Safety, Tolerability, and Outcomes of VelpatasvirR/SofosbuvirR in Treatment of Chronic Hepatitis C Virus during Pregnancy (STORC)

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University of Pittsburgh IND Sponsor: Catherine Chappell, MD, MS
All other participating sites: IND exempt or CTA under Health Canada

Protocol Chair: Catherine Chappell, MD, MS

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LIST OF ABBREVIATIONS AND ACRONYMS

ALT	Alanine transaminase
AST	Aspartate transaminase
CTA	Clinical Trial Application
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCLP	Good Clinical Laboratory Practices
GCP	Good Clinical Practices
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IND	Investigational New Drug
INR	International normalized ratio
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Interim Study Review
VEL	Velpatasvir
SOF/VEL	Sofosbuvir/Velpatasvir
mL	Milliliter
PK	Pharmacokinetic
PSRT	Protocol Safety Review Team
PTID	Participant identification number
REB	Research Ethics Board
RNA	Ribonucleic acid
SAE	Serious adverse event
SOF	Sofosbuvir
SOP	Standard operating procedure(s)
SSP	Study-specific Procedure(s)

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PROTOCOL SUMMARY

Short Title:	Sofosbuvir/Velpatasvir Treatment of Chronic Hepatitis C during Pregnancy
Clinical Phase:	Phase 4
IND Sponsor:	Each site investigator holds an IND/IND Exemption/CTA
Protocol Chair:	Catherine Chappell, MD, MS
Sample Size:	Approximately 100 women and their infants
Study Population:	Pregnant women, 18-45 years old, diagnosed with chronic hepatitis C infection who are between 12 + 0 and 29 + 6 weeks of gestation at screening, and infants born to the enrolled participants
Study Design:	Multi-center, single-arm Phase 4 study
Study Duration:	Approximately 24 weeks per maternal participant and approximately one year of infant participant follow-up
Study Medication:	Fixed-dose combination tablet of sofosbuvir 400 mg and velpatasvir 100 mg (SOF/VEL)
Study Regimen:	Maternal participants will take SOF/VEL one tablet once daily starting between 20 + 0 and 30 + 0 weeks of gestation for 12 weeks (84 days)

Primary Objectives:

1. To evaluate the sustained virologic response 12 weeks after completion of SOF/VEL treatment (SVR12) in women treated during pregnancy.
2. To evaluate impact of antenatal treatment with SOF/VEL on the gestational age at delivery for women who received SOF/VEL for HCV treatment during pregnancy.

Primary Endpoints:

1. Maternal HCV RNA PCR 12 weeks after completion of SOF/VEL treatment (HCV RNA PCR below the lower limit of quantification will be considered evidence of SVR12).
2. Preterm delivery (spontaneous and iatrogenic) prior to 37 weeks' gestation.

Secondary Objectives:

1. To evaluate the maternal safety of HCV treatment during pregnancy with SOF/VEL.
2. To evaluate the neonatal safety of HCV treatment during pregnancy with SOF/VEL.
3. To determine the rate of HCV perinatal transmission among women treated with SOF/VEL during pregnancy according to HIV co-infection status.

Secondary Endpoints:

1. Maternal safety defined as
    - Maternal adverse events
    - Pregnancy and delivery outcomes
        - stillbirth or intrauterine fetal demise
        - intrapartum hemorrhage
        - postpartum hemorrhage
        - hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia with and without severe features, eclampsia)
        - gestational diabetes
        - intrauterine growth restriction
        - cholestasis of pregnancy
        - severe maternal morbidity (defined by CDC[1])
        - maternal admission to the intensive care unit
        - maternal death

2. Neonatal/Infant safety defined as
    - Severe neonatal morbidity with admission to neonatal intensive care unit
        - Perinatal *preterm* (<37 weeks) composite defined as fetal or neonatal death, severe bronchopulmonary dysplasia (grade 3), intraventricular hemorrhage grades III-IV, necrotizing enterocolitis (proven – Bell Stage 2A or greater), periventricular leukomalacia, retinopathy of prematurity stage III-V, or proven sepsis (early or late)
        - Perinatal *term* (>= 37 weeks) composite defined as fetal or neonatal death, respiratory support , Apgar score ≤ 3 at 5 minutes, hypoxic ischemic encephalopathy, seizure, infection (sepsis or pneumonia), birth trauma, meconium aspiration syndrome, intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support

- Admission to the neonatal intensive care unit
- Neonatal death
- Major malformations, defined as structural abnormalities with medical, surgical or cosmetic importance
- Weight, length, and head circumference at birth (by exam or chart review), 8 weeks, six months and 12 months
- Neurodevelopmental assessments at 6 months and 12 months by Ages & Stages Questionnaires®

3. Infant HCV RNA PCR viral load at 8 weeks, 6 months and 12 months

Table 1: Study Visit Schedule

	Maternal Study Visit	Gestational Age (Weeks + Days)/Timing †
V1	Screening	12+0 to 29+6
V2	Enrollment*	20+0 to 30+0
V3	Safety check/Med dispense	4 weeks ± 7 days after treatment start
V4	Safety check/Med dispense	8 weeks ± 7 days after treatment start
V5	End of Treatment	Within 7 days after last dose
	Delivery Visit^	
V6/iV	Post-treatment for SVR12	12 weeks ± 4 days after last dose
	Infant Study Visit	Infant Age
V6/iV	Infant Visit 1	8 weeks ± 6 weeks
iV2	Infant Visit 2	6 months ± 1 month
iV3	Infant Visit 3	12 months ± 1 month

†These are target windows. If the participant cannot be seen within these windows, she should be seen as soon as possible. A delayed visit will not be considered a protocol deviation.
*Start SOF/VEL and continue for 12 weeks (84 days)
^The Delivery Visit may occur before or after V5

Screening and Enrollment visits are separate visits and therefore should not occur on the same day.

Ideally, once a participant starts study medication (V2, Enrollment), study visits while on study medication should be scheduled 28 days apart or as close to 28 days as possible.

1 KEY ROLES

1.1 Funders and Protocol Chair

Funder: Gilead Sciences

Protocol Chair: Catherine Chappell, MD MSc

1.2 Laboratories

Clinical: This study will utilize the clinical laboratories designated on the FDA1572 or Qualified Investigator undertaking Health Canada form at each study site.

Next generation HCV genomic deep sequencing (which will only be done in the instance of a treatment failure or perinatal HCV transmission):

Dr. Jordan Feld's lab
MaRS Discovery Tower
C/O Atif Zahoor
101 College Street, 10-356
Toronto, ON
M5G 1L7

2 INTRODUCTION

2.1 Chronic Hepatitis C Infection in Pregnancy

A rising prevalence of acute and chronic hepatitis C virus (HCV) infection has been one of the most significant consequences of the opioid epidemic. Injection drug use among reproductive-aged persons is now the leading cause of new HCV infections[2] and has resulted in a dramatic rise in prevalence of HCV among pregnant women[3]. From 2006 to 2012 the rate of HCV among young people ≤ 30 years old increased by 364% in central Appalachian states hit hardest by the opioid epidemic such as Kentucky, Tennessee, Virginia and West Virginia[4]. Chronic HCV can lead to liver disease and cirrhosis[5] and is the leading cause of mortality from a nationally notifiable infection (NNI) in the US, surpassing all 60 other NNIs combined[6]. Infants born to women with HCV have a 4-7% risk of perinatal HCV infection[7], and are at increased risk for congenital anomalies, low birth weight, and neonatal intensive unit (NICU) care[3,8,9]. HCV-exposed infants also have a greater risk of adverse neurologic outcomes,[10] although these findings may be confounded by maternal substance use. Therefore, it is biologically plausible that treatment of HCV during pregnancy could improve both pregnancy and neonatal outcomes in addition to prevention of perinatal HCV transmission.

HCV cure provides significant health benefits outside of pregnancy. The goal of HCV treatment is to render HCV undetectable in the serum, liver tissue and mononuclear cells[11-13]. Sustained virologic response (SVR12) is defined as the absence of detectable HCV RNA in the serum at least 12 weeks after the completion of therapy. SVR12 has been shown to be a durable predictor of HCV cure when HCV RNA is collected for five years or more[14,15]. Patients cured of HCV experience significant health benefits including decreased liver inflammation and improvement in fibrosis and cirrhosis[16]. Additionally, SVR12 is associated with a 70% reduction in the risk of hepatocellular carcinoma and a 90% reduction in the risk of liver-related mortality and need for liver transplantation[17]. Furthermore, treatment of persons who use injection drugs can prevent ongoing transmission of HCV, or "treatment as prevention[18]." For these reasons, the joint American Association for the Study of Liver Disease (AASLD) and the Infectious Diseases Society of America (IDSA) treatment guidelines recommend that *all HCV-infected persons* be treated[19]. Despite this recommendation, pregnant women are excluded because the safety and efficacy of treatment during pregnancy has not been established.

Pregnant women are a priority population in HCV elimination efforts. In 2016, the World Health Organization (WHO) adopted the goal of eliminating hepatitis as a major public threat by 2030 by reducing hepatitis incidence from 6-10 to 0.9 million cases, and to reduce annual hepatitis deaths from 1.4 to 0.5 million[20]. In the national response to the WHO goal, the Department of Health and Human Services National Viral Action Plan 2017-2020 specifically includes pregnant women as a priority population due to the risk of perinatal transmission[21]. Although avoidance of certain obstetric procedures, such as amniotomy and invasive fetal monitoring, may

decrease perinatal HCV transmission, evidence is lacking[22]. Perinatal transmission of HCV is thought to occur around the time of parturition. Thus, curative HCV treatment during pregnancy could be the most effective intervention to prevent perinatal transmission.

