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

Date	May 28, 2021
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Subject	Combined Clinical Review, Cross-Discipline Team Leader Review and Division Director Summary Review
NDA# and Supplement#	208341/Supplement 17; 214187 (Original)
Applicant	Gilead Sciences, Incorporated.
Date of Submission	December 15, 2020
PDUFA Goal Date	June 14, 2021
Proprietary Name	Epclusa®
Established or Proper Name	Sofosbuvir/Velpatasvir (SOF/VEL)
Dosage Form(s)	Oral tablets: ▪ 400 mg of sofosbuvir and 100 mg of velpatasvir ▪ 200 mg sofosbuvir and 50 mg of velpatasvir Oral pellets: ▪ 200 mg sofosbuvir and 50 mg of velpatasvir ▪ 150 mg sofosbuvir and 37.5 mg of velpatasvir
Applicant Proposed Indication(s)/Population(s)	Pediatric Patients 3 to < 6 years of age: For treatment of genotype 1, 2, 3, 4, 5 or 6 chronic HCV infection
Applicant Proposed Dosing Regimen(s)	Weight based dosing (see Table 2)
Recommendation on Regulatory Action	Approval

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1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The pharmacokinetic (PK), safety, and efficacy data submitted in this supplemental New Drug Application (sNDA) under NDA 208341 and the initial marketing application under NDA 214187 for 200 mg/50 mg and 150mg/37.5 mg oral pellets formulation support approval of sofosbuvir/velpatasvir (Epclusa®, SOF/VEL) for the treatment of chronic hepatitis C virus infection in children 3 to < 6 years of age and provides for an age-appropriate pediatric formulation. Throughout the review of this sNDA and NDA, no deficiencies that would preclude approval were identified. Epclusa was studied in a multicenter, open-label, non-comparative trial (Study GS-US-342-1143) in which 216 children (102 children 12 to < 18 years; 73 children 6 to < 12 years old, and 41 children 3 to < 6 years old), were enrolled and followed for 24 weeks , after completion 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 SOF/VEL were evaluated. The SOF/VEL dose selection was weight-based, and formulation was selection based on the participant's ability to swallow tablets; those who could not swallow tablets were administered the pellets formulation. The study consisted of the three cohorts: Cohort 1 (12 to < 18 years); Cohort 2 (6 to < 12 years) and Cohort 3 (3 to < 6 years). SOF/VEL is approved for children 6 to < 18 years (Cohorts 1 and 2). Only data for Cohort 3 are presented in this review.

The key objective of this pediatric study was to identify a dose(s) for use in pediatric patients based on targeting an exposure in children that is similar to the approved adult doses. The observed exposures from VEL, SOF, and SOF major metabolite, GS-331007, in Cohort 3 were similar to those seen in the older children (6 to < 18 year old), and in adults. Therefore, the efficacy of SOF/VEL is extrapolated from the adult to pediatric population 3 years and older. Other objectives for the study include to describe the safety of SOF/VEL in pediatric subjects; and collect virologic outcome (efficacy).

The efficacy outcome for the overall group, as measured by sustained virologic response 12 weeks after treatment completion (SVR12), was 82.9% (34/41); with an SVR12 of 87.5% (28/32) for genotype 1; 50% (3/6) for genotype 2; 100% (2/2) for genotype 3; and 100% (1/1) for genotype 4. Alanine aminotransferase (ALT) normalization was also observed. A total of 7 subjects (17.1%) did not achieve SVR12 due to drug discontinuation, without evidence of virologic failure. Of these 7 children, 5 discontinued the drug on Day 1 due to adverse reactions –vomiting or spitting up of drug (likely due to unplatability of the drug); one discontinued the treatment on Day 7 due to non-compliance; and one discontinued study drug on Day 20 due to other adverse reactions.

SOF/VEL was generally found to be safe and reasonably 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 severity, though there was a greater proportion of children 3 to < 6 years old who expereinced vomiting (15%) and spitting up (10%), compared to the older age groups.

In conclusion, the benefit of SOF/VEL for the treatment of chronic hepatitis C virus infection outweighs the risks, as demonstrated in this study; and approval of SOF/VEL (sofosbuvir/velpatasvir, Epclusa®) for the treatment of chronic hepatitis C virus infection in children 3 to < 6 years of age is recommended by the review team. I, the signatory authority for this application, concur with the recommendations made by the multi-disciplinary review team.

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 CHC 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, it can lead to the development of serious or fatal complications by early adulthood. This can result in a debilitating disease 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 years. However it is poorly tolerated with unfavorable safety profile, and is curative in only about half of children. 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® (a fixed dose combination (FDC) of ledipasvir [LDV] and SOF) is approved in pediatric patients 3 years and older with chronic HCV infection 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 (a FDC of glecaprevir and pibrentasvir) is approved for pediatric patients	Four treatments are available for adolescents; fewer for children less than 12 years of age. Some of the available therapies require coadministation with RBV under certain circumstances. • Pegylated interferon/ribavirin is only approximately 50% effective, is injectable (pegylated interferon), and is associated with many serious adverse reactions. • Sovaldi® and Harvoni® need to be combined with ribavirin (RBV) under certain circumstances; RBV is associated with toxicities. • Mavyret is available for children 12 years and older and is currently under review for children 3 – 12 years of age with PDUFA goal date of June 10, 2021.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	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.	
• Benefit	• To support an efficacy claim for the use of SOF/VEL for the treatment of children with CHC infection 3 to < 6 years old, the applicant submitted efficacy and safety results from a single study (Study/Trial GS-US-342-1143), which is a Phase 3, open-label, non-comparator trial to evaluate a 12-week regimen of SOF/VEL. • In this study, 41 subjects aged 3 years to less than 6 years of age with chronic HCV infection genotype 1 (n=32), genotype 2 (n=6), genotype 3 (n=2) and genotype 4 (n=2) were treated with SOF/VEL once daily for 12 weeks in treatment-naive subjects. Among the proportion (~25%) of participants evaluated, no cirrhosis was detected. • The study demonstrated the effectiveness of SOF/VEL among those who received treatment. While the overall sustained virolocal response at week 12 (SVR12) was 82.9% (34/41), the SVR12 was 100% among the 34 subjects who completed treatment. A total of 87.5% of patients with genotype 1, 50% with genotype 2, 100% with genotype 3 and 100% with genotype 4 who received the treatment achieved SVR12 which is an indication of complete viral clearance and cure. Additionally, among subjects who achieved SVR12, normalization of ALT was observed. • Seven subjects 17.1% (7/34) did not achieve SVR12 due to early drug discontinuation, and had no evidence of virologic failure.	SOF/VEL was efficacious in clearing HCV in children 3 to < 6 years old. This viral clearance led to a ALT normalization in all the children who achieved SVR12. Long-term studies in children and adults have demonstrated that clearance of HCV (spontaneosly or by treatment) eliminates hepatic inflammation and prevents or reduces long-term complications such as fibrosis, cirrhosis, liver failure and hepatocellular cancer (HCC) complications. Therefore, long-term viral suppression in children 3 to < 6 years old can reasonably be presumed to prevent or lead to fewer complications later in their life.
• Risk and Risk Management	Few adverse events were observed with Epclusa (SOF/VEL); the most common adverse reactions were vomiting, product use issues (spitting up of drug), fatigue and irritability. All events were mild or moderate in severity (Grade 1 or 2). No drug-related serious adverse events no deaths were reported. Of the 7 children who discontinued the drug, 5 discontinued it on Day 1 due to	The frequency and severity of the adverse events observed in this study were similar to those noted in adolescents and adults. Based on the totality of safety data for SOF/VEL, no Risk Evaluation and Mitigation Strategy

