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

Date	February 18, 2020
From	William B. Tauber, MD, 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#	208341 Supplement Number 14
Applicant	Gilead Sciences, Incorporated.
Date of Submission	September 19, 2019
PDUFA Goal Date	March 19, 2020
Proprietary Name	Epclusa®
Established or Proper Name	SOFOSBUVIR/VELPATASVIR (SOF/VEL)
Dosage Form(s)	Oral tablets: ▪ 400 mg sofosbuvir and 100 mg velpatasvir ▪ 200 mg sofosbuvir and 50 mg velpatasvir
Applicant Proposed Indication(s)/Population(s)	Pediatric Patients 6 to <18 years of age: For the treatment of chronic hepatitis C (HCV) genotype 1,2,3,4, 5, or 6infection
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Table 11)
Recommendation on Regulatory Action	Approval

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1. Executive Summary

1.1. Summary of Regulatory Action

This supplemental new drug application (NDA) is intended to expand the indicated population for Epclusa® (sofosbuvir and velpatasvir; SOF/VEL) FDC (Fixed Drug Combination) to include subjects 6 years old and older or weighing at least 17 kg.

This submission also serves as a Prior Approval Supplement to support the addition of a new tablet strength 200 mg/50 mg tablets.

The NDA was reviewed by the multi-disciplinary 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/VEL will be approved for children six years of age and older or weighing at least 17 kg with HCV genotype 1, 2, 3, 4, 5, or 6 infection.

- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin

The Applicant submitted a multicenter, open-label, non-comparative trial (1143) in which 175 children (102 children 12 to <18 years old, 73 children 6 to <12 years old) were enrolled, treated for 12 weeks and followed for 24 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 SOF/VEL were evaluated. The SOF/VEL dose was based on the child's age.

Adolescents received the current adult dosage of 400 mg/100 mg (SOF/VEL) tablet once daily. Children 6 to <12 years of age received the 200 mg/50 mg (SOF/VEL) daily tablet.

The Applicant was interested in weight-band dosing with adult dosage administered for subjects weighing ≥ 35 kg. Exposures of SOF, GS-331007 and VEL in adolescents were compared to historical data in adults collected in SOF/VEL clinical studies. GS-331007 AUC_{tau} and C_{max} and VEL AUC_{tau} and C_{tau} were within the predefined equivalence boundary of 70% to 200%. The SOF AUC_{tau} and C_{max} and VEL C_{max} in subjects 12 to <18 years of age were higher than observed in the adult population.

Exposures of SOF, GS-331007 and VEL in children 6 to <12 years of age were compared to historical data in adults collected in SOF/VEL clinical studies. Sofosbuvir C_{max}, VEL C_{max} and VEL C_{tau} were not fully contained within the predefined equivalence boundary of 70% to 200 %. Specifically the SOF C_{max} value exceeded the equivalence boundary and the VEL_{tau} was too low.

The Applicant summary analysis documented SOF exposures were higher and VEL C_{tau} were lower. They conducted analyses to see if lower weight band (e.g., ≥30 kg) for adult dose would improve VEL C_{tau}. With the ≥30 kg weight band, VEL C_{tau} exposures increased; however, further increases in SOF exposures were noted. The safety of the higher SOF exposures was supported by data from 6 children who were <35 kg and received the adult dose for because the dosages were age rather than weight driven.

The efficacy outcomes, as measured by SVR 12 were 95% for adolescents and 93% for children 6 to <12 years of age. One child in the 12 to <18 year old group became pregnant, discontinued and relapsed. One child in the 6 to <12 year old group experienced virologic failure.

The Safety data indicated that Epclusa® is safe and well tolerated, no deaths, SAEs or related Grade 3 or 4 events, two D/Cs, The commonly observed AEs in children were similar to those seen in adults and were mild in severity. Overall the benefit risk assessment is favorable.

1.2. 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 U.S. 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	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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	limitations in a person's professional and personal activities, disability, reduced healthy life expectancy, and potential years of life lost.
Current Treatment Options Pediatrics	• 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. • Sovaldi® (SOF) is approved in patients 3 years of age and older with HCV genotype 2 or 3 without cirrhosis or with compensated cirrhosis for use in combination with ribavirin. • Harvoni® (an FDC of ledipasvir [LDV] and SOF) is approved in pediatric patients 3 and older with HCV genotype with: o Genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis o Genotype 1 infection with decompensated cirrhosis for use with ribavirin o Genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis, for use with ribavirin. • Mavyret (an FDC of glecaprevir and pibrentasvir) is approved for pediatric patients 12 years of age and older or weighing at least 45 kg with HCV genotype 1, 2, 3, 4, 5 or 6 infection or genotype 1 infection who previously were treated with an HCV NS5A inhibitor or an NS3/4A protease inhibitor but not both.	Four treatments are available for adolescents; fewer for less than 12 years of age and need to be combined with RBV for certain patients and durations • Pegylated interferon/ribavirin is only effective in about half the cases, is injectable (pegylated interferon), and has many serious side-effects. • Sovaldi® and Harvoni® need to be combined with ribavirin (RBV) for certain patients and durations of treatment are variable according to genotype and presence of cirrhosis. RBV has significant toxicities, durations of treatment vary.
Benefit	• To support an efficacy claim for the use of SOF/VEL for the treatment of CHC infection in children 6 to <18 years old, the applicant submitted the 24 Week efficacy and safety results from a single study (Study Trial GS-US-342-1143), which is a Phase 2, open-label, non-comparator trial. • In this study, 175 subjects (treatment-naïve and treatment-experienced) in two groups aged 6 years to less than 12 years (73 subjects) and 12 years to less than 18 years of age (102 subjects) with chronic HCV genotype 1, 2, 3, 4, or 6 were treated with SOF/VEL once daily for 12 weeks. No cirrhosis was	SOF/VEL was highly efficacious in clearing HCV in children 6 to <18 years old. Given long-term studies in children adults, clearance of HCV (spontaneously or by treatment) stops resultant liver inflammation and prevents or reduces long-term complications such as fibrosis, cirrhosis, liver

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	detected but only approximately 50% of subjects were assessed for the presence of cirrhosis. • The study demonstrated a high efficacy among those in both groups who received treatment. In the 12 to <18 year old group the SVR 12 rate for genotype 1 was 93% and 100% for the remaining genotypes 2, 3, 4, 6. For the 6 to 12 year old group, the SVR 12 rates for genotype 1 were 93%, genotype 3 90% and 100% for genotypes 2, and 4. • In adults SOF/VEL is approved for HCV genotype 5; however, no genotype 5 pediatric subjects were enrolled. This is not unexpected owing to the scarcity of genotype 5. HCV genotype does not affect SOF/VEL exposure and previous trials in adults have demonstrated an equivalent SOF/VEL exposure is efficacious in adults with chronic HCV genotype 5. Therefore, the submitted PK data are adequate to support the efficacy of SOF/VEL for treatment of HCV genotypes 5 in patients 6 years old 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)	failure and hepatocellular complications. It is reasonable to assume that long-term viral suppression in children 6 to <18 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 population.
Risk and Risk Management	SOF/VEL had a few mild side-effects in both age groups, the most common of which in the 12 to <18 year were headache, fatigue and nausea and in the 6 to <12 group the most common events were vomiting, cough, headache and, fatigue. All of the events were categorized as either mild or moderate (Grade 1 or 2 Adverse Events). There were no drug related SAE in the 12 to <18 years group and a single drug-related Serious Adverse Event in the 6 to <12 years group (auditory hallucinations) and no deaths. 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 adults. The safety results were similar between the age cohorts. Based on the available safety profile for SOF/VEL, no Risk Evaluation and Mitigation Strategy (REMS) is recommended at this time.

