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APPLICATION NUMBER:

214187Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY
REVIEW(S)

**DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW**

**NDA: 214187 SDN: 001 (Original) eCTD: 0001; sNDA: 208341 S-17 SDN: 800 eCTD: 0156
DATE REVIEWED: 1/28/2021**

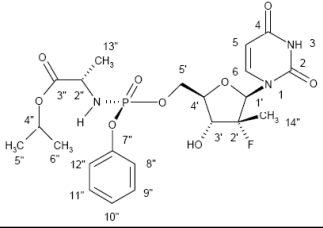
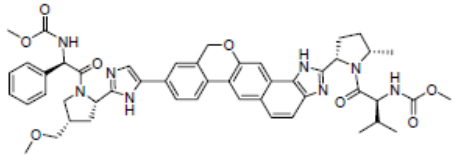
Reviewer: Patrick R. Harrington, Ph.D.

Date Submitted: 12/15/2020

Date Received: 12/15/2020

Date Assigned: 12/16/2020

Sponsor: Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Product Names (Class)	Sofosbuvir (GS-7977) (Uridine Nucleotide Analogue HCV NS5B Polymerase Inhibitor)	Velpatasvir (GS-5816) (HCV NS5A Inhibitor)
Structures		
Chemical Names	(S)- Isopropyl 2-((S)-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy)(phenoxy)phosphorylamino) propanoate	Methyl {(2S)-1-[(2S,5S)-2-(9-{2-[(2S,4S)-1-[(2R)-2-[(methoxycarbonyl) amino]-2-henylacetyl]-4-(methoxymethyl)pyrrolidin-2-yl]-1H-imidazol-5-yl)-1,11-dihydroisochromeno[4',3':6,7]naphtho[1,2-d]imidazol-2-yl)-5-methylpyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
Molecular formula	$C_{22}H_{29}FN_3O_9P$	$C_{49}H_{54}N_8O_8$
Molecular weight	529.46	883.00

Drug Category: Antiviral

Indication: Treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection

Dosage Form/Route of administration: SOF/VEL fixed-dose combination tablet or pellets/oral

Supporting documents: Clinical Virology review of [NDA 208341 S-14](#) by Dr. Takashi Komatsu; NDA 214187 SDN 10 (updated labeling), NDA 208341 SDN 847 (updated labeling)

Abbreviations: GT, genotype; HCV, hepatitis C virus; LiPA, Line Probe Assay; LLOQ, lower limit of quantification; NGS, next generation sequencing; PMR, post-marketing requirement; RAP(/V), resistance-associated polymorphism(/variant); SOF, sofosbuvir; SVR, sustained virologic response; VEL, velpatasvir;

1. CONCLUSIONS AND LABELING RECOMMENDATIONS

This set of submissions consists of a new sNDA (208341 S-17) to expand the sofosbuvir (SOF)/velpatasvir (VEL) ([Epclusa®](#)) indication to include the treatment of pediatric patients 3 years of age and older, and a new NDA (214187) for a new pediatric formulation of SOF/VEL pellets.

sNDA 208341 S-17 and NDA 214187 are approvable from a Clinical Virology perspective. Minor changes were proposed for Section 12.4 Microbiology, which are acceptable to this reviewer. We have no

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recommended additions or edits to the prescribing information to forward to the sponsor.

From a Clinical Virology perspective, this set of submissions also satisfies 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."

2. BACKGROUND

The fixed-dose combination of sofosbuvir (SOF, uridine nucleotide analogue NS5B polymerase inhibitor) and velpatasvir (VEL, NS5A inhibitor) (SOF/VEL), marketed as [Epclusa®](#), was approved in 2016 for the treatment of chronic HCV genotype (GT) 1-6 infection. The current indication includes treatment of adult and pediatric patients 6 years and older or weighing at least 17 kg.

In support of the expanded indication to include pediatric subjects aged 3 to < 6 years, the sponsor provided the final clinical study report and datasets from clinical trial GS-US-342-1143, "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." Data from this trial for adolescent subjects 12 to <18 years old and pediatric subjects 6 to <12 years old were previously submitted and reviewed; see the Clinical Virology review of [NDA 208341 S-14](#) by Dr. Takashi Komatsu for details.

This review covers the submitted clinical virology and drug resistance data from pediatric patients aged 3 to <6 years of age enrolled in clinical trial GS-US-342-1143.

