (n=28) | Total (n=41) |
|---|---|---|---|
| Mean Age in years at baseline (range) | 8 (6, 11) | 9 (6, 11) | 8 (6, 11) |
| Sex Number (%) | | | |
| Male | 3 (23.1%) | 8 (28.6%) | 11 (26.8%) |
| Female | 10 (76.9%) | 20 (71.4%) | 30 (73.2%) |
| Race: Number (%) | | | |
| White | 9 (69.2%) | 20 (71.4%) | 29 (70.7%) |
| African American or Black | 0 | 0 | 0 |
| Asian | 2 (15.4%) | 6 (21.4%) | 8 (19.5%) |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Other | 2 (15.4%) | 2 (7.1%) | 4 (9.8%) |
| Ethnicity: Number (%) | | | |
| Hispanic or Latino | 2 (15.4%) | 4 (14.3%) | 6 (14.6%) |
| Not Hispanic or Latino | 11 (84.6%) | 23 (82.1%) | 34 (82.9%) |
| Not Disclosed | 0 | 1 (3.6%) | 1 (2.4%) |
| Region | | | |
| US | 8 (61.5%) | 10 (35.7%) | 18 (43.9%) |
| Non-US | 5 (38.5%) | 18 (64.3%) | 23 (56.1%) |

Source: Clinical Study Report GS-US-334-1112: Table 16. Pages 88-89.

Baseline HCV disease characteristics are shown in Table 4.

**Table 4. Baseline HCV Characteristics (6 to < 12 years Old)**

| Number of Subjects | Genotype 2 (n=13) | Genotype 3 (n=28) | Total (n=41) |
|---|---|---|---|
| HCV genotype | | | |
| Genotype 2 | 13 (100.0%) | 0 | 13 (31.7%) |
| Genotype 2 (no confirmed subtype) | 2 (15.4%) | 0 | 2 (4.9%) |
| Genotype 2a/2c | 4 (30.8%) | 0 | 4 (9.8%) |
| Genotype 2b | 7 (53.8%) | 0 | 7 (17.1%) |
| Genotype 3a | 0 | 28 (100.0%) | 28 (68.3%) |
| Cirrhosis | | | |
| No | 3 (23.1%) | 2 (7.1%) | 5 (12.2%) |
| Unknown | 10 (76.9%) | 26 (92.9%) | 36 (87.8%) |
| IL28B | | | |
| CC | 4 (30.8%) | 10 (35.7%) | 14 (34.1%) |
| CT | 7 (53.8%) | 14 (50.0%) | 21 (51.2%) |
| TT | 2 (15.4%) | 4 (14.3%) | 6 (14.6%) |
| Baseline HCV RNA ($log_{10}$/mL) | | | |
| Mean (range) | 5.8 (4.6, 6.7) | 5.7 (2.2, 7.8) | 5.7 (2.2, 7.8) |
| Baseline ALT (U/L) | | | |
| Mean (range) | 40 (14, 114) | 60 (21, 583) | 54 (14, 583) |
| Prior HCV Treatment | | | |
| Treatment naïve | 13/13 (100.0%) | 27/28 (96.4%) | 40/41 (97.6%) |
| Treatment Experienced | 0/13 | 1/28 (3.6%) | 1/41 (2.4%) |
| Mode of HCV Infection | | | |
| Vertical transmission | 13 (100.0%) | 27 (96.4%) | 40 (97.6%) |
| Unknown | 0 | 1 (3.6%) | 1 (2.4%) |

Source: Clinical Study Report GS-US-334-1112: Table 17. Pages 90-91.

#### 7.1.3. Efficacy Results at Week 12 after Discontinuation of Treatment (6 to < 12 years old)

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 who received SOF+RBV x 12 weeks was 100% (95% CI: 75.3% to 100.0%) and for the 28 subjects with genotype 3 who received SOF+RBV x 24 weeks was 100% (95% CI: 87.7% to 100.0%). 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 PEG-IFN to treat chronic HCV.

Further analysis of the primary endpoint by subgroup (race, ethinicity, gender, etc) was not meaningful given that all subgroups had a 100% SVR12 and only a descriptive presentation was provided (Source: Clinical Study Report GS-US-334-1112, Tables 37 & 38, pages 117-119).

The virologic response at different endpoints was a secondary efficacy endpoint. Virologic response at each on treatment study visit is shown in Table 5. As demonstrated in this table, there were no treatment breakthroughs and no treatment failures.

**Table 5. Number and Percentage of Subjects with HCV RNA <LLOQ by On Treatment Visit and by Genotype**

| | Genotype 2 (n=13) | Genotype 3 (n=28) |
|---|---|---|
| Baseline | 0/13 | 0/28 |
| Week 1 | 6/13 (46.2%) | 11/28 (39.3%) |
| Week 2 | 10/13 (76.9%) | 22/28 (78.6%) |
| Week 4 | 13/13 (100.0%) | 27/28 (96.4%) |
| Week 8 | 13/13 (100.0%) | 27/28 (96.4%) |
| Week 12 | 13/13 (100.0%) | 28/28 (100.0%) |
| Week 16 | N/A | 28/28 (100.0%) |
| Week 20 | N/A | 28/28 (100.0%) |
| Week 24 | N/A | 28/28 (100.0%) |
| Post-Treatment Week 4 (SVR4) | 13/13 (100.0%) | 28/28 (100%) |
| Post-Treatment Week 4 (SVR12) | 13/13 (100.0%) | 28/28 (100%) |
| Post-Treatment Week 4 (SVR24) | 13/13 (100.0%) | 28/28 (100%) |

Source: Clinical Study Report GS-US-334-1112: Table 36, page 116, and Table 39. Pages 120-121.