2.2 Rationale

Pregnancy is a critical window of opportunity for HCV screening and treatment. Pregnancy may be the ideal time to provide HCV treatment due to enhanced maternal investment in neonatal health outcomes as has been demonstrated for maternal HIV infection. A meta-analysis of adherence to antiretroviral therapy during and after pregnancy showed a statistically significant difference in adherence during pregnancy (75.5%) compared to the postpartum period (53.0%)[23]. Recently the CDC and the USPSTF have recommended that pregnant women be screened for HCV during each pregnancy, so this may be the time when many women learn that they have chronic HCV.[24,25] In a retrospective cohort study of 369 pregnant women who were HCV seropositive at our institution from 2009 to 2012, 285 (77%) were referred to hepatology for postpartum treatment, but only 71 (25%) attended the consultation and only 6 (1.6%) were treated in the first year postpartum[26]. Furthermore, in an ongoing study of postpartum HCV treatment with SOF/VEL paired with medication-assisted treatment (MAT) at our institution, 6 (50%) of 12 enrolled participants were lost to follow-up prior to treatment completion[27]. *Thus, pregnancy may be the ideal period for enhanced HCV treatment adherence and engagement.*

Preliminary data: Phase 1 trial of ledipasvir/sofosbuvir (LDV/SOF) treatment in pregnancy demonstrated promising preliminary results.[28] Between June 2017 and October 2018, 9 pregnant women between 23-24 weeks' gestation with chronic genotype 1 infection were treated with LDV 90mg- SOF 400mg daily for 12 weeks. Three intensive PK visits were performed at 25-26, 29-30, and 33-34 weeks' gestation. Plasma was collected pre-dose and at 0.5, 1, 2, 3, 4, 5, 8 and 12 hours post-dose to measure LDV, SOF and GS-331007 (the inactive metabolite of SOF) by validated HPLC-MS/MS methods[29]. Of 29 women screened, 20 were excluded due to genotype 2 or 3 infection (n=10), ongoing illicit drug use (n=4), declined participation (n=3), intention to deliver off-site (n=2), and an APRI score of >1 (n=1). All 9 participants were white, with a median age of 31 years. Eight women acquired HCV due to injection drug use (of whom 4 were receiving medication assisted treatment for opioid use disorder) and one was perinatally infected. All nine (100%) participants were cured and there were no adverse events greater than grade 2 related to LDV/SOF. There were no significant differences between the PK parameters at each gestational age timepoint[28].

In this first study of HCV treatment during pregnancy, LDV/SOF was safe and effective with similar LDV and SOF PK exposure in pregnancy to non-pregnant

adults. While there was lower inactive metabolite (GS-331007) exposure, this was likely due to increased glomerular filtration rate during pregnancy.

2.3 SOF/VEL Fixed Dose Combination

2.3.1 Description

Sofosbuvir is described chemically as (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. It has a molecular formula of $C_{22}H_{29}FN_3O_9P$ and a molecular weight of 529.45. Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥2 mg/mL across the pH range of 2–7.7 at 37C and is slightly soluble in water[30].

Velpatasvir is described chemically as methyl {(1*R*)-2-[(2*S*,4*S*)-2-(5-{2- [(2*S*,5*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-5-methylpyrrolidin-2-yl]- 1,11-dihydro[2]benzopyrano[4',3':6,7]naphtho[1,2-*d*]imidazol-9-yl}-1*H*-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of $C_{49}H_{54}N_8O_8$ and a molecular weight of 883.0.

Each tablet contains sofosbuvir 400 mg and velpatasvir 100 mg. The tablets include the following inactive ingredients: copovidone, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

2.3.2 Mechanism of Action

Sofosbuvir is a nucleotide prodrug that is metabolized to the pharmacologically active metabolite GS-461203, which is incorporated into HCV RNA by NS5B polymerase where it acts as a chain terminator. Velpatasvir inhibits the HCV NS5A protein and sofosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase, which are essential for viral replication.

Sofosbuvir has demonstrated pangenotypic antiviral activity, with EC50 values against HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a, of 40, 110, 50, 15, 50, 40, 15, and 14 nmol/L, respectively in HCV replicon assays. Velpatasvir has potent pangenotypic antiviral activity against HCV genotypes 1a, 1b, 2a, 2b, 3a, 4a, 4d, 5a, 6a, and 6e with EC50 values of 0.014, 0.016, 0.016, 0.006, 0.004, 0.009, 0.004, 0.054, 0.009, respectively. The combination SOF/VEL has potent activity against HCV genotypes 1, 2, 3, 4, 5, and 6[30].

2.4 Clinical Studies

2.4.1 Clinical Studies of Sofosbuvir/Velpatasvir for the Treatment of HCV

Approximately 1035 participants without cirrhosis or with compensated cirrhosis have been enrolled in several multicenter, Phase 3 trials to assess the efficacy of treatment with SOF/VEL for 12 weeks in patients with genotypes 1, 2, 3, 4, 5, and 6 chronic HCV in ASTRAL-1, ASTRAL-2 and ASTRAL-3 (Table 2). ASTRAL-1 was a randomized, double-blind, placebo-controlled trial that evaluated 12 weeks of treatment with SOF/VEL compared to placebo in participants with genotype 1, 2, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis[31]. ASTRAL-2 was a randomized, open-label trial that evaluated 12 weeks of SOF/VEL compared to 12 weeks of SOF plus ribavirin in subjects with genotype 2 infection[32]. ASTRAL-3 was a randomized, open-label trial that evaluated 12 weeks of SOF/VEL compared to 24 weeks of SOF plus ribavirin in genotype 3 infection[32]. Approximately 40% (over 400 participants) in these trials were women. There were no on-treatment virologic failures reported (persistent viremia while actively taking SOF/VEL), however 13 (1%) participants experienced virologic failure after treatment or relapse, most commonly among participants with genotype 3 infection. Another 12 (5%) participants failed to achieve SVR12 due to non-adherence, adverse reaction (n=2) or another reason for treatment interruption (Table 2).

Table 2: Virologic outcome of a 12-week course of SOF/VEL for the treatment of HCV infection in participants without cirrhosis or with compensated cirrhosis from ASTRAL-1, ASTRAL-2, and ASTRAL-3

geno-type	Total n	SVR12 n	SVR12 rate	on-treatment virologic failure	after-treatment virologic Failure	Other
1	328	323	98%	0	2 (1%)	3 (1%)
2	238	237	100%	0	0	1(<1%)
3	277	264	95%	0	11(4%)	2 (1%)
4	116	116	100%	0	0	0
5	35	34	97%	0	0	1 (1%)
6	41	41	100%	0	0	0

Safety

The safety and tolerability of SOF/VEL has been evaluated in the Phase 3 trials described above. Overall, SOF/VEL was well tolerated by patients with chronic HCV infection (N=1035); only 2 participants (0.2%) permanently discontinued treatment due to adverse events. The most common adverse reactions (adverse events assessed as causally related by the investigator and occurring in at least 10% of participants) were headache and fatigue. Adverse reactions, all grades, observed in greater than or equal to 5% of participants receiving 12 weeks of SOF/VEL treatment in ASTRAL-1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving SOF/VEL, 79% had an adverse reaction of mild severity (Grade 1). With the exception of asthenia, each of these adverse reactions occurred at a similar frequency or more frequently in the placebo arm compared to SOF/VEL recipients; asthenia was reported by 3% versus 5% for the placebo and SOF/VEL groups, respectively. The adverse reactions observed in participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater

than or equal to 5% of participants treated with SOF/VEL in ASTRAL-3. In ASTRAL-1, rash occurred in 2% of participants treated with SOF/VEL and in 1% of participants taking placebo. All rashes were mild or moderate in severity. In ASTRAL-1, depressed mood occurred in 1% of participants treated with SOF/VEL and was not reported by any placebo participants; all reports of depressed mood were mild or moderate[30].

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Additionally, post-marketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered with a sofosbuvir-containing regimen. Additionally, a fatal cardiac arrest occurred in a patient taking amiodarone that was co-administered with sofosbuvir.

Laboratory abnormalities:
Lipase Elevations: In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3 times the upper limit of normal were observed in 3% and 1% of participants treated with SOF/VEL and placebo, respectively, and in 6% and 3% of participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively[30].

Creatine Kinase: In ASTRAL-1, isolated, asymptomatic creatine kinase elevations greater than or equal to 10 times the upper limit of normal were reported in 1% and 0% of participants treated with SOF/VEL and placebo, respectively, and in 2% and 1% of participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively.

2.4.2 Animal Studies of Sofosbuvir and Velpatasvir During Pregnancy

There are no adequate studies of SOF/VEL in pregnant women. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with the components sofosbuvir or velpatasvir at exposures greater than the recommended human dose. During organogenesis in the mouse, rat, and rabbit, systemic exposures (AUC) to velpatasvir were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the recommended human dose, while exposures to the predominant circulating metabolite of sofosbuvir (GS-331007) were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the recommended human dose[30].

Velpatasvir: Velpatasvir 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

velpatasvir during gestation were approximately 31 (mice), 6 (rats), and 0.4 (rabbits) times the exposure in humans at the recommended human dose.

Sofosbuvir: Sofosbuvir 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 sofosbuvir (GS-331007) during gestation were approximately 4 (rats) and 10 (rabbits) times the exposure in humans at the RHD.

2.5 Rationale for Study Design

There is currently no published experience with SOF/VEL in pregnant women, although there were no effects on fetal development observed in mice, rats and rabbits with doses higher than those given for treatment of hepatitis C in humans in data submitted to the FDA. There are reassuring data from our prior study of treatment of pregnant women with LDV/SOF. Because LDV/SOF is not approved for treatment of genotypes 2 and 3, it is imperative to evaluate a pan-genotypic regimen. In highly-affected areas such as West Virginia, genotypes 2 and 3 constitute up to 30% of cases. In this study, treatment will be initiated during the second trimester, reducing the risk of SOF/VEL exposure during organogenesis, ensuring viral supression and a majority of the treatment is completed by delivery, and thus minimizing the risk of perinatal transmission.

