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

Date	August 27, 2019
From	Samer El-Kamary, MD, MPH, Medical Officer Kimberly Struble, PharmD, Cross-Discipline Team Leader Debra Birnkrant, MD, Division Director
Subject	Combined Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Memo
NDA# and Supplement#	205834/Supplement 29 212477
Applicant	Gilead Sciences, Incorporated.
Date of Submission	February 28, 2019
PDUFA Goal Date	August 28, 2019
Proprietary Name	Harvoni
Established or Proper Name	Ledipasvir/Sofosbuvir (LDV/SOF)
Dosage Form(s)	Oral tablets: ▪ 45 mg ledipasvir and 200 mg sofosbuvir Oral pellets: ▪ 45 mg ledipasvir and 200 mg sofosbuvir ▪ 33.75 mg ledipasvir and 150 mg sofosbuvir
Applicant Proposed Indication(s)/Population(s)	Pediatric Patients 3 to < 12 years of age: For treatment of genotype 1, 4, 5 and 6 HCV infection
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Table 2)
Recommendation on Regulatory Action	Approval

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I. Executive Summary

Summary of Regulatory Action

The new drug application (NDA) for HARVONI® (ledipasvir/sofosbuvir; LDV/SOF) 33.75 mg/150 mg and 45 mg/200 mg oral pellets and the supplemental NDA for LDV/SOF 45/200 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. LDV/SOF will be approved for children three years of age and older with:

- Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- Genotype 1 infection with decompensated cirrhosis, in combination with ribavirin
- Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, in combination with ribavirin.

The Applicant submitted a multicenter, open-label, non-comparative trial in which 124 children (90 children 6 to < 12 years old, and 34 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 LDV/SOF dose was based on the child's weight, with tablets for those who could swallow them and pellets for the younger age groups. The LDV exposure, 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 LDV/SOF in adults and adolescents.

The efficacy outcome, as measured by sustained virologic response 12 weeks after treatment discontinuation (SVR12) was 98.3% (119/121) for genotype 1 and 100% (3/3) for genotype 4, and they also normalized their alanine aminotransferase (ALT). Only two subjects did not achieve SVR12 and did not normalize their ALT (one had a virologic failure [relapse] and another one had discontinued treatment due to unplatability of the drug). LDV/SOF 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. • 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. • 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. • There is no vaccine and no post-exposure immunoprophylaxis available for HCV.	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. • 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 younger than 12 years of age 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. 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 LDV/SOF (Harvoni) for the treatment of children with 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-337-1116), which is a Phase 3, open-label, non-comparator trial. • In this study, 126 subjects aged 3 years to less than 12 years of age with chronic HCV infection genotype 1 (n=120), and genotype 4 (n=3) were treated with LDV/SOF once daily for 12 weeks (treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis); one subject with genotype 1 was treated with LDV/SOF once daily for 24 weeks (treatment experienced with cirrhosis); and two subjects with genotype 3 (n=2) were treated with LDV/SOF + ribavirin (RBV) for 24 weeks. • Given that Harvoni is not approved for treatment of genotype 3, the efficacy of genotype 3 was not taken into consideration, and only the safety data related to these two subjects was assessed. These were also the only two subjects in this cohort to receive RBV, thereby providing information on safety and tolerability of RBV with LDV/SOF for 24 weeks . • The study demonstrated a high efficacy among those who received treatment. A total of 98.3% of patients with genotype 1, and 100% with genotype 4 who received the treatment achieved a sustained virolocal response at week 12 (SVR12) which is an indication of complete viral clearance and cure. Also, all subjects who achieved SVR12 achieved ALT normalization. • In HCV-infected adults, LDV/SOF is approved to treat patients with genotype 5 or 6; however, no genotype 5 or 6 pediatric subjects were enrolled in the current trial. HCV genotype does not affect LDV/SOF exposure and previous trials in adults have demonstrated that an equivalent LDV/SOF exposure is efficacious in adults with chronic HCV genotype 5 and 6. Therefore, the submitted PK data are adequate to support the efficacy of LDV/SOF for treatment of HCV genotypes 5 or 6 in patients 3 years of age and older. A similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1 infection who have decompensated cirrhosis (Child-Pugh B or C) and for pediatric patients	LDV/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 achieved SVR12, which is reflective of reduced hepatic inflammation. 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. The SVR12 results were similar between the age cohorts and also similar with the adult and adolescent population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with HCV genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis	
Risk and Risk Management	LDV/SOF had a few mild side-effects, the most common of which were vomiting, headache, fatigue, nausea, pyrexia, abdominal pain, cough,vomiting 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. 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. The safety results were similar between the age cohorts and also similar with the adolescent population. Based on the available safety profile for LDV/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 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 of LDV/SOF is favorable as demonstrated by the high SVR12 rates (98.3% (119/121) for genotype 1 and 100% (3/3) for genotype 4). LDV/SOF 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 availability of LDV/SOF for children less than 12 years of age is a major public health benefit and offers children three years of age and older with HCV genotype 1, 4, 5 and 6 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-337-1116. 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-337-1116 Synopsis, Section 12.1
		☒	Observer reported outcome (ObsRO)	Clinical study report CSR for Study GS-US-337-1116 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		Module 2.5, Section 2.5; GS-US-337-1116

			GS-US-337-1116.	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.

Ledipasvir/sofosbuvir (LDV/SOF, Harvoni®) was first approved for commercial marketing in the United States (US) on 10 October 2014, and is indicated for the treatment of genotype 1, 4, 5, or 6 HCV infection. The marketing application for LDV/SOF was updated on 07 April 2017 in the US to expand the indication for the treatment of patients 12 years of age and older, or weighing at least 35 kg, with genotype 1, 4, 5, or 6 HCV infection. A country-specific protocol amendment was created to allow for the enrollment of pediatric subjects with genotype 3 in Europe to receive LDV/SOF+RBV x 24 weeks. Because LDV/SOF is not approved for genotype 3 adults in the United States, no genotype 3 pediatric subjects were enrolled in the US, and they were not included in this clinical review.

In this supplemental NDA, LDV/SOF was evaluated in a single open-label, uncontrolled, pharmacokinetic (PK), safety, and efficacy trial in 124 children 3 to less than 18 years old in four countries (US, UK, Australia and New Zealand). 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 LDV/SOF, 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 (NDA 205834) fulfills the following outstanding post-marketing requirements (PMR) under the Pediatric Research Equity Act (PREA):

- PMR 2780-1 under PREA to provide data for 3 to <18 year old HCV-infected children.
- PMR 2983-1 and 2985-1 to evaluate the PK, safety and HCV treatment response of LDV/SOF in children 3 to <18 years of age.

The efficacy supplement also supports a new oral pellet formulation for children (NDA 212477) mg tablet and is a response to the pediatric written request.