Conclusions Regarding Benefit and Risk

The overall benefit-risk assessment of SOF/VEL is favorable. SVR12 values were greater than 90% in all genotypes for both age groups. SOF/VEL was safe and well-tolerated with no related Grade 3 or 4 events, serious adverse events or deaths. The most commonly observed adverse events were similar to those seen in adults and were mild in nature.

The availability of SOF/VEL for pediatric patients 6 to less than 18 years or weighing at least 17 kg is a major health benefit. Neither SOF or LDV/SOF are approved for all genotypes and for certain genotypes or cirrhosis status use with RBV or a duration longer than 12 weeks is needed. SOF/VEL offers children six years of age and older infected with any HCV genotype (1,2,3,4,5 or 6) without cirrhosis or with compensated cirrhosis a safe, effective, 12 week option without the need for RBV. SOF/VEL is also approved for use in pediatric patients 6 years of age or older or weighing at least 17 kg with HCV genotypes 1, 2, 3, 4, 5, or 6 with decompensated cirrhosis for use in combination with RBV.

1.3. Patient Experience Data

The table below presents where Patient Experience Data Relevant to this Application is described in Study GS-US-342-1143. See Appendix 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-342-1143 Synopsis, Section 7.5.2.6. Not reviewed*
		♦	Observer reported outcome (ObsRO)	*Clinical study report CSR for Study GS-US-342-1143. Synopsis section. This was not reviewed.*
		□	*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 granule formulation were assessed in Study GS-US-342-1143. Swallowability assessment at screening up to Day 1 using placebo tablets similar in size to SOF/VEL for both cohorts studied. Quality of Life Assessment in CSR, section 7.5.2.6. Neither were reviewed in this supplement.		Module 2.5, Section 2.3; GS-US-342-1143 Sections 2.3.1 and 2.3.2
□	*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 an average 1% in 2015, for a total of 71 million individuals. Globally, there are an estimated 2.1 to 3.5 million children 15 years of age or younger with chronic HCV. The prevalence varies by geographic location, with an estimated prevalence of 0.4% in Europe and the United States (U.S.), for a total of forty-six thousand children in the U.S.; and up to 6% in resource-limited countries.

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. 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.

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. 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.

Currently available treatment for children younger than 12 years of age with chronic HCV infection includes both pegylated interferon (IFN) ribavirin combination (RBV) therapy and direct acting antivirals (DAA). Treatment with IFN/ RBV is associated with lower activity and significant toxicity which limit their usefulness. DAAs currently applicable to the CHC pediatric 3 years old or older populations include Sofosbuvir, LDV/SOF (Harvoni®) and Mavyret® for adolescents. HCV genotype has had impact upon the activity and duration of therapy of some of the DAAs. SOF/VEL is unique in having activity against all 6 genotypes with a standard therapy duration of 12 weeks.

Electronic materials submitted included two ongoing Clinical Study Reports (CSR) corresponding to the two age groups studied. Group 1 corresponds to the 12 to <18 year old group and Group 2 corresponds to children 6 to <12 years of age. These CSRs were submitted with accompanying datasets as required.

- PMR 3092-1 is for 12 to less than 18 years of age This PMR has been fulfilled with this sNDA.
- PMR 3092-2 is for 3 to <12 years. This PMR is not fulfilled by this sNDA at this time because the data in children 3 to <6 years of age was not included

This supplement includes data from the Interim Study GS-US-342-1143. SVR 4 and SVR 24 of both groups were not summarized in this submission. (b) (4) [redacted] Only data for pediatric subjects 6 to <18 years old are presented in this clinical review.

2.1. Product Information

Tablets

A new lower strength tablet was submitted with this application. EPCLUSA is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analogue of HCV NS5B polymerase and velpatasvir is an

HCV NS5A inhibitor. Each 200/50 mg tablet contains 200 mg sofosbuvir and 50 mg velpatasvir.

2.2. Summary of Regulatory Activity Related to Submission

In the U.S., Study GS-US-342-1143 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/VEL in the treatment of HCV infection was submitted to the FDA to New Drug Application (NDA) 208341 on 28 October 2015.
- A written Request (WR) for studies of SOF/VEL in pediatric subjects 3 to <18 years old was received on 02 September 2016.
- The terms of the WR were further negotiated and Gilead agreed to the terms of the pediatric WR.

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 U.S. Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312).

2.3. Summary of Study Protocol

Trial GS-US-342-1143 is entitled, “A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir (SOF/VEL) in Adolescents and Children with Chronic HCV Infection.” The study design designates two groups differentiated by age. Group 1 had a single cohort of subjects between the ages of 12 and <18 years, Group 2 subjects had 2 cohorts, 2 and 3. Cohort 2 included children between the ages of 6 to <12 years old and Cohort 3 includes children 3 to <6 years of age. No data from group 3 was submitted.

Approximately 200 subjects were planned for enrollment, 100 adolescents and 100 children between 3 years of age and <12 years of age. Up to 40 individuals could be treatment experienced. Group 1 subjects received the adult dosage of 400 mg/100 mg SOF/VEL. Group 2 received the new formulation of 200 mg/50 mg SOF/VEL. No data regarding Cohort 3 (ages 3 to <6 years old) were submitted.

The PK Lead-In Phase

The PK lead-in phase evaluated and confirmed the age-appropriate SOF/VEL dose for both age groups by analyzing the PK, safety and antiviral activity of SOF/VEL through 7 days of dosing. Additional subjects were enrolled into the treatment phase upon

confirmation of the appropriateness of the dose from the PK lead-in phase. At least 17 subjects were planned to be enrolled into each of the 2 PK lead in cohorts. Treatment experienced subjects were excluded from PK lead-in phase. Subjects who completed the PK lead-in phase were immediately enrolled into the treatment

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 SOF/VEL dose from the PK lead-in phase.

In this submission, the main inclusion criteria for enrolled children from 6 to <18 years of age included: evidence of chronic HCV infection through the presence of one of the following in the previous six months: positive HCV genotyping (positive genotype 1,2, 3, 4, 5 or 6). Subjects had an HCV RNA level ≥1,000 IU/mL.

Exclusion criteria included: subjects co-infected with HIV, acute hepatitis A, or hepatitis B decompensated liver disease, defined as INR >1.2 times the upper limit of normal, platelets <50,000 mm^3, albumin <3.5 g/dL, alpha- fetoprotein >50 ng/mL, serum creatinine >1.5 mg/dL or eGFR <90 mL/min/1.73 m^2, evidence of hepatocellular carcinoma or other malignancy fetoprotein >50 ng/mL, serum creatinine >1.5 mg/dL or eGFR <90 mL/min/1.73 m^2 and evidence of hepatocellular carcinoma or other malignancy.

Subjects in the study received SOF/VEL once daily as oral tablets as shown in Table 1. Dosing was done by age. The final approved dosage weight bands are in the label and in Section 11 below.

Pharmacokinetics Sampling Scheme

For the subjects in the PK lead-in phase, intensive serial PK blood samples were collected at the Day 7 visit at the following time points: 0 (predose [≤ 30 minutes prior to dosing]), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose. During the treatment phase, a single sparse PK blood sample was collected from all subjects any time at Weeks 1 (excluding subjects who rolled over from the PK lead-in phase) and 12. Additionally, 2 sparse PK samples were collected at Weeks 4 and 8, unless the subject was participating in the optional intensive PK substudy, at predose and between 15 minutes to 4 hours postdose. For subjects 12 to <18 years old who participated in the optional intensive PK substudy, intensive serial PK blood samples were collected at Week 4 or 8 at the following time points: 0 (predose [≤ 30 minutes prior to dosing]), 0.5, 1, 2, 3, 4, 6, 8, and 12 hours postdose. The PK of SOF, SOF metabolites (GS-566500 and GS-331007), and VEL were assessed.