**ALT normalization (6 to < 12 years)**
ALT normalization is defined as ALT > ULN at baseline and ALT ≤ ULN at each visit during and after treatment with SOF. Overall, 48.8% of subjects (20 of 41) had ALT > ULN at baseline. Normalization of ALT was observed in 100.0% of subjects with genotype 2 HCV infection treated for 12 weeks and 93.3% of subjects with genotype 3 HCV infection treated for 24 weeks by Week 2. Normalization of ALT was 100.0% in subjects in the genotype 3 HCV infection by Week 4.

## 7.2. Cohort 3: 3 to < 6 years old

### 7.2.1. Disposition of Subjects

Fourteen subjects were screened; 13 of these were enrolled and received study drug. This included 5 subjects with Genotype 2 who were enrolled to receive SOF (200mg) + RBV for 12 weeks; and 8 subjects who were enrolled to receive SOF (200 mg) + RBV for 24 weeks. Twelve of 13 subjects (92.3%) completed treatment, one genotype 2 subject discontinued treatment due to an Adverse Event of product use issue (the subject spit up the dose) and "abnormal product taste". All but one clinical site enrolled patients, with no more than 1-5 patients per site. A total of 2 important protocol deviations occurred in 2 subjects during the study. Both subjects had a single important deviation. One important protocol deviation was a deviation of informed

consent and the second one was for incorrect dose. None of these protocol deviations affected the overall quality or interpretation of the study data.

#### 7.2.2. Demographic and Baseline Characteristics

The Full Analysis Set included 13 subjects. Demographics and baseline characteristics are shown in Table 6.

**Table 6. Demographics and Baseline Characteristics**

| Number of Subjects | Genotype 2 (n=5) | Genotype 3 (n=8) | Total (n=13) |
|---|---|---|---|
| Mean Age in years (range) | 4 (3, 5) | 5 (3, 5) | 4 (3, 5) |
| Sex Number (%) | | | |
| Male | 1 (20.0%) | 2 (25.0%) | 3 (23.1%) |
| Female | 4 (80.0%) | 6 (75.0%) | 10 (76.9%) |
| Race: Number (%) | | | |
| White | 3 (60.0%) | 6 (75.0%) | 9 (69.2%) |
| African American or Black | 1 (20.0%) | 0 | 1 (7.7%) |
| Asian | 0 | 1 (12.5%) | 1 (7.7%) |
| Native Hawaiian or Pacific Islander | 0 | 0 | 0 |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Other | 1 (20.0%) | 1 (12.5%) | 2 (15.4%) |
| Ethnicity: Number (%) | | | |
| Hispanic or Latino | 1 (20.0%) | 0 | 1 (7.7%) |
| Not Hispanic or Latino | 4 (80.0%) | 8 (100.0%) | 12 (92.3%) |
| Region | | | |
| US | 4 (80.0%) | 5 (62.5%) | 9 (69.2%) |
| Non-US | 1 (20.0%) | 3 (37.5%) | 4 (30.8%) |

Source: Clinical Study Report GS-US-334-1112: Table 21. Page 97.

Baseline HCV disease characteristics are shown in Table 7.

**Table 7. Baseline HCV Characteristics (3 to < 6 years Old)**

| Number of Subjects | Genotype 2 (n=5) | Genotype 3 (n=8) | Total (n=13) |
|---|---|---|---|
| HCV genotype | | | |
| Genotype 2 | 5 (100.0%) | 0 | 5 (38.5%) |
| Genotype 2 (no confirmed subtype) | 1 (20.0%) | 0 | 1 (7.7%) |
| Genotype 2b | 4 (80.0%) | 0 | 4 (30.8%) |
| Genotype 3a | 0 | 8 (100.0%) | 8 (61.5%) |
| Cirrhosis | | | |
| No | 1 (20.0%) | 1 (12.5%) | 2 (15.4%) |
| Unknown | 4 (80.0%) | 7 (87.5%) | 11 (84.6%) |
| IL28B | | | |
| CC | 2 (40.0%) | 1 (12.5%) | 3 (23.1%) |
| CT | 2 (40.0%) | 7 (87.5%) | 9 (69.2%) |
| TT | 1 (20.0%) | 0 | 1 (7.7%) |
| Baseline HCV RNA ($log_{10}$/mL) | | | |
| Mean (range) | 5.8 (4.5, 7.2) | 5.1 (4.4, 5.6) | 5.4 (4.4, 7.2) |
| Baseline ALT (U/L) | | | |
| Mean (range) | 28 (17, 51) | 33 (11, 76) | 31 (11, 76) |
| Prior HCV Treatment | | | |
| Treatment Naive | 5/5 (100.0%) | 8/8 (100.0%) | 13/13 (100.0%) |
| Treatment Experienced | 0/5 | 0/8 | 0/13 |
| Mode of HCV Infection | | | |
| Vertical transmission | 5 (100.0%) | 6 (75.0%) | 11 (84.6%) |
| Unknown | 0 | 2 (25.0%) | 2 (15.4%) |

Source: Clinical Study Report GS-US-334-1112: Table 22. Pages 99-100.

#### 7.2.3. Efficacy Results at Week 12 after Discontinuation of Treatment (3 to < 6 years old)

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 5 subjects with genotype 2 who received SOF+RBV x 12 weeks was 80% (95% CI: 28.4% to 99.5%) of subjects (4 of 5) and for the 8 subjects with genotype 3 who received SOF+RBV x 24 weeks was 100% (95% CI: 63.1% to

100.0%). One of 5 subjects with genotype 2 HCV infection treated for 12 weeks (20.0%) did not achieve SVR12 due to premature discontinuation of the study drug due to AEs of spitting up drug and abnormal product taste. An attempt to temporarily discontinue treatment and restart it later failed and the child continued to spit up and was permanently discontinued on Day 3.