This supplement provides the final data from Study GS-US-337-1116 through post-treatment Week 24 from in a Final Clinical Study Report (CSR) for evaluating the proposed indication for LDV/SOF in the treatment of genotype 1 and 4 chronic HCV infection for all children 3 to < 18 year old. Although the protocol allowed for the enrollment of genotypes 5 and 6, none could be enrolled. **Only data for pediatric subjects 3 to < 12 years old are presented in this clinical review.** *Data for the adolescent age group 12 to < 18 years old were presented in the GS-US-337-1116 Interim CSR submitted in 2016, and the LDV/SOF was approved for that age group in 2017. For a full clinical review of the data for adolescent subjects 12 to < 18 years old, please refer to Dr. Virginia Sheikh's review in the original NDA 205834.*

2.1. Product Information

Tablets

HARVONI tablets are fixed-dose combination tablets containing ledipasvir and sofosbuvir for oral administration. Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase. Each 90 mg/400 mg tablet contains 90 mg ledipasvir and 400 mg sofosbuvir. Each 45 mg/200 mg tablet contains 45 mg ledipasvir and 200 mg sofosbuvir.

Pellets

HARVONI oral pellets are for oral administration, supplied as small, orange pellets in unit-dose packets. Each unit-dose of HARVONI oral pellets contains either 45 mg ledipasvir and 200 mg sofosbuvir or 33.75 mg ledipasvir and 150 mg sofosbuvir

2.2. Summary of Regulatory Activity Related to Submission

In the US, Study GS-US-336-1117 was conducted in accordance with postmarketing requirements under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).

- The agreed pediatric plan for LDV/SOF in the treatment of HCV infection was submitted to the FDA to Investigational New Drug (IND) 115268 on 02 January 2014(Serial No. 0119) and to New Drug Application (NDA) 205834 on 08 February 2014(Seq No. 0000).
- A Written Request (WR) for studies of LDV/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. 0177).

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-337-1116, entitled, *A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination +/- Ribavirin in Adolescents and Children with Chronic HCV-Infection*; is a two-phase, pharmacokinetic, safety and efficacy study of ledipasvir/sofosbuvir (LDV/SOF) for the treatment of pediatric subjects with genotype 1, 4, 5 or 6 chronic HCV infection. The trial was designed to enroll 220 pediatric subjects from 3 to <18 years of age sequentially by descending age cohort (100 adolescents subjects 12 to < 18 years of age; and 120 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 2016 and was approved for this adolescent age group in 2017. ***This current 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 one of the following treatments based on country of enrollment, HCV genotype, prior treatment experience, and cirrhosis status. A country-specific protocol amendment was created to allow for the enrollment of pediatric subjects with genotype 3 in Europe to receive LDV/SOF+RBV x 24 weeks. However, since LDV/SOF is not approved for genotype 3 in the United States, they were not included in section 7.1.3 for Efficacy assessment. Otherwise they were included in Section 7.1.2 for their demographic and Baseline Characteristics and in Section 8.0 for Safety. . Subjects received the following regimen based on past treatment, presence of cirrhosis and HCV genotype:

- Treatment naive with or without cirrhosis:
  - Subjects with genotype 1, 4, 5 or 6: LDV/SOF x 12 weeks
- Treatment experienced without cirrhosis:
  - Subjects with genotype 1, 4, 5 or 6: LDV/SOF x 12 weeks
  - Subjects with genotype 3: LDV/SOF+RBV x 24 weeks
- Treatment experienced with cirrhosis:
  - Subjects with genotype 1: LDV/SOF x 24 weeks
  - Subjects with genotype 4, 5 or 6: LDV/SOF x 12 weeks
  - Subjects with genotype 3: LDV/SOF+RBV x 24 weeks

The trial was conducted in two phases. The first phase was a 10-day 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 LDV/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 LDV/SOF for 12 weeks in HCV-infected pediatric subjects infected with genotype 1, 4, 5 or 6 without cirrhosis, and those with genotype 1 and cirrhosis to be treated with LDV/SOF for 24 weeks. 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 PK lead-in phase evaluated and/or confirmed the dose of LDV/SOF by analyzing PK and safety of LDV/SOF administered through 10 days of dosing for each cohort. The age cohorts, each with at least 10 treatment-naive subjects without history of cirrhosis were sequentially enrolled with the following weight limits:

- 6 to < 12 years old weighing ≥ 17 kg and < 45 kg
- 3 to < 6 years old with (at least 4 subjects weighing ≥ 17 kg and at least 4 subjects weighing < 17 kg)

Intensive PK and safety results through Day 10 of treatment for each cohort were reviewed to confirm the appropriateness of the evaluated LDV/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. Additional treatment-naive or treatment-experienced subjects were enrolled into the treatment phase upon confirmation of the age-appropriate LDV/SOF dose from the PK lead-in phase. No weight limits applied to the additional subjects enrolled in the treatment phase.

In this submission, the main inclusion criteria for enrolled children from 3 to <12 years of age included: evidence of chronic HCV infection through the presence of one of the following in the previous six months: positive anti-HCV antibody test, positive HCV RNA, or positive HCV genotyping (positive genotype 1, 4, 5 or 6). 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 weight ≥ 17 kg and < 45 kg and be treatment naïve and non-cirrhotic. Exclusion criteria included: 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. Evidence of hepatocellular carcinoma or other malignancy.

Subjects in this study protocol received LDV/SOF orally once daily as oral tablets or pellets as shown in the Table 1 (two subjects with genotype 3 received LDV/SOF+RBV). RBV was administered by tablet or oral solution as shown in Table 2:

Table 1: Dosage of LDV/SOF by Weight in Study Protocol GS-US-337-1116

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Pellets
≥ 45	LDV/SOF (90/400 mg) orally once daily
≥ 17 and < 45	LDV/SOF (45/200 mg) orally once daily
< 17	LDV/SOF (33.75/150 mg orally once daily

Source: Summarized from Clinical Study Report GS-US-337-1116: Text – Pages 44, 47, 48

LDV/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 (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. Source: protocol

Intensive PK and safety results from the PK lead-in phase of each cohort confirmed the appropriateness of the LDV/SOF dose for the treatment phase for that age group.

All subjects were to complete the following visits: screening, Day 1, Weeks 1, 2, 4, 8, and 12 (and Weeks 16, 20, and 24 for the 24-week treatment group) during the treatment phase followed by post-treatment visits 4, 12, and 24 weeks after discontinuation of therapy. For subjects who participated in the PK lead-in phase, the first visit in the treatment phase was the Week 2 visit.

Subjects 3 to < 6 years old providing (parental) written consent were eligible for participation in an optional intensive PK substudy. Intensive serial PK blood samples were collected at Week 4 or 8 at the following time points: 0 (predose), 0.5, 1, 2, 3, 4, 5, 8, and 12 hours postdose (with predose also serving as t = 24). Subjects providing separate and specific consent were eligible for participation in the pharmacogenomics substudy. A blood sample was drawn for this substudy at the Day 1 visit or at any time during the study.

The primary efficacy endpoint was sustained virologic response at post-treatment week 12 (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, proportion of subjects with HCV RNA < LLOQ by study visit while on treatment and during the posttreatment follow-up period, HCV RNA log10 IU/mL and changes from baseline through end of treatment, the proportion of subjects with virologic failure, and the proportion of subjects with alanine aminotransferase (ALT) normalization..

