GILEAD | Medical Information

Epclusa® (sofosbuvir/velpatasvir) Use in Pregnancy

This document is in response to your request for information regarding the use of Epclusa® (sofosbuvir/velpatasvir [SOF/VEL]) for the treatment of HCV in women who are pregnant.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any recommendation on its clinical relevance or use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Summary

Product Labeling[1]

No adequate human data are available to establish whether SOF/VEL poses a risk to pregnancy outcomes.

Clinical Data on the Use of SOF/VEL in Pregnancy

The ongoing, phase 4, open-label, single-arm STORC study is assessing safety and efficacy outcomes of chronic HCV treatment with SOF/VEL once daily for 12 weeks during pregnancy.[2] Interim data showed a 100% maternal SVR rate and no perinatal transmission with SOF/VEL. No SAEs were related to SOF/VEL. Two participants discontinued SOF/VEL.[3]

In a study conducted to assess whether a test-and-treat model with SOF-based regimens for pregnant women who were actively using drugs improved HCV treatment starts and SVR rates, the overall SVR rate among pregnant women evaluated in the third trimester was 100%. All participants self-reported complete adherence, and no cases of vertical transmission were reported.[4]

In a phase 1, open-label PK study evaluating SOF/VEL in 10 pregnant women, VEL exposures and SOF C_{max} were similar between the pregnant participants and the non-pregnant reference cohort. The SVR12 rate was 100% (n=8 with SVR visit), and none of the 8 infants with HCV RNA data had detectable values, including 4 infants who completed 12 months of follow-up. Maternal AEs included headache, nausea, vomiting, heartburn, and fatigue. One AE (vomiting) resulted in treatment discontinuation. Among the infants, there were 2 preterm births (<37 weeks of gestation) and 3 neonatal intensive care unit admissions.[5]

Pregnancy Registry

The TiP-HepC Registry is an observational study to assess the mother-infant outcomes of exposures to DAAs during pregnancy.

Please consider submitting information to the Registry at:
Treatment in Pregnancy for Hepatitis C (TiP-HepC) Clinical Case Registry (emory.edu).

Product Labeling[1]

Warnings and Precautions

Risks associated with RBV and SOF/VEL combination treatment

If SOF/VEL is administered with RBV, the warnings and precautions for RBV apply to this combination regimen. Refer to the RBV prescribing information for a full list of the warnings and precautions for RBV.

Use in Specific Populations

Pregnancy

Risk summary

If SOF/VEL is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information for more information on RBV-associated risks of use during pregnancy.

No adequate human data are available to establish whether SOF/VEL poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components of SOF/VEL at exposures greater than those in humans at the RHD. During organogenesis in the mouse, rat, and rabbit, systemic exposures (AUC) to VEL were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the RHD, while exposures to the predominant circulating metabolite of SOF (GS-331007) were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the RHD. In rat pre/postnatal development studies, maternal systemic exposures (AUC) of VEL and GS-331007 were approximately 5 times the exposures of each component in humans at the RHD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

SOF was administered orally to pregnant rats (up to 500 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation Days 6 to 18 and 6 to 19, respectively, and also to rats (oral doses up to 500 mg/kg/day) on gestation Day 6 to lactation/post-partum Day 20. No significant effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. The systemic exposures (AUC) of the predominant circulating metabolite of SOF (GS-331007) during gestation were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the RHD.

VEL was administered orally to pregnant mice (up to 1000 mg/kg/day), rats (up to 200 mg/kg/day) and rabbits (up to 300 mg/kg/day) on gestation Days 6 to 15, 6 to 17, and 7 to 20, respectively, and also to rats (oral doses up to 200 mg/kg) on gestation Day 6 to lactation/post-partum Day 20. No significant effects on embryo-fetal (mice, rats, and rabbits) or pre/postnatal (rats) development were observed at the highest doses tested. The

systemic exposures (AUC) of VEL during gestation were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the RHD.

Females and males of reproductive potential

If SOF/VEL is administered with RBV, the information for RBV with regards to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information for additional information.

Patient Counseling Information

Advise patients to avoid pregnancy during combination treatment with SOF/VEL and RBV and for 6 months after completion of treatment. Inform patients to notify their healthcare provider immediately in the event of a pregnancy.