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	adverse reactions of vomiting or spitting up of drug (likely due to poor platability); one discontinued the treatment on Day 7 due to non-compliance; and one discontinued the drug on Day 20 due to oher adverse reactions. SOF/VAL had no notable effects on development or growth (baseline to posttreatment Week 12) in Tanner stage, bone age, height, weight and body mass index (BMI) percentiles, and vital signs.	(REMS) is recommended at this time.

Patient Experience Data

Patient Experience Data for Epclusa in children 3 to < 6 years old with chronic HCV infection were collected within the clinical trials. The table below summarizes Patient Experience Data Relevant to this Application, as described in Study GS-US-342-1143. 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-342-1143, Section 12.1
		♦	Observer reported outcome (ObsRO)	CSR for Study GS-US-342-1143, Section 12.1
		□	Clinician reported outcome (ClinRO)	-
		□	Performance outcome (PerfO)	-
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		-
	□	Patient-focused drug development or other stakeholder meeting summary reports		-
	□	Observational survey studies designed to capture patient experience data		-
	□	Natural history studies		-
	□	Patient preference studies (e.g., submitted studies or scientific publications)		-
	♦	Other: (Please specify) Swallowability of oral tablets and palatability of oral pellet formulation were assessed in Study GS-US-342-1143.		Module 2.5 (Clinical Overview), Section 2.5; GS-US-342-1143 CSR, Sections 8.1.4, 8.2.4.
□	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. -			

Treatment Phase
Subjects who completed the PK lead-in phase were immediately enrolled into the treatment phase with no interruption of study drug administration. Additional subjects were enrolled into the treatment phase upon confirmation of the appropriateness of the dose from the PK lead-in phase.

Approximately 100 subjects, including subjects from Cohort 1 of the PK lead-in phase, were planned to be enrolled into Group 1:

- **Group 1 (12 to < 18 years old):** Subjects received SOF/VEL FDC 400/100 mg (total dose) orally, once daily for 12 weeks.

Approximately 100 subjects, including subjects from Cohort 2 (6 to < 12 years old) and Cohort 3 (3 to < 6 years old) of the PK lead-in phase, were planned to be enrolled into Group 2:

- **Group 2 (6 to < 12 years old):** Subjects received SOF/VEL FDC 200/50 mg (total daily dose) orally, once daily for 12 weeks.
- **Group 2 (3 to < 6 years old):**
  - Subjects weighing ≥ 17 kg received SOF/VEL FDC 200/50 mg (total daily dose) orally, once daily for 12 weeks.
  - Subjects weighing < 17 kg received SOF/VEL FDC 150/37.5 mg (total daily dose) orally, once daily for 12 weeks.

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

After completing all required study visits, all subjects (those who attained SVR24 and those who did not attain SVR24 and did not initiate other experimental or approved anti-HCV therapy) were eligible to enroll into a registry study (GS-US-334-1113) to be followed for a total of 5 years for assessments of growth, quality of life, and long-term viral suppression (if applicable).

2.4. Protocol Amendments

The original study protocol (June 20, 2016) was amended 4 times. Key changes to the protocol for each amendment were as follows:

2.4.1 Amendment 1

The protocol was first amended on 20 September 2016, prior to any subjects being screened, to reflect the following key changes:

- Added clarification that all adverse events (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

2.4.2 Amendment 2

The protocol was amended for the second time on December 1, 2016, prior to any subjects being screened, to reflect the following key changes:

- Added serial hepatitis B virus (HBV) DNA monitoring for any subject with hepatitis B core antibody (HBcAb)-positive status at screening, per a US Food and Drug Administration Drug Safety Communication
- Added formulation, packaging, labeling, storage, and handling information for the SOF/VEL 200/50-mg and placebo tablets

2.4.3 Amendment 3

The protocol was amended for the third time on August 31, 2017, following completion of Cohort 1, to reflect the following key changes:

- 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
- Clarified that the non-tablet formulation information would be included in a future protocol amendment once it was available and would be submitted for approval prior to dosing of subjects
- Updated the dosing instructions in the case of vomiting to align with the SOF/VEL label
- 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)

2.4.4 Amendment 4

The protocol was amended for the fourth time on June 15, 2018, following completion of Cohort 2, to reflect the following key changes:

- 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
- Updated the schedule of assessments (Appendix 2 of the clinical study protocol [Appendix 16.1.1]) for consistency

3. Product Quality

Oral tablets are already approved for use in adolescents and adults (400 mg sofosbuvir/100 mg velpatasvir). A new lower strength tablet (200 sofosbuvir/50 mg velpatasvir), and Oral pellets (200 mg sofosbuvir/50 mg velpatasvir; 150 mg sofosbuvir/37.5 mg velpatasvir) were developed for use in children and submitted as part of the current sNDA. *Please refer to the review of Chemistry, Manufacturing and Control (CMC) in NDA 208341/NDA 214187 for additional information.*

3. Nonclinical Pharmacology/Toxicology

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

4. Clinical Pharmacology

The Office of Clinical Pharmacology has reviewed the information provided by the Applicant in NDA 214187 as well as NDA 208341 and recommends approval for the new EPCLUSA oral pellet formulation. They agreed with the Applicant's proposal that the:

- SOF/VEL pellet formulation was comparable to the SOF/VEL tablet formulation under fasted conditions based on the findings from the Phase 1 relative bioavailability study (Study GS-US-342-1142).
- To-be-marketed SOF/VEL pellet formulation can be administered without regard to food.
- Population PK analysis and simulations support the proposed weight band-based dosing regimen of 150 mg/37.5 mg once daily for SOF/VEL in pediatric patients with body weight < 17 kg.
- Changes to the label be made to lower the minimum age for treatment eligibility to 3 years and to remove the lower weight cutoff of at least 17 kg.