The study will be completed in 8 or 9 visits (6 maternal visits and 3 infant visits) which should easily align with routine prenatal and postpartum visits (Table 1). We plan to screen patients between 12+0 and 29+6 weeks of gestation confirmed by ultrasound (ultrasound will be performed prior to enrollment). HCV RNA level to confirm the patient has active infection will be obtained. Laboratory evaluation of liver function including CBC, PT/INR, hepatic panel, creatinine/eGFR, creatine kinase and lipase will be obtained, to evaluate for renal insufficiency, decompensated cirrhosis and baseline elevations of lipase and creatine kinase. Hepatitis B virus (HBV) antigen will be performed to look for evidence of active HBV infection. Medical history and demographic information will also be collected at screening. If the following inclusion and exclusion criteria are met, then the patient will be enrolled into the study between 20+0 and 30+0 weeks' gestation and initiate a 12-week course of SOF/VEL.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objectives:

1. To evaluate the sustained virologic response 12 weeks after completion of SOF/VEL treatment (SVR12) in women treated during pregnancy.

2. To evaluate impact of antenatal treatment with SOF/VEL on the gestational age at delivery for women who received SOF/VEL for HCV treatment during pregnancy.

3.2 Primary Endpoints:

1. Maternal HCV RNA PCR 12 weeks after completion of SOF/VEL treatment (HCV RNA PCR below the lower limit of quantification will be considered evidence of SVR12)
2. Preterm delivery (spontaneous and iatrogenic) prior to 37 weeks' gestation

3.3 Secondary Objectives:

1. To evaluate the maternal safety of HCV treatment during pregnancy with SOF/VEL
2. To evaluate the neonatal safety of HCV treatment during pregnancy with SOF/VEL
3. To determine the rate of HCV perinatal transmission among women treated with SOF/VEL during pregnancy according to HIV co-infection status

3.4 Secondary Endpoints

1. Maternal safety defined as
    - Maternal adverse events
    - Pregnancy and delivery outcomes
        - stillbirth or intrauterine fetal demise
        - intrapartum hemorrhage
        - postpartum hemorrhage
        - hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia with and without severe features, eclampsia)
        - gestational diabetes
        - intrauterine growth restriction
        - cholestasis of pregnancy
        - severe maternal morbidity (defined by CDC[1])
        - maternal admission to the intensive care unit
        - maternal death
2. Neonatal/Infant safety defined as
    - Severe neonatal morbidity admission to neonatal intensive care unit
        - Perinatal *preterm* (<37 weeks) composite defined as fetal or neonatal death, severe bronchopulmonary dysplasia (grade 3), intraventricular hemorrhage grades III-IV, necrotizing enterocolitis (proven – Bell Stage 2A or greater), periventricular leukomalacia, retinopathy of prematurity stage III-V, or proven sepsis (early or late)
        - Perinatal *term* (>= 37 weeks) composite defined as fetal or neonatal death, respiratory support, Apgar score ≤ 3 at 5

minutes, hypoxic ischemic encephalopathy, seizure, infection (sepsis or pneumonia), birth trauma, meconium aspiration syndrome, intracranial or subgaleal hemorrhage, or hypotension requiring vasopressor support

- Admission to the neonatal intensive care unit
- Neonatal death
- Major malformations, defined as structural abnormalities with medical, surgical or cosmetic importance
- Weight, length, and head circumference at birth (by exam or chart review), 8 weeks, six months and 12 months
- Neurodevelopmental assessments at 6 months and 12 months by Ages & Stages Questionnaires ®

3. Infant HCV RNA PCR viral load at 8 weeks, 6 months and 12 months

4 STUDY TIMELINE

4.1 Time to Complete Accrual

The approximate time to complete study enrollment is expected to be 12 months.

4.2 Expected Duration of Participation

The expected duration for maternal participants is approximately 24 weeks, not including the screening window. Infants will be followed for a full year after birth; therefore, follow-up after enrollment is approximately one year and 4 months. Maternal study data will be collected from the participant and/or her medical records through the Post-Treatment (SVR12) Visit (V6). Maternal participants who experience adverse events (AEs) at the Post- Treatment Visit (V6) that are clinically significant or related to study product/participation will be followed beyond V6 until a clinically acceptable resolution or stabilization of the AE(s) is confirmed and documented. The follow-up may be done via phone as applicable. Similarly, infant study data will be collected through the 12-month follow-up visit (iV3). Infants who have AEs at the iV3 visit that are clinically significant or related to study product/participation and have not resolved or stabilized will be followed beyond iV3 until a clinically acceptable resolution or stabilization of the AE(s) is confirmed and documented. The follow-up may be done via phone as applicable.

5 STUDY POPULATION

5.1 Selection of the Study Population

5.1.1 Recruitment and Retention

Recruitment will take place at multiple study sites and according to the site's recruitment SOP. All recruitment materials and procedures will be approved prior to use by the site/local IRB/REB.

The importance of retention will be stressed to the participant at each visit as part of protocol adherence counseling and as per the site's retention SOP. Once a participant is enrolled, the study staff will make every effort to retain the participant in follow-up. If a participant is lost to follow-up or is discontinued from the study prior to the completion of the final maternal visit evaluating SVR12, then an additional/replacement participant will be enrolled into the study from any participating site.

5.2 Inclusion Criteria

Women must meet all the following criteria to be eligible for inclusion in the study. Any exclusionary laboratory values can be repeated at a later date within the

screening window. If the repeated laboratory values meet inclusion criteria, then the participant can be enrolled. If there is concern that the participant's health status has changed between the screening visit and the enrollment visit or if there is a clinical concern by the study investigators, the screening laboratories can be repeated prior to enrollment.

1) Age 18 through 45 years (inclusive) at screening
2) Able and willing to provide written informed consent and take part in the study procedures
3) Able and willing to provide adequate locator information, defined as at least two other alternate contacts
4) HCV antibody seropositivity with detectable HCV RNA viral load at screening
5) Chronic HCV infection of at least 6 months by laboratory report or participant reported medical history as determined by the site PI/designee, or if duration of HCV cannot be determined then the participant can be enrolled if there is no clinical evidence of acute hepatitis C infection (defined by CDC as presence of jaundice or total bilirubin >/= 3.0 mg/dL/51 μmol/L or ALT >200IU/L)
6) Singleton pregnancy at 20 + 0 to 30 + 0 weeks' gestation at enrollment with gestational dating confirmed by ultrasound
7) Having a comprehensive anatomy scan with no evidence of major structural abnormalities as defined by the CDC birth surveillance toolkit (https://www.cdc.gov/ncbddd/birthdefects/surveillancemanual/chapters/chapter-4/chapter4-1.html) or an anomaly that would significantly impact delivery timing or neonatal outcomes as determined by the Protocol Safety Review Team (PSRT) prior to enrollment
8) Documented negative Hepatitis B testing for current infection (negative HBsAg test) prior to enrollment
9) If living with HIV, must be on antiretroviral therapy with HIV viral load <50 copies/mL/40 IU/mL on the most recent HIV viral load test within 30 days before enrollment and agree to continue antiretroviral therapy throughout study participation
10) If taking acid-suppressant medication(s), willing and able to either discontinue administration during the 12-week period of study treatment or to follow specific dosing instructions for concomitant use with SOF/VEL
11) Per participant report at screening and enrollment, agrees not to participate in other research studies involving investigational medications or investigational medical devices for the duration of study participation (does not include duration of infant participation). Note: maternal participants can participate in research studies that include standard of care medications.

5.3 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

1) Participant report of any of the following at screening or enrollment:
    a. Previous DAA treatment for HCV (prior interferon-based treatment is acceptable) without documentation of SVR12 (HCV RNA below the lower limit of quantification at least 24 weeks after DAA initiation)
    b. Use of any medications contraindicated with concurrent use of velpatasvir or sofosbuvir according to the most current EPCLUSA® package insert[30]
    c. Plans to relocate away from the study site area in the next 16 months and unable/unwilling to return for study visits
    d. History of cirrhosis documented or reported by previous liver biopsy, imaging tests or on at least 2 noninvasive laboratory tests of fibrosis, including compensated cirrhosis
2) Reports participating in any other research study involving investigational medications or investigational medical devices within 60 days or less prior to enrollment (does not include research studies involving standard of care medications)
3) Known fetal chromosomal abnormality prior to enrollment (confirmed by chorionic villus sampling or amniocentesis)
4) Clinically significant and habitual non-therapeutic drug use, not including marijuana, as determined by site PI/designee at screening and enrollment
5) At screening and enrollment, as determined by site PI/designee, any significant, uncontrolled, active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease other than HCV (or HIV as outlined in eligibility criteria)
6) Any of the following laboratory abnormalities at screening:
    a. Aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 10 times the upper limit of normal
    b. Hemoglobin less than 9 g/dL (90 g/L)
    c. Platelet count less than 90,000 per mm^3 ($90{,}000 \times 10^9$/L)
    d. International normalized ratio (INR) > 1.5
    e. Creatinine greater than 1.4 mg/dL (124 μmol/L)
7) If living with HIV, CD4 count less than 200 cells/mm^3 within 6 months of enrollment.
8) Any other condition that, in the opinion of the site PI/designee, would preclude appropriate informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives.

6 STUDY MEDICATION

6.1 Regimen

Each participant will take a 12-week course (84 consecutive days) of SOF/VEL(400 mg of sofosbuvir and 100 mg of velpatasvir), one tablet by mouth once daily.

6.2 Administration

Study medication will be dispensed at V2 (Enrollment), V3 and V4 visits. Participants will be given instructions on timing of the dose, what to do if a dose is missed and how to store the medication. If a dose is missed, the participant should take the dose as soon as it is remembered, but only one dose per day (24-hour period). Participants will be instructed to take the medication each day as close to the same time as possible. SOF/VEL can be taken with or without food. Participants will be given adherence tips, such as setting an alarm on their phone, linking medication time to another daily activity, etc. Participants will be instructed to call the study staff immediately if they run out of medication or if they lose the study medication. In this case, all possible efforts will be made to get the participant study medication as soon as possible which may be outside the visits listed above.