Further analysis of the primary endpoint by subgroup (race, ethinicity, gender, etc) showed that all subgroups had a high SVR12 (Source: Clinical Study Report GS-US-334-1112, Tables 47 & 48, pages 128-130). The high SVR12 rate observed overall, with no cases of virologic failure, precluded meaningful interpretation of subgroup analyses. High SVR12 rates were achieved in all subgroups, among both subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype 3 HCV infection treated for 24 weeks.

The virologic response at different endpoints was a secondary efficacy endpoint. Virologic response at each time point on treatment study visit is shown in Table 8. Data starting from Week 2 includes only those who received the treatment (the subject who discontinued the study due to spitting up did so at Day 3). As demonstrated in this table, there were no treatment breakthroughs and no treatment failures among those who received the treatment.

**Table 8. Number and Percentage of Subjects with HCV RNA <LLOQ by On Treatment Visit and by Genotype**

| | Genotype 2 (n=13) | Genotype 3 (n=28) |
|---|---|---|
| Baseline | 0/5 | 0/8 |
| Week 1 | 2/4 (50.0%) | 3/8 (37.5%) |
| Week 2 | 3/4 (75.0%) | 7/8 (87.5%) |
| Week 4 | 3/4 (75.0%) | 8/8 (100.0%) |
| Week 8 | 4/4 (100.0%) | 8/8 (100.0%) |
| Week 12 | 4/4 (100.0%) | 8/8 (100.0%) |
| Week 16 | N/A | 8/8 (100.0%) |
| Week 20 | N/A | 8/8 (100.0%) |
| Week 24 | N/A | 8/8 (100.0%) |
| Post-Treatment Week 4 (SVR4) | 4/5 (80.0%) | 8/8 (100%) |
| Post-Treatment Week 4 (SVR12) | 4/5 (80.0%) | 8/8 (100%) |
| Post-Treatment Week 4 (SVR24) | 4/5 (80.0%) | 8/8 (100%) |

Source: Clinical Study Report GS-US-334-1112: Table 46, Page 127 and Table 49, Pages 131-132.

**ALT normalization (3 to < 6 years)**

ALT normalization is defined as ALT > ULN at baseline and ALT ≤ ULN at each visit during and after treatment with SOF. Overall, 23.1% of subjects (3 of 13) had ALT > ULN at baseline. The 1 subject with genotype 2 HCV infection with ALT > ULN at baseline discontinued the study on Day 3. Normalization of ALT was observed in the remaining 2 subjects with genotype 3 HCV infection by Week 1.

**Overall Efficacy Summary and Conclusions (3 to 12 years old)**

The efficacy of sofosbuvir in combination with ribavirin in children with chronic HCV due to genotype 2 or 3 was demonstrated in this open-label, 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 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 doses in pediatric patients 3 to < 12 years of age 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 children 3 to < 12 years with chronic HCV genotype 2 or genotype 3 infection. Furthermore, given the similar pharmacokinetics and exposures compared to adults, the use of Sovaldi in combination with ribavirin to treat HCV-infected adults in genotype 2 or 3 for up to 48 weeks or until the time of liver transplantation was extended to children 3 years and older based on the adult safety data, and the

# 8. Safety

The data submitted support the safety and tolerability of sofosbuvir in combination with ribavirin in pediatric subjects 3 to < 12 years old with chronic HCV infection. The applicant has submitted safety data from 54 pediatric subjects 3 to < 12 years old (Cohort 2 = 41 subjects 6 to < 12 years old; and Cohort 3 = 13 subjects 3 to < 6 years) 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 54 subjects. The types of Adverse Events observed were similar to the types of AEs observed in adolescents and 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 and who attained SVR24, or those who did not attain SVR24 and did not initiate other experimental or approved anti-HCV therapy, could enroll in a long term registry (Study GS-US-334-1113) for assessment of growth, quality of life, and long-term viral suppression (if applicable).

This Clinical Study Report summarized the safety data for the 12 or 24 weeks 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 who completed the study and 12 week post-treatment period were included in the safety evaluation.

Safety Data from Cohort 1 (12 to < 18 years old) was already reviewed and the drug approved for use in this age group in 2017. *Please refer to Dr. Melisse Taylor's review for the full review in the original NDA 204671.*

The following is a summary of the disposition and demographics of study subjects and the assessment of efficacy for each of the remaining cohorts separately (Cohort 2 = 41 subjects 6 to < 12 years old; and Cohort 3 = 13 subjects 3 to < 6 years).

### 8.1. Cohort 2: 6 to < 12 years old

Table 9 presents the overall summary of AEs for subjects 6 to < 12 years old by treatment group. The majority of subjects (35 of 41, 85.4%) experienced at least 1 AE (9 of 13, [69.2%] subjects with genotype 2 HCV infection treated for 12 weeks; and 26 of 28 [92.9%] subjects with genotype 3 HCV infection treated for 24 weeks).