For full details, please refer to Dr. Abhay Joshi's Clinical Pharmacology Review, archived on May 21, 2021.

5. Clinical Microbiology

Analyses of baseline HCV NS5A and NS5B resistance-associated polymorphisms were conducted for 33 subjects in the 3 to < 6-year age group. This analysis excluded the 7 subjects who did not achieve SVR12 for reasons not attributed to virologic failure. While NS5A and NS5B resistance-associated polymorphisms were detected in 18% (6/33) and 3% (1/33) of subjects, respectively, all 33 subjects with or without detected NS5A and NS5B resistance-associated polymorphisms achieved SVR12. There was no evidence that sofosbuvir resistance had emerged during the study period. *Please refer to Dr. Patrick Harrington's Clinical Microbiology Review for full 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 Quantitative Test, v2.0 was used to quantify HCV RNA in this study.

A total of 216 children (102 children 12 to < 18 years; 73 children 6 to < 12 years old, and 41 children 3 to < 6 years old), were enrolled and followed for 12 weeks after discontinuation of study treatment. The planned enrollment was 200 for the entire population, targeting 100 from the adolescents age cohort, and the remaining 100 from 3 to <12 years old age group.

White	32 (78.0%)
African American or Black	3 (7.3%)
Asian	0
Native Hawaiian or Pacific Islander	0
American Indian or Alaskan Native	0
Other	5 (12.2%)
Not Permitted	1 (2.4%)
Ethnicity: Number (%)	
Hispanic or Latino	4 (9.8%)
Not Hispanic or Latino	36 (87.8%)
Not Permitted	1 (2.4%)
Region	
US	38 (92.7%)
Non-US	3 (7.3%)

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-342-1143, Table 22. Page 101-102.

Overall, the majority of subjects were infected through vertical transmission (97.6%). The majority of subjects had genotype 1 HCV infection (78.0% [1a = 70.7%, 1b = 4.9%, and 1c = 2.4%]) or genotype 2 HCV infection (14.6%), and the majority of the subjects (73.2%) had IL28B non-CC genotype (CT = 48.8%, TT = 24.4%). All subjects were treatment naïve and no subjects had known cirrhosis based on prior biopsy or clinical history. The majority of subjects had baseline HCV RNA < 800,000 IU/mL (51.2%), with a mean (SD) value of 5.9 (1.06) log10 IU/mL. The mean (SD) baseline ALT value was 60 (42.2) U/L, and 41.5% of subjects had baseline ALT values > 1.5 x ULN. The mean (SD) baseline eGFR using the Schwartz formula was 152.1 (29.70) mL/min/1.73 m^2 (Table 2).

Table 2. Baseline HCV Characteristics (3 to < 6 years Old)

Disease Characteristic	**3 to < 6 Years Old SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)**
HCV genotype	
Genotype 1	32 (78.0%)
Genotype 1a	29 (70.7%)
Genotype 1b	2 (4.9%)
Genotype 1c	1 (2.4%)
Genotype 2	6 (14.6%)

Genotype 2 (No confirmed subtype)	1 (2.4%)
Genotype 2a	1 (2.4%)
Genotype 2b	4 (9.8%)
Genotype 3	2 (4.9%)
Genotype 3a	2 (4.9%)
Genotype 4	1 (2.4%)
Genotype 4a	1 (2.4%)
Cirrhosis	
Yes	0
No	10 (24.4%)
Not determined	31 (75.6%)
IL28B	
CC	10 (24.4%)
CT	30 (73.2%)
TT	10 (24.4%)
Missing	1 (2.4%)
Baseline HCV RNA (log_{10}/mL)	
Mean (range)	5.9 (1.1, 7.3)
Baseline ALT (U/L)	
Mean (range)	60 (12, 245)
Prior HCV Treatment	
Treatment Naive	41/41 (100.0%)
Treatment Experienced	0/41
Mode of HCV Infection	
Vertical transmission	40 (97.6%)
Blood product transfusion + Vertical transmission	1 (2.4%)
Unknown	0

Source: Analysis of ADSL ADAM dataset and Clinical Study Report GS-US-342-1143: Table 23. Page 103-104.

6.3 Efficacy Results at Week 12 after Treatment Completion

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 41 subjects who received SOF/VEL x 12 weeks was 82.9% (95% CI: 67.9% to 92.8%) of pediatric subjects aged 3 to < 6 years old (34 of 41) achieved SVR 12.

- In subjects with genotype 1 HCV infection, a total of 28 of 32 subjects (87.5%) who received SOF/VEL FDC (200/50 mg or 150/37.5 mg) achieved SVR12.
- In subjects with genotype 2 HCV infection, 3 of 6 subjects (50.0%) who received SOF/VEL FDC (200/50 mg or 150/37.5 mg) achieved SVR12.
- All subjects (100%) with genotype 3 (n = 2) and 4 (n = 1) HCV infection who received SOF/VEL FDC (200/50 mg or 150/37.5 mg) achieved SVR12

Among the subjects who completed the study treatment, SVR12 was achieved in 100% (34/34) of subjects. Due to the very high SVR12 rate that was observed, with no cases of virologic failure among those who completed the study, precluded meaningful interpretation thorugh further analysis of the primary endpoint by subgroup (race, ethinicity, gender, disease characteristic, genotype, etc) (Source: Clinical Study Report GS-US-342-1143, Tables 48, 49 and 50, pages 150-156).

A total of 7 subjects (17.1%) did not achieve SVR12 due to early discontinuation of treatment, not due to virologic failure (see Section 7.1 Discontinuations due to Adverse Events in this review for a detailed description).

The virologic response at different timepoints was a secondary efficacy endpoint. Virologic response at each time point on treatment study visit is shown in Table 3. The denominator includes only those who were on treatment at each time point. As summarized in the table, there were no treatment breakthroughs and no virologic treatment failures among subject who received the treatment (ie, breakthrough, rebound, or nonresponse).