3. CLINICAL TRIAL GS-US-342-1143

Study Design

Clinical trial GS-US-342-1143 was a 2-part study evaluating the PK, safety, and antiviral activity of SOF/VEL in pediatric subjects aged 3 to <18 years with chronic HCV infection. The study consisted of a PK lead-in phase and a treatment phase within each age group. Approximately 200 subjects were planned to be enrolled: approximately 100 adolescent subjects 12 to <18 years old and approximately 100 pediatric subjects 3 to <12 years old. The PK lead-in phase evaluated and confirmed age-appropriate SOF/VEL doses by analyzing the PK, safety, and antiviral activity of SOF/VEL through 7 days of dosing. Subjects who completed the PK lead-in phase were immediately enrolled into the treatment phase with no interruption of study drug administration until the appropriateness of the dose had been confirmed by PK and safety results from the PK lead-in phase.

All HCV GTs were eligible. Subjects could be either treatment-naïve or treatment-experienced, except that prior receipt of an HCV NS5A inhibitor was exclusionary. Subjects could be noncirrhotic or have compensated cirrhosis. Coinfection with HIV, acute hepatitis A virus, or hepatitis B virus (HBV surface antigen positive) was exclusionary.

Among subjects aged 3 to <6 years, two different SOF/VEL doses were evaluated. Subjects weighing ≥ 17 kg received SOF/VEL 200/50 mg QD, while subjects weighing <17 kg received SOF/VEL 150/37.5 mg QD. The planned treatment duration was 12 weeks.

All subjects were to be followed to Post-Treatment Week 24. After completing all required study visits, all subjects 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).

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HCV RNA levels in plasma were measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan HCV Quantitative Test, v2.0, which has a lower limit of quantification of 15 IU/mL. HCV genotype was determined at screening using the VERSANT® HCV Genotype 2.0 Line Probe Assay (LiPA). Genotype and subtype were subsequently confirmed or refined by BLAST analysis of HCV NS5A and NS5B sequences. Resistance analyses based on next generation nucleotide sequencing (NGS) were conducted by (b) (4) on baseline samples for all subjects (no subjects in this age group experienced virologic failure). Baseline HCV amino acid polymorphisms were reported based on a 15% assay sensitivity cutoff.

Subject Population (3 to <6-year age group)

Baseline subject characteristics for the GS-US-342-1143 3 to <6-year age group are summarized in Table 1 (compiled by reviewer). A total of 41 subjects were enrolled and received at least 1 dose of study drug.

Table 1. Baseline characteristics of GS-US-342-1143 study population (3 to <6-year age group).

	N (%)
Age (years)	
3	10 (24%)
4	11 (27%)
5	20 (49%)
Tx history	
Treatment-Naive	41 (100%)
Cirrhosis	
Unknown	31 (76%)
Non-Cirrhotic	10 (24%)
HCV Genotype/Subtype*	
1a	29 (71%)
1b	2 (5%)
1c	1 (2%)
2-unknown subtype	1 (2%)
2a	1 (2%)
2b	4 (10%)
3a	2 (5%)
4a	1 (2%)
WEIGHT (kg) Median (Range)	19.2 (12.9-35)
Baseline HCV RNA (Log ₁₀ IU/mL) Median (Range)	5.9 (undet.-7.3)

*38/41 results confirmed or refined by nucleotide sequencing analysis; all others based on LiPA assay.

Efficacy Results (3 to <6-year age group)

Efficacy results based on SVR12 are summarized in Table 2 (FDA analysis). The overall SVR12 rate was 82.9% (34/41). Of the 7 subjects who did not achieve SVR12, none were due to reported virologic failure. All 7 subjects discontinued treatment early after 1 (n=3), 2, (n=1), 5, (n=1), 7 (n=1), or 20 (n=1) days.

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Table 2. SVR12 rates in GS-US-342-1143 (3 to <6-year age group).

	SVR12 Rate
All Subjects	82.9% (34/41)
All GT1	87.5% (28/32)
1a	25/29
1b	2/2
1c	1/1
All GT2	50% (3/6)
2	0/1
2a	1/1
2b	2/4
All GT3	100% (2/2)
3a	2/2
All GT4	100% (1/1)
4a	1/1

Baseline Resistance Analyses (3 to <6-year age group)

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, as well as one subject who had an HCV RNA level of 9,970 IU/mL at Screening but undetected HCV RNA at Baseline.

