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APPLICATION NUMBER:

214187Orig1s000

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

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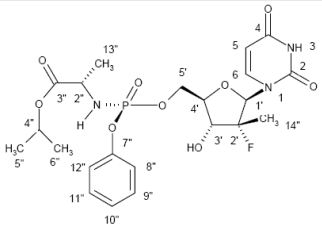
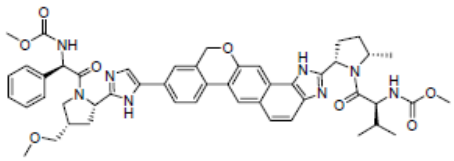
DIVISION OF ANTIVIRALS, CDER/OND/OID
CLINICAL VIROLOGY REVIEW
NDA: 214187 **SDN:** 001 (Original) **eCTD:** 0001; **sNDA:** 208341 S-17 **SDN:** 800 **eCTD:** 0156
DATE REVIEWED: 1/28/2021

Reviewer: Patrick R. Harrington, Ph.D.
Date Submitted: 12/15/2020 **Date Assigned:** 12/16/2020
Date Received: 12/15/2020

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-naive 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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