Safety was monitored by assessment of Adverse Events, concomitant medications, clinical safety, laboratory tests, Tanner staging, and growth. Safety was analyzed using descriptive statistics. Trial GS-US-336-1117 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 (10 July 2014) was amended 6 times. Key changes to the protocol for each amendment were as follows:

- The protocol was amended for the first time on 7 February 2014; key changes in this amendment included the removal of Russia as a study site from the trial; updating the futility rule to suspend enrollment if 3 or more of the first 10 subjects enrolled have viral breakthrough or are nonresponders at or prior to Week 8. Included genotype 3 as an exclusion criteria. Additional changes included administrative updates, formulation, packaging and storage updates.
- The protocol was amended for the second time on 8 December 2014. Key changes in Amendment 2 included updates to the design and statistical analysis to include a treatment period of 24 weeks with LDV/SOF for treatment-experienced subjects with cirrhosis, to comply with the approved US prescribing information. Additional adminsitrative and formatting and minor updates were made.
    - Amendment 2.1 (specific to UK only): The protocol was next amended on 9 January 2015 to include an update in the study design and staitistical analysis to include a treatment period of 24 weeks with LDV/SOF+RBV for treatment-experienced and/or cirrhotic subjects with genotype 3 HCV infection, to comply with the approved UK prescribing information; added weigh-based ribavirin dosing and other instructions related to inclusion, exclusion criteria and stopping rules for subjects receiving ribavirin.
    - Amendment 2.2 (specific to UK only): The protocol was next amended on 1 April 2015 to update inclusion/exclusion criteria.
- The protocol was amended for the third time on 28 May 2015. Key changes in this amendment included an update to clarify that genotype 3 subjects would only be enrolled in the UK. Updates were made to the eclusion criteria and statistical analysis. Amiodarone was added to the disallowed agents in the prior and concomitant medications section. Other clarifications and minor updates were made.
- The protocol was amended for the fourth time on 15 March 2016. This amendment included an update of the study design and staistical analysis to include genotypes 5 and 6 after supporting data from adults became available. Additional clarifications and minor updates were made.
- The protocol was amended for the fifth time on 4 November 2016. Changes made in this amendment included information regarding oral granule formulation dosing, labeling,

packagaing and storage; added Phase 1 bioavailability data to support use of oral granule formulation; added additional hepatitis B virus (HBV) serological testing (HBsAb and HBcAb) at screening and specified that serial HBV DNA monitoring for any subjects who were HBcAb positive at screening, per a FDA communication.

- The protocol was amended for the sixth time on 8 June 2017. Changes were made to update the study design and statistical section to increase the number of subjects from 200 to 220; added a palatability assessment for LDV/SOF oral granules at Day 1 for subjects 3 to < 6 years old; and included an optional intensive PK substudy, for subjects 3 to < 12 years who provided written consent. Additional formatting and minor grammatical corrections and updates were made throughout the document.

3. Product Quality

Oral tablets are already approved for use in adolescents and adults (90 mg LDV/400 mg SOF; and 45 mg LDV/200 mg SOF). A new formulation in the form oral pellets (45 mg LDV/200 mg SOF; and 33.75 mg LDV/150 mg SOF), were developed for use in children. *Please refer to the original review of Chemistry, Manufcaturing and Control (CMC) in NDA 205834 and NDA 212477 for additional information.*

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data was submitted, see original NDA 205834 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 120 subjects enrolled into the 3 to < 12 years old group, a 2-sided 95% CI of the SVR12 rate would extend at most 5.4% in both directions from the observed SVR12 rate assuming the expected SVR12 rate is 90%.

A total of 124 subjects were enrolled in to the 3 to < 12 year old group (34 enrolled in the 3 to < 6 year old group, and 90 in the 6 to < 12 year old group). This exceeded the planned sample of 120 subjects needed for the statistical analysis.

The following is a summary of the disposition and demographics of study subjects and the assessment of efficacy for each of the two cohorts separately (6 to < 12 years and 3 to < 6 years).

7.1. 6 to < 12 years old cohort

7.1.1. Disposition of Subjects

Ninety seven subjects were screened; 92 of these were enrolled and received study drug. This included 87 subjects with Genotype 1; two subjects with genotype 4 who were enrolled to receive LDF/SOF for 12 weeks (treatment naive/experienced without cirrhosis; or treatment naive with cirrhosis); one subject with genotype 1 who received LDV/SOF for 24 weeks (treatment experienced with cirrhosis), and 2 subjects with genotype 3 treated with LDV/SOF + RBV for 24 weeks. All 92 subjects completed treatment. The two genotype 3 subjects were enrolled and treated in Europe (United Kingdom). However, since LDV/SOF is not approved for genotype 3 in the United States, they were not included in this review in section 7.1.3 for Efficacy assessment. Otherwise they were included in Section 7.1.2 for their Demographic and Baseline Characteristics and in Section 8.0 for Safety.

All sites enrolled patients, with no more than 1-8 patients per site. A total of of 11 important protocol deviations occurred in 9 subjects during the study. Of the 9 subjects, 7 subjects had a single important deviation and 2 subjects had 2 important deviations. The majority of important protocol deviations were for deviations of informed consent (9 of 11 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 92 subjects. Demographics and baseline characteristics are shown in Table 3.

Characteristic	LDV/SOF x 12 weeks (n=89)*		LDV/SOF x 24 weeks**	LDV/SOF + RBV x 24 weeks	Total (n=92)
	Genotype 1 (n=87)	Genotype 4 (n=2)	Genotype 1 (n=1)	Genotype 3 (n=2)	
Mean Age in years at baseline (range)	8.6 (6,11)	2 (7, 11)	1 (11, 11)	9 (7,11)	9 (6, 11)
Sex Number (%)					
Male	51 (56.7%)	2 (100%)	0	1 (50%)	54 (58.7%)
Female	36 (40.0%)	0	1 (100%)	1 (50%)	38 (41.3%)
Race: Number (%)					
White	68 (76%)	2 (100%)	1 (100%)	2 (100%)	73 (79.3%)
African American or Black	7 (7.8%)	0	0	0	7 (7.6%)
Asian	5 (5.6%)	0	0	0	5 (5.4%)
Native Hawaiian or Pacific Islander	2 (2.2%)	0	0	0	2 (2.2%)
Other	5 (5.6%)	0	0	0	5 (5.4%)
Ethnicity: Number (%)					
Hispanic or Latino	9 (10.0%)	0	0	0	9 (9.8%)
Not Hispanic or Latino	74 (82.2%)	1 (50%)	1 (100%)	2 (100%)	78 (84.8%)
Not Disclosed	4 (4.4%)	1 (50%)	0	0	5 (5.4%)
Region					
US	69 (76.7%)	1 (50%)	0	0	70 (76.1%)
Non-US	18 (20%)	1 (50%)	1 (100%)	2 (100%)	20 (23.9%)

Source: Analysis of ADSL ADAM dataset.
*Treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

Baseline HCV disease characteristics are shown in Table 4.