Table 3. Number and Percentage of Subjects with HCV RNA <LLOQ by Treatment Visit

	3 to < 6 Years Old SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)
Baseline	1/41 (2.4%)
Week 1	14/38 (36.8%)
Week 4	32/35 (91.4%)
Week 8	34/34 (100%)
Week 12	34/34 (100%)
Post-Treatment Week 4 (SVR4)	34/34 (100%)
Post-Treatment Week 12 (SVR12)	34/34 (100%)
Post-Treatment Week 24 (SVR24)	34/34 (100%)

Source: Extracted from Clinical Study Report GS-US-342-1143: Table 48, page 150; Table 51, Pages 158-159; and Table 15.9.7, Pages 360 and 364.

ALT normalization

ALT normalization is defined as (defined as ALT> ULN at baseline and ALT ≤ ULN at each visit) during and after treatment with SOF/VEL. Decreases from baseline in median ALT were observed for the duration of treatment and at the post-treatment Week 4 visit. During treatment, median changes from baseline ranged from −29 U/L to −24 U/L..

Virologic Resistance
Pretreatment NS5A and NS5B NI RAVs were observed in 18.2% (6/33) and 3.3% (1/33) of subjects, respectively, with virologic outcome who were included in the Resistance Analysis Population in pediatric subjects 3 to < 6 years old. The presence of pretreatment NS5A and/or NS5B RAVs did not impact treatment outcome as all subjects with pretreatment RAVs achieved SVR12 and SVR24. No on-treatment breakthrough or relapse was observed through posttreatment Week 12 or posttreatment Week 24. Please refer to Section 5. Clinical Microbiology in this review.

Overall Efficacy Summary
The efficacy of SOF/VEL in children with chronic HCV infection was demonstrated in this open-label, noncomparator trial. At 12 weeks after completion of study treatment, a sustained virologic response (SVR12) was demonstrated in 82.9% (95% CI: 67.9% to 92.8%) of pediatric subjects (34/41). The response rate is consistent with the antiviral response observed in studies of treatment-naive adults. A total of 7 subjects (17.1%) and did not achieve SVR12 due to early treatment discontinuation, not due to virologic failure (see Section 7.1 Discontinuation due to Adverse Events in this review).

7. Safety

The applicant has submitted safety data from 41 pediatric subjects 3 to < 6 years old who received at least one dose of SOF/VEL in Trial GS-US-342-1143.

Duration of Treatment
The duration of treatment was 12 weeks with a follow-up of 12 weeks after the end of treatment, and 80.5% (33 of 41) of subjects received SOF/VEL for 12 weeks. The types of Adverse Events (AEs) observed were mostly similar to the types of AEs observed in adolescents and adults with chronic HCV infection who received SOF/VEL in Phase 3 studies; though gastrointestinal adverse reactions were reported more commonly compared to subjects 6 years of age and older. 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.

This Clinical Study Report summarized the safety data for the 12 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 6 to < 18 year old age group was already reviewed and the drug approved for use in this age group in 2020. *Please refer to Dr. William Tauber's detailed review archived on March 19, 2020, in the original NDA 208341. .*

The following is a summary of the assessment of safety for the remaining age group (Cohort 3) with 41 subjects aged 3 to < 6 years. Adverse events were mapped according to Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1.

7.1. Adverse Events

Table 4 presents the overall summary of AEs for subjects 3 to < 6 years old. The majority of pediatric subjects 3 to < 6 years old (78.0%, 32 of 41) experienced at least 1 AE, and 39.0% (16 of 41 subjects) had a treatment-related AE. All AEs were Grade 1 (mild) or 2 (moderate) in severity. No subjects experienced Grade 3 or Grade 4 AEs. No subjects had any serious adverse events (SAEs). Five subject (12.2%) had an AE that led to premature discontinuation of study drug. No subjects had AEs that led to interruption of study drug. No deaths occurred during the study. There were no AEs consistent with progression of liver disease such as AEs of HCC or hepatic liver decompensation. No subjects with genotypes 5 or 6 were enrolled in this age group; and no subjects with known cirrhosis were enrolled.

Table 4. Overall Summary of Adverse Events (Safety Analysis Set)

Adverse Events	**3 to < 6 Years Old SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)**
Any TEAE*	32 (78.0%)
Maximum Toxicity Grade	
Grade 1 (mild)	32 (78.0%)
Grade 2 (moderate)	3 (7.3%)
Grade 3 (severe)	0
Grade 4 (life-threatening)	0
Deaths	0
Any SAE	0
Drug-related SAE	0
Drug-related TEAEs	16 (39.0%)
Drug-related Grade 2 TEAE	1 (2.4%)
Drug-related Grade 3 TEAE	0
TEAE Leading to Premature Discontinuation	5 (12.2%)*
TEAE Leading to Temporary Interruption	0

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-342-1143: Table 73. Page 199.
TEAE: Treatment Emergent Adverse Event; SAE: Serious Adverse Event
* Discontinued treatment due to vomiting or product use issue (spitting up study drug), most likely due to palatability of pellets in young children.

Common Adverse Events

Table 5 presents a summary of treatment-related AEs reported in at least 5% of subjects 3 to < 6 years old by preferred term. The most commonly reported AEs were vomiting (26.8%, 11 subjects), and cough, pyrexia, and rhinorrhea (14.6%, 6 subjects each). Other AEs reported were diarrhea, fatigue, and nasal congestion (12.2%, 5 subjects each); product use issues (9.8%, 4 subjects), and decreased appetite (7.3%, 3 subjects). All AEs of vomiting resolved on the same day as onset and 4 of 6 subjects that had an AE of vomiting associated with taking the study drug completed 12 weeks of treatment

Table 5. Treatment Related Adverse Events in at Least 5% of Subjects

Adverse Events	3 to < 6 Years Old SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41)
Total # of AEs	32 (78.0%)
Vomiting	11 (26.8%)
Cough	6 (14.6%)
Pyrexia	6 (14.6%)
Rhinorrhea	6 (14.6%)
Diarrhea	5 (12.2%)
Fatigue	5 (12.2%)
Nasal congestion	5 (12.2%)
Products use issue	4 (9.8%)
Decreased appetite	3 (7.3%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-342-1143: Table 74, Page 200.