Clinical Data on Use of SOF/VEL in Pregnancy

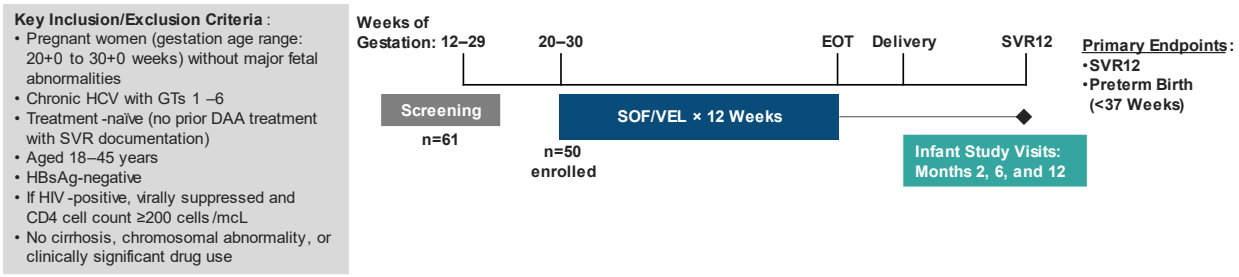
Open-Label STORC Study

Study design and demographics

The ongoing, phase 4, open-label, single-arm STORC study is assessing safety and efficacy outcomes of chronic HCV treatment with SOF/VEL once daily for 12 weeks during pregnancy. Delivery outcomes, viral response, safety profile, and infant outcomes were evaluated in the SOF/VEL-treated participants. The primary endpoints of this study were SVR12 and preterm birth (defined as <37 weeks; Figure 1).[2]

As of October 28, 2024, 50 participants were enrolled; 44 participants delivered, and 46 completed study medication, with 35 completing bloodwork to assess for SVR. Baseline characteristics included a median (range) age of 31 (18–40) years. Injection or inhalant drug use was the most common mode of HCV acquisition (n=31 [62%]). Participant races included the following: White, 84% (n=41); multiracial, 6% (n=3); Asian, 4% (n=2); Native American, 2% (n=1); Black, 2% (n=1); and Rohingya, 2% (n=1). Hispanic/Latino ethnicity was reported in 12% of participants (n=6). The median (range) gestational age at enrollment was 25 weeks + 4 days (20+3 to 30+0).[3]

Figure 1. STORC Study: Study Design[2,3]



Abbreviations: CD=clusters of differentiation; EOT=end of treatment; HBsAg=hepatitis B surface antigen.
Note: HCV VL and AEs were assessed during SOF/VEL treatment and through SVR12. For 12 months postdelivery in infants, HCV VL and AEs were assessed, and physical exams and growth and neurodevelopment assessments were given.

Interim results[3]

Interim data showed a 100% maternal SVR12 rate among the 35 participants who completed SVR assessment and no perinatal transmission in the 26 infants with available data. Of the 44 deliveries, 6 (13.6%) were preterm, including 2 with premature rupture of membranes at 36 + 4 weeks of gestation; 1 each with premature rupture of membranes and spontaneous preterm labor at 36 + 2 weeks of gestation; 1 with spontaneous preterm labor with breech presentation at 33 + 5 weeks of gestation; and 1 with spontaneous preterm labor with marginal placental abruption at 33 + 4 weeks of gestation. There were no reports of cholestasis.

There were 218 AEs reported in mothers and 183 AEs reported in infants. Forty mothers experienced AEs that were deemed related to SOF/VEL, including the following: nausea/vomiting (n=18); GERD and fatigue (each, n=7); headache (n=5); and elevated CK level, light sensitivity, numbness in fingers, arthralgias, insomnia, and diarrhea (each, n=1). There were 13 SAEs reported in mothers and 19 in infants; none were deemed related to SOF/VEL. Four congenital anomalies were reported: Hirschsprung disease, retrognathia, pyloric stenosis, and preauricular skin tag (each, n=1). Two participants discontinued SOF/VEL (nausea/vomiting, n=1; participant initiated, n=1).

HCV Treatment Initiation in the Third Trimester[4]

Study design

A study was conducted to assess whether a test-and-treat model with SOF-based regimens for treating pregnant women with HCV in their third trimester who were actively using drugs (defined as use within the past 6 months) improved HCV treatment starts and SVR rates (N=14). Participants were referred to a combination hepatology and addiction medicine clinic from addiction centers, syringe exchanges, high-risk obstetrics, Planned Parenthood, incarceration systems, and drug courts. Appointments with case managers and social workers were scheduled within 3 days, and additional services (eg, addiction therapy, medically assisted therapy, and HIV/PrEP management) were included. Test-and-treat approaches included same-day start, Medicare next-day rapid start, and next-day telemedicine start.