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

Disease Characteristic	LDV/SOF x 12 weeks (n=89)*		LDV/SOF x 24 weeks**	LDV/SOF + RBV x 24 weeks	Total (n=92)
	Genotype 1 (n=87)	Genotype 4 (n=2)	Genotype 1 (n=1)	Genotype 3 (n=2)	
HCV genotype					
Genotype 1					
Genotype 1 (no confirmed subtype)	1 (1.1%)	0	0		1 (1.1%)
Genotype 1a	76 (84.4%)	0	1 (100%)	0	77 (83.7%)
Genotype 1b	10 (11.1%)	0	0	0	10 (10-.9%)
Genotype 3		0	0	2 (100%)	2 (2.2%)
Genotype 4		2 (100%)	0	0	2 (2.2%)
Cirrhosis					
No	32 (36.8%)	1 (50%)	0	2 (100%)	35 (38.0%)
Yes	1 (1.1%)	0	1 (50%)	0	2 (2.2%)
Unknown	54 (62.1%)	1 (50%)	1 (50%)	0	55 (59.8%)
IL28B					
CC	23 (25.8%)	0	0	0	23 (25.0%)
CT	51 (57.3%)	2 (100%)	0	2 (100%)	55 (59.8%)
TT	12 (13.5%)	0	1 (100%)	0	13 (14.1%)
Baseline HCV RNA (log_{10}/mL)					
Mean (range)	6.0 (4.6, 7.3)	6.0 (5.8, 6.2)	6.2 (6.2, 6.2)	5.7 (5.5, 5.9)	6.0 (4.6, 7.3)
Baseline ALT (U/L)					
Mean (range)	65.9 (14, 255)	44 (26, 62)	94 (94, 94)	70 (58, 82)	66 (14, 255)
Prior HCV Treatment					
Treatment naïve	70 (77.8%)	0	1 (100%)	0	72 (78.3%)
Treatment experienced	17 (18.9%)	2 (100%)	0	2 (100%)	20 (21.7%)
Mode of HCV Infection					
Vertical transmission	84 (93.3%)	2 (100%)	1 (100%)	2 (100%)	89 (96.7%)

Blood product transfusion	1 (1.1%)	0	0	0	1 (1.1%)
Unknown	2 (2.2%)	0	0	0	2 (2.2%)

Source: Data analysis of ADSL ADAM dataset in Study GS-US-337-1116.
*Treatment naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

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. In this section, only the 90 subjects with genotypes 1 and 4 were assessed. The two subjects with genotype 3 were excluded. The SVR12 for the 87 subjects with genotype 1 who received LDV/SOF x 12 weeks was 98.9% (86/87) and for the 2 subjects with genotype 4 who received LDV/SOF x 12 weeks it was 100%) (2/2); and for the one subject with genotype 1 with cirrhosis who LDV/SOF x 24 weeks it was 100% (1/1). Overall, the SVR12 for genotype 1 was 87/88 (98.9%). One subject (1.1%, 1 of 90), who was treatment naive with genotype 1a HCV infection and cirrhosis, relapsed after completion of treatment with LDV/SOF for 12 weeks . The subject relapsed at the post-treatment Week 4 visit and was reported to have 97.6% study drug adherence.

Although the primary statistical analysis of SVR12 was descriptive, the SVR12 for genotypes 1 and 4 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 individuals except one had a 100% SVR12 and only a descriptive presentation was provided (Source: Clinical Study Report GS-US-3374-1116, Tables 41 & 42, pages 121-124).

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 was only one treatment failure (relapse at SVR4).

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

	LDV/SOF x 12 weeks (n=89)*		LDV/SOF x 24 weeks**	Total (n=90)
	Genotype 1 (n=87)	Genotype 4 (n=2)	Genotype 1 (n=1)	
Baseline	0/87	0/2	0/1	0/90
Week 1	27/87 (31.0%)	0/2	0/1	27/90 (30.0%)
Week 2	62/87 (71.3%)	2/2 (78.6%)	1/1 (100%)	62/90 (68.9%)
Week 4	84/87 (96.6%)	2/2 (100%)	1/1 (100%)	87/90 (96.7%)
Week 8	87/87 (100%)	2/2 (100%)	1/1 (100%)	90/90 (100%)
Week 12	87/87 (100%)	2/2 (100%)	1/1 (100%)	90/90 (100%)
Week 16	N/A	N/A	1/1 (100%)	90/90 (100%)
Week 20	N/A	N/A	1/1 (100%)	90/90 (100%)
Week 24	N/A	N/A	1/1 (100%)	90/90 (100%)
Post-Treatment Week 4 (SVR4)	86/87 (98.9%)	2/2 (100.0%)	1/1 (100%)	89/90 (98.9%)
Post-Treatment Week 4 (SVR12)	86/87 (98.9%)	2/2 (100.0%)	1/1 (100%)	89/90 (98.9%)
Post-Treatment Week 4 (SVR24)	86/87 (98.9%)	2/2 (100.0%)	1/1 (100%)	89/90 (98.9%)

Source: Data analysis of ADEFF ADAM dataset in Study GS-US-337-1116; and extracted from Clinical Study Report GS-US-337-1116: Text page 117, and Tables 38, 39, 40 and 43 (pages 118 to 120, 125-126).
*Treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

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 LDV/SOF. In the LDV/SOF x 12 week group, 80.9% of subjects (72 of 89) had ALT > ULN at baseline. Normalization of ALT was observed in 93.1% (67 of 72 subjects) at Week 4. Of the remaining 5 subjects, 3 had normalized ALT at Week 8, 1 had normalized ALT at post-treatment Week 4, and 1 who experienced virologic failure did not have normalized ALT. The 1 subject in the LDV/SOF x 24 week groups had ALT > ULN at baseline and had normalized ALT at Week 12. *Hence, all subjects normalized their ALT except for the one subject who had virologic failure.*

7.2. 3 to < 6 years old cohort

7.2.1. Disposition of Subjects

Thirty six subjects were screened; 34 of these were enrolled and received study drug. This included 33 subjects with Genotype 1 and one subject with Genotype 4, all of whom who were enrolled to receive LDV/SOF for 12 weeks. No subjects with genotypes 3, 5 or 6 were enrolled

in this age group. Thirty three of 34 subjects (97.1%) completed treatment, one genotype 1 subject discontinued treatment due to an Adverse Event of "abnormal product taste". All sites enrolled patients, with no more than 1-8 patients per site. A total of 5 important protocol deviations occurred in 5 subjects during the study. The only important protocol deviation that occurred in more than one subject was for treatment compliance. Relevant protocol deviations were proportionally distributed among study sites. None of these protocol deviations affected the overall quality or interpretation of the study data.

7.2.2. Demographic and Baseline Characteristics

The Full Analysis Set included 34 subjects. Demographics and baseline characteristics are shown in Table 6.

Table 6. Demographics and Baseline Characteristics

Characteristic	Genotype 1 (n=33) or Genotype 4 (n=1)
Mean Age in years (range)	4 (3, 5)
Sex Number (%)	
Male	10 (29.4%)
Female	24 (70.6%)
Race: Number (%)	
White	27 (79.4%)
African American or Black	1 (2.9%)
Asian	2 (5.9%)
Native Hawaiian or Pacific Islander	0
American Indian or Alaskan Native	0
Other	4 (11.8%)
Ethnicity: Number (%)	
Hispanic or Latino	6 (17.6%)
Not Hispanic or Latino	28 (82.4%)
Region	
US	29 (85.3%)
Non-US	5 (14.7%)

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-337-1116, Table 23. Page 99-100.