The primary efficacy endpoint was SVR12. SVR12 is 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 pubertal staging, and growth. Safety was analyzed using descriptive statistics. Trial GS-US-342-1143 was reviewed for efficacy, safety and tolerability, and pharmacokinetics.

2.3.1. Protocol Amendments

The original study protocol (10 July 2014) was amended 4 times. Key changes to the protocol for each amendment were as follows:

The protocol was amended for the first time on 20 September 2016; key changes in this amendment included:

Amendment 1

- Clarification that all AEs will be recorded with a focus on those AEs leading to study drug discontinuation for evaluation of the primary safety endpoint
- Updated the SOF/VEL stopping criteria to align with the LDV/SOF and SOF laboratory stopping criteria in adult and pediatric clinical studies
- Added eligibility criteria pertaining to liver enzymes and bilirubin to align with the exclusion criteria parameters in SOF/VEL adult clinical studies
- Clarified that only the subject is required to complete the acceptability questionnaire at Day 1 but may be completed by the parent or legal guardian if the subject is unable to read
- Clarified that the Day 3 study visit will be performed over the phone and the site will assess the subject's dosing compliance by reviewing the dosing diary remotely with the subject or parent or legal guardian
- Added SOF/VEL Acceptability Questionnaire assessment to the early termination visit
- Appendix 3 (Management of Clinical and Laboratory AEs) was removed due to discrepancy in the protocol stopping rules within the protocol

Amendment 2

The protocol was amended for the second time on 10 December 2016. Key changes in Amendment 2 included: hepatitis B virus monitoring for any subject with hepatitis B core antibody positive at screening as per FDA Safety communication; added formulation, packaging, labeling storage and handling for SOF/VEL 200/50 mg.

Amendment 3

The protocol was next amended the third time on 31 August 2017 following completion of Cohort 1 to reflect the following key change.

- Added clinical pharmacology data and safety results from Cohort 1 from the PK lead-in phase supporting the dose for subjects 12 to <18 years old (Group 1) in the treatment phase and dose determination for Cohort 2 (6 to <12 years old) in the PK lead-in phase
- Added an optional intensive PK substudy for adolescent subjects 12 to <18 years old enrolled in the treatment phase at Week 4 or 8 to support development of the population PK model
- Additional time points were added to the intensive PK assessment for Cohort 3 (subjects 3 to <6 years old) to support characterization of PK of all analytes in the youngest Studies GS-US-342-1553 and GS-US-342-1146 since both of these studies were not included in the SOF/VEL investigator's brochure (IB) age group
- Added clarification of the sparse PK sample at Weeks 1, 4, 8, and 12
- Added a second sparse PK sample at Weeks 4 and 8 for all enrolled subjects
- Clarified the non-tablet formulation information will be included in a future protocol amendment once it was available and will be submitted for approval prior to dosing of subjects
- Added biomarker testing to align with the Gilead Sciences (Gilead) protocol template
- Updated the background information to include Studies GS-US-342-1553 and GS-US-342-1146 since both of these studies were not included in the SOF/VEL investigator's brochure (IB)

Amendment 4

Added clinical pharmacology data from Cohort 2 from the PK lead-in phase supporting the dose for subjects 3 to <6 years old (Cohort 3) in the PK lead-in phase

- Added dosing instructions for subjects 3 to <6 years old
- Added information on the oral granule formulation, including the dose for each age group and dosing instructions
- Added subject dosing diary for subjects who were administered oral granules Clarified dosing instructions for subjects 6 to <12 years old
- Clarified collection of parental height

- Clarified requirements for the complete physical examination and symptom-directed physical examination
- Updated the disallowed and concomitant medication table to align with the table in the most recent SOF/VEL FDC IB (Edition 5.0; dated 12 December 2017)
- Updated the list of PK parameters to align with regulatory commitments
- Updated the schedule of assessments (Appendix 2 of the Clinical Study Protocol) for consistency

2.4. Product Quality

Oral SOF/VEL tablets are already approved for use in adults (400 mg sofosbuvir/100 mg velpatasvir). A new lower strength tablet (200 mg sofosbuvir/50 mg velpatasvir) was developed for use in children. Please refer to the original review and to the sNDA review of Chemistry, Manufacturing and Control (CMC) in NDA 208341 for additional information.

3. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology data was submitted, see original NDA 208341for full details.

4. Clinical Pharmacology

Exposures in pediatric subjects were different from the exposures observed with adults as demonstrated by higher SOF exposures and lower VEL C_{tau}. Further details are discussed in Section 7.4. Please refer to Dr. Hazem Hassan's Clinical Pharmacology Review for full details.

5. Clinical Microbiology

There was a single instance of viral resistance with velpatasvir (NS5A inhibitor) among group 2 subjects. Please refer to Dr. Takashi Komatsu's Clinical Microbiology Review for details.

6. Clinical/Statistical: Efficacy

The primary statistical analysis was descriptive. The key efficacy endpoint is SVR12 defined as HCV RNA<LLOQ (i.e., <15 IU/mL) 12 weeks after discontinuation of the study drug in the Full Analysis Set (FAS). The COBAS® AmpliPrep/COBAS® TaqMan®HCV test v2.for use with the High Pure System were used to measure HCV RNA. No inferential statistics were used for efficacy endpoint.

A total of 175 subjects were enrolled into the 6 to <18 year old group (102 enrolled in the 12 to <18 years old and 73 enrolled into the 6 to <12 year old group). The planned enrollment was 200 for the entire population with 100 for the adolescents and the remaining 100 shared by the two cohorts of Cohorts (2) 6 to <12 years old and cohort (3) 3 to <6 years old.

The following is a summary of the disposition, demographics and characteristics of study subjects and the assessment of efficacy for each of the two cohorts separately (12 to <18 years and 6 to <12 years).

6.1. Cohort 1: 12- to <18-Year-Old Subjects

6.1.1. Disposition of Subjects

A total of 103 subjects were screened; 102 subjects were enrolled and received study drug. All subjects were treated with SOF/VEL for 12 weeks. All subjects except one who became pregnant completed the treatment course. Following treatment, subjects were evaluated at 4, 12 and 24 weeks off treatment.

A total of 21 of the 24 sites administered study drug to this age group. There were 3 sites participating in Study 1143 which did not enroll subjects. The 21 sites submitting subjects had a had a mean and median of 5 subjects each per site.

Protocol Violations

A total of 20 protocol violations occurred in 18 subjects during the study. The most prevalent protocol deviation regarded informed consent either initial or reconsenting which occurred in 10 sites. The next major category occurring in 4 subjects was for the subject not managed according to protocol. This mostly involved sample drawing windows. The last protocol deviations were study medication errors occurring in 4 subjects. There were no documented negative consequences of these protocol violations.

The site incidence of relevant protocol deviations was generally low except for Center 09292 which experienced 7 instances of protocol deviation (mostly related to informed consent or re-consenting issues) involving 5 subjects. There is no evidence that these protocol deviations affected the overall quality or interpretation of the study data.

Swallowability Assessment

Based on the swallowability assessment, a total of 92 subjects were able to swallow the SOF/VEL FDC 400/100-mg placebo tablet, and 10 subjects were not able to swallow the SOF/VEL FDC 400/100-mg placebo tablet but were able to swallow the 200/50-mg placebo tablets. No adolescent subject received oral granules.