**Table 9. Overall Summary of Adverse Events (6 to < 12 Years Old) (Safety Analysis Set)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=13) | Genotype 3 SOF + RBV x 24 weeks (n=28) | Total (N=41) |
|---|---|---|---|
| Any TEAE* | 9 (69.2%) | 26 (92.9%) | 35 (85.4%) |
| Maximum Toxicity Grade | | | |
| Grade 1 (mild) | 8 (61.5%) | 20 (71.4%) | 28 (68.3%) |
| Grade 2 (moderate) | 1 (7.7%) | 6 (21.4%) | 7 (17.1%) |
| Grade 3 (severe) | 0 | 0 | 0 |
| Grade 4 (life-threatening) | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 |
| Any SAE | 0 | 0 | 0 |
| Drug-related SAE | 0 | 0 | 0 |
| Drug-related TEAEs | 4 (30.8%) | 9 (32.1%) | 13 (31.7%) |
| Drug-related Grade 2 TEAE | 0 | 1 (3.6%) | 1 (2.4%) |
| Drug-related Grade 3 TEAE | 0 | 0 | 0 |
| TEAE Leading to Premature Discontinuation | 0 | 0 | 0 |
| TEAE Leading to Temporary Interruption | 0 | 1 (3.6%)* | 1 (2.4%) |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 62. Page 156.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
*Grade 1 AE of vomiting led to an interruption of SOF/RBV x 1 day

**Common Adverse Events**

Table 10 presents a summary of AEs reported for at least 10% of subjects 6 to < 12 years old in either treatment group by preferred term. Overall, the most commonly reported AEs across subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype 3 HCV infection treated for 24 weeks were vomiting (15.4% and 39.3%, respectively), headache (30.8% and 28.6%, respectively), fatigue (23.1% and 17.9%, respectively), and cough (7.7% and 25.0%, respectively).

**Table 10. Overall Summary of Common Adverse Events in at Least 10% of Subjects by Treatment Group (6 to < 12 Years Old)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=13) | Genotype 3 SOF + RBV x 24 weeks (n=28) |
|---|---|---|
| Total # of 35 AEs in 41 subjects | 9 (69.2%) | 26 (92.9%) |
| Commonest AEs | | |
| Vomiting | 2 (15.4%) | 11 (39.3%) |
| Headache | 4 (30.8%) | 8 (28.6%) |
| Fatigue | 3 (23.1%) | 5 (17.9%) |
| Cough | 1 (7.7%) | 7 (25.0%) |
| Nasopharyngitis | 1 (7.7%) | 4 (14.3%) |
| Decreased appetite | 2 (15.4%) | 2 (7.1%) |
| Diarrhea | 1 (7.7%) | 3 (10.7%) |
| Rhinorrhea | 1 (7.7%) | 3 (10.7%) |
| Nausea | 0 | 4 (14.3%) |
| Oropharyngeal pain | 0 | 4 (14.3%) |
| Pyrexia | 0 | 4 (14.3%) |
| Abdominal pain | 0 | 3 (10.7%) |
| Contusion | 0 | 3 (10.7%) |
| Gastroenteritis | 0 | 3 (10.7%) |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 63. Page 157.

**Adverse Drug Reactions (Related to Study Drug)**

Table 11 presents a summary of Adverse Drug Reactions (ADR) reported in > 1 subject 6 to < 12 years old in either treatment group by preferred term. The 3 most commonly reported ADRs across subjects with genotype 2 HCV infection treated for 12 weeks and subjects with genotype

3 HCV infection treated for 24 weeks were headache (7.7% and 14.3%, respectively), fatigue (23.1% and 3.6%, respectively), and decreased appetite (15.4% and 7.1%, respectively).

**Table 11. Treatment Related Adverse Events in > 1 Subject by Treatment Group (6 to < 12 Years Old)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=13) | Genotype 3 SOF + RBV x 24 weeks (n=28) |
|---|---|---|
| Total of 13 Treatment-Related AEs in 41 subjects | 4 (30.8%) | 9 (32.1%) |
| Commonest AEs | | |
| Headache | 1 (7.7%) | 4 (14.3%) |
| Fatigue | 3 (23.1%) | 1 (3.6%) |
| Decreased appetite | 2 (15.4%) | 2 (7.1%) |
| Nausea | 0 | 3 (10.7%) |
| Arthralgia | 0 | 2 (7.1%) |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 64. Page 158

**Deaths**
There were no deaths reported in the study.

Serious Adverse Events (SAEs)
There were no treatment-emergent serious adverse events for subjects 6 to < 12 years old.

**Discontinuations due to Adverse Events**
There were no discontinuations due to adverse events among subjects 6 to < 12 years old. There was one temporary interruption of study drug for one day due to a Grade 1 AE of vomiting.

**Drug-Related Adverse Events with Severe or Life-threatening Intensity**
None. All AEs were Grade 1 or 2 in severity.

**Laboratory Abnormalities**
The majority of subjects had at least 1 laboratory abnormality (26/41, 63.4%). All lab abnormalities were Grade 1 or 2 except for 1 subject (Genotype 3, who had a Grade 3 increased INR not associated with an AE). No subject with genotype 2 or genotype 3 HCV infection had Grade 3 or 4 hematology laboratory abnormalities. There was 1 subject with postbaseline hemoglobin < 10 g/dL (protocol guideline for RBV dose reduction/modification) and no subject with postbaseline hemoglobin < 8.5 g/dL. One subject, with a baseline hemoglobin value of 12.7 g/dL had a Grade 2 decrease in hemoglobin to 9.9 g/dL at Week 4 followed by return to a normal hemoglobin level at Week 8 and for the remainder of the study. Decreased hemoglobin is a known effect of RBV therapy. No clinically meaningful changes from baseline in neutrophils,

lymphocytes, hemoglobin, reticulocytes, and platelets were observed in either treatment regimen. No subject with genotype 2 HCV infection had Grade 3 or 4 chemistry laboratory abnormalities. One subject with genotype 3 HCV infection had a Grade 3 laboratory abnormality of increased INR (1 of 28 subjects, 3.6%) at Study Weeks 2, 4, and 20. The INR was Grade 0 to Grade 1 at all other time points and was Grade 0 at Week 24. No AEs were associated with this laboratory abnormality.

**Other Adverse Events**
There was no notable effect of treatment on development or growth (baseline to post-treatment Week 24) in Tanner stage, bone age, height, weight and BMI percentiles. There was no notable change from baseline to post-treatment Week 24 in vital signs (Systolic Blood Pressure, Diastolic Blood Pressure or pulse).