Baseline HCV disease characteristics are shown in Table 7.

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

Disease Characteristic	Genotype 1 (n=33) or Genotype 4 (n=1)
HCV genotype	
Genotype 1	33 (97.1%)
Genotype 1 (no confirmed subtype)	0
Genotype 1a	28 (82.4%)
Genotype 1b	5 (14.7%)
Genotype 4	1 (2.9%)
Cirrhosis	
No	14 (41.2%)
Unknown	20 (58.8%)
IL28B	
CC	10 (29.4%)
CT	16 (47.1%)
TT	6 (17.6%)
Missing	2 (5.9%)
Baseline HCV RNA (log_{10}/mL)	
Mean (range)	6.0 (4.8, 7.3)
Baseline ALT (U/L)	
Mean (range)	62 (25, 130)
Prior HCV Treatment	
Treatment Naive	34/34 (100.0%)
Treatment Experienced	0/34
Mode of HCV Infection	
Vertical transmission	34 (100.0%)
Unknown	0

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-337-1116: Table 24. Page 101-102.

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 33 subjects who received LDV/SOF x 12 weeks with genotype 1 was 97.0% (32/33) and for the one subject with genotype 4 was 100% (1/1). One of 33 subjects with genotype 1 HCV infection did not achieve SVR12 due to

premature discontinuation of the study drug due to AEs of spitting up drug and abnormal product taste from Day 2 to Day 5, and the the drug was permanently discontinued on Day 5.

The very high SVR12 rate that was observed, with no cases of virologic failure, precluded meaningful interpretation thorugh further analysis of the primary endpoint by subgroup (race, ethinicity, gender, etc) (Source: Clinical Study Report GS-US-337-1116, Tables 54 & 55, pages 137-139).

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 5). As demonstrated in this table, there were no treatment breakthroughs and no treatment failures among the 3 to < 6 year old subject who received the treatment.

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

	Genotype 1 (n=33) or Genotype 4 (n=1)
Baseline	0/34
Week 1	10/34 (29.4%)
Week 2	26/33 (78.8%)
Week 4	32/33 (97.0%)
Week 8	33/33 (100%)
Week 12	33/33 (100%)
Post-Treatment Week 4 (SVR4)	33/34 (97.1%)
Post-Treatment Week 12 (SVR12)	33/34 (97.1%)
Post-Treatment Week 24 (SVR24)	33/34 (97.1%)

Source: Clinical Study Report GS-US-337-1116: Tables 52, 53, Pages 135-136 and Table 56, Pages 140.

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 LDV/SOF. At baseline, 79.4% of subjects (27 of 34), had ALT > ULN at baseline. Normalization of ALT was observed in 96.0% (24 of 25 subjects with nonmissing values) at Week 4. Of the remaining 3 subjects, 1 subject had normalized ALT at post-treatment Week 4, 1 subject with missing ALT value at Week 4 had normalized ALT at Week 1, and *1 subject who prematurely discontinued study drug did not achieve SVR12 and did not normaliz their ALT.*

Overall Efficacy Summary (3 to 12 years old)
The efficacy of LDV/SOF in children with chronic HCV due to genotype 1 or 4 was demonstrated in this open-label, uncontrolled trial. At 12 weeks after discontinuation of study treatment, a sustained virologic response was demonstrated in 97.0% (32/33) of subjects with

HCV due to genotype 1 and in 100% (1/1) in the subject with genotype 4; the response rate is consistent with the antiviral response observed in studies of treatment-naive adults. Although the protocol was amended to allow for enrollment of genotypes 5 and 6, none could be enrolled during the trial.

8. Safety

The applicant has submitted safety data from 126 pediatric subjects 3 to < 12 years old (92 subjects 6 to < 12 years old; and 34 subjects 3 to < 6 years) who received at least one dose of LDV/SOF in Trial GS-US-337-1116. The duration of follow-up was 12 weeks after discontinuation of treatment for all 126 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 LDV/SOF±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-337-1116 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. All subjects who completed the study and 12 week post-treatment period were included in the safety evaluation.

Safety Data from 12 to < 18 year old age group was already reviewed and the drug approved for use in this age group in 2017. *Please refer to Dr. Virginia Sheikh'sreview for the full review in the original NDA 205834.*

The following is a summary of the disposition and demographics of study subjects and the assessment of efficacy for each of the remaining age groups separately (90 subjects 6 to < 12 years old; and 34 subjects 3 to < 6 years).

8.1. 6 to < 12 years old cohort

Table 9 presents the overall summary of AEs for subjects 6 to < 12 years old by treatment group. In this group, the two subjects with genotype 3 were included in the review to assess safety. The total number of subjects reviewed were 92. The majority of subjects (65 of 92, 70.7%) experienced at least 1 AE. 62 of 89, (69.7)% of subjects with genotype 1 HCV infection; 1 of 2 [50%] subjects with genotype 4 treated for 12 weeks; 1 of 1 [100%] subject with genotype 1 HCV infection treated for 24 weeks); and 2 of 2 subjects in the LDV/SOF+RBV treated for 24 weeks experienced at least 1 AE.

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

	LDV/SOF x 12 weeks (n=89)*		LDV/SOF x 24 weeks**	LDV/SOF + RBV x 24 weeks	Total (n=92)
Adverse Events (Number of subjects)	**Genotype 1 (n=87)**	**Genotype 4 (n=2)**	**Genotype 1 (n=1)**	**Genotype 3 (n=2)**	
Any TEAE	61 (70.1%)	1 (50%)	1 (100%)	2 (100%)	65 (70.7%)
Maximum Toxicity Grade					
Grade 1 (mild)	60 (69.0%)	1 (50%)	1 (100%)	2 (100%)	65 (70.7%)
Grade 2 (moderate)	14 (16.1%)	0	0	0	14 (15.2%)
Grade 3 (severe)	0	0	0	0	0
Grade 4 (life-threatening)	0	0	0	0	0
Deaths	0	0	0	0	0
Any SAE	2 (2.2%)	0	0		2 (2.2%)
Drug-related SAE	0	0	0	0	0
Drug-related TEAEs	22 (25.3%)	1 (50%)	0	2 (100%)	25 (27.2%)
Drug-related Grade 2 TEAE	1 (1.1%)	0	0	0	1 (1.1%)
Drug-related Grade 3 TEAE	0	0	0	0	0
TEAE Leading to Premature Discontinuation of LDV/SOF	0	0	0		0
Premature Discontinuation of RBV	N/A	N/A	N/A	0	0
TEAE Leading to Temporary Interruption of LDV/SOF	0	0	0		0
TEAE Leading to Temporary Interruption of RBV	N/A	N/A	N/A	0	0

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-337-1116: Table 72. Page 166.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
*Treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

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 were headache (18.5%), pyrexia (17.4%), abdominal pain (15.2%) and fatigue (15.2%).