Adverse Drug Reaction (Related to Study Drug)

Table 6 presents a summary of Adverse Drug Reactions (ADR) reported in > 1 subject 3 to < 6 years old in either treatment group by preferred term. The most common treatment-related AEs reported for ≥ 5% of subjects were vomiting (14.6%, 6 subjects), product use issue (9.8%, 4 subjects), and fatigue (7.3%, 3 subjects).

Table 6. Treatment Related Adverse Events in > 1 Subject

Adverse Events	3 to < 6 Years Old SOF/VEL (200/50 or 150/37.5 mg) 12 Weeks (N = 41))
Number of subjects experiencing an ADR	16 (39.0%)
Vomiting	6 (14.6%)
Product use issue	4 (9.8%)
Fatigue	3 (7.3%)

Irritability	2 (4.9%)

Source: Data Analysis of ADAE ADAM dataset and Clinical Study Report GS-US-342-1143: Table 75, Page 201

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
A total of 7 of 41 subjects (17.1%) did not achieve SVR12 and were categorized by the Applicant as "other." Of these, the Applicant determined that only one subject had discontinued treatment due to an AE:

- One subject discontinued study drug on Day 20 due to adverse events of decreased appetite, irritability, psychomotor hyperactivity, and product use issue (reported term: spitting up study drug); his virologic outcome was "other" with early treatment discontinuation not due to virologic failure listed as the reason.

However, based on the clinial team's review of the data, we determined that another four subjects had also discontinued treatment due to an AE, bringing the total to 5 (12.2%) subjects.

- These four subjects discontinued the drug on Day 1 due to an adverse events [vomiting or product use issue (spitting up drug)] that were considered by the Applicant to be related to the study drug. These four subjects were described by the Applicant to have discontinued study drug due to "Other" reasons including:
    - One subject being noncompliant with study drug.
    - One due to investigator discretion
    - One subject was lost to follow up
    - One subject discontinued study drug due to withdrawal of parent/guardian assent.

None had follow-up assessments.

In addition to the above five subjects who discontinued treatment due to an AE, the following two subjects discontinued the drug due to the following reasons:

- One subject discontinued the study drug on Day 7 due to being noncompliant.
- One subject discontinued the drug on Day 1 due to investigator discretion

Interruption of Study Drug due to Adverse Events
No pediatric subjects 3 to < 6 years old experienced any AE leading to interruption of study drug during this study

Laboratory Abnormalities
All laboratory abnormalities were treatment emergent (hematology, chemistry). Overall, 16 of 36 (44.4%) pediatric subjects 3 to < 6 years old had a graded laboratory abnormality. The maximum abnormality grade for most of the pediatric subjects 3 to < 6 years old was Grade 1 (36.1%, 13 of 36 subjects); overall, the incidence of Grade 2 laboratory abnormalities was 5.6% (2 of 36 subjects), the incidence of Grade 3 laboratory abnormalities was 2.8% (1 of 36 subjects), and there were no Grade 4 laboratory abnormalities.

A Grade 3 increase in alkaline phosphatase was reported in a 3 year old subject (2.8%) at Day 84, which was resolved by the post-treatment Week 4 visit; the subject was asymptomatic and the investigator attributed the result to hyperalkaline phosphatemia of infancy.

No clinically meaningful changes from baseline in neutrophils, lymphocytes, hemoglobin or platelets were observed. No Grade 3 or 4 ALT, AST, bilirubin, creatine kinase or lipase elevations were reported.

Vital Signs, Physical Findings, and Other Observations Related to Safety
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).

Other Analyses Related to Safety
Neuropsychiatric assessment was conducted using the PedsQL™ 4.0 SF15 psychosocial domain-related scores. Overall, no statistically significant ($p < 0.05$) mean changes were noted in the following categories:

- Physical health summary scores:
- During treatment (baseline to end-of-treatment [EOT]) or
- During follow-up (EOT through posttreatment Week 24)
- Per the subject reports and parent reports

Psychosocial health summary scores (Emotional, Social and School functioning domains):

- During treatment (baseline to EOT) or
- During follow-up (EOT through posttreatment Week 24)
- Per the subject reports and parent reports

No significant impact on general or disease health-related Quality of Life was reported.

Summary of Safety in Subjects 3 to < 6 years old
Overall, treatment with SOF/VEL for 12 weeks was generally safe and well tolerated in pediatric subjects 3 to < 6 years old. The majority of pediatric subjects 3 to < 6 years old (78.0%, 32 of 41) had at least 1 AE. The most commonly reported AEs were vomiting (26.8%, 11 subjects), and cough, pyrexia, and rhinorrhea (14.6%, 6 subjects each). All AEs were Grade 1 or 2 in severity. Five subjects (12.2%) had an AE that led to premature discontinuation of study drug. No Grade 3 or 4 AEs, SAEs, or AEs that led to interruption of study drug were reported. No deaths were reported during the study for pediatric subjects 3 to < 6 years old.

Overall, 16 pediatric subjects 3 to < 6 years old had a graded laboratory abnormality. There were no Grade 3 or 4 hematology laboratory abnormalities reported, and no clinically meaningful changes from baseline in neutrophils, lymphocytes, hemoglobin, and platelets. No Grade 3 creatine kinase elevations or lipase elevations were reported, and no Grade 4 chemistry laboratory abnormalities of any kind. A Grade 3 increase in alkaline phosphatase was reported in a 3 year old subject (2.8%) at Day 84, which was resolved by the posttreatment Week 4 visit; the subject was asymptomatic and the investigator attributed the result to hyperalkaline phosphatemia of infancy. There were no reported Grade 3 or 4 elevations in ALT, AST or total bilirubin. Coincident with viral suppression, decreases from baseline in median ALT and AST

were observed for the duration of treatment and at the posttreatment Week 4 visit. There were no notable changes in total bilirubin values from baseline that were observed.

Hence, the maximum laboratory abnormality grade for most of the pediatric subjects 3 to < 6 years old was Grade 1 (36.1%, 13 of 36 subjects); overall, the incidence of Grade 2 laboratory abnormalities was 5.6% (2 of 36 subjects), the incidence of Grade 3 laboratory abnormalities was 2.8% (1 of 36 subjects), and there were no Grade 4 laboratory abnormalities.

No notable effects of study treatment were observed on development or growth as assessed by changes from baseline through posttreatment Week 24 in Tanner pubertal stages, height, weight, and BMI percentiles and radiographic bone age.

No notable changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, pulse, respiration, or body temperature) were observed during the study.