**Summary of Safety in Subjects 6 to < 12 years old**
All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. No subjects experienced SAEs. No deaths were reported. No subject prematurely discontinued SOF due to an AE. One subject with genotype 3 HCV infection treated for 24 weeks experienced a Grade 1 AE of vomiting that led to an interruption of SOF and RBV dosing for 1 day. There were no AEs consistent with progression of liver disease, such as AEs of hepatocellular carcinoma or hepatic decompensation.

### 8.2. Cohort 3: 3 to < 6 years old

Table 12 presents the overall summary of AEs for subjects 3 to < 6 years old by treatment group. All subjects (13 of 13, 100%) experienced at least 1 AE.

**Table 12. Overall Summary of Adverse Events (3 to < 6 Years Old) (Safety Analysis Set)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=5) | Genotype 3 SOF + RBV x 24 weeks (n=8) | Total (N=13) |
|---|---|---|---|
| Any TEAE* | 5 (100.0%) | 8 (100.0%) | 13 (100.0%) |
| Maximum Toxicity Grade | | | |
| Grade 1 (mild) | 5 (100.0%) | 5 (62.5%) | 10 (76.9%) |
| Grade 2 (moderate) | 0 | 3 (37.5%) | 3 (23.1%) |
| Grade 3 (severe) | 0 | 0 | 0 |
| Grade 4 (life-threatening) | 0 | 0 | 0 |
| Deaths | 0 | 0 | 0 |
| Any SAE | 0 | 1 (12.5%)* | 1 (7.7%) |
| Drug-related SAE | 0 | 0 | 0 |
| Drug-related TEAEs | 4 (80.0%) | 1 (12.5%) | 5 (38.5%) |
| Drug-related Grade 2 TEAE | 0 | 1 (12.5%) | 1 (7.7%) |
| Drug-related Grade 3 TEAE | 0 | 0 | 0 |
| TEAE Leading to Premature Discontinuation | 1 (20.0%)[$] | 0 | 1 (7.7%) |
| TEAE Leading to Temporary Interruption | 2 (40%)[#$] | 1 (12.5%)[#] | 3 (23.1%) |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 67. Page 170.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
*SAE in one GT3 subject – hospitalization due to RBV treatment overdose on Day 83 – stopped SOF/RBV until Day 92. Remained asymptomatic and was considered resolved on Day 102. [#]Two subjects interrupted SOF/RBV for 1 day due to Grade 1 vomiting. [$] Discontinued treatment due to abnormal taste

**Common Adverse Events**

Table 13 presents a summary of treatment-related AEs reported in at least 2 subjects 3 to < 6 years old in either treatment group by preferred term. Overall, the most commonly reported AEs across subjects with genotype 2 HCV infection treated for 12 weeks or genotype 3 HCV infection treated for 24 weeks were vomiting (60.0% and 37.5%, respectively) and diarrhea (40.0% and 37.5%, respectively).

**Table 13. Treatment Related Adverse Events in at Least 2 Subjects by Treatment Group (3 to < 6 Years Old)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=5) | Genotype 3 SOF + RBV x 24 weeks (n=8) |
|---|---|---|
| Total # of 13 AEs in 13 subjects | 5 (100.0%) | 8 (100.0%) |
| Vomiting | 3 (60.0%) | 3 (37.5%) |
| Diarrhea | 2 (40.0%) | 3 (37.5%) |
| Decreased appetite | 0 | 3 (37.5%) |
| Arthropod bite | 0 | 2 (25.0%) |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 68, Page 171.

**Adverse Drug Reaction (Related to Study Drug)**

Table 14 presents a summary of Adverse Drug Reactions (ADR) reported in at least 2 subjects 3 to < 6 years old in either treatment group by preferred term. Overall, the most commonly reported ADR in > 1 subject (2 of 5 subjects) was vomiting (40.0%).

**Table 14. Treatment Related Adverse Events in > 1 Subject by Treatment Group (3 to < 6 Years Old)**

| Adverse Events | Genotype 2 SOF + RBV x 12 weeks (n=5) | Genotype 3 SOF + RBV x 24 weeks (n=8) |
|---|---|---|
| Total of 5 Treatment-Related AEs in 13 subjects | 4 (80.0%) | 1 (12.5%) |
| Vomiting | 2 (40.0%) | 0 |

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-334-1112: Table 69, Page 172

**Deaths**

There were no deaths reported in the study.

**Serious Adverse Events (SAEs)**

One subject (12.5%) with genotype 3 HCV infection treated for 24 weeks experienced an SAE of accidental overdose of ribavirin on study Day 83 which required hospitalization for monitoring. The subject remained asymptomatic and the event was assessed as not related to study drug by the investigator. The SAE resolved on study Day 102. The SAE led to interruption of SOF and RBV from Day 83 to Day 92. SOF was restarted on Day 92; RBV dose was initially restarted at a lower dose on Day 92 and full dose was reintroduced on Day 102.

**Discontinuations due to Adverse Events**

One subject with genotype 2 HCV infection treated for 12 weeks discontinued study drug and study due to AEs. This subject, 4 years old, experienced a Grade 1 AE of vomiting of both SOF pellets and RBV oral solution, on Day 1. Study drug was not administered on Day 2. Study drug

administration was again attempted on Day 3 when the subject experienced a Grade 1 AE of product use issue (reported term spitting up dose) for both SOF pellets and RBV oral solution and a Grade 1 AE of abnormal product taste for SOF pellets, resulting in study drug and study discontinuation on Day 3.