6.3 Supply and Accountability

6.3.1 Supply

Gilead Sciences will supply the study medication that is manufactured under Good Manufacturing Practices as FDA approved bulk product. The product will be shipped to each designated site pharmacy location from the drug distributer.

6.3.2 Storage and Dispensing

SOF/VEL should be stored at room temperature below 30°C (86°F).[30] The site investigational pharmacist or designee will maintain documentation of temperature in the area where the study medication is stored. Study medications will be dispensed at each site according to the study pharmacy manual and their site SOP for medication provision.

The site pharmacist or designee will dispense enough study medication to last until the next scheduled visit and an additional (emergency/extra) supply. The study medication will be dispensed to the study staff, then subsequently provided directly to the study participant.

6.3.3 Accountability

At each investigational site, the pharmacist or designee will maintain complete accountability records of all study SOF/VEL received and dispensed. Unused

product should be brought back to the study site by participants at each visit and sent to the pharmacy for documentation and quarantine, according to the site SOP. All available unused study medications will be returned to the distributor/Gilead Sciences or destroyed or as instructed by Gilead after the study is completed.

6.3.4 Retrieval of Study Medication

Participants will be instructed to return any unused medication at each visit. If the participant fails to return unused medication at a scheduled visit, reasonable attempts will be made and documented to obtain the unused medication from the participant (i.e. at an unscheduled visit or the following study visit). Unused medication will be accounted for by study staff and documented in the participant's research record and then returned to the site pharmacy for documentation and quarantine, per site SOP or site standards.

6.4 Concomitant Medications

Participants may use non-prohibited concomitant medications during the study. All concomitant medications reported throughout the course of the study will be recorded and will include prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations. Each reported concomitant medication will be reviewed to ensure the participant is not using prohibited medications (i.e. St. John's wort, carbamazepine, efavirenz) as referenced in the EPCLUSA® package insert. At each visit, participants will be asked if they have initiated any new medications or changed any reported medications. If the participant reports using acid suppressing medications, she will be given the option of discontinuing use during the 12-week period of SOF/VEL administration or following specific dosing instructions regarding correct timing of acid suppressing medication use according to the EPCLUSA® package insert.

7 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is presented in Appendix 1. Any clinical or laboratory information collected as a part of the participant's routine clinical care occurring on the same day as the study visit does not need to be repeated and can be collected from the participant's medical record.

7.1 Pre-screening

Sites may perform pre-screening activities as per local standards/local IRB/REB approval. Activities may include:

- Pre-screening medical records for minimum criteria (i.e. age, gestational age, HCV status)
- Use of screening scripts to provide information about the study to individuals who are interested

- Use of IRB/REB approved materials (i.e. ads, flyers, videos, social media posts)

Process information (e.g., number of potential participants contacted, number presumptively eligible) will be recorded and stored at the study site to inform recruitment activities.

Participants will be encouraged to include her partner and/or family members in discussions about study participation as desired.

7.2 Visit 1- Screening (V1)

Potential participants will be encouraged to speak with their primary care/OB provider to determine whether to initiate HCV treatment during pregnancy before enrolling in the study.

Written informed consent will be obtained before any screening procedures are initiated. Screening can take place anytime within the screening gestational age window (12+0 to 29+6 weeks) with gestational age being determined by available clinical information and confirmed by ultrasound prior to enrollment. The screening visit questionnaire will include information about the diagnosis of HCV, any past or ongoing HCV risk factors, and any past HCV care or treatment. If an anatomy ultrasound has not been performed by the time of the screening visit, then it should be performed prior to enrollment as part of routine obstetric care. The study team may assist the participant in scheduling this ultrasound. Multiple visits may be needed to complete all required screening procedures as necessary.

The actual screening visit may occur anytime during the protocol defined screening window of 12+0 to 29+6 weeks. Routine clinical care laboratory values collected up to 4 weeks prior to the **date of the screening visit** may be used for screening purposes. In this case, any STORC screening required laboratory tests that were not done as part of clinical care within 4 weeks should be drawn at the time of the STORC Screening Visit. Any exclusionary laboratory values can be repeated at a later date within the screening window. If the repeated laboratory values meet inclusion criteria, then the participant can be enrolled. If there is concern that the participant's health status has changed between the screening and the enrollment visit or if the study investigators have concerns about the woman's health status, the screening laboratories can be repeated prior to enrollment.

Table 3: Screening Visit (V1)

Visit 1- Screening Visit	
Component	**Procedures**
Administrative and Regulatory	• Assess eligibility • Review and obtain written informed consent • ICF Comprehension Assessment • Assign participant ID (PTID) • Sign appropriate medical record releases (i.e. to obtain records from prenatal care and outside records as necessary) • Collect locator information • Collect demographic information • Visit questionnaire • Provide reimbursement for study visit • Schedule next visit
Clinical	• Collect medical history & review and print medical/prenatal records including documentation of previous hepatitis C treatment, if applicable • Review and obtain documentation of previous liver biopsy, liver imaging and/or noninvasive measures of fibrosis, if applicable • Collect concomitant medications • Perform full physical examination, including Fetal Heart Tones (FHTs) • Confirm gestational dating (by available clinical information but must be confirmed by ultrasound prior to enrollment)
Local Laboratory Tests	• Collect blood: • Complete blood count (CBC) with differential and platelets* • HCV antibody and RNA viral load* • HCV genotype (if not available) • Hepatic function panel (AST, ALT, albumin, total and direct bilirubin, alkaline phosphatase)* • Creatinine/eGFR * • If living with HIV, perform HIV RNA PCR (viral load) if not done within 30 days of screening and CD4 cell count if not done within 6 months of screening*** • Hepatitis B virus testing (HBsAg, anti-HBc, anti-HBs) if not done as part of routine prenatal care • PT/INR* • Lipase* • Creatine kinase*

***If greater than 30 days between screening and enrollment, HIV RNA PCR must be repeated/available and within eligibility criteria to enroll
*Results of routine clinical care laboratory testing conducted within 4 weeks of screening visit date may be used towards the screening visit.

7.3 Visit 2- Enrollment (V2)

The following procedures will occur at the enrollment visit (V2). The visit questionnaire includes any changes in the participant's medical history and any new or ongoing HCV risk factors. During the enrollment visit the participant will be given instructions on taking the study medication.

Table 4: Enrollment (V2)

Enrollment Visit- Visit 2 (V2)	
Component	**Procedures**
Administrative and Regulatory	• Confirm eligibility • Review/update locator information • Visit Questionnaire • Provide counseling regarding protocol adherence • Provide reimbursement for study visit • Schedule next visit
Clinical	• Review/update medical history • Review/update concomitant medications • Document pre-existing conditions • Perform modified physical examination, including FHTs
Study Medication	• Provide instructions regarding study medication/daily use • Provide study medication and observe first dose (day 1) of medication in office
Local Laboratory Tests	• Collect blood: • HCV RNA viral load • Blood sample for HCV genomic deep sequencing (collected but only used in the case of treatment failure) or stored sample for future use, as applicable • If living with HIV and more than 30 days between screening and enrollment, HIV RNA PCR must be repeated prior to enrollment (if a clinical HIV viral load within 30 days of enrollment is not available)

7.4 Follow-up Visits

7.4.1 Visit 3 and 4

The following procedures will occur at visits 3 and 4 to assess the safety and tolerability of study medication. The visit questionnaire will assess any changes in the participant's medical history and any new or ongoing HCV risk factors. Participants will also be reminded to call the research staff when they present to the hospital for delivery.

Table 5: Follow-up Visits (V3 and V4)

Follow-up Visits 3 and 4	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit questionnaire • Provide modified counseling regarding protocol adherence • Provide reimbursement for study visit • Schedule next visit as applicable
Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination, including FHTs • Record/update AEs • Provide available test results (if applicable) • Instruction about contacting study staff when in labor/being admitted to labor and delivery
Study Medication	• Collect and perform accountability of unused study medication (if applicable) • Provide study medication • Review instructions for daily use

Local Laboratory Tests	• Collect blood: • CBC with differential and platelets (V3) • Hepatic function panel (AST, ALT, albumin, total and direct bilirubin, alkaline phosphatase) (V3) • PT/INR (V3) • Creatinine/eGFR (V3) • Lipase (V3) • Creatine kinase (V3) • HCV RNA viral load (V3, V4) • Blood sample for HCV genomic deep sequencing (collected but only used in the case of a treatment failure) or stored sample for future use (V3), as applicable

7.4.2 End of Treatment Visit (V5)

The following procedures will occur at the End of Treatment visit. This visit will be scheduled within 7 days of completion of the 12-week course of study medication. The purpose of this visit will be to collect any remaining study medication and to assess and follow-up on any adverse events. The visit questionnaire will assess any changes in the participant's medical history and any new or ongoing HCV risk factors. Participants will also be reminded to call the research staff when they present to the hospital for delivery.

Table 6: End of Treatment Visit

End of Treatment Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit Questionnaire • Protocol adherence counseling, including delivery visit instructions • Provide reimbursement
Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination, including FHTs • Record/update AEs • Provide available test results (if applicable)
Study Medication	• Collect and perform accountability of remaining study medication
Local Laboratory Tests	• Collect blood for: • HCV RNA viral load • Blood sample for HCV genomic deep sequencing (collected but only used in the case of treatment failure) or stored sample for future use, as applicable

7.4.3 Delivery Visit (in person or phone visit and chart review)

Participants will be instructed to contact the study staff when they are in labor/admitted to labor and delivery, regardless of delivery location; a family member or friend may provide this information to study staff. If the participant has not yet completed study medication, she will be instructed to bring the remaining medication with her to the hospital to continue daily dosing and avoid missed doses. If necessary and possible, additional doses may be dispensed during admission if the participant did not bring study medication with her and is unable to access it.