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

Adverse Events	LDV/SOF x 12 weeks	(n=89)*	LDV/SOF x 24 weeks*	LDV/SOF + RBV x 24 weeks	Total (n=92)
	Genotype 1 (n=87)	Genotype 4 (n=2)	Genotype 1 (n=1)	Genotype 3 (n=2)	
Commonest AEs					
Headache	16 (18.4%)	1 (50%)	0	1 (50%)	18 (19.6%)
Pyrexia	15 (17.2%)	0	0	1 (50%)	16 (17.4%)
Abdominal pain	14 (16.1%)	0	0	0	14 (15.2%)
Fatigue	12 (13.8%)	1 (50%)	0	1 (50%)	14 (15.2%)
Cough	12 (13.8%)	0	1(100%)	1 (50%)	14 (15.2%)
Vomiting	12 (13.8%)	1 (50%)	0	1 (50%)	14 (15.2%)
Diarrhea	10 (11.5%)	1 (50%)	0	0	11 (12.0%)
Nausea	10 (11.5%)	0	0	1 (50%)	11 (12.0%)
Oropharyngeal pain	10 (11.5%)	0	0	0	10 (10.9%)

Source: Data Analysis of ADAE ADAM dataset of Study GS-US-337-1116.
*Treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

Adverse Drug Reactions (Related to Study Drug)

Table 11 presents a summary of Adverse Drug Reactions (ADR) in > 1 subject 6 to < 12 years old in either treatment group by preferred term. The 3 most commonly reported treatment related ADRs were headache (12%), fatigue (9.8%), and nausea (6.5%).

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

Adverse Events	LDV/SOF x 12 weeks (n=89)*		LDV/SOF x 24 weeks**	LDV/SOF + RBV x 24 weeks	Total (n=92)
	Genotype 1 (n=87)	Genotype 4 (n=2)	Genotype 1 (n=1)	Genotype 3 (n=2)	
Commonest AEs					
Headache	10 (11.5%)	0	0	1 (50%)	11 (12.0%)
Fatigue	7 (8.1%)	1	0	1 (50%)	9 (9.8%)
Nausea	6 (6.9%)	0	0	0	6 (6.5%)
Dizziness	3 (3.4%)	0	0	0	3 (3.3%)
Decreased appetite	2 (2.3%)	0	0	0	2 (2.2%)

Source: Data Analysis of ADAE ADAM dataset of Study GS-US-337-1116
*Treatment Naive with/without cirrhosis; or treatment experienced without cirrhosis
**Treatment experienced with cirrhosis

Deaths
There were no deaths reported in the study.

Serious Adverse Events (SAEs)
Three treatment-emergent SAEs and 1 nontreatment-emergent SAE were reported in 1 subject in the LDV/SOF 12 week group. The subject experienced treatment-emergent SAEs of Grade 2 tooth abscess on Day 13, Grade 2 abdominal pain on Day 25, and Grade 2 gastroenteritis on Day 89, and a nontreatment-emergent SAE of allergic edema 167 days after the end of treatment. None of the events were assessed by the investigator as related to study drug or led to dose modification. All events resolved.

Discontinuations due to Adverse Events
There were no discontinuations due to adverse events among subjects 6 to < 12 years old.

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

Laboratory Abnormalities and
The majority of subjects had at least 1 laboratory abnormality reported (57.3% [51 of 89] of subjects in the LDV/SOF 12 week group, 100.0% [1 of 1] of subjects in the LDV/SOF 24 week group, and 50% [1 of 2] of subjects in the LDV/SOF+RBV 24 weeks). For all but 4 subjects, the maximum laboratory abnormality grade was Grade 1 or Grade 2. Grade 3 and 4 laboratory

abnormalities were reported for 4.3% (4 of 92) of subjects, all of whom were in the LDV/SOF 12 week group. A Grade 3 decrease in hemoglobin by >4.5 gm/dl was reported for one subject (Baseline hemoglobin was 18.3 gm/dl) but remained within the normal range at all time points (>12 gm/dl); and a Grade 4 decrease in neutrophils at Week 1 then was normal after that, all of whom were in the LDV/SOF 12 week group. No clinically meaningful changes from baseline in neutrophils, lymphocytes, hemoglobin, reticulocytes, or platelets were observed. No Grade 3 or 4 ALT, AST, bilirubin, creatine kinase or lipase elevations were reported.

Other Adverse Events
There were no notable effects of treatment on development or growth (baseline to post-treatment Week 24) in Tanner stage, bone age, height, weight and Body Mass Index (BMI) percentiles, and vital signs. 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
Overall, treatment with LDV/SOF for 12 or 24 weeks was generally safe and well tolerated by subjects 6 to < 12 years of age, regardless of genotype. All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. The majority of subjects had at least 1 laboratory abnormality reported, the maximum laboratory abnormality grade was Grade 1 or Grade 2. A Grade 4 laboratory abnormality was reported for decreased neutrophils, which was isolated and transient. One subject experienced SAEs that were not drug related. No deaths were reported. No subject prematurely discontinued LDV/SOF due to an AE. The commonest Adverse Events were mild in nature and similar to those seen in adolescents and adults. There were no AEs consistent with progression of liver disease, such as AEs of hepatocellular carcinoma or hepatic decompensation. There were no effects of treatment on development, growth or vital signs.

8.2. 3 to < 6 years old cohort

Table 12 presents the overall summary of AEs for subjects 3 to < 6 years old by treatment group. The majority of subjects (25 of 34, 73.5%) experienced at least 1 AE. No subjects with genotypes 3, 5 or 6 were enrolled in this age group.

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

Adverse Events	Genotype 1 (n=33) or Genotype 4 (n=1)
Any TEAE*	25 (73.5%)
Maximum Toxicity Grade	
Grade 1 (mild)	25 (73.5%)
Grade 2 (moderate)	4 (11.8%)
Grade 3 (severe)	0
Grade 4 (life-threatening)	0
Deaths	0
Any SAE	0
Drug-related SAE	0
Drug-related TEAEs	10 (29.4%)
Drug-related Grade 2 TEAE	0
Drug-related Grade 3 TEAE	0
TEAE Leading to Premature Discontinuation	1 (2.9%)*
TEAE Leading to Temporary Interruption	0

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-337-1116: Table 78. Page 11.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
* Discontinued treatment due to abnormal taste on Day 5.

Common Adverse Events

Table 13 presents a summary of treatment-related AEs reported in at least 10% of subjects 3 to < 6 years old in either treatment group by preferred term. Overall, the most 3 commonly reported AEs were vomiting (23.5%), and pyrexia and cough (each 20.6%).

Table 13. Treatment Related Adverse Events in at Least 1% of Subjects by Treatment Group (3 to < 6 Years Old)

Adverse Events	Genotype 1 (n=33) or Genotype 4 (n=1)
Total # of AEs	25 (73.5%)
Vomiting	8 (23.5%)
Pyrexia	7 (20.6%)
Cough	7 (20.6%)
Rhinorrhea	6 (17.6%)
Streptococcal pharyngitis	4 (11.8%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-337-1116: Table 79, Page 182.

Adverse Drug Reaction (Related to Study Drug)
Table 14 presents a summary of Adverse Drug Reactions (ADR) reported in > 1 subject 3 to < 6 years old in either treatment group by preferred term. Overall, the most commonly reported ADR was product taste abnormal (8.8%).