**Drug-Related Adverse Events with Severe or Life-threatening Intensity**
None. All AEs were Grade 1 or 2 in severity.

**Laboratory Abnormalities and Other Adverse Events**
The majority of Subjects had at least 1 laboratory abnormality (10/12, 83.3%). All lab abnormalities were Grade 1 or 2. There was no notable effect of treatment on development or growth (baseline to post-treatment Week 24) in Tanner stage, bone age, height, weight and BMI percentiles. There was no notable change from baseline to post-treatment Week 24 in vital signs (Systolic Blood Pressure, Diastolic Blood Pressure or pulse).

**Summary of Safety in Subjects 3 to < 6 years old**
All subjects had at least 1 AE (100%). All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject with genotype 3 HCV infection experienced an SAE (accidental RBV overdose) resulting in interruption of treatment with SOF and RBV for 8 days. One subject with genotype 2 HCV infection prematurely discontinued SOF and RBV due to AEs (product use issue and abnormal product taste), and 2 subjects with genotype 2 HCV infection experienced Grade 1 AEs of vomiting that led to an interruption of SOF dosing for 1 day. No deaths were reported. There were no AEs consistent with progression of liver disease, such as AEs of HCC or hepatic decompensation.

### 8.3. Special Populations

The pediatric Chronic Hepatitis C (CHC) subjects evaluated in Study GS-US-334-1112 represent a special patient population, and no additional special subgroup analyses were performed given the low number of subjects that would be included in each subgroup.

### 8.4. Drug Interactions

No new findings relevant to the coadministration of SOF with other drugs are submitted with this update to the marketing application.

### 8.5. Use in Pregnancy and Lactation

No notable new findings relevant to use of SOF concomitantly with pregnancy or lactation were submitted with this update to the marketing application. No pregnancies were reported for pediatric CHC subjects in Study GS-US-334-1112.

## 9. Advisory Committee Meeting

An Advisory Committee Meeting was not held for this supplemental NDA application. No significant issues were raised to warrant a public discussion.

# 10. Pediatrics

See section 7.0 for discussion regarding efficacy and Section 8.0 for discussion regarding safety.

The Study was reviewed by the Pediatric Review Committee (PeRC) for the pediatric assessment and they agreed with our approval determination and that no additional Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMC) were indicated based on review of the data.

The Study was reviewed and approved for pediatric exclusivity by the Pediatric Exclusivity Board, and Exclusivity was granted as recommended by the Division.

# 11. Other Relevant Regulatory Issues

## 11.1 Submission Quality and Integrity

The quality and integrity of the submission were adequate. From a clinical review perspective, the submission was well organized and reasonable to navigate. The Division did not consult the Office of Scientific Investigations (OSI) for clinical inspection of the trial sites.

## 11.2 Compliance with Good Clinical Practices

As per the Sponsor, the clinical study included in this submission was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Council for Harmonisation (ICH) guideline for Good Clinical Practice (GCP), applicable governmental regulatory requirements, and in compliance with the respective protocols. These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312) and the European Community Directive 2001/20/EC.

The protocol, protocol amendments, administrative letters, and any accompanying material provided to the subject (such as advertisements, subject information sheets, subject dosing diaries, or descriptions of the study used to obtain informed consent/assent) were submitted by each investigator to a duly constituted independent ethics committee (IEC) or institutional review board (IRB) for review and approval before study initiation. Protocol amendments and all revisions to the consent form, assent form, or study subject information sheet after initial IEC/IRB approval were submitted by the investigator to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. The Sponsor maintains copies of all IEC/IRB approval letters in the trial master file.

## 11.3 Financial Disclosures

Gilead Sciences has submitted Form FDA 3454, which certifies that the Applicant (Study Sponsor) did not enter into any financial relationships with principle or sub-investigators. The

form included an attachment containing the names of principal investigators and sub-investigators for study GS-US-334-1112 who have attested to the absence of financial interests or arrangements described in 21 CFR Part 54.4(a)(3). There were a total of 201 investigators (41 Principal Investigators and 160 Sub-Investigators), all of whom certified that they have no disclosable financial interests. None of the investigators are Gilead employees. See the Appendix 2 for the Clinical Investigator Financial Disclosure Review.

# 12. Labeling

The USPI (United States Prescribing Information) and PPI (Patient Package Insert) have been agreed to and are summarized below.

The labeling has been updated to reflect changes in the indication, extending the population to chronic HCV genotype 2 or 3 infected pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis. The changes with this efficacy supplement primarily affected the following sections. These changes were accepted by Gilead. (b) (4)

(b) (4)

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

*This section was updated to reflect the changes made to the label as described below.*

**1 INDICATIONS AND USAGE**

*The following section was updated:*

Pediatric Patients:

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

**2 DOSAGE AND ADMINISTRATION**

**2.3 Recommended Dosage in Pediatric Patients 3 Years of Age and Older with Genotype 2 or 3 HCV**

*It was noted during the review that the recommended dosage in labeling differed from the protocol specified doses.*

***D***

(b) (4)

*This section was modified to extend the indication to children 3 years and older. Tables describing recommended treatment regimens by age, weight and genotype were revised for clarity. The word* (b) (4) *was changed to 'pellets' as a more accurate description of the formulation based on the USP 1151 Pharmaceutical Dosage Forms. The label was also revised to specify that non-acidic soft foods,* (b) (4) *be used with the oral pellets. Also, use of Sovaldi* in combination with ribavirin to treat HCV-infected adults in *genotype 2 or 3* for up to 48 weeks or until the time of liver

transplantation *was extended to children 3 years and older based on the adult safety data, and the similar pharmacokinetics and exposures compared to adults.*

*The revised language in this section is as follows:*

> The recommended treatment regimen, duration and recommended dosage for SOVALDI combination therapy is provided in Table 2 and Table 3. Table 4 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. Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs. Administer SOVALDI in combination with ribavirin for up to 48 weeks or until the time of liver transplantation, whichever occurs first, to prevent post-transplant HCV reinfection *[see Use in Specific Populations (8.8)].*

**Table 2. Recommended Treatment Regimen and Duration in Pediatric Patients 3 Years of Age and Older with Genotype 2, or 3 HCV**

| | 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 4 for weight-based ribavirin dosing recommendations.