The delivery visit may occur in person, for participants who are delivering at the hospital associated with the study site. For participants who are delivering at a non-

associated clinic or at a time in which the study staff is unable to provide an in person visit, the visit may be conducted utilizing information contained in the delivery medical records and/or by participant report. The date of this delivery visit will be the date the study staff makes the first contact with the participant during her delivery admission, regardless if procedures occur over more than one day. Participants who deliver at an outside location will be contacted by phone as close to delivery as possible to complete the applicable delivery visit study procedures (i.e. questionnaire, update locator information, update medical history). The delivery visit date for these participants will be the date of the completed phone call. Available medical records to obtain delivery outcomes/variables will be reviewed for all participants, regardless of delivery location. A copy of the delivery records will be placed in the participant's research chart. In the event that the participant delivers at the hospital associated with the clinical site and is still taking study medication, then procedures from previously scheduled visits (V3 or V4) can be performed. Regardless of location of delivery, participants who are still on study medication at

the time of delivery will be encouraged to continue on the medication to complete the full 12-week course (84 doses) of study medication.

Table 7: Delivery Visit

Delivery Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit Questionnaire • Protocol adherence counseling (for mother and infant) • Provide reimbursement, as applicable • Schedule next visit
Clinical (Maternal)	• Review/update medical history • Review/update concomitant medications • Provide available test results (if applicable) • Perform modified physical examination (or obtain from medical record) • Record/update AEs
Study Medication	• Study medication use/adherence (if still on study medication) • Dispense study medication, as applicable, to complete 12-week course (if still on study medication)
Clinical (Infant)	• Record concomitant medications • Full physical examination (may be done via chart review)
Medical Record Review for Delivery Outcomes	• Type of pregnancy outcome • Gestational age at pregnancy outcome • If delivery, type of delivery (e.g., vaginal, vaginal forceps-assisted, • vaginal vacuum-assisted, cesarean section) • Delivery medications • Complications related to pregnancy outcome – Delivery complications (e.g., intrapartum and/or postpartum hemorrhage, hypertension, admission to the neonatal ICU) – Other complications not related to delivery
Baseline Infant Information*	• Demographics • Sex • Weight • Length • Head circumference • Apgar scores
Local Laboratory Test**	• Collect blood: • Maternal HCV RNA viral load

*All baseline infant information may be extracted from the infant medical record as available.
**Laboratory test performed as applicable for participants who deliver at site hospitals.

7.4.4 Post-Treatment (SVR12) (V6) Visit

The following procedures will occur at the Post-Treatment (SVR12) visit (V6), which should be scheduled 12 weeks ± 4 days from the last dose of study medication. The V6 visit can occur simultaneously with the 8-week Follow-up Visit for the infant (iV1), as applicable. This is the last scheduled clinic visit specifically for the mother. If an HCV RNA test is not obtained at the V6 visit or abstracted from the medical record

within the V6 visit window or later, then the participant is NOT evaluable and will be replaced with a new participant.

Table 8: Post Treatment (V6)

Visit 7 (V6) Post Treatment Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit questionnaire • Provide reimbursement
Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination • Record/update AEs • Provide available test results from delivery, as applicable
Laboratory	• Collect blood: • CBC with platelets and differential • Hepatic function panel (AST, ALT, albumin, total and direct bilirubin, alkaline phosphatase) • PT/INR • Creatinine/eGFR • Lipase • Creatine kinase • HCV RNA viral load* • Blood sample for HCV genomic deep sequencing (collected and only used in the case of treatment failure) or stored sample for future use, as applicable.

*If the participant does not come to the V6 visit, then the HCV RNA viral load may be abstracted from the medical record if it occurs during the visit window or later. If the HCV RNA is detectable then every effort should be made to have the participant return for a blood sample for HCV genomic deep sequencing.

7.4.5 Infant Follow-Up Visits (iV1, iV2, iV3)

After delivery, infants will be seen at the following time points:
iV1: 8 weeks ± 6 weeks
iV2: 6 months ± 1 month
iV3: 12 months ± 1 month

The following procedures will occur at the Infant Follow-Up Visits (iV1, iV2, iV3). If blood sampling is not possible, then the results can be collected from the infant's medical record if available. Results of physical and developmental exams will be shared with the mother, and if necessary, with the infant's routine healthcare

provider. Referrals, for instance for early intervention, will be made as indicated by pediatric study staff.

Table 9: Infant Follow-Up Visits (iV1, iV2, iV3)

Visit iV1, iV2, iV3 Infant Follow-Up Visits	
Component	**Procedures**
Administrative and Regulatory	• Review/update mother/guardian locator information • Review infant demographics (iV1) • Sign release(s) for medical records for infant, as applicable • Provide reimbursement • Schedule next visit (iV2, iV3) • Review schedule of infant follow-up visits • Protocol adherence counseling
Clinical	• Review/update medical history* • Document pre-existing conditions (iV1)* • Review/update concomitant medications* • Record/update AEs • Age-appropriate physical examination by pediatrician or designee, including growth assessment (weight, length, and head circumference)*** • Developmental Exam (Ages and Stages Questionnaire®); with referrals as indicated • Provide available laboratory test results, as applicable
Laboratory	• Collect infant blood • HCV RNA (iV1, iV2, iV3) • HCV genomic deep sequencing (only if HCV RNA is detectable)**

*May be collected from the medical record as applicable
**If HCV RNA is detectable at iV1, iV2 or iV3, then HCV genomic deep sequencing should be collected/stored. If infant is at high-risk of HCV perinatal transmission, then an additional sample can be drawn at the time of the HCV RNA test and stored until the HCV RNA test has resulted. If the HCV RNA result is undetectable, then the stored sample will be discarded.
***An age-appropriate physical exam is required during the infant study visit. However, if the infant participant misses a visit, then an age-appropriate physical exam may be abstracted from the medical records if it occurs during the visit window.

7.5 Follow-up Procedures for Participants Who Permanently Discontinue Study Medication

Participants will be permanently discontinued from study medication for significant laboratory abnormalities or adverse events as outlined in section 9.3 and 9.4, or if they choose to discontinue study medication. The participant will be asked to continue in the study and complete applicable remaining study procedures for safety purposes, including maternal and infant study procedures. To reduce burden on the participant and prevent lost to follow-up, in person visits can be converted to telephone visits for the collection of adverse events and safety labs can be collected from the medical record as performed for standard of care.

Participants who are permanently discontinued from study medication will be instructed to return any remaining study medication. All protocol-specified study procedures will continue for safety except the following:

- Provision of study medication
- Provision of medication use/adherence counseling

The following procedures will be performed at the visit at which study medication use is permanently discontinued or at the next in person visit:

- HCV viral load
- HCV genomic deep sequencing (collected and used as necessary) or stored sample for future use, as applicable
- Medical history review
- Concomitant medication review
- Record/update AEs
- Modified physical examination including vital signs, if indicated.

If an in person visit is not possible, applicable information may be retrieved from their routine care medical chart as appropriate.

7.5.1 Interim Visits

Interim visits may be performed at any time during the study. Study procedures may be repeated at interim visits as clinically indicated. All interim contacts and visits will be documented in participants' study records and on applicable eCRFs.

7.6 Adherence Counseling and Assessment

Adherence counseling regarding the study protocol will be performed at each applicable study visit. Additionally, investigators may use text messaging, follow-up phone calls, email, and/or meeting study participants at their regular clinic visits in order to improve adherence to study medication and procedures. At the follow-up visits (V3 and V4), all unused medication will be counted, recorded and returned to the study staff and handled according to the site SOP. Participants will receive written instructions on how and when to take the medication and directions on how to store the medication as well as what to do if the medication is lost or stolen. Research staff will recommend that participants take the study medication consistently at a time convenient for their schedule. If a participant forgets to take a dose, she should take the missed dose as soon as she remembers but should not take more than one tablet of SOF/VEL per day (24-hour period).

7.7 Clinical Evaluations and Procedures

Maternal

Physical exams will include the following assessments:

- General appearance
- Height^ and Weight
- Vital signs: temperature, pulse, blood pressure, respirations
- Fundal height (if gestational age > 20 weeks)
- Abdomen*
- Head, Eye, Ear, Nose and Throat (HEENT)*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*

- Extremities*
- Skin*
- Neurological*
- Symptom-directed examination at all follow-up visits
- Fetal Heart Tones**

^obtained at Screening Visit only
*obtained at Screening Visit and prn
**Performed for mother at screening, enrollment, V3, V4, V5, and prn)

Infant

- Age-appropriate physical exam
- Weight, length, head circumference
- Ages and Stages Questionnaire® (iV1, iV2, iV3)

7.8 Laboratory Evaluations

Site clinical laboratory

- Maternal Blood
  - Hepatitis B virus testing (HBsAg, anti-HBc, anti-HBs) if not done as part of routine prenatal testing
  - HCV RNA viral load
  - Hepatitis C genotype, as applicable
  - CBC with differential and platelets
  - Creatinine/eGFR
  - Hepatic function panel: AST, ALT, albumin, total and direct bilirubin, alkaline phosphatase
  - PT/INR
  - Lipase
  - Creatine kinase
  - HIV viral load and CD4 count, as part of screening/eligibility as needed

- Infant Blood
  - HCV RNA viral load

Dr. Feld's Lab

- Maternal blood and infant blood
  - Next Generation Sequencing (prn) OR if maternal sample not used for sequencing, it may be used for future use at the study site of collection if participant agrees

7.9 Specimen Collection and Processing

The study site will adhere to the standards of good clinical laboratory practice and local standards for proper collection, processing, labeling, transport, and storage of specimens.