No significant impact on general or disease health-related Quality of Life.

7.2. Special Populations

The pediatric Chronic Hepatitis C (CHC) subjects evaluated in Study GS-US-342-1143 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.

7.3. Drug Interactions

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

7.4. 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. No pregnancies were reported for pediatric CHC subjects in Study GS-US-342-1143.

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 7.0 for the discussion regarding efficacy, and Section 8.0 for the discussion regarding safety.

Study GS-US-342-1143 fulfills the following PMR issued under the Pediatric Research Equity Act (PREA) in the initial approval letter dated June 28, 2016 for Epclusa NDA 208341:

- PMR 3092-2: Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of sofosbuvir and velpatasvir in pediatric subjects 3 through less than 12 years of age with chronic hepatitis C virus infection.

FDA previously waived the pediatric study requirements from birth to less than 3 years because necessary studies are impossible or highly impractical. This is because spontaneous HCV clearance is possible and very few patients in this age group require treatment.

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 presented to the Pediatric Exclusivity Board, and Pediatric Exclusitivity was granted.

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 due to the following reasons:

- This is a pediatric trial with PK, an objective measure, as the pivotal endpoint.
- There wass no site that enrolled a disproportionately large number of cases compared to the rest that would affect the outcome of the study. Forty one subjects were enrolled at 21 US sites (n=38), 2 Italian sites (n=2) and 1 UK site (n=1). Each site enrolled 1-2 subjects except for Site #09159 that enrolled 3, and Site #01733), also in the US that enrolled 5.
- There were only 7 important protocol deviations, mostly due to violation of inclusion/exclusion criteria. They were determined to not affect the outcome of the study.

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time given that OSIS inspected the site in (b) (4) which falls within the surveillance interval. The inspection was conducted under the following submissions: Non Responsive
See No Action Indicated (NAI) memo by Kimberly Miller, RPM, on February 18, 2021.

10.2 Compliance with Good Clinical Practices

As per the Applicant, the clinical study included in this submission (GS-US-342-1143) was conducted under a US investigational new drug (IND) application and in accordance with recognized international scientific and ethical standards, including but not limited to the International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) guideline for Good Clinical Practice (GCP) (Sections 7.6 and 8.1.2), and the original principles embodied in the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa). These standards are consistent with the requirements of the US Code of Federal Regulations (CFR) Title 21, Part 312 (21CFR312), subpart D, " Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, Part 54, 1998, 21 CFR part 56, 1998, the European Union Clinical Trials Directive 2001/20/EC, and Good Clinical Practice Directive 2005/28/EC, as well as other local legislation.

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 Applicant 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 133 investigators (27 Principal Investigators and 106 Sub-Investigators), all of whom certified that they have no disclosable financial interests, except for one investigator who certified having received "Significant payment of sorts ≥ $25,000" for whom Forms FDA 3455 and Minimization of Bias Form were submitted and are acceptable. None of the investigators are Gilead employees. See Appendix 2 for the Clinical Investigator Financial Disclosure Review.

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 infection with genotype 1, 2, 3, 4, 5, or 6 in pediatric patients 3 years of age and older without cirrhosis or with compensated cirrhosis; or with decompensated cirrhosis for use in combination with ribavirin. The changes with this efficacy supplement primarily affected the following sections. The Applicant is in agreement with the final labeling revisions.

Throughout the label, reference to "weight at least 17 kg" was deleted given that 12 subjects weighed < 17 kg completed the study uneventfully, of whom 10 completed the study, with the lowest weight in a subject being 12.9 kg. Also, the age was changed to 3 years and older instead of 6 years and older. The total number of children in all three cohorts (3 to < 6 years, 6 to < 12 years and 12 to < 18 years) was updated to 216 children (from 175).

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, 2, 3, 4, 5, or 6 infection:*
  - *without cirrhosis or with compensated cirrhosis*
  - *with compensated cirrhosis, for use in combination with ribavirin*

Rationale: In chronic HCV-infected adults and children 6 years and older, SOF/VEL is approved to treat patients with genotype 1, 2, 3, 4, 5 or 6 without cirrhosis or with compensated cirrhosis (Child-Pugh A); and for patients with decompensated cirrhosis (Child-Pugh B or C) in combination with ribavirin. 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 genotypes 1 to 6. Therefore, the submitted PK data are adequate to support the efficacy of SOF/VEL for treatment of HCV of any genotype in patients 3 years of age and older. A similar rationale is used to support dosing recommendations for pediatric patients with compensated cirrhosis (Child Pugh A), or with decompensated cirrhosis (Child-Pugh B or C).

This section was updated as follows based on these recommendations:

> EPCLUSA is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adults and pediatric patients 3 years of age and older with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection (1):
> - without cirrhosis or with compensated cirrhosis
> - with decompensated cirrhosis for use in combination with ribavirin

2 DOSAGE AND ADMINISTRATION

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

This section was modified to extend the indication to children 3 years and older, and to include treatment with oral pellets. The following sentences were added and the modification made by the review team is underlined:

> Take EPCLUSA oral pellets or tablets once daily with or without food. In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability related to palatability

The title for Table 2 was updated to include oral pellets and was renamed "Dosing for Pediatric Patients 3 Years and Older with Genotype 1, 2, 3, 4, 5, or 6 HCV Using EPCLUSA Tablets or Oral Pellets". In the table, the equivalent dosage using pellets was added for each weight group (less than 17 kg, 17 to less than 30, and at least 30 kg).

2.5 Preparation and Administration of Oral Pellets

The following paragraph was added by the Applicant. It was modified by the review team by adding the underlined text.

> See the EPCLUSA oral pellets full Instructions for Use for details on the preparation and administration of EPCLUSA oral pellets.
>
> Do not chew EPCLUSA oral pellets to avoid a bitter aftertaste. EPCLUSA oral pellets can be taken directly in the mouth or with food (See Instructions for Use). In pediatric patients less than 6 years of age, administer the oral pellets with food to increase tolerability related to palatability. Sprinkle the oral pellets on one or more spoonfuls of

non-acidic soft food at or below room temperature. Examples of non-acidic foods include pudding, chocolate syrup, and ice cream. Take EPCLUSA oral pellets within 15 minutes of gently mixing with food and swallow the entire contents without chewing.