> The recommended dosage of SOVALDI in pediatric patients 3 years and older with genotype 2 or 3 HCV using SOVALDI tablets (with or without food) or oral pellets (with non-acidic soft food) is based on weight (3), and is to be taken orally once daily in combination with ribavirin *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3) and Clinical Studies (14.5)]* d. SOVALDI pellets can be taken in pediatric patients who cannot swallow the tablet formulation *[see Dosage and Administration (2.4)].*

**Table 3 Dosing for Pediatric Patients 3 Years and Older Using SOVALDI Tablets or Oral Pellets**

| Body Weight (kg) | Dosing of SOVALDI Tablets or Oral Pellets | SOVALDI Daily Dose |
|---|---|---|
| at least 35 | one 400 mg tablet once daily<br>or<br>two 200 mg tablets once daily<br>or<br>two 200 mg packets of pellets once daily | 400 mg per day |
| 17 to less than 35 | one 200 mg tablet once daily<br>or<br>one 200 mg packet of pellets once daily | 200 mg per day |
| less than 17 | one 150 mg packet of pellets once daily | 150 mg per day |

**Table 4 Recommended Dosing for Ribavirin in Combination Therapy with SOVALDI for Pediatric Patients 3 Years and Older**

| Body Weight (kg) | Ribavirin Daily Dosage[a] |
|---|---|
| less than 47 | 15 mg per kg per day<br>(divided dose AM and PM) |
| 47–49 | 600 mg per day<br>(1 x 200 mg AM, 2 x 200 mg PM) |
| 50–65 | 800 mg per day<br>(2 x 200 mg AM, 2 x 200 mg PM) |
| 66–80 | 1000 mg per day<br>(2 x 200 mg AM, 3 x 200 mg PM) |
| greater than 80 | 1200 mg perday<br>(3 x 200 mg AM, 3 x 200 mg PM) |

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

### 2.4 Preparation and Administration of Oral Pellets

*This section was revised to clarify the types of foods that can be given with oral pellets.*

> Do not chew SOVALDI pellets. If SOVALDI pellets are administered with food, sprinkle the pellets on one or more spoonfuls of non-acidic soft food or liquid at or below room temperature. Examples of non-acidic foods include chocolate pudding, chocolate syrup, mashed potato, and ice cream. Take SOVALDI pellets within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.

*A comment was sent to the Sponsor requesting that the RBV dosing in Table entitled "Recommended Dosing for Ribavirin in Combination Therapy with SOVALDI for Pediatric Patients 3 Years of Age and Older" be revised to match the most recent version of the protocol.*

### 3. Dosage and Administration

*This section was revised to include the new 200 mg tablet formulation and the 150 mg and 200 mg pellet formulations. The word* (b) (4) *was changed to "pellets".*

### 6.1 Clinical Trials Experience

*In this section, under "Adverse Reactions in Pediatric Subjects 3 Years of Age and Older", The following sentences were added:*

> The adverse reactions observed were consistent with those observed in clinical studies of SOVALDI plus ribavirin in adults. Among pediatric subjects 3 years (b) (4) taking SOVALDI in combination with ribavirin oral solution, decreased appetite was observed in (b) (4) subjects *[see Clinical Studies 14.5)]*.

### 7.2 Drugs without Clinically Significant Interactions with SOVALDI

*The language was revised to align with the language in the HARVONI, EPCLUSA and VOSEVI USPIs, which all include Sovaldi in their combinations.*

> Based on drug interaction studies conducted with SOVALDI, no clinically significant drug interactions have been either observed or are expected when SOVALDI is combined with the following drugs *[see Clinical Pharmacology (12.3)]:* cyclosporine, darunavir/ritonavir, efavirenz, emtricitabine, methadone, oral contraceptives, raltegravir, rilpivirine, tacrolimus, or tenofovir disoproxil fumarate.

### 8.4 Pediatric Use

*Some minor changes were made in this section to expand the indication to pediatric subjects 3 years and older based on the results of Study GS-US-334-1112 and for consistency with revisions in Sections 6.1, 12.3 and 14.6 of the Full Prescribing Information (FPI).*

### 11 DESCRIPTION

*Additional information was added describing the new 200 mg tablet formulation and the 150 mg and 200 mg oral pellets.*

### 12 CLINICAL PHARMACOLOGY
### 12.3 Pharmacokinetics

Pediatric Patients

*Under this section, the text was edited to extend the indication to children 3 years and older. The Table entitled "Pharmacokinetic Properties of SOVALDI in HCV-infected Pediatric Subjects 3 Years of Age and Older" was edited* (b) (4)

(b) (4)

### 14 CLINICAL STUDIES
### 14.1 Description of Clinical Trials

*Under this section, the trial information was updated to include the total number of children enrolled from 3 to < 18 years old in Study GS-US-334-1112. Also, the Table entitled "Trials*

*Conducted with SOVALDI with Peginterferon Alfa and/or Ribavirin in Subjects with Chronic HCV Genotype 1, 2, 3, or 4 Infection" was updated to include Study GS-US-334-1112.*

### 14.5 Clinical Trial in Pediatrics (Study 1112)

*This section was updated with the most recent data in the Final Clinical Study Report and the accompanying datasets. The number enrolled and treated in the 12 to < 18 year old group was updated* (b) (4) *given that this was the final correct number, and the accompanying percentages were revised. The following two sections on the 6 to < 12 years old and the 3 to < 6 years old were added:*

*Subjects 6 Years to <12 Years of Age:* SOVALDI was evaluated in 41 subjects 6 years to <12 years of age with HCV genotype 2 (N = 13) or genotype 3 (N = 28) infection. The median age was (b) (4) years (range: 6 to 11); 73% of the subjects were female; 71% were White and 20% were Asian; 15% were Hispanic/Latino; mean body mass index was 19 kg/m2 (range: 13 to 32 kg/m2); mean weight was 34 kg (range 15 to 80 kg); 98% were treatment naive; 46% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no subjects had known cirrhosis. The majority of subjects (98%) had been infected through vertical transmission. The SVR12 rate was 100% (13/13) in genotype 2 and 100% (28/28) in genotype 3 subjects.). No subjects experienced on-treatment virologic failure or relapse.