7.10 Biohazard Containment

As the transmission of hepatitis C and other blood-borne pathogens can occur through contact with contaminated needles, blood and other bodily fluids, appropriate blood and secretion precautions will be employed by all personnel during blood draws and processing and handling of all specimens for this study as recommended by the CDC and National Institutes of Health (NIH). Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site study investigators are responsible for the evaluation, documentation and reporting of all adverse events, for continuous close safety monitoring of all study participants and for alerting the Protocol Safety Review Team (PSRT) if any unexpected concerns arise. The PSRT will be comprised of, at the minimum, the following: protocol chair, the site PIs, an independent safety physician, a pediatric co-Investigator, data management statistician, and a Gilead Sciences representative. The data management team at the data coordinating center will prepare routine AE and clinical data reports for review by the PSRT monthly and will meet in person or via conference call approximately every three months or as needed throughout the study period to review safety data, discuss product management, and to address any potential safety concerns.

Evaluation of safety concerns will be conducted at the site as clinically indicated. All adverse events will be documented and followed to their resolution or until clinically stable. Site investigators are responsible for notifying the Protocol Chair and PSRT if unexpected and/or serious adverse events occur. The Protocol Chair will notify Gilead Sciences, as applicable. Each site is responsible for reporting adverse events to their own local IRB/REB as required by their local guidelines.

8.2 Clinical Data and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the Protocol Chair and PSRT if any unexpected safety concerns arise.

Participant safety is also monitored at the data coordinating center level through a series of routine reviews conducted by the data management team as well as the PSRT. The data management team at the coordinating center will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. The PSRT will review clinical data reports on a monthly basis, beginning at approximately one month from the first

enrollment. In addition to the monthly safety data reviews, the PSRT will convene on an approximate quarterly basis to review the AE report and on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, external experts representing expertise in the fields of obstetrics, neonatology, infectious diseases, hepatology, statistics and medical ethics may be invited to join the safety review. A recommendation to pause or stop the trial may be made at this time or at any such time that the safety review team agrees that an unacceptable type and/or frequency of AEs has been observed.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational medication and which does not necessarily have a causal relationship with the investigational medication. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational medication, whether or not considered related to the medication. The term “investigational medication” for this study refers to the study medication. This definition of an adverse event is applied to all study participants from the time of enrollment, which is the time the participants begin taking the study medication.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience throughout their participation in the study. They will be instructed to seek medical care with their local primary care physician/obstetrical team, as necessary. Participants may have an unscheduled visit with the site PI/study clinicians as necessary or desired in applicable circumstances. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be requested and required data elements will be abstracted and recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically as deemed appropriate by a site PI/designee until the occurrence resolves (returns to baseline) or stabilizes. Study site staff will document AEs reported by or observed in enrolled study participants by severity and presumed relationship to investigational medication, including gradable laboratory findings. AE severity and laboratory tests will be graded per the most recent version of the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Certain adverse events are expected as a consequence of pregnancy as well as labor and delivery. These events may be found in the Clinical Management SSP. In addition, the Clinical Management SSP will also provide guidance for adverse event grading for pregnancy-associated adverse events that occur during pregnancy, such as bleeding, pregnancy induced hypertension, chorioamnionitis. This SSP will also provide guidance adverse event reporting for infants that were exposed to opioids.

For any serious adverse events (SAEs) that are continuing at a participant's study exit visit, the site PI/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the site PI/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit, or any new ≥ Grade 3 AEs uncovered at the last visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case-by-case basis.

8.3.2 Serious Adverse Events

An SAE will be defined as an AE that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

8.3.3 Adverse Event Relationship to Study Medication

Relatedness is an assessment made by the site PI/designee of whether or not the event is related to the study agent.

- *Related:* There is a reasonable possibility that the AE may be related to the study medication
- *Not Related:* There is not a reasonable possibility that the AE is related to the study medication

8.4 Adverse Event Reporting Requirements

8.4.1 Reporting Requirements for this Study

All adverse events will be reported to Gilead Sciences on a monthly basis by the Data Management Team. All serious adverse events that are considered unexpected and related to the study medication will be reported to the respective site Institutional Review Board as applicable and per local reporting guidelines, and

the FDA at the time of annual renewal or before if it meets FDA reporting requirements and will follow Health Canada reporting requirements. As such, during the course of the clinical trial, the sponsor will inform the Minister of any serious unexpected adverse drug reaction that has occurred within or outside Canada by i) 15 days of becoming aware of the information if neither fatal nor life threatening, and ii) within 7 days of becoming aware of the information if fatal or life threatening.

The site PI will notify the Protocol Chair and PSRT within 7 days of becoming aware of the SAE. The Protocol Chair will be responsible for notifying Gilead Sciences within 15 days of becoming aware of the event.

8.4.2 Grading Severity of Events

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

8.5 Regulatory Requirements

Information on all applicable AEs will be included in reports to the FDA and Health Canada, and other applicable government and regulatory authorities. The site PI or designee will submit AE information in accordance with the requirements of the respective site IRB/REB.

8.6 Social Harms Reporting

Although every effort will be made to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms may result. Social harms that are judged by the study investigators to be serious or unexpected will be reported to the Protocol Chair and Gilead Sciences and to the respective site IRB/REB.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study medication are outlined in this section. In addition, detailed information regarding specific adverse events can be found in the Clinical Management SSP. In general, the site PI/designee will only discontinue study medication in consultation with the Protocol Chair and independent safety physician if they feel that the risk of study medication continuation outweighs the benefits of study medication continuation. All permanent discontinuations will be documented on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.3.1.

9.2 Dose Modification Instructions

No dose modifications will be permitted in this study.

9.3 General Criteria for Permanent Discontinuation of Study Medication

A participant will be permanently discontinued from medication use by the site PI/designee for any of the following reasons:

- Upon confirmation with a second result of a 5-fold or greater increase in ALT or AST at the V3 visit compared to baseline result (Screening visit) and must be greater that 3-fold higher than the upper limit of normal and cannot be attributed to another cause (such as cholestasis of pregnancy, preeclampsia, etc.).
- Any increase of ALT or AST above baseline (Screening visit) at the V3 visit that is accompanied by development of new ascites, jaundice (total bilirubin >3.0 mg/dL/51 µmol/L) or hepatic encephalopathy, that cannot be attributed to another cause.
- Upon confirmation with a second result of a 3-fold or greater increase in ALT or AST accompanied by direct bilirubin >2x the upper limit of normal that cannot be attributed by another cause.
- Participant is unable or unwilling to comply with required study procedures
- Participant might be put at undue risk to their safety and well-being by continuing medication use, according to the judgment of the study investigators.

The study investigators will consult with the PSRT prior to all study medication discontinuation. Both the independent safety physician and one of the hepatologist site principal investigators must review the case prior to stopping the medication.

9.4 Permanent Discontinuation in Response to Adverse Events

Grade 1 or 2
In general, a participant who develops a Grade 1 or 2 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 dated July 2017 regardless of relationship to study medication may continue study medication use.

Grade 3
For participants who develop a Grade 3 AE as defined by the DAIDS Table for Version 2.1 dated July 2017 that is judged by the study investigators to be unrelated to study medication, the study medication may continue. The study medication must

be permanently discontinued for participants who develop a Grade 3 AE judged by a site PI/designee to be related to the study medication.

Grade 4
If a participant develops a Grade 4 AE as defined by the current DAIDS Table for Grading Adult and Pediatric Adverse Events and the AE is determined to be related to study medication, then study medication must be permanently discontinued.

9.5 HIV-1 Infection

If HIV seroconversion occurs during the time of study medication use, the study medication may continue.

9.6 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The study investigators also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures (see section 9.3 for further details). Participants also may be withdrawn if Gilead Sciences, government or regulatory authorities, including the FDA, Health Canada, PSRT or site IRBs/REBs or the Protocol Chair terminate the study prior to its planned end date. Detailed reasons for the withdrawal of a participant will be documented in the research record. Every reasonable effort will be made to continue to follow the participant as scheduled for safety.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 4, single-arm, open label cohort study of treatment for chronic HCV infection during pregnancy in approximately 100 HCV-infected pregnant women receiving a 12-week (84 day) course of SOF/VEL and their infants. Maternal participants will be considered evaluable if they have a HCV viral load result at the Post-Treatment visit (V6) or have a HCV viral load drawn from clinical care that occurs during or any time after the V6 visit window. Pregnancy and neonatal outcomes will be compared to a historical cohort of pregnant women with active HCV from each of the participating study sites.

10.2 Study Endpoints

Pregnant women meeting all of the eligibility criteria in sections 5.2 and 5.3 will be enrolled into the study and followed prospectively through approximately 12 weeks after the last dose of study medication. Infants will be enrolled upon delivery and followed prospectively through approximately one year of age. Maternal and infant study endpoints are described in detail in Section 3.

10.3 Sample Size

The sample size of approximately 100 participants was chosen in order to determine if a clinically meaningful difference exists between the prospective treatment cohort and the historical or published comparison groups regarding preterm birth <37+0 weeks' gestation and maternal SVR12.

To estimate the sample size required for maternal SVR12, a baseline SVR12 of 97% was used. This estimate was based on a 30% prevalence of HCV genotype 3 among young persons and the published rate of SVR12 for all genotypes[33]. For maternal SVR, using an exact binomial test with a nominal 10% one-sided significance level will have 82% power to detect the difference between the Null hypothesis proportion, π_0 of 97% (published rate of SVR12 with SOF/VEL) and the Alternative proportion, π_1, of 92% when the sample size is 100.

For the primary neonatal outcome of preterm birth <37+0 weeks' gestation, using Fisher's exact test a sample size of 100 will identify a difference of 13 percentage points in preterm birth rates (80% power 2-sided alpha = .05). The published preterm birth rate of 23% among HCV+ pregnant women at the University of Pittsburgh was used to calculate this estimate[34].

10.4 Data Collection and Analysis

10.4.1 Study Data Collection

All study data will be entered into the REDCap electronic data capture system maintained by the University of Pittsburgh.