3 DOSAGE FORMS AND STRENGTHS

In this section the Applicant added the following information regarding the newly available pellets in their two dosage forms. It was accepted by the review team without modifications

EPCLUSA is available as tablets or pellets for oral use. Each dosage form is available in two dose strengths:

- 400 mg/100 mg Tablets: pink, diamond-shaped, film-coated tablet debossed with “GSI” on one side and “7916” on the other side. Each tablet contains 400 mg of sofosbuvir and 100 mg of velpatasvir.
- 200 mg/50 mg Tablets: pink, oval-shaped, film-coated tablet debossed with “GSI” on one side and “S/V” on the other side. Each tablet contains 200 mg of sofosbuvir and 50 mg of velpatasvir.
- 200 mg/50 mg Pellets: white to off-white pellets in unit-dose packets. Each packet contains 200 mg of sofosbuvir and 50 mg of velpatasvir.
- 150 mg/37.5 mg Pellets: white to off-white pellets in unit-dose packets. Each packet contains 150 mg of sofosbuvir and 37.5 mg of velpatasvir.

6.1 Clinical Trials Experience

In this section, under “Adverse Reactions in Pediatric Subjects 3 Years of Age and Older”, the following paragprah was added to differentiate between the increased gastrointestinal adverse reactions in children younger than 6 years compared to the older age groups, and to indicate that five subjects (not one subjects as described by the Applicant in the Clinical Study Report) had discontinued treatment due to Adverse Reactions. Modifications made by the review team are underlined:

> Among the 41 pediatric subjects less than 6 years of age, gastrointestinal adverse reactions were reported more commonly compared to subjects 6 years of age and older. Vomiting and product use issue (spitting up the drug) were reported in 15% and 10% of subjects, respectively; these adverse reactions were mild (Grade 1 or 2) and led to treatment discontinuation in 5 (12%) subjects.

8.4 Pediatric Use

The following 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-342-1143 and for consistency with revisions in Sections 6.1, 12.3 and 14.7 of the Full Prescribing Information (FPI). Modifications made by the review team are underlined:

> 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 3 years of age and older without cirrhosis or with compensated cirrhosis have been established in an open-label, multicenter clinical trial (Study 1143, N=216; 190 treatment-naïve, 26 treatment-experienced). No clinically meaningful

differences in pharmacokinetics were observed in comparison to those observed in adults.

The safety and effectiveness in pediatric subjects were comparable to those observed in adults. However, among the 41 pediatric subjects less than 6 years of age, vomiting and product use issue (spitting up the drug) were reported more frequently (15% and 10%, respectively; all Grade 1 or 2) compared to subjects 6 years of age and older. Five subjects (12%) discontinued treatment after vomiting or spitting up the drug.

11 DESCRIPTION

Additional information was added describing the new SOF/VEL pellets and the following paragraph was added. It was accepted by the review team without modification.

Pellets

EPCLUSA oral pellets are for oral administration, supplied as small, white to off-white pellets in unit-dose packets. Each unit-dose of EPCLUSA oral pellets contains either 200 mg sofosbuvir and 50 mg velpatasvir or 150 mg sofosbuvir and 37.5 mg velpatasvir and the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The oral pellets are film-coated with a coating material containing the following inactive ingredients: amino methacrylate copolymer, colloidal silicon dioxide, hypromellose, *L*-tartaric acid, polyethylene glycol, stearic acid, talc, and titanium dioxide.

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. Please see the detailed Clinical Pharmacology Review by Dr. Abhay Joshi, archived on May 21, 2021, for additional information.

12.4 Microbiology

Some minor modifications were made under the subsection "Pediatrics" regarding the percentage of subjects with pretreatment baseline resistant NS5A and and NS5B nucleoside inhibitor RAPs (resistance-associated polymorphisms), all of whom achieved SVR following 12 weeks of treatment with Epclusa. Please see the detailed Microbiology Review for additional information.

14 CLINICAL STUDIES
14.7 Clinical Trial in Pediatric Subjects

This section was updated with the most recent data from the Final Clinical Study Report and the accompanying datasets. The number of subjects treated in the 3 to < 18 year old group used to determine efficacy was updated from 173 to 214. Furthermore, a statement that pediatric subjects received weigh-based recommended dosage was deleted since it did not reflect the study conduct. The following subsection on the 3 to < 6 years old was added. Modifications made by the review team are underlined:

Subjects 3 Years to <6 Years of Age: EPCLUSA was evaluated in 41 treatment-naïve subjects 3 years to <6 years of age with genotype 1, 2, 3, or 4 HCV infection. The median

age was 4 years (range: 3 to 5); 59% of the subjects were female; 78% were White, 7% were Black; 10% were Hispanic/Latino; mean body mass index was 17.0 kg/m^2 (range: 13.9 to 22.0 kg/m^2); mean weight was 19 kg (range: 13 to 35 kg); 49% 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 78%, 15%, 5%, and 2%, respectively; no subjects had known cirrhosis. The majority of subjects (98%) had been infected through vertical transmission.

The SVR rate among all subjects was 83% (34/41); with 88% (28/32) in subjects with genotype 1 HCV infection, 50% (3/6) in subjects with genotype 2 HCV infection, and 100% in subjects with genotype 3 (2/2) and genotype 4 (1/1) HCV infection. None of the 34 subjects who completed the treatment had virologic failure. Of the remaining seven subjects who did not achieve SVR12, five discontinued treatment on Day 1, one on Day 7, and one on Day 20.

16 HOW SUPPLIED/STORAGE AND HANDLING

This section was revised to include the following description for new SOF/VEL oral pellets. The revisions were accepted by the review team without modifications.

Oral Pellets
EPCLUSA oral pellets, 200 mg/50 mg, are white to off-white pellets supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-2204-1).
EPCLUSA oral pellets, 150 mg/37.5 mg, are white to off-white pellets supplied as unit-dose packets in cartons. Each carton contains 28 packets (NDC 61958-2205-1).

- Store below 30 °C (86 ºF).
- Do not use if carton tamper-evident seal or packet has been opened or damaged.

The following subsections in "Patient Information" handout were revised for consistency with changes made in the Full Prescribing Information (FPI) mentioned above.

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

An "INSTRUCTIONS FOR USE" handout was created to provide instructions on how to take EPCLUSA oral pellets both with and without food.

12. 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 based on the data reviewed.