6.1.2. Demographic and Baseline Characteristics

The Full Analysis Set included 102 subjects. Demographics and baseline characteristics are shown in Table 1 below.

The mean age was 15 years. the majority of subjects had been infected through vertical transmission (89.2%). The majority of subjects (72.5%) had IL28B non-CC genotype (CT = 53.9%, TT = 18.6%). The majority of subjects were treatment naive (78.4%), and no subjects had known cirrhosis based on prior biopsy or clinical history. The majority of subjects had HCV RNA ≥ 800,000 IU/mL (57.8%), with a mean (SD) baseline HCV RNA value of 6.1 (0.59) log10 IU/mL. The mean (SD) baseline alanine aminotransferase (ALT) value was 44 (35.7) U/L, and 19.6% of subjects had baseline ALT values >1.5 x upper limit of normal (ULN). The mean (SD) baseline estimated glomerular filtration rate (eGFR) using the Schwartz formula was 163.3 (30.05) mL/min/1.73m^2.

Table 1. Demographics and Baseline Characteristics for Subjects Ages 12 to <18 Years

Characteristic	SOF/VEL (400/100 mg) x 12 Weeks N=102
Race	
White	74 (72.5%)
Asian	11 (10.8%)
Black or African American	9 (8.8%)
Other	5 (4.9%)
Sex	
Male	50 (49.0%)
Female	52 (51.0%)
HCV viral genotype	
1	75 (73.5%)
2	6 (5.9%)
3	12 (11.8%)
4	2 (2.0%)
5	0
6	6 (5.9%)
Cirrhosis	
Yes	0
No	40 (39.2%)
Not determined	62 (60.8%)
Weight	
Mean	60.6 kg
Median	56.9 kg

6.1.3. Efficacy Results SVR 12 (12- to <18-Year-Old Subjects)

The primary efficacy endpoint was SVR12. All subjects completed study drug treatment except for a single individual who discontinued due to pregnancy. A total of 97 completed 12 week post study drug treatment. One subject remained in study but had not yet completed the 12 week follow-up evaluation at the time of supplement submission.

The SVR 12 rate was 93% (71/76) in subjects with genotype 1 HCV infection and 100% in subjects with genotype 2 (6/6), genotype 3 (12/12), genotype 4 (2/2), and genotype 6 (6/6) HCV infection. One subject discontinued treatment at Week 4 and subsequently relapsed; the other four subjects who did not achieve SVR12 did not meet virologic failure criteria (lost to follow-up. The Applicant did not summarize SVR 4 and SVR 24 results for either cohort in this interim submission (b) (4)

Although the primary statistical analysis of SVR 12 was descriptive, it is noted that the SVR 12 results in this group are similar to historical controls in adults treated with Epclusa ® for HCV infection

ALT Normalization (12- to <18-Year-Old Subjects)

ALT normalization is defined as ALT>ULN at baseline and ALT≤ ULN at each visit during and after treatment with SOF/VEL. At baseline 40% of subjects (41 of 102) had ALT > ULN. Normalization of ALT was observed in 90% (37 of 41) of subjects by Week

4. Of the remaining 4 subjects an additional subject had normalized ALT at Week 8. The remaining 3 subjects continued to demonstrate ALT values above the ULN throughout the period of observation. The HCV viral titers were negative in these three. The cause of the residual ALT elevations in the three were not determined but did not appear to be indicative of virologic failure.

Table 2. ALT Normalization in Subjects 12 to <18 Years of Age

Time Point	N (%) >ULN N=102
Baseline	41/102 (40%)
Treatment week 1	6/41 (15%)
Treatment week 4	4/41 (10%)
Treatment week 8	3/39 (8%)
Treatment week 12	3/40 (8%)
Follow-up week 4	3/32 (9%)

6.2. Cohort 2: 6- to <12-Year-Old Subjects

6.2.1. Disposition of Subjects

A total of 73 subjects 6 to <12 years of age were screened. All screened subjects were enrolled in study 1143. All subjects were treated with SOF/VEL for 12 weeks. Most subjects completed the study treatment (94.5%). All post treatment subjects were evaluated at 4, 12 and 24 weeks off treatment.

Seventy-one subjects of the seventy-three total were administered SOF/VEL 200 mg/50 mg tablets daily.

Two subjects received granules (SOF/VEL 50 mg/12.5 mg) for a total of 200 mg/50 mg. The reason for the granules was difficulty swallowing the tablet formulation. One subject of the two received 24 hours of granules and the other subject received the remainder of 12 week treatment.

A total of 5 of 71 subjects (7.0%) who received the low-dose tablet formulation during the study did not achieve SVR12. Of these, 1 subject (1.4%) with HCV genotype 1a had on-treatment virologic failure (nonresponse), and 4 subjects (5.6%) were categorized as “other.”

Of the 4 subjects categorized as “other,” 2 subjects (1 with genotype 1a and 1 with genotype 3a HCV infection) were lost to follow-up. The two remaining “other” subjects both with genotype 1a HCV infections either discontinued study drug due to an AE of product use issue (reported term: spitting up investigational product), or are pending a posttreatment Week 12 visit at the time of this analysis.

Protocol Violations

A total of 9 protocol deviations occurred in 7 subjects during the study. These protocol violations occurred at 7 among the 26 sites participating in the 6 to <12 year old group.

The most prevalent protocol deviation was study medication errors occurring in 6 subjects. Both increased dosage and inadequate doses were observed. The next deviation in incidence involving 4 individuals was mismanagement of protocol. The final protocol deviation was a single incident of informed consent error.

The incidence of relevant protocol deviations was generally low with one or at most two instances per patient at a study site. There is no evidence that these protocol deviations affected the overall quality or interpretability of the study data.

Swallowability Assessment

A total of 70 pediatric subjects 6 to <12 years old who were only administered SOF/VEL FDC (200/50 mg) tablets completed the acceptability questionnaire on Day 1 and at Week 12 or early termination. On Day 1, 58 of 70 subjects (82.9%) either did not taste the study drug or reported the taste as palatable (score marked ≥ 40), and 63 of 70 subjects (90.0%) reported the ease of taking study drug as acceptable (score marked ≥ 40). At Week 12 or early termination, 59 of 70 subjects (84.3%) either did not taste the study drug or reported the taste as palatable, 70 of 70 subjects (100.0%) reported the ease of taking study drug as acceptable, and 67 of 70 subjects (95.7%) reported the ease of taking 1 tablet each day as acceptable. (score marked ≥ 40).

6.2.2. Demographics and Baseline Characteristics of Subjects

The Full Analysis Set included 73 subjects. Only 71 subjects received the low dose tablet throughout the study. The remining 2 subjects had swallowing difficulties and received the granules instead of the low dose tablet. Demographics and baseline characteristics are shown in Table 3 below.

Most subjects were infected with HCV by vertical transmission (94.4%). The subjects were predominantly female (53.5%) and white (90.1%), and not Hispanic or Latino,(87.3%), with a mean age of 8 years (range: 6−11). The mean baseline BMI was 17.4 kg/m2 (range: 12.8−30.9), and the mean baseline body weight was 29.7 kg (range: 18.4−77.9). There were no important demographic or baseline characteristic differences between the low dose tablet only recipients and the recipients of granules, acknowledging the numbers of the latter were very low.