The HCV NS5A resistance-associated polymorphisms were defined by the sponsor as specific amino acid changes that conferred >2.5-fold reduced phenotypic susceptibility to NS5A inhibitors. These specific polymorphisms are summarized in Table 3 (GS-US-342-1143 Study Report pg. 162).

Table 3. Sponsor-defined NS5A resistance-associated polymorphisms (or “variants”, i.e., “RAVs”).

Genotype	HCV Reference Sequence Name	NS5A RAVs
1a	HCV1a_H77_NC_004102	K24A/E/G/N/R M28A/G/T/V Q30ANY L31F/I/M/V P32L S38F H58D/L/N A92K/P/T Y93ANY
1b	HCV1b_Con1_AJ238799	Q24K/R L28V R30H/Q/S L31F/I/M/V P32L P58D/R/T A92K Y93ANY
2a	HCV2a_JFH1_AB047639	T24A/P/S F28A/C/S/V L31F/I/M/V P58D/S/T C92A/K/N/R/S/T Y93ANY
2b	HCV2b_MD2b10_AY232748	S24T L28F/V L31I/M/V P58A/D C92A/S/T Y93ANY
3	HCV3a_S52_GU814263	M28A/G/T/V A30E/G/H/K/S/V L31F/I/M/V P58D/G Y93ANY
4	HCV4_ED43_GU814265	K24G/R L28A/M/S/T/V L30E/G/H/K/R/S/T M31F/I/V P58D/L/S A92K/T Y93ANY

RAV = resistance-associated variant

Nucleotide analogue NS5B polymerase inhibitor resistance-associated polymorphisms were defined as: S96T, N142T, L159F, E237G, S282-any, C289I/L, L320F/I/V, and V321A/I.

Based on these listings, excluding the 7 subjects without SVR12 virologic outcome results, NS5A and NS5B

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resistance-associated polymorphisms were detected in 18% (6/33) and 3% (1/33) of subjects, respectively (FDA analysis). Note that full-length NS5B sequence analysis data were available from 30 of these 33 subjects; the other 3 subjects had a short fragment analyzed that did not cover all pre-specified resistance-associated positions. Therefore, the sponsor's denominator for NS5B analysis was 30 subjects, not 33 subjects. Nevertheless, all 33 subjects with or without detected NS5A and NS5B resistance-associated polymorphisms achieved SVR12.

SVR24 Results (all age groups)

All 34 subjects in the 3 to <6 year-age group who achieved SVR12 also achieved SVR24 (FDA analysis). It does not appear that the sNDA/NDA submission included HCV RNA datasets for the 12 to <18-year and 6 to <12-year age groups to confirm durability of SVR12. However, according to the GS-US-342-1143 final study report, all subjects in these age groups who achieved SVR12 also achieved SVR24 (97/97 and 68/68, respectively).

4. LABELING

The sponsor proposed only a minor edit to Section 12.4 of the Eplusa prescribing information, to update the numbers of subjects identified with baseline resistance-associated polymorphisms in clinical trial GS-US-342-1143:

Pediatrics

In Study 1143, the presence of NS5A and NS5B RAPs did not impact treatment outcome; all pediatric subjects 3^(b) years of age and older with baseline NS5A RAPs (^(b)₍₄₎ 15%; ^(b)₍₄₎ 29/^(b)₍₄₎ 199) or NS5B nucleoside⁽⁴⁾ inhibitor RAPs (3%; ^(b)₍₄₎ 6/^(b)₍₄₎ 195) achieved SVR following 12 weeks treatment with EPCLUSA.

Incorporating the results from the 3 to <6-year group with the numbers currently described in the Eplusa label, the denominators for subjects analyzed for baseline NS5A and NS5B resistance-associated polymorphisms would be 198 and 194, each of which differs by 1 subject from the sponsor's updated labeling. This discrepancy has no substantive impact and is presumably due to an updated result from one of the other age groups.

The sponsor's proposed edits to Section 12.4 Microbiology are acceptable from a Clinical Virology perspective.

5. SIGNATURE AND CONCURRENCES

Patrick R. Harrington, Ph.D.
Senior Clinical Virology Reviewer

CONCURRENCE

DAV/Clin Virol TL/J O'Rear

Date: _____

cc: DAV/RPM/Lindheimer

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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04/19/2021 12:24:34 PM

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