Results

The overall SVR rate among pregnant women who had available data was 100% (8/8). Eleven of the 14 participants received SOF/VEL, including 7 who began treatment on the same day test-and-treat approach. Of the 11 participants who received SOF/VEL, 6 achieved SVR, 2 were lost to follow-up, and 3 are pending SVR assessment. All participants self-reported complete adherence. No cases of vertical transmission were reported.

Open-Label PK Study

Study design, participant disposition, and demographics

A phase 1, open-label, single-center study evaluated the PK profile of 12 weeks of SOF/VEL in pregnant compared with non-pregnant women with chronic HCV infection. Delivery outcomes, viral response, and safety profile were also evaluated in the SOF/VEL-treated participants.[5,6] Study participants were HIV-negative and between 23 and 25 weeks of gestation at enrollment (Table 1). Eleven participants were enrolled in the study, and 10 participants were included in the primary PK analysis; 1 participant was excluded due to discontinuation of study treatment due to AEs after 2 doses. All participants had HCV GT 1 or GT 3, and most acquired HCV via drug use.[5]

The PKs of SOF/VEL were evaluated at Weeks 3, 6, and 9 of treatment. Exposures to VEL, SOF, and the GS-331007 metabolite in plasma were compared with historical PK data in 25 non-pregnant women treated with SOF/VEL in registrational trials. Infants were enrolled at delivery, and HCV VL, AEs, physical exams, growth, and neurodevelopment were assessed.[5] Another analysis compared levels of 007-TP (the active form of SOF; collected before dosing during Weeks 3, 6, and 9 of treatment) in DBS and PBMCs in study participants with those collected from 58 non-pregnant participants who received LDV/SOF in another study; levels may be used as a surrogate of drug activation in various tissue types and a measure of adherence to SOF-based treatment.[6]

Table 1. Baseline Demographics and Disease Characteristics (Chappell et al)[6]

Key Demographics and Characteristics	Pregnant Participants (N=10)
Age, median (range), years	31 (25–39)
Race, White/Black, n (%)	9 (90)/1 (10)
SCr, median (range), mg/dL	0.5 (0.4–0.6)
GFR, median (range), mL/min/1.73 m^2	126 (122–141)
Hematocrit, median (range), %	36.1 (33.2–37.8)

PK results

VEL PK parameters and SOF C_{max} were similar between pregnant and non-pregnant participants; however, SOF AUC was 38% higher in the group of pregnant participants than in the non-pregnant reference group. The GS-331007 AUC and C_{max} were 38% and 43% lower, respectively, in the pregnant participant group than in the non-pregnant reference group (Table 2). Study authors attributed differences observed between groups in SOF and GS-31007 exposures to slowed gastrointestinal motility and increased renal clearance during pregnancy.[5]

Table 2. PK Parameters in Pregnant Participants and Non-Pregnant Reference Group[5]

PK Parameters		Pregnant Participants (N=10)[a]	Non-Pregnant Participants (N=25)[b]	%GMR (90% CI)
SOF	AUC_T, GM (CV%), h × ng/mL	2039.62 (29.75)	1483.83 (66.43)	1.38 (1.06–1.78)
	C_{max}, GM (CV%), ng/mL	1455.09 (43.92)	1226.16 (59.46)	1.19 (0.88–1.6)
GS-331007	AUC_T, GM (CV%), h × ng/mL	9588.94 (18.75)	15,361.31 (22.35)	0.62 (0.55–0.71)
	C_{max}, GM (CV%), ng/mL	752.66 (21.85)	1312.17 (32.55)	0.57 (0.49–0.67)
VEL	AUC_T, GM (CV%), h × ng/mL	3244.45 (39.89)	3570.65 (72.04)	0.91 (0.67–1.23)
	C_{max}, GM (CV%), ng/mL	381.93 (38.35)	449.39 (77.12)	0.85 (0.63–1.15)
	C_T, GM (CV%), ng/mL	40.56 (49)	49.77 (66.37)	0.82 (0.59–1.13)

Abbreviations: AUC_T=area under the concentration-time curve of the dosing interval; C_T=concentration at the end of the dosing interval; CV=coefficient of variation; GMR=geometric mean ratio.
[a]GM from 2 PK visits from individual participants' PK parameters were summarized.
[b]Historical intensive PK data from non-pregnant women from registrational trials who were administered SOF/VEL.