10.4.2 Analysis of Maternal Safety

Pregnancy and delivery outcomes will be compared to a historical control group of pregnant women with active HCV (defined as a detectable HCV RNA) that delivered at the same hospitals where the study participants are enrolled. This retrospective cohort data will be collected using a separate protocol. Differences in frequency of each outcome will be determined by Fisher's exact test. Further, an adjusted analysis based on the collected maternal factors will be conducted in order to determine if any of the findings were related to treatment with SOF/VEL or due to a confounder using regression methods. In addition, all adverse events will be reported descriptively, noting relationship to the study medication as well as any grade 3 or 4 adverse events.

10.4.3 Analysis of Neonatal Safety

Neonatal outcomes will be compared to a historical control group of infants who had perinatal HCV exposure. Differences in frequency of each outcome will be

determined by Fisher's exact test. Further, an adjusted analysis based on the collected maternal factors will be conducted in order to determine if any of the findings were related to treatment with SOF/VEL or due to a confounder using regression methods. In addition, all adverse events will be reported descriptively, noting relationship to the study medication as well as any adverse events grade 3 or 4.

10.4.4 Analysis of HCV Endpoints

The maternal SVR12 rate in the study will be compared to the historical SVR12 rate published in the literature of 97% for non-cirrhotic patients with an approximately 30% prevalence of genotype 3 infection[33] using a one-sided exact binomial test. The reported rate of perinatal transmission in HCV mono-infection is between 4-7% as noted in a large metanalysis, and is approximately double that for pregnant women with HIV co-infection[7]. We will compare the rates of perinatal transmission in our study to these historic rates using a one-sided binomial test of proportions and will stratify by HIV status if there is sufficient enrollment of HCV/HIV co-infected participants.

10.5.4 Data and Safety Monitoring Plan

No formal Data and Safety Monitoring Board oversight is planned for this single-arm study; however, the PSRT, as described in section 8.1, will provide oversight. Reviews of adverse events by the PSRT will take place every month. Additionally, Reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and review of the adverse events will take place approximately every 3 months in person or via a conference call, and as needed. At the time of these reviews, or at any other time, the PSRT may recommend that the study proceed as designed, proceed with design modifications, or be halted/discontinued.

10.5.5 Next Generation Sequencing

On an as needed basis for treatment failures or in the case of perinatal HCV exposures, sequencing of the baseline and post-treatment samples will be carried out using Next Generation Sequencing (NGS) with the Illumina MiSeq platform using a full genome sequencing assay (E1 to NS5B) that works across all 6 major HCV genotypes. Baseline and post-treatment samples will be aligned and compared in HVR1, NS5B and the 5'UTR. If results are equivocal with these 3 regions, additional regions will be compared to allow for determination of relapse versus reinfection. After applying quality control measures to the raw NGS data, the specific haplotypes and their frequencies will be determined using the Global Hepatitis Outbreak and Surveillance Technology (GHOST) platform. Genetic distances between sequences will be calculated and any sequences with a distance of less than the experimentally determined threshold of 0.037 will represent relapse (same virus) and anything at or above this threshold will represent reinfection with a different HCV strain. The

presence of resistance associated substitutions (RAS) in NS3, NS5A and NS5B and their frequency will also be evaluated on pre- and post-treatment samples.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Coordinating Center Responsibilities

Study questionnaires will be developed by data management. The Data Coordinating Center is responsible for maintaining and updating the study questionnaires/RedCap database as needed and for notifying all sites of any updates/changes.

The Data Coordinating Center Statistician or designee will routinely monitor all data entered in the RedCap system. Query reports will be generated and provided to each site on at least a monthly basis. Notification and resolution of queries will be performed according to the coordinating center data management plan. The Protocol Chair will be promptly notified by the Data Coordinating Center statistician of any concerning trends or missing data.

11.2 Source Documents and Access to Source Data/Documents

Each site will maintain source data/documents in accordance with current Good Clinical Practice Guidelines as described by the International Conference on Harmonization (https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials)/(https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-clinical-practices.html)

The study teams will maintain and securely store complete, accurate and current study records. Study records will be maintained on site for the entire period of study implementation.

In accordance with U.S. regulations regarding testing investigational medications, the study investigators will maintain all study documentation for at least two years following the date of marketing approval for the indication of HCV treatment in pregnancy. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the U.S. FDA is notified. For research involving children, records shall be retained at least until the pediatric subject reaches the age of 23. For Canadian sites the sponsor shall maintain all records related to the clinical trial for a period of 15 years.

11.3 Quality Control and Quality Assurance

The study sites will conduct quality control and quality assurance procedures in accordance with site SOPs.

12 CLINICAL SITE MONITORING

Up until the time that PPD, Inc. begins monitoring for the multi-site protocol, local monitoring will be performed according to the site's local monitoring plan. The local monitoring plan must be submitted to the Coordinating Center prior to site activation. The local monitoring may be performed by delegates from local/site IND offices or independent monitors. Local plans should include:

- Review local regulatory files, including required essential documents
- Review informed consents for accurate version and completeness
- Verify eligibility
- Perform source document verification to ensure the accuracy and completeness of study data entry, including local laboratory results
- Review and verify accurate and complete documentation and reporting of adverse events.
- Verify proper storage, dispensing, and accountability of investigational study medications.

PPD, Inc. will begin monitoring for all sites once all applicable plans are in place (i.e., contracts, monitoring plans, etc.). Monitoring will be conducted according to the monitoring plan agreed upon by PPD, Inc. and the Protocol Chair. Site monitoring by PPD, Inc. may be conducted in person and/or remotely. All sites must continue to abide by their local institutional policies and procedures and PPD, Inc. will monitor sites per the monitoring plan.

As each local site PI is responsible for submission of their independent IND/CTA to the FDA/Health Canada, all local site requirements for monitoring and FDA/Health Canada regulations in regards to IND/CTA holders are the responsibility of the site PI. Any monitoring and audit reports are to be emailed to the coordinating center regulatory contact upon receipt.

The study investigators also will allow inspection of all study-related documentation by authorized representatives of Gilead Sciences, FDA, Health Canada, IRBs/REBs, PPD, Inc., and applicable Canadian and U.S. regulatory authorities.

13 HUMAN SUBJECTS PROTECTIONS

Study investigators will make efforts to minimize risks to participants. Informed consent will be reviewed in detail with potential participants and all questions will be adequately answered prior to obtaining written informed consent. Informed consent will be obtained prior to performing any study related procedures. All eligibility criteria will be verified prior to initiation of investigational product. Recruitment will begin after the protocol has been submitted to the FDA (as applicable) or Health Canada and after receiving IRB/REB approval and completing requirements of the coordinating center for site activation. The study investigators will permit audits by the Gilead Sciences, the FDA, Health Canada, site IRBs/REBs, and other Canadian and U.S. regulatory authorities or any of their appointed agents.

13.1 Institutional Review Boards

The site study staff will ensure that the protocol, informed consent form, and study-related documents (such as participant education and recruitment materials) are reviewed and approved by the respective site IRB/REB prior to starting the study. Any amendments to the protocol or informed consent will be approved by the appropriate IRB/REB prior to implementation.

13.2 Study Coordination

This study is a multi-center study with Catherine Chappell holding the IND at the University of Pittsburgh and the other sites have received an IND exemption from the FDA, their local IRB/REB, or will obtain a Health Canada CTA. Each site will receive IRB/REB approval from their local IRB/REB. Each study site is responsible for understanding and complying with their local and state research guidelines, regulations and laws.

University of Pittsburgh/UPMC Magee-Womens Hospital will provide coordination for the study.

Close coordination between the study teams is necessary to track recruitment, enrollment, retention, AEs and unanticipated problems in a timely manner and to address other issues that may arise. The PSRT will address issues related to study eligibility, AE management/reporting and unanticipated problems as needed to ensure consistency. Rates of accrual, protocol adherence, retention, and AE incidence will be reported by data management and monitored closely by Data Coordinating Center as well as the PSRT.

13.3 Risk Benefit Statement

13.3.1 Risks

General/Maternal

As with any research study, there may be adverse events for the maternal participant or the fetus/infant that are currently unknown and certain of these unknown risks could be permanent, severe or life-threatening.

There are no published studies of SOF/VEL in pregnant women. However, there has been one study of a sofosbuvir-containing regimen (ledipasvir/sofosbuvir) in 9 pregnant women.[26] There were no adverse events greater that grade 2 that were related to ledipasvir/sofosbuvir for the pregnant women and no related adverse events for the infant. There have been animal studies done in rats and rabbits as detailed in section 2.4.2. No effects on fetal development have been observed in rats and rabbits at the highest doses tested. However, animal reproductive studies are not always predictive of human responses.

It is also not known if SOF/VEL is present in human breast milk and there are no clinical studies of SOF/VEL during breastfeeding. The safety of SOF/VEL administration during breastfeeding is unknown. Participants who are still on study medication at the time of delivery and plan to breast feed, will be counseled about the lack of clinical data versus the benefits of breastfeeding. Participants will be encouraged to breast feed if they desire given the health benefits of both the infant and the mother and will have the option to stop or continue taking SOF/VEL after counseling. Participants will be encouraged to talk to their pediatrician if desired.

There is a potential risk that the hepatitis C virus may become resistant to SOF/VEL because the dose may not be adequate for treating pregnant women with hepatitis C or if the participant does not complete the entire 12 weeks of study medication. If resistance occurs, this may limit the choices of effective therapy after pregnancy for the participant and/or possibly her infant.

Overall, SOF/VEL was well tolerated by patients with chronic HCV infection (N=1035) with only 2 participants (0.2%) permanently discontinued treatment due to adverse events. These are detailed in Section 2.4.1, including the risk of hepatitis B virus (HBV) reactivation reported in HCV/HBV coinfected patients.

Phlebotomy may lead to bleeding, discomfort, bruising, swelling and/or infection at the site and feelings of dizziness or faintness.