13. Recommended Comments to the Applicant

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

14. References

Borgia SM, Hedskog C, Parhy B, Hyland RH, Stamm LM, Brainard DM, et al. Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes. J Infect Dis 2018;218:1722-

EPCLUSA®, Gilead Sciences Inc. EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised November. 2017:

HARVONI®, Gilead Sciences Inc. HARVONI® (ledipasvir and sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised November. 2017:

Indolfi G, Easterbrook P, Dusheiko G, El-Sayed MH, Jonas MM, Thorne C, et al. Hepatitis C Virus Infection in Children and Adolescents. Lancet Gastroenterol Hepatol 2019.

Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology 2015;61 (1):77-87.

Modin L, Arshad A, Wilkes B, Benselin J, Lloyd C, Irving WL, et al. Epidemiology and Natural History of Hepatitis C Virus Infection Among Children and Young People. J Hepatol 2019;70:371-8.

Schmelzer J, Dugan E, Blach S, Coleman S, Cai Z, DePaola M, et al. Global Prevalence of Hepatitis C Virus in Children in 2018: A Modelling Study. Lancet Gastroenterol Hepatol 2020:1-19.

SOVALDI®, Gilead Sciences Inc. SOVALDI® (sofosbuvir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised: November. 2017:

The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–76.

Vosevi®, Gilead Sciences Inc. VOSEVI® (sofosbuvir, velpatasvir, and voxilaprevir) tablets, for oral use. US Prescribing Information. Foster City, CA. Revised: November. 2017:

World Health Organization (WHO). Hepatitis C Fact Sheet. Available at: http://www.who.int/news-room/fact-sheets/detail/hepatitis-c. 18 July. 2018b.

Appendix 1

Patient Experience Data for Epclusa in children 3 to < 6 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-342-1143).

- Quality of life data were collected via completion of the PedsQL™ Pediatric Quality of Life Inventory V4.0 Short Form (SF15) by the study subject and/or their parent/guardian. The SF15 questionnaire represented 4 domains: physical, emotional, social and school functioning, with the emotional, social and school functioning domains representing the psychosocial health summary. The quality of life assessments were completed at Day 1, end of treatment, early termination (if applicable), and posttreatment Weeks 12 and 24. Separate survey instruments were administered by age group, including the Teen Report (ages 13-18), Child Report (ages 8-12), Young Child Report (ages 5-7), and Toddlers (ages 2-4). In the submitted data from the 3 to < 6 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).

- Tablet formulation acceptability was evaluated via a swallowability assessment of the tablet formulation by subjects aged 6 to < 12 years old and 12 to < 18 years old (but none of the 3 to < 6 years old).
    - A total of 91 subjects 12 to < 18 years old performed the swallowability assessment with the SOF/VEL 400/100-mg tablet and completed the assessment questionnaire. On Day 1, 91 subjects (96.7%) either did not taste the drug or reported it as palatable. Eleven of the 102 of the subjects also performed the swallowability assessment with the SOF/VEL 200 mg/50 mg tablet. On Day 1, 9 of 11 subjects (81.8%) either did not taste the study drug or reported the taste as palatable.
    - All 73 subjects 6 to < 12 years old, a total of 72/73 (98.6%) were able to swallow the 200 mg/50 mg tablet . One subject experienced an AE of vomiting on Day 1. On Day 1, 59 of 71 subjects (83.1%) either did not taste the study drug or reported the taste as palatable.
- Pellet formulation acceptability:
    - None of the 12 to < 18 year old adolescent subjects received SOF/VEL FDC 400/100-mg oral pellets (8 x 50/12.5-mg packets) in this study.
    - SOF/VEL pellets were administered orally to pediatric subjects 6 to < 12 years old in Group 2 at a dose of 200/50 mg (as 1 x 200/50-mg FDC tablet or as 4 x 50/12.5-mg packets containing pellets) once daily. The selection of formulation was based on a swallowability assessment using placebo tablets.
    - SOF/VEL was administered orally to all pediatric subjects 3 to < 6 years old and weighing ≥ 17 kg in Group 2 at a dose of 200/50 mg (4 x 50/12.5-mg packets containing pellets) once daily. SOF/VEL was administered orally to pediatric subjects 3 to < 6 years old and weighing < 17 kg in Group 2 at a dose of 150/37.5 mg (3 x 50/12.5-mg packets containing pellets) once daily. Of the 27 subjects

who completed the acceptability questionnaire, reported on Day 1 that 18/27 (66.7%) either did not taste the study drug or reported the taste as palatable.
  - A total of 25 parents/caregivers of pediatric subjects 3 to < 6 years old who were administered SOF/VEL FDC (200/50 mg) oral granules completed the acceptability questionnaire at Week 12 or early termination. At Week 12 or early termination, 17/25 (68.0%) reported that the subject either did not taste the study drug or reported the taste as palatable.
  - A total of seven subjects discontinued treatment. Four subjects experienced an AE of vomiting/spitting up on Day 1 and discontinued the treatment. One subject experienced adverse reactions on Day 20 and discontinued treatment. One subject discontinued due to an investigator discretion, and one subject due to non-compliance on Day 7.

- <u>The following labeling changes were made based on this data:</u>
  - The following sentence was added in Sections 2.4 and 2.5 of the label "*Due to tolerability related to palatability, administer the oral pellets with food in pediatric patients less than 6 years of age*". Also, in Section 2.5 the following statement was added "*Do not chew EPCLUSA oral pellets to avoid a bitter aftertaste*."

Appendix 2

Clinical Investigator Financial Disclosure Review

Application Number: NDA 214187/208341

Submission Date(s): December 15, 2020

Applicant: Gilead Sciences, Inc.

Product: Sofosbuvir/Velpatasvir (Epclusa)

Reviewer: Samer El-Kamary, MD, MPH

Date of Review: April 29, 2021

Covered Clinical Study (Name and/or Number):
"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" (Study Number: GS-US-342-1143 [Group 2, Cohort 3])

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 133 (27 Principal Investigators and 106 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): 1		
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: 1 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 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 133 Investigators for Study GS-US-342-1143 are employed by the Sponsor. One of the investigators, representing <1% (1/133) of the total number of investigators, have disclosable financial interests/arrangements which the Sponsor defined as 'Significant payment of other sorts > $25,000' for whome forms FDA 3455 and Minimization of Bias Form were submitted and are acceptable.

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 one investigator who had financial interests or arrangements with the Sponsor, represent <1% of all investigators and is at one site which enrolled only (b) (6) patients or (b) (6)% (b) (6) /41) of all patients enrolled in the study. In conclusion, the likelihood that the trial results we e 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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