Table 3. Demographics and Baseline Characteristics for Subjects Ages 6 to <12 Years

Characteristic	SOF/VEL (200/50 mg) x 12 Weeks N=71
Race	
White	66 (90.4%)
Asian	1 (1.4%)
Black or African American	4 (5.5 %)
Other	2 (2.7%)
Sex	
Male	35 (48%)
Female	38 (52%)
HCV viral genotype	
1	56 (76.7%)
2	2 (2.7%)
3	11 (15.1%)
4	4 (5.5%)
5	0
6	0
Cirrhosis	
Yes	0
No	30 (42.3%)
Not determined	41 (57.7%)
Weight	
Mean	29.7 kg
Median	26.7 kg

6.2.3. Efficacy Week 12 After Discontinuation of Treatment (6- to <12-Year-Old Subjects)

The primary efficacy endpoint was the SVR 12. The SVR 12 for all subjects 6 to <12 years regardless of HCV virus genotype was 93%.The SVR 12 results per genotypes were: genotype 1 was 51/56 (91%); genotype 3 was 10/11 (91%); and genotypes 2 and 4 were 6/6 (100%).Overall 5 subjects did not achieve SVR12. One of the 5 displayed an on-treatment virologic failure, another was not able to tolerate the investigational product and discontinued treatment, two were lost to follow-up, one has not completed post treatment assessments at time of submission.

ALT Normalization (6- to <12-Year-Old Subjects)

ALT normalization is defined as ALT>ULN at baseline and ALT≤ ULN at each visit during and after treatment with SOF/VEL. At baseline 74% of subjects (54 of 73) had ALT > ULN. Normalization of ALT was observed in 92% (48 of 52) of subjects by Week 4. Of the remaining 4, two achieved normalization of ALT by Week 8. The final two individuals continued to have ALT values above the ULN. HCV viral assays determined one individual was experiencing viral failure with recurrent infection. The cause of the ALT elevation in the other subject was not determined

Table 4. ALT Normalization in Subjects 6 Years to <12 Years of Age

Time Point	N (%) >ULN N=73
Baseline	54/73 (74%)
Treatment week 1	15/51 (29%)
Treatment week 4	4/52 (8%)
Treatment week 8	2/29 (4%)
Treatment week 12	2/49 (4%)
Follow-up week 4	2/38 (5%)

6.3. Overall Efficacy Summary (6- to <18-Year-Old Subjects)

The efficacy of SOF/VEL in children with chronic HCV due to genotype 1, 2, 3, 4 or 6 was demonstrated in this open-label, uncontrolled trial. SVR12 was demonstrated in 95.0% of subjects of subjects ages 12 to <18 (97/102) and 93% of subjects 6 to <12 years of age (66/71). The response rate is consistent with the antiviral response observed in studies of treatment-naive adults. Although the protocol allowed enrollment of genotype 5, none were enrolled during the trial. Genotype 5 is very uncommon but SOF/VEL has demonstrated clinical activity in adults and therefore because the PK is similar for all genotypes the efficacy in adults with Genotype 5 infection was extrapolated to children. A similar rationale was used to extrapolate the efficacy to children with decompensated cirrhosis.

7. Safety

The applicant has submitted safety data from 175 pediatric subjects 6 to <18 years old (102 subjects 12 to <18 years old; and 73 subjects 6 to <12 years) who received at least one dose of SOF/VEL in Trial GS-US-342-1143. The duration of follow-up was 12 weeks after discontinuation of treatment for all 175 subjects. The types of Adverse Events (AEs) observed were similar to the types of AEs observed in adults with chronic HCV infection who received SOF/VEL 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 used.

7.1. Safety Data Subjects 12 to <18 Years

Table 5 presents the overall summary of AEs (without regard to causality) and adverse drug reactions (ADRs) at least possibly related for subjects 12 to <18 years of age by treatment group. Nearly 78% of subjects experienced a Treatment Emergent Adverse Event (TEAE). The majority of AE severities were either grade 1 or 2 severity. There were 2 unrelated SAEs and 3 unrelated Grade 3 AEs occurring in the same 2 subjects concerning suicidal ideation and attempts.

Table 5. Overall Summary of Adverse Events 12 to <18 Years Old, Cohort 1

Adverse Event	SOF/VEL 400/100 mg x 12 Weeks N=102
Any TEAE	77 (75.5%)
Maximum toxicity grade	
Grade 1 (mild)	64 (63%)
Grade 2 (moderate)	10 (9.8%)
Grade 3 (severe)	3 (3%)
Grade 4 (life threatening)	0
Death	0
SAEs	2 (2%)
Drug related SAEs	0
Drug related AEs (ADRs)	41 (40%)

There were no Grade 3 or 4 ADRs, no premature discontinuation ADRs or treatment interruption due to an ADR**.**

SAEs Narratives

- 13-year-old female experienced Grade 3 suicidal ideation study day 55. No interruption of study drug. New drug for attention deficit hyperactivity disorder recently started. Parents attributed symptoms to social stressors at school.

Reviewer comment: Agree with Investigator's assessment not likely related.

- 14-year-old female had ongoing Grade 3 SAE of suicidal ideation on day 69. Grade 4 Suicide attempt occurred day 59 and 75. Symptoms relieved by Study Day 80. No interruption of study drug administration and AE was not related to study drug.

Reviewer comment: The provided narratives do not indicate a relationship between these SAEs and study drugs.

Table 6. ADRs >1 Subjects Ages 12 to <18 Years Old

Adverse Drug Reaction	SOF/VEL 400/100 mg x 12 Weeks N=102
Number % subjects with treatment related AE	41 (40.2%)
Headache	18 (17.6%)
Fatigue	16 (15.7%)
Nausea	15 (14.7%)
Dizziness	5 (4.9%)
Abdominal pain	4 (3.9%)
Abdominal pain upper	4 (3.9%)
Diarrhea	2 (2.0%)

Table 7 presents a summary of AEs (without regard to causality) reported for at least 5% of subjects ages 12 to <18 years.

Table 7. Common AEs (≥5%) in Subjects Ages 12 to <18 Years Without Regard to Relatedness

Adverse Event	SOF/VEL 400/100 mg x 12 Weeks N=102
Headache	30 (29.4%)
Fatigue	22 (21.6%)
Nausea	17 (16.7%)
Upper abdominal pain	10 (9.8%)
Pyrexia	10 (9.8%)
Cough	9 (8.8%)
Dizziness	9 (8.8%)
Oropharyngeal pain	9 (8.8%)
Vomiting	9 (8.8%)
Diarrhea	7 (6.9%)
Abdominal pain	6 (5.9%)
Nasal congestion	6 (5.9%)

Graded Laboratory Abnormalities

Overall, 44 adolescent subjects 12 to <18 years old had a graded laboratory abnormality. The maximum abnormality grade for most these subjects was Grade 1 (34.3%, 35/102 subjects) or Grade 2 (3.9%, 4 of 102 subjects); overall, the incidence of Grade 3 laboratory abnormalities was 4.9% (5 of 102 subjects) and there were no Grade 4 laboratory abnormalities. The only Grade 3 laboratory abnormality that occurred in >1 subject was Grade 3 decreased neutrophils (2.0%, 2 of 102 subjects). One subject has a medical history of neutropenia with an ongoing AE of neutropenia and the other subject had an isolated Grade 3 decrease in neutrophils. The laboratory abnormalities observed during treatment appear not clinically significant.

Discontinuations

There were no discontinuations due to AEs in subjects ages 12 to <18 years

Interruptions

There were no interruptions due to AEs in subjects ages 12 to <18 year

Deaths

No deaths occurred during the conduct of the clinical trial.

7.2. Safety Data Group 2: Ages 6 to <12 Years

Table 8 presents the overall summary of AEs for subjects 6 to <12 years old by treatment group. Approximately 81% of subjects experienced at least one AE during the conduct of the trial. The severities of the AEs were mostly grade 1 and 2. There were 2 SAEs, Grade 2 constipation and auditory hallucinations.