In DBS, GM (95% CI) levels of 007-TP at Weeks 3, 6, and 9 of treatment were 340 (287–403), 340 (278–418), and 356 (275–461) fmol/punch, respectively; 007-TP levels in PBMCs were 2111 (1096–4066), 2808 (1559–5058), and 2212 (1267–3864) fmol/10^6 cells. Levels of 007-TP in PBMCs were similar or higher in pregnant study participants than in non-pregnant participants treated with LDV/SOF; DBS levels were approximately 50% lower among pregnant study participants than among non-pregnant participants, which study investigators concluded may have been due to hemodilution.[6]

Efficacy[5]

Eight of the 10 pregnant participants in the study had an SVR12 visit, and 100% of those achieved SVR12. Of the 10 infants enrolled at delivery (2 were lost to follow-up after delivery and 1 was lost to follow-up after the first infant visit), none of the 8 infants with HCV RNA data had detectable HCV RNA.

Safety[5]

There were 12 treatment-related maternal AEs (headache, n=4; nausea, n=3; vomiting, n=2; heartburn, n=2; fatigue, n=1). One AE (ie, vomiting) resulted in treatment discontinuation. In infants, there were 2 preterm (<37 weeks of gestation) births and 3 neonatal intensive care unit admissions.

Pregnancy Registry

The TiP-HepC Registry is an observational study assessing mother-infant outcomes of exposures to DAAs during pregnancy. The registry was developed by the Coalition for Global Hepatitis Elimination at the Task Force for Global Health. Funding for the registry is provided by the US Centers for Disease Control and Prevention. Data will be reviewed twice yearly by the TiP-HepC Scientific Advisory Committee, which is composed of a panel of experts in the field. Registry data will be analyzed and released twice yearly through the TiP-HepC Community of Practice. Please consider submitting information to the Registry at Treatment in Pregnancy for Hepatitis C (TiP-HepC) Clinical Case Registry (emory.edu).

References

1. Enclosed. Gilead Sciences Inc, EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use. US Prescribing Information. Foster City, CA.
2. Chappell C, Charles J, Smid M, et al. Safety, Tolerability, and Outcomes of Sofosbuvir/Velpatasvir in Treatment of Chronic Hepatitis C Virus during Pregnancy: interim results from the STORC study [Poster 5018]. Paper presented at: American Association for the Study of Liver Diseases (AASLD); November 10-14, 2023; Boston, Massachusetts.
3. Chappell C. Safety, Tolerability, and Outcomes of SofosbuviR/Velpatasvir in Treatment of Chronic Hepatitis C Virus during Pregnancy: Interim results from the STORC study [Oral presentation 222]. Presentation at: The Liver Meeting, American Association for the Study of Liver Diseases; 15-19 November, 2024; San Diego, CA.
4. Martinez A, Springer S, Hossein-Javaheri N, Formato T, Clark M. Hepatitis C Management of Women in the Third Trimestrer of Pregnancy in La Bodega [Poster 1475]. Presented at: The Liver Meeting, American Association for the Study of Liver Diseases; 15-19 November, 2024; San Diego, CA.
5. Chappell CA, Kiser JJ, Randolph R, et al. Sofosbuvir/ Velpatasvir Pharmacokinetics in Pregnant Women Hepatitis C Virus [Poster 597]. Presented at: Conference on Retroviruses and Opportunistic Infections; February 19-22, 2023; Seattle, Washington
6. Chappell CA, Brooks KM, Kiser JJ, et al. Intracellular Sofosbuvir Concentrations in Pregnant Women With Hepatitis C Virus [Poster 00710]. Presented at: Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6, 2024; Denver, CO.

Abbreviations

007-TP=uridine triphosphate
AE=adverse event
AUC=area under the concentration-time curve
C_{max}=maximum measured concentration
DAA=direct-acting antiviral
DBS=dried blood spots
GERD=gastroesophageal reflux disease
GM=geometric mean
GS-331007=predominant circulating metabolite of SOF
GT=genotype
LDV=ledipasvir
PBMC=peripheral blood mononuclear cells
PK=pharmacokinetic
PrEP=pre-exposure prophylaxis
RBV=ribavirin
RHD=recommended human dose
SAE=serious adverse event
SOF=sofosbuvir
STORC=SOF/VEL Treatment of Chronic Hepatitis C During Pregnancy
SVR=sustained virologic response
SVR12=sustained virologic response 12 weeks after end of treatment
TiP-HepC=Treatment In Pregnancy for Hepatitis C
VEL=velpatasvir
VL=viral load

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Epclusa US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

☎ 1-866-MEDI-GSI (1-866-633-4474) or 🖱 www.askgileadmedical.com

Adverse Event Reporting

Please report all adverse events to:

Gilead Global Patient Safety ☎ 1-800-445-3235, option 3 or
🖱 www.gilead.com/utility/contact/report-an-adverse-event

FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or 🖱 www.accessdata.fda.gov/scripts/medwatch

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