*Subjects 3 Years to <6 Years of Age:* SOVALDI was evaluated in 13 subjects 3 years to <6 years of age with HCV genotype 2 (N = 5) or genotype 3 (N = 8) infection. The median age was 4 years (range: 3 to 5); 77% of the subjects were female; 69% were White, 8% were Black, and 8% were Asian; 8% were Hispanic/Latino; mean body mass index was 15 kg/m2 (range: 13 to 17 kg/m2); mean weight was 17 kg (range 13 to 19 kg); 100% were treatment naive; 23% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; and no subjects had known cirrhosis. The majority of subjects (85%) had been infected through vertical transmission. The SVR12 rate was 80% [4/5] in genotype 2 subjects and 100% [8/8] in genotype 3 subjects. No subjects experienced on-treatment virologic failure or relapse. One subject prematurely discontinued study treatment due to an adverse event.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

*This section was revised to include the description for the Sovaldi 200 mg oral tablet, and the 150 mg and 200 mg oral pellets.*

**Patient Information**
**What is SOVALDI?**
**How should I take SOVALDI?**
**How should I give SOVALDI oral pellets to my child?**
**How should I store SOVALDI?**
**What are the ingredients in SOVALDI?**

*These Sections were revised for consistency with changes made in the FPI.*

## 13. Postmarketing Recommendations

*Risk Evaluation and Management Strategies (REMS)*

No recommendation for a REMS is indicated.

*Postmarketing Requirements (PMRs) and Commitments (PMCs)*

No PMRs or PMCs are indicated.

# 14. Recommended Comments to the Applicant

No additional comments need to be communicated to the Applicant at this time.

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# Appendix 1

Patient Experience Data for Harvoni in children 3 to < 12 years old with HCV infection were collected within the clinical trials. The following is a summary of the data collected in this study (GS-US-334-1112).

- Quality of life data were collected via completion of the PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) by the study subject and/or their parent/guardian. The SF15 questionnaire represented 4 domains: physical, emotional, social and school functioning, with the emotional, social and school functioning domains representing the psychosocial health summary. the following is a general summary of the findings in the three age groups studied. In both groups, 3 to < 6 years old and 6 to < 12 years old, there were no statistically significant ($p < 0.05$) mean changes in physical or psychosocial functioning scores in either treatment group per either the parent's reports or the subject's reports during treatment (baseline to EOT) or during follow up (end of treatment to posttreatment Week 24).

- Formulation acceptability was evaluated via a swallowability assessment of the tablet formulation by subjects aged 6 to < 12 years old to determine if they should be given the tablet or oral pellet formulation and via a palatability assessment of the oral pellet formulation on Day 1 by subjects who received that formulation. In Study GS-US-334-1112, among the 6 to < 12 year olds, one subject inadvertently performed the swallowability assessment with the 400 mg SOF tablet, but was subsequently administered SOF 100 mg tablets. Of the remaining 40 subjects, 34 of 40 (85%) who performed the swallowability assessment with the 100 mg tablet were able to swallow it. The remaining 6 subjects were administered SOF as 4 x 50 mg capsules containing the SOF pellets. Of the 7 subjects who were administered oral pellets, 3 subjects (42.9%) were able to taste the pellets. All 3 subjects were able to complete treatment.

# Appendix 2

Clinical Investigator Financial Disclosure Review

Application Number: NDA 204671/212480

Submission Date(s): February 28, 2019

Applicant: Gilead Sciences, Inc.

Product: Sofosbuvir (Sovaldi)

Reviewer: Samer El-Kamary, MD, MPH

Date of Review: April 4, 2019

Covered Clinical Study (Name and/or Number):
*A Phase 2, Open-Label, Multicenter, Multi-cohort, Single-Arm Study to Investigate the Safety and Efficacy of Sofosbuvir + Ribavirin in Adolescents and Children with Genotype 2 or 3 Chronic HCV Infection (Study Number: GS-US-334-1112 [Group 2])*

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from applicant) |
| Total number of investigators identified: 201 (41 Principal Investigators and 160 Sub-Investigators) | | |
| 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): 3 | | |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0<br>Significant payments of other sorts: 3<br>Proprietary interest in the product tested held by investigator: 0<br>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: | Yes ☒ | No ☐ (Request explanation from applicant) |

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

*The Sponsor adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for Industry, Financial Disclosure by Clinical Investigators, and by 21 CFR 54.4.*

*None of the 201 Investigators for Study GS-US-334-1112 are employed by the Sponsor. Three of the investigators, representing 1.5% (3/201) of the total number of investigators, have disclosable financial interests/arrangements which the Sponsor defined as 'Significant payment of other sorts > $25,000'.*

(b) (6)

[redacted]

[1] See https://www.fda.gov/media/85293/download.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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KIMBERLY A STRUBLE
08/27/2019 02:35:32 PM
Signing on behalf of Samer El-Kamary MD MPH clinical reviewer. I concur with the review

DEBRA B BIRNKRANT
08/27/2019 03:48:18 PM