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

Adverse Events	Genotype 1 (n=33) or Genotype 4 (n=1)
Number of subjects experiencing an ADR	10 (29.4%)
Product taste abnormal	3 (8.8%)
Fatigue	2 (5.9%)
Vomiting	2 (5.9%)
Insomnia	2 (5.9%)
Upper abdominal pain	2 (5.9%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-337-1116: Table 80, Page 183

Deaths
There were no deaths reported in the study

Serious Adverse Events (SAEs)
No treatment emergent SAEs were reported in the study.

Discontinuations due to Adverse Events
One subject discontinued study drug due to an AE (Table 15.11.5.1). This subject, 3 years old, experienced a Grade 1 AE of product taste abnormal from Days 2 through 5. The subject's last dose was administered on Day 5, after which study drug was discontinued

Laboratory Abnormalities
The majority of Subjects had at least 1 laboratory abnormality (24/34, 70.6%). All lab abnormalities were Grade 1 or 2. No Grade 3 or 4 hematology laboratory abnormalities were reported in subjects 3 to < 6 years old. No clinically meaningful changes from baseline in neutrophils, lymphocytes, hemoglobin, reticulocytes, or platelets were observed. No Grade 3 or 4 ALT, AST, bilirubin, creatine kinase or lipase elevations were reported.

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 3 to < 6 years old
Treatment with LDV/SOF for 12 weeks was generally safe and well tolerated by subjects 3 to < 6 years of age. The majority of subjects (25 of 34, 73.5%) experienced at least 1 AE. The 3 most commonly reported AEs were vomiting (23.5%), and pyrexia and cough (each 20.6%). All AEs were Grade 1 (mild) or Grade 2 (moderate) in severity. One subject prematurely discontinued LDV/SOF due to a Grade 1 AE of product taste abnormal on Day 5.

The majority of subjects 3 to < 6 years old had at least 1 laboratory abnormality reported (24 of 34, 70.6%). All laboratory abnormalities were Grade 1 or Grade 2 in severity. No notable effects of study treatment on development or growth were observed in either treatment group. No notable changes from baseline in vital signs were observed during the study.

8.3. Special Populations

The pediatric Chronic Hepatitis C (CHC) subjects evaluated in Study GS-US-337-1116 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 LDV/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 LDV/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-337-1116.

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-337-1116 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 194 investigators (33 Principal Investigators and 161 Sub-Investigators), of which 4 investigators certified that they have no disclosable financial interests. None of the investigators are Gilead employees. See 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 1, 4, 5 and 6 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. A separate Instructions For Use (IFU) document will be requested from the Sponsor within 15 days after approval

Expanded dosing recommendations

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

1 INDICATIONS AND USAGE

Based on the adult safety data, and the similar pharmacokinetics and exposure compared to adults, the following dosing recommendations were extended to children 3 years and older.

- *genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis*
- *genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin*
- *genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin*

Rationale: In HCV-infected adults, LDV/SOF is approved to treat patients with genotype 5 or 6; and LDV/SOF ± RBV is approved for patients with genotype 1 infection who have decompensated cirrhosis (Child-Pugh B or C); and patients with genotype 1 or 4 who were liver transplant recipients without cirrhosis or with compensated cirrhosis (Child-Pugh A). HCV genotype does not affect LDV/SOF exposure and previous trials in adults have demonstrated that an equivalent LDV/SOF exposure is efficacious in adults with chronic HCV genotype 5 and 6. Therefore, the submitted PK data are adequate to support the efficacy of LDV/SOF for treatment of HCV genotypes 5 or 6 in patients 3 years of age and older. A similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1 infection who have decompensated cirrhosis (Child-Pugh B or C) and for pediatric patients with HCV genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis.

This section was updated as follows based on these recommendations:

HARVONI is indicated for the treatment of adults and pediatric patients 3 years of age and older with chronic hepatitis C virus (HCV) *[see Dosage and Administration (2.2 and 2.3) and Clinical Studies (14)]*:

- genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis
- genotype 1 infection with decompensated cirrhosis, for use in combination with ribavirin
- genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use in combination with ribavirin

2 DOSAGE AND ADMINISTRATION

2.2 Recommended (b) (4) Patients 3 Years of Age and Older with Genotype 1, 4, 5 or 6 HCV

This section was modified to extend the indication to children 3 years and older, and to include the expanded recommendations described above. The revised language in this section is as follows:

Table 1 shows the recommended HARVONI treatment regimen and duration based on patient population. Relapse rates are affected by baseline host and viral factors and differ between treatment durations for certain subgroups *[see Clinical Studies (14)].*

For patients with HCV/HIV-1 coinfection, follow the dosage recommendations in Table 1 *[see Clinical Studies (14)].* Refer to *Drug Interactions (7)* for dosage recommendations for concomitant HIV-1 antiviral drugs.

Table 1 Recommended Treatment Regimen and Duration for HARVONI in Patients 3 Years of Age and Older with Genotype 1, 4, 5, or 6 HCV

HCV Genotype	Patient Population	Treatment Regimen and Duration
Genotype 1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks[a]
	Treatment-experienced[b] without cirrhosis	HARVONI 12 weeks
	Treatment-experienced[b] with compensated cirrhosis (Child-Pugh A)	HARVONI 24 weeks[c]
	Treatment-naïve and treatment-experienced[b] with decompensated cirrhosis (Child-Pugh B or C)	HARVONI + ribavirin[d] 12 weeks
Genotype 1 or 4	Treatment-naïve and treatment-experienced[b] liver transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Pugh A)	HARVONI + ribavirin[d] 12 weeks

Genotype 4, 5, or 6	Treatment-naïve and treatment-experienced[b], without cirrhosis or with compensated cirrhosis (Child-Pugh A)	HARVONI 12 weeks

a. HARVONI for 8 weeks can be considered in treatment-naïve genotype 1 patients without cirrhosis who have pretreatment HCV RNA less than 6 million IU/mL *[see Clinical Studies (14.2)]*.
b. Treatment-experienced adult and pediatric subjects have failed a peginterferon alfa +/- ribavirin based regimen with or without an HCV protease inhibitor.
c. HARVONI + ribavirin for 12 weeks can be considered in treatment-experienced genotype 1 patients with cirrhosis who are eligible for ribavirin *[see Dosage and Administration (2.3 and 2.4) and Clinical Studies (14.2)]*.
d. See *Dosage and Administration 2.3 and 2.4* for ribavirin dosage recommendations.

2.4 Recommended Dosage in Pediatric Patients 3 Years of Age and Older

It was noted during the review that the recommended dosage in labeling differs from the protocol specified dosing.

(b) (4)

The recommended dosage of HARVONI in pediatric patients 3 years of age and older with genotype 1, 4, 5, or 6 HCV using HARVONI tablets or oral pellets is based on weight (Table 2). Table 3 provides the weight-based dosage of ribavirin when used in combination with HARVONI for pediatric patients. Take HARVONI tablets or pellets (with or without food) once daily [see Dosage and Administration (2.5), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]. HARVONI pellets can be taken in pediatric patients who cannot swallow the tablet formulation.