Table 8. Overall Summary of AEs and ADRs Ages 6 to <12 Years

Adverse Event	SOF/VEL 200/50 mg x 12 Weeks N=73
Any TEAE	59 (80.8%)
Maximum toxicity grade	
Grade 1 (mild)	51 (64%)
Grade 2 (moderate)	4 (5%)
Grade 3 (severe)	2 (2.7%)
Grade 4 (life threatening)	0
Death	0
SAEs	2 (2.7%)
Drug related SAEs	1 (1.4%)
Drug related AEs	25 (34.2%)
Drug related Grade 3 AEs	1 (1.4%)
Premature discontinuations	2 (2.7%)
Temporary interruptions	3 (4.1%)

SAEs Narratives

- One subject with a medical history of ongoing chronic constipation experienced a Grade 2 SAE of constipation on Day 3, which was assessed as not related to study drug. The subject was hospitalized and treated with macrogol, potassium chloride, sodium bicarbonate, sodium chloride, and sodium sulfate. The event resolved on Day 5 without interruption of study drug
- One subject, a 6-year-old female with a medical history of asthma experienced a Grade 3 SAE of auditory hallucinations on Day 37, which was assessed as related to study drug. Study drug was discontinued on Day 39, and the event resolved on posttreatment Day 10. This subject also experienced a nonserious, Grade 2 AE of negative thoughts from Days 31 through 34 which was assessed as related to

Reviewer comments: Of the two SAEs, one was an episode of unrelated constipation occurring in an individual with chronic constipation. The other was an multiple day instance of auditory hallucinations that were assessed as related to study drug by the investigator. This reviewer agrees with the Investigator's assessment.

Table 9 describes ADRs experienced by children 6 to <12 years old. Overall, ADRs were less prevalent among the 6 to <12 years old subjects compared to the adolescents. The pattern of ADR entities were similar.

Table 9. ADRs Subjects Ages 6 to <12 Years

Adverse Drug Reaction	SOF/VEL 200/50 mg x 12 Weeks N=73
Number % subjects with ADRs ages 6 to <12 years	25 (34.2%)
Fatigue	8 (11%)
Headache	5 (6.8%)
Abdominal pain	3 (4.1%)
Abdominal pain upper	3 (4.1%)
Diarrhea	3 (4.1%)
Irritability	2 (2.7%)
Product use issue	2 (2.7%)

Table 10 presents a summary of AEs occurring in at least 5% of subjects ages 6 to <12 years. Overall the most commonly reported AE across subjects are cited in the table below:) The mixture of most common AEs in the 6 to <12 years old differs from the adolescent with prominence of vomiting.

Table 10. Common AEs (≥5%) Subjects Ages 6 to <12 Years

Adverse Event	SOF/VEL 200/50 mg x 12 Weeks N=73
Vomiting	12 (16.4%)
Cough	11 (15.1%)
Headache	11 (15.1%)
Fatigue	9 (12.3%)
Abdominal pain	9 (12.3%)
Pyrexia	8 (11%)
Nasopharyngitis	7 (9.6%)
Rash	7 (9.6%)
Upper respiratory tract infection	7 (9.6%)
Diarrhea	6 (8.2%)
Epistaxis	6 (8.2%)
Nausea	5 (6.8%)

Graded Laboratory Abnormalities

- 27 of 73 subjects did have graded lab abnormalities. Maximum grade one severity for 34%, or Grade two 4.2%. No Grade 3 or 4 hematology laboratory abnormalities were reported in pediatric subjects
- No pediatric subject 6 to <12 years old had postbaseline hemoglobin <10 g/dL

Discontinuations

2 subjects had AEs that led to premature discontinuations:

- 1 subject experienced product use issues- spitting up investigational product on Study Day one leading to interruption of dosing to Study Day 7 when subject experienced another Grade 1 product use issue and dosing was discontinued.
- One subject experienced Grade 3 SAE auditory hallucinations study drug discontinued

Interruptions

Three Group 2 subjects experienced treatment interruptions:

- 2/3 experienced retching with substitution of granules for tablets. One resulted in discontinuation after 24 hours and the other resumption with granules on Day 56 to complete 12 Weeks.
- Remaining subject described in discontinuation above.

Deaths

There were no deaths reported in the study.

Summary of Safety in Subjects 6- to <12 Years Old

Overall, treatment with SOF/VEL for 12 weeks was generally safe and well tolerated. Overall (38% 27/71) of subjects had a graded laboratory abnormality. There were no Grade 3 or Grade 4 laboratory abnormalities.

7.3. Other Adverse Events

There were no notable effects of treatment on development or growth (baseline to post-treatment Week 12) 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 12 in vital signs (Systolic Blood Pressure, Diastolic Blood Pressure or pulse).

7.4. Weight-Based Exposure and Safety Issues

For pediatric patients 6 to less than 18 years of age, a weight band-based dosing regimen was proposed (200/50 mg for 17 to less than 35 kg and 400/100 mg for >35 kg). Based on a population PK analyses, the following observations were made in pediatric patients who received EPCLUSA.

- SOF exposures were consistently higher (approximately 2-fold) in comparison to adults and also to the SOVALDI and HARVONI pediatric programs.
- GS-331007 and VEL exposures for the >35 kg weight band are comparable to those in adults
- Lower (approximately 30%) GS-331007 AUC and VEL C_{tau} values were observed in the 17 to <35 kg weight band compared to adults

No clear explanation was evident for the increased SOF exposures in pediatric subjects. To avoid lower C_{tau} values of VEL and potentially compromise efficacy, both the Applicant and FDA simulated exposures of SOF, GS-331007 and VEL with different weight bands (e.g., 200/50 mg for 17 to <30 kg and 400/100 mg for >30 kg). The simulated exposures show that if a 400/100-mg dose is given to children weighing >30 kg, the percentage of subjects with VEL C_{tau} values below the 5th percentile of adults would decrease from 14% to 6%. Consequently, a modest increase is projected in the percentage of subjects with AUC_{tau} and C_{max} above the 95th percentile of adults for SOF, GS-331007 and VEL. Please refer to the Clinical Pharmacology review for further details.

Next, we reviewed the available safety data to support the adult dose (400/100 mg) and the increased SOF AUC and C_{max} exposures in children weighing >30 kg. Dosing in Study 1143 was based on age and not weight. Children 12 years of age and older were to receive the adult dose (400/100 mg) and children <12 years of age received 200/50 mg. Overall, six adolescent subjects with body weight less than 35 kg received SOF/VEL 400 mg/100 mg. Of these six subjects, three experienced adverse events and three did not. The adverse events experienced were unremarkable consisting of mild

fatigue, nausea, headache in two and moderate constipation, fever, pink eye in the remaining subject.

There were no exposure-response relationships between SOF, GS-331007 and VEL exposure parameters and selected adverse events identified in any clinical trial to date. Therefore, the increased SOF exposures are not clinically significant, and the safety data are reasonable to support the 400/100 mg dose in children weight >30 kg.

Table 11. SOF/VEL Weight Band Doses Utilized in Study 1143

	No. of Subjects Exposed, n (%)	
	Cohort 1[a] (N=103)	Cohort 2[b] (N=73)
Baseline Weight	SOF/VEL: 400 mg/100 mg	SOF/VEL: 200 mg/50 mg
≥35 kg	97/103 (94%)	17/73 (23%)
<35 kg	6/103 (6%)	56/73 (77%)

[a] Cohort 1 includes subjects 12 to <18 years of age
[b] Cohort 2 includes subjects 6 to <12 years of age

7.5. Drug Interactions

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

7.6. Use in Pregnancy and Lactation

No notable new findings relevant to use of SOF/VEL concomitantly with pregnancy or lactation were submitted with this update to the marketing application. One of the 175 subjects (b) (6) 17 years of age) participating in group 1 of GS-US-342-1143 became pregnant. The subject withdrew from participation. Pregnancy occurred during her first trimester. This pregnancy resulted in induced abortion. No birth defects were noted in the fetus.