Table 2 Dosing for Pediatric Patients 3 Years and Older Using HARVONI Tablets or Oral Pellets

Body Weight (kg)	Dosing of HARVONI Tablets or Oral Pellets	HARVONI Daily Dose
at least 35	one 90 mg/400 mg tablet once daily or two 45 mg/200 mg tablets once daily or two 45 mg/200 mg packets of pellets once daily	90 mg/400 mg per day
17 to less than 35	one 45 mg/200 mg tablet once daily or one 45 mg/200 mg packet of pellets once daily	45 mg/200 mg per day
less than17	one 33.75 mg/150 mg packet of pellets once daily	33.75 mg/150 mg per day

2.5 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 HARVONI pellets. If HARVONI pellets are administered with food, sprinkle the pellets on one or more spoonfuls of non-acidic soft food (b) (4) or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, mashed potato, and ice cream. Take HARVONI pellets within 30 minutes of gently mixing with food and swallow the entire contents without chewing to avoid a bitter aftertaste.

6.1 Clinical Trials Experience

In this section, under "Adverse Reactions in Pediatric Subjects 3 Years of Age and Older", the age was changed to 3 years and older instead of 12 years and older.

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-337-1116 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 LDV/SOF 45 mg/200 mg tablet formulation and the LDV/SOF 45 mg/200 mg and LDV/SOF 33.75/150 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 the Components of HARVONI in HCV-Infected Pediatric Subjects 3 Years of Age and Older" was edited to remove age groups from the first column since weight-based dosing is adopted for subjects 3 Years of Age and Older, and to be consistent with Table 3 in section 2 "DOSAGE AND ADMINISTRATION" which does not include age groups.

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-337-1116. Also, the Table entitled "Trials Conducted with HARVONI with or without Ribavirin in Subjects with Chronic HCV Genotype 1, 4, 5, or 6 Infection" was updated to include Study GS-US-337-1116.

14.6 Clinical Trial in Pediatric Subjects

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 from 226 to 223, after excluding the three genotype 3 patients (one subject in the 12 to < 18 years old group, and two subjects in the 6 to < 12 years old group) given that the drug is not approved for adults and adolescents with genotype 3 in the United States. 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: HARVONI was evaluated in 90 subjects 6 years to <12 years of age with HCV genotype 1 or 4 infection. Among these subjects, 72 (80%) were treatment-naïve and 18 (20%) were treatment-experienced. Eighty-nine of the subjects (87 with genotype 1 HCV infection and 2 with genotype 4 HCV infection) were treated with HARVONI for 12 weeks, 1 subject with genotype 1 HCV infection was treated with HARVONI for 24 weeks. The median age was 9 years (range: 6 to 11); 59% of the subjects were male; 79% were White, 8% were Black, and 6% were Asian; 10% were Hispanic/Latino; mean body mass index was 18 kg/m2 (range: 13 to 31kg/m2); mean weight was 33 kg (range 18 to 76 kg); 59% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 86% had genotype 1a HCV infection; 2 subjects (1 treatment-naïve, 1 treatment-experienced) had known compensated cirrhosis. The majority of subjects (97%) had been infected through vertical transmission.

The SVR rate was 99% (86/87) in subjects with genotype 1 HCV infection and 100% (2/2) in subjects with genotype 4 HCV infection. (b) (4) genotype 1 subject treated with HARVONI for 24 weeks. The one subject (genotype 1) who did not achieve SVR12 and relapsed had been treated with HARVONI for 12 weeks.

Subjects 3 Years to <6 Years of Age: HARVONI was evaluated in 34 subjects 3 years to <6 years of age with HCV genotype 1 (N = 33) or genotype 4 (N = 1) infection. All of the subjects were treatment-naïve and treated with HARVONI for 12 weeks. The median age was 5 years (range: 3 to 5); 71% of the subjects were female; 79% were White, 3% were Black, and 6% were Asian; 18% were Hispanic/Latino; mean body mass index was 17 kg/m2 (range: 13 to 25 kg/m2); mean weight was 19 kg (range 11 to 34 kg); 56% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 82% had genotype 1a HCV infection; no subjects had known cirrhosis. All subjects (100%) had been infected through vertical transmission.

The SVR rate was 97% (32/33) in subjects with genotype 1 HCV infection and (b) (4) subjects with genotype 4 HCV infection. 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 new LDV/SOF 45 mg/200 mg tablet formulation and the LDV/SOF 45 mg/200 mg and LDV/SOF 33.75/150 mg oral pellets.

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

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-337-1116).

- 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. In both age groups, 3 to < 6 year olds and 6 to < 12 year olds, there were no statistically significant ($p < 0.05$) mean changes in physical or psychosocial functioning scores in any treatment group based on either the subject or parent reports during treatment (baseline to end of treatment) or during the follow-up (end of treatment to posttreatment).

- 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-337-1116, 84 of the 92 subjects 6 to < 12 years old who were enrolled performed the swallowability assessment with the 22.5/100-mg placebo tablet; 83 of the 84 subjects (98.8%) were able to swallow the tablet. No subjects 6 to < 12 years old dosed with the LDV/SOF FDC (22.5/100-mg) tablet formulation experienced AEs associated with acceptability or palatability.

No labeling was proposed based on this data.

Appendix 2

Clinical Investigator Financial Disclosure Review

Application Number: NDA 205834/212477

Submission Date(s): February 28, 2019

Applicant: Gilead Sciences, Inc.

Product: Ledipasvir/Sofosbuvir (Harvoni)

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 Study to Investigate the Safety and Efficacy of Ledipasvir/Sofosbuvir Fixed Dose Combination ± Ribavirin in Adolescents and Children with Chronic HCV-Infection (Study Number: GS-US-337-1116 [Group 2])

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 194 (33 Principal Investigators and 161 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): 4		
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: 4 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:	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 194 Investigators for Study GS-US-337-1116 are employed by the Sponsor. Four of the investigators, representing 2% (4/194) of the total number of investigators, have disclosable financial interests/arrangements which the Sponsor defined as 'Significant payment of other sorts > $25,000'.

The investigator financial disclosures do not raise questions about the integrity of the data. The primary efficacy endpoint includes PK parameters (PK Lead-in Phase), and the viral load assessed at week 12 (SVR12), which are objective laboratory measurements that are assessed at two separate laboratories and not vulnerable to investigator bias. While the AE assessment is performed by the investigators and their staff in this open-label study, the Sponsor states that 100% of the source documents will be verified by a Clinical research Associate (CRA) working on behalf of the Sponsor. The CRA is then able to evaluate whether the investigator is under-reporting or over-reporting the incidence of AEs, and any discrepancy will be reported promptly to the Sponsor.

Hence, the fact that the main laboratory efficacy endpoints are objectively measured by third party laboratories and that the CRA monitor reviews the patient's source documents would minimize the potential for investigator bias to play a role. Finally, the 4 investigators who had financial interests or arrangements with the Sponsor, represent 2% of all investigators and are all at one site which enrolled only 3 patients or 2.4% (3/126) of all patients enrolled in the study. In conclusion, the

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

likelihood that the trial results were biased based on financial interests is minimal and should not affect the approvability of the application.

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.

/s/

KIMBERLY A STRUBLE
08/27/2019 02:28:09 PM
Signing off on behalf of Samer El-Kamary MD, MPH, clinical review. I concur with the review

DEBRA B BIRNKRANT
08/27/2019 03:47:44 PM