8. 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.

9. Pediatrics

See Section 6 for discussion regarding efficacy and Section 7 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.

This application did not go to the exclusivity board – [redacted] (b) (4) .

10. Other Relevant Regulatory Issues

10.1. 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 because too few subjects were enrolled per site and the basis of approval was matching PK in children to adults.

10.2. 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 U.S. 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.

10.3. 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-342-1143 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 125 investigators (26 Principal Investigators and 99 Sub-Investigators), None of the investigators are Gilead employees. Please see Appendix for more details.

11. 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 infected pediatric patients 6 to <18 years of age without cirrhosis or with compensated cirrhosis or with decompensated cirrhosis used in combination with ribavirin. The changes with this efficacy supplement primarily affected the following sections.

11.1. Highlights of Prescribing Information

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

1 INDICATIONS AND USAGE

The indication was expanded to pediatric patients as follows.

EPCLUSA is indicated for the treatment of adults and pediatric patients 6 years of age and older or weighing at least 17 kg with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection [see Dosage and Administration (2.2, 2.3, 2.4) and Clinical Studies (14)]:

- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin.

The changes to the indication is supported by results from Study 1143 and SOF, GS-331007 and VEL exposures in adults and pediatric patients.

As mentioned in section 7.2.3 (efficacy) subjects with HCV genotype 5 and pediatric subjects with decompensated cirrhosis were not enrolled in the trial. However, the indication was expanded to these subgroups because:

- HCV genotype does not affect SOF/VEL exposure and previous trials in adults have demonstrated that an equivalent SOF/VEL exposure is efficacious in adults with chronic HCV genotype 5. Therefore, the submitted PK data are adequate to support the efficacy of SOF/VEL for treatment of patients 6 years of age and older or weighing at least 17 kg with HCV genotype 5

- Similar rationale is used to support dosing recommendations for pediatric patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

2 DOSAGE AND ADMINISTRATION

This section was reorganized to include 2.2 Recommended Treatment Regimen and Duration in Patients 6 Years of Age and Older or Weighing at Least 17 kg, section 2.3 to outline adult dosing (no changes to this section) and section 2.4 Recommended Dosage in Pediatric Patients 6 Years of Age and Older or Weighing at Least 17 kg as shown in the Tables from the label below.

Additionally, dosing recommendations for pediatric patients with decompensated cirrhosis was included and requires coadministration with RBV, therefore, RBV dosing recommendations consistent with the Sovaldi and Harvoni label were included in this section. Additionally, the weight bands were modified from at leas (b) (6) kg to at least 30 kg and from 17 to less than (b) (4) kg to 17 to less than 30 kg as described in section 8.4.

Table 1. Recommended Treatment Regimen and Duration in Patients ≥6 Years of Age or Weighing ≥ 17 kg With Genotype 1, 2, 3, 4, 5 or 6 HCV

Patient Population	Treatment Regimen and Duration
Treatment naïve and treatment experienced without cirrhosis and with compensated cirrhosis (Child-Pugh A)	EPCLUSA 12 weeks
Treatment naïve and treatment experienced with decompensated cirrhosis (Child-Pugh B or C)	EPCLUSA + ribavirin 12 weeks

2.4 Recommended Dosage in Pediatric Patients 6 Years of Age and Older or Weighing at Least 17 kg

> The recommended dosage of EPCLUSA in pediatric patients 6 years of age and older or weighing at least 17 kg is based on weight and provided in Table 2. Table 3 provides the weight-based dosage of ribavirin when used in combination with EPCLUSA for pediatric patients. Take EPCLUSA once daily with or without food *[see Use in Specific Populations (8.4), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]*.

Table 2. Dosing for Pediatric Patients ≥6 Years or Weighing ≥17 kg With Genotype 1, 2, 3, 4, 5, or 6 HCV

Body Weight (kg)	Dosing of EPCLUSA	EPCLUSA Daily Dose
At least 30	One 400 mg/100 mg tablet once daily or two 200 mg/50 mg tablets once daily	400 mg/100 mg per day
17 to less than 30	One 200 mg/50 mg tablet once daily	200 mg/50 mg per day

Table 3. Recommended Dosing for Ribavirin in Combination Therapy With EPCLUSA for Pediatric Patients 6 Years and Older

Body Weight (kg)	Oral Ribavirin Daily Dosage
Less than 47	15 mg per kg per day (divided dose AM and PM)
47-49	600 mg per day (1x200 mg AM, 2x200 mg PM)
50-65	800 mg per day (2x200 mg AM, 2 x200 mg PM)
66-80	1, 000 mg per day (2x200 mg AM, 3x200 mg PM)
Greater than 80	1,200 mg per day (3x200 mg AM, 3x200 mg PM)

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

6.1 Clinical Trials Experience

This section was updated to include a summary of the adverse reactions in children as follows:

> Adverse Reactions in Pediatric Subjects 6 Years of Age and Older
> The safety assessment of EPCLUSA in pediatric subjects 6 years of age and older is based on data from a Phase 2, open-label clinical trial (Study 1143) that enrolled 175 subjects who were treated with EPCLUSA for 12 weeks. The adverse reactions observed were consistent with those observed in clinical trials of EPCLUSA in adults *[see Clinical Studies (14.5)]*.

8.4 Pediatric Use

This section was updated as follows to summarize the basis of approval in pediatric patients 6 years of age and older or weighing at least 17 kg.

The pharmacokinetics, safety, and effectiveness of EPCLUSA for treatment of HCV genotype 1, 2, 3, 4, or 6 infection in treatment-naïve and treatment-experienced pediatric patients 6 years of age and older or weighing at least 17 kg without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1143, N=175; 149 treatment-naïve, 26 treatment-experienced). No clinically meaningful differences in pharmacokinetics were observed in comparison to those observed in adults. The safety and effectiveness were comparable with those observed in adults *[see Dosage and Administration (2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)].*

The safety and effectiveness of EPCLUSA for treatment of HCV genotype 5 in pediatric patients 6 years of age and older or weighing at least 17 kg without cirrhosis or with compensated cirrhosis are supported by sofosbuvir, GS-331007, and velpatasvir exposures in adults and pediatric patients *[see Dosage and Administration (2.2 and 2.4), Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14.6)]*. Similar rationale is used to support dosing recommendations for pediatric

patients with HCV genotype 1, 2, 3, 4, 5, or 6 infection who have decompensated cirrhosis (Child-Pugh B or C).

In patients with severe renal impairment, including those requiring dialysis, exposures of GS-331007, the inactive metabolite of sofosbuvir, are increased *[see Clinical Pharmacology (12.3)]*. No data are available regarding the safety of EPCLUSA in pediatric patients with renal impairment *[see Use in Specific Populations (8.6)]*.

The safety and effectiveness of EPCLUSA have not been established in pediatric patients less than 6 years of age.

11 DESCRIPTION

In section 11 a simple visual description of the two formulations tablets was added as follows.

EPCLUSA is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an NS5A inhibitor.

Each 400 mg/100 mg tablet contains 400 mg sofosbuvir and 100 mg velpatasvir and each 200 mg/50 mg contains 200 mg sofosbuvir and 50 mg velpatasvir.

(b) (4)

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

This section was updated as follows to include the PK data from Study 1143.

The pharmacokinetics of sofosbuvir, GS-331007, and velpatasvir were determined in HCV genotype 1, 2, 3, 4, or 6 infected pediatric subjects 6 years of age and older receiving a daily dose of EPCLUSA as described below in Table (b) (4). Geometric mean SOF AUC_{tau} and C_{max} and VEL C_{max} values were 72%, 75%, and 85% higher in pediatric subjects $\geq$30 kg, and 73%, 81%, and 109% higher in pediatric subjects 17 to <30 kg compared to those observed in adults. This difference was not considered clinically significant. GS-331007 exposures and velpatasvir AUC_{tau} and C_{tau} values in pediatric subjects were similar to those observed in adults.

Table (b) (4). PK of Sofosbuvir and Velpatasvir in Infected Pediatric Patients 6 Years and Older

			Geometric Mean (% CV)		
Weight Group	**Dose**	**PK Parameter**	**Sofosbuvir**	**GS-331007**	**Velpatasvir**
≥30 kg	400/100 mg	C_{max} (ng/ml)	946 (93.3)	1140 (24.5)	416 (34.8)
		AUC_{tau}(ng/ml)	2040 (83.3)	13100 (27.4)	3810 (40.3)
		C_{trough}(ng/ml)	NA	NA	35 (87.2)
17 to <30 kg	200/50 mg	C_{max}(ng/ml)	974 (70.8	1040 (29.8)	470 (33.6)
		AUC_{tau}(ng/ml)	2050 (59.0)	10800 (27.9)	3460(27.5)
		C_{trough}(ng/ml)	NA	NA	33 (51.2)

The pharmacokinetics of sofosbuvir, GS-331007 and velpatasvir have not been established in pediatric subjects less than 6 years of age or weighing less than 17 kg *[see Use in Specific Populations (8.4) and Clinical Studies (14.5)]*.

12.4 Microbiology

This section is largely unchanged. Under the subsection Effect of Baseline HCV Polymorphisms on Treatment Response, Subsection Pediatrics the following language has been added:

> In Study 1143, the presence of NS5A and NS5B RAPs did not impact treatment outcome; all pediatric subjects 6 years of age and older with baseline NS5A RAPs (14%; 23/165) or NS5B nucleoside inhibitor RAPs (3%; 5/164) achieved SVR following 12 weeks treatment with EPCLUSA.

Rationale

At the 15% assay cutoff, pretreatment NS5A RAVs were detected in 7 of 67 subjects (10.4%). All 7 subjects with baseline NS5A RAVs achieved SVR12. Overall, 66 of 67 subjects (98.5%) achieved SVR12. One subject had on-treatment virologic failure (nonresponse) during SOF/VEL treatment; this subject had genotype 1a HCV infection, was treatment naive, and had no NS5A RAVs detected at baseline.

At the 15% deep sequencing assay cutoff, pretreatment NS5B RAVs were not detected in any of the 67 subjects. One subject had on-treatment virologic failure (nonresponse) during SOF/VEL treatment; this subject had genotype 1a HCV infection, was treatment naive, and had no NS5B NI RAVs detected at baseline.

14 CLINICAL STUDIES

14.6 Clinical Trial in Pediatric Subjects

This section was updated with the most recent data from the two interim Clinical Study Reports and the accompanying datasets corresponding to the two age groups 12 to <18 years and 6 to <12 years old. The demographic and clinical trial data presented for the two groups (Group (1) 12 to <18 years and Group (2) 6 to <12 years) participating in Clinical Study1143 are accurately reported. The following sections were added:

The efficacy of EPCLUSA once daily for 12 weeks was evaluated in an open-label trial (Study 1143) in 173 genotype 1, 2, 3, 4, or 6 HCV treatment-naïve (N=147) or treatment-experienced (N=26) pediatric subjects 6 years of age and older without cirrhosis or with compensated cirrhosis.

Subjects 12 Years to <18 Years of Age: EPCLUSA was evaluated in 102 subjects 12 years to <18 years of age with genotype 1, 2, 3, 4, or 6 HCV infection. Among these subjects, 80 (78%) were treatment-naïve and 22 (22%) were treatment-experienced. The median age was 15 years (range: 12 to 17); 51% of the subjects were female; 73% were White, 9% were Black, and 11% were Asian; 14% were Hispanic/Latino; mean body mass index was 23 kg/m2 (range: 13 to 49 kg/m2); mean weight was 61 kg (range 22 to 147 kg); 58% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; the proportions of subjects with genotype 1, 2, 3, 4, or 6 HCV infection were 74%, 6%, 12%, 2%, and 6%, respectively; no subjects had known cirrhosis. The majority of subjects (89%) had been infected through vertical transmission. The SVR rate was 93% (71/76) in subjects with genotype 1 HCV infection and 100% in subjects with genotype 2 (6/6), genotype 3 (12/12), genotype 4 (2/2), and genotype 6 (6/6) HCV infection. One subject discontinued treatment at Week 4 and subsequently relapsed; the other four subjects who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

Subjects 6 Years to <12 Years of Age: EPCLUSA was evaluated in 71 subjects 6 years to <12 years of age with genotype 1, 2, 3, or 4 HCV infection. Among these subjects, 67 (94%) were treatment-naïve and 4 (6%) were treatment-experienced. The median age was 8 years (range: 6 to 11); 54% of the subjects were female; 90% were White, 6% were Black, and 1% were Asian; 10% were Hispanic/Latino; mean body mass index was 17 kg/m2 (range: 13 to 31 kg/m2); mean weight was 30 kg (range 18 to 78 kg); 48% had baseline HCV RNA levels greater than or equal to 800,000 IU per mL; the proportions of subjects with genotype 1, 2, 3, or 4 HCV infection were 76%, 3%, 15%, and 6%, respectively; no subjects had known cirrhosis. The majority of subjects (94%) had been infected through vertical transmission.

The SVR 12 rate was 93% (50/54) in subjects with genotype 1 HCV infection, 91% (10/11) in subjects with genotype 3 HCV infection, and 100% in subjects with genotype 2 (2/2) and genotype 4 (4/4) HCV infection. One subject had on-treatment virologic failure; the other four subjects who did not achieve SVR12 did not meet virologic failure criteria (e.g., lost to follow-up).

12. Postmarketing Recommendations

12.1. Risk Evaluation and Management Strategies (REMS)

No recommendation for a REMS is indicated.

12.2. Postmarketing Requirements (PMRs) and Commitments (PMCs)

No PMRs or PMCs are indicated.

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14. Appendix: Clinical Investigator Financial Disclosure Review

Clinical Investigator Financial Disclosure Review

Application Number: NDA 208341/ Supplement 14

Submission Date(s): September 19, 2019

Applicant: Gilead Sciences, Inc.

Product: Sofosbuvir/Velpatasvir (Epclusa)

Reviewer: William Tauber, MD

Date of Review: February 18, 2020

Covered Clinical:
"A Phase 2, Open-Label, Multicenter, Multi-cohort Study to Investigate the Safety and Efficacy of Sofosbuvir/Velpatasvir in Adolescents and Children with Chronic HCV Infection"

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 125 (26 Principal Investigators and 99 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): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

The Applicant states there were no principal and/or sub-investigators who are participating or have participated in the covered clinical study (GS-US-342-1143) that have received financial interest or arrangements as described in 21CFR 54.4(a)(3). As such no Forms FDA 3455 are included in this submission.

Clinical Reviewer:

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 125 Investigators for Study GS-US-342-1143 are employed by the Sponsor

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 Applicant states that 100% of the source documents will be verified by a Clinical Research Associate (CRA) working on behalf of the Applicant. 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 Applicant.

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. In conclusion, the 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/

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03/19/2020 12:30:52 PM

KIMBERLY A STRUBLE
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