Participation in clinical research includes the risks of confidentiality loss. Participants will be asked to provide personal/protected health information (PHI). All attempts will be made to keep PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see PHI. All paper records will be kept in a locked file cabinet or maintained in a locked room at each study site and electronic files/databases will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to participant PHI. Any presentations and publications will not include any information that could identify individual participants. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the study sponsor, Gilead Sciences, the US Food and Drug Administration (FDA), and Health Canada.

<u>Fetus/infant</u>:
There are no published data on use of this medication during pregnancy so the effects on a fetus/unborn child are not known. The study medication may cross the placenta, exposing the fetus to the study medication. It is unknown whether a fetus/unborn infant whose mother took SOF/VEL during pregnancy will develop normally or have adverse effects.

Obtaining blood samples from the infant may cause them to cry, cause bleeding, bruising or a clot at the site, and may be distressful to watch the infant have blood drawn.

13.3.2 Benefits

This study is a safety study of use of SOF/VEL in pregnancy and as such the study medication may not treat HCV in pregnancy as it may not be the correct dose. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to evidence-based guidance for the treatment of chronic hepatitis C infection in pregnancy and the prevention of perinatal HCV transmission.

13.4 Informed Consent Process

Written informed consent will be obtained from each study participant prior to performing study procedures. Consent may be obtained electronically if approved by the local IRB/REB and utilizing an IRB/REB approved mechanism. In obtaining and documenting informed consent, the study investigators will comply with applicable local and U.S. regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Participants will be provided with a copy of the informed consent form.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of importance to this study:

- The risks and unknown efficacy of the study medications in this population
- The importance of daily adherence to the study medication
- The importance of adherence to the study visit and procedure schedule
- The potential risks of study participation (and what to do if such risks are experienced)
- The potential benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

13.5 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the fullest extent possible. All study-related information will be stored securely at the study site with access limited to the study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number (PTID) only to the extent possible to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored securely and may be stored separately. REDCap employs various methods to protect the data stored in the software application’s backend database against data breaches.

These methods are described in a document accessible on the REDCap website (URL: https://projectredcap.org/wpcontent/resources/REDCapTechnicalOverview.pdf). Each end user is assigned a unique username and password and access to the study databases is controlled by the study's data management personnel. Appropriate firewall and virus scanning software are installed and updated routinely. Forms, lists, logs, appointment books, and any other documents that link participants' ID numbers (PTID) to identifying information will be stored securely with access limited to study staff. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the U.S. federal government, including the FDA, and U.S. regulatory authorities
- Representatives from Health Canada or other Canadian regulatory authorities.
- Representatives of Gilead Sciences
- Representatives of the sites delegated to conduct local monitoring
- PPD, Inc.
- Study staff
- University of Pittsburgh IRB and site local IRB/REB

13.6 Special Populations

13.6.1 Pregnant Women

Pregnant women will be offered enrollment in this study in accordance with guidelines set forth in the US 45 CFR 46.

13.6.2 Children

Infant procedures will begin at the time of delivery if delivered at a site hospital or at iV1 visit if infant delivered outside of the site hospital in accordance with guidelines set forth in the US 45 CFR 46 and DAIDS policy (http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/enrollingchildrenrequirements.pdf).

13.7 Compensation

Participants will be compensated for their time and effort, and/or be reimbursed for travel to study visits and time away from work. Reimbursement amounts will be specified in the site's informed consent form. Compensation may include parking/bus passes, assistance with transportation, and additional incentives for making study appointments per site, as applicable.

13.8 Study Discontinuation

The study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to: investigators, funding agency, the IND/CTA sponsors and regulatory authorities. Study participants will be contacted, as applicable, and will be informed of any changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, regulatory authorities and/or FDA/Health Canada.

14 PUBLICATION POLICY

The study investigators will be responsible for presentation and publication of the results of this study. The manuscript draft will be sent to Gilead Sciences 30 days prior to submission for their review and approval by the Protocol Chair.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS (Mother)

	SCR (V1)	ENR (V2)	Visits 3 & 4 (V3, V4)	End of Treatment (V5)	Delivery**	Post treatment (V6)
ADMINISTRATIVE AND REGULATORY						
Informed consent	X					
Assess informed consent comprehension	X					
Assignment of PTID	X					
Locator information	X	X	X	X	X	X
Demographic information	X					
Visit Questionnaire	X	X	X	X	X	X
Eligibility assessment	X					
Eligibility confirmation		X				
Reimbursement	X	X	X	X	X	X
Record/ update AEs			X	X	X	X
Schedule next visit	X	X	X		X	
Protocol adherence counseling		X	X	X	X	X
Medication use/adherence counseling		X	X		*	
CLINICAL						
Medical history, review/obtain records	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Document pre-existing conditions	X	X				
Physical examination	X(full)	X(modified)	X (modified)	X(modified)	+ (modified)	X (modified)
Fetal Heart Tones	X	X	X	X		
Provide available test results	X	X	X	X	X	X
Collect Pregnancy Outcomes/MR review					X	
LABORATORY						
HCV RNA viral load	X	X	X	X	X	X
HCV Genotype	*					
HBV Testing	*					
CBC with diff and platelets	X		X (V3)			X
Creatinine	X		X (V3)			X
Hepatic Function Panel	X		X (V3)			X
Lipase	X		X (V3)			X
Creatine kinase	X		X (V3)			X
PT/INR	X		X (V3)			X
HIV Viral Load and CD4 count	#					
Blood Sample (future use/sequencing prn)		X	X (V3)	X		X
STUDY MEDICATION						
Provision of Study Medication		X	X		*	
Collect Remaining Study Medication				X		

*If indicated

+May be performed or obtained from medical record

**May be performed during hospital admission for participants who deliver at an accessible facility or applicable procedures conducted by phone and information may also be collected via medical record review

^ If still on study medication at the time of delivery

if indicated for HIV+ participants

APPENDIX II: SCHEDULE OF STUDY VISITS AND EVALUATIONS (Infant)

	Delivery***	iV1 (Month 1-3)	iV2 (Month 6)	iV3 (Month 12)
ADMINISTRATIVE AND REGULATORY				
Assignment of PTID	X			
Locator information	X	X	X	X
Demographic information		X		
Record Release for Infant	*	*	*	*
Reimbursement	X	X	X	X
Record/update AEs		X	X	X
Schedule next visit	X	X	X	
CLINICAL				
Medical history **	X	X	X	X
Obtain Medical Record	X	X	X	X
Concomitant medications**	X	X	X	X
Document pre-existing conditions**	X	X		
Physical examination **	X	X	X	X
Collect growth parameters **		X	X	X
Collect Baseline Information**	X			
Provide available test results		X	X	X
Developmental Exam/Assessment		X	X	X
LABORATORY				
HCV RNA viral load		X	X	X
HCV sequencing		*	*	*

*If indicated (HCV sequencing only required if HCV RNA is detectable)
**May be obtained from medical record as applicable
*** May be performed during hospital admission for infants born at study site hospitals or applicable procedures conducted by phone with mother for infants who deliver at outside locations. For all participants, a chart review of the delivery records will be done as part of the delivery visit.

Reference List

1. Center for Disease Control, Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. How Does CDC Identify Severe Maternal Morbidity?. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/smm/severe-morbidity-ICD.htm. Accessed on October 30, 2020. .
2. Morse A, Barritt ASt, Jhaveri R. Individual State Hepatitis C Data Supports Expanding Screening Beyond Baby Boomers to All Adults. Gastroenterology 2018;154:1850-1 e2.
3. Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. Hepatitis C Virus Infection Among Women Giving Birth - Tennessee and United States, 2009-2014. MMWR Morb Mortal Wkly Rep 2017;66:470-3.
4. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged </=30 years - Kentucky, Tennessee, Virginia, and West Virginia, 2006-2012. MMWR Morb Mortal Wkly Rep 2015;64:453-8.
5. Goldberg D, Ditah IC, Saeian K, et al. Changes in the Prevalence of Hepatitis C Virus Infection, Nonalcoholic Steatohepatitis, and Alcoholic Liver Disease Among Patients With Cirrhosis or Liver Failure on the Waitlist for Liver Transplantation. Gastroenterology 2017;152:1090-9 e1.
6. Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising Mortality Associated With Hepatitis C Virus in the United States, 2003-2013. Clin Infect Dis 2016;62:1287-8.
7. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis 2014;59:765-73.
8. Connell LE, Salihu HM, Salemi JL, August EM, Weldeselasse H, Mbah AK. Maternal hepatitis B and hepatitis C carrier status and perinatal outcomes. Liver Int 2011;31:1163-70.
9. Pergam SA, Wang CC, Gardella CM, Sandison TG, Phipps WT, Hawes SE. Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. Am J Obstet Gynecol 2008;199:38 e1-9.
10. Salemi JL, Whiteman VE, August EM, Chandler K, Mbah AK, Salihu HM. Maternal hepatitis B and hepatitis C infection and neonatal neurological outcomes. J Viral Hepat 2014;21:e144-53.
11. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis C and sustained response to interferon-alpha therapy. Ann Intern Med 1997;127:875-81.
12. Coppola N, De Pascalis S, Pisaturo M, et al. Sustained virological response to antiviral treatment in chronic hepatitis C patients may be predictable by HCV-RNA clearance in peripheral blood mononuclear cells. J Clin Virol 2013;58:748-50.
13. Garcia-Bengoechea M, Basaras M, Barrio J, et al. Late disappearance of hepatitis C virus RNA from peripheral blood mononuclear cells in patients with chronic hepatitis C in sustained response after alpha-interferon therapy. Am J Gastroenterol 1999;94:1902-5.
14. Swain MG, Lai MY, Shiffman ML, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology 2010;139:1593-601.
15. Manns MP, Pockros PJ, Norkrans G, et al. Long-term clearance of hepatitis C virus following interferon alpha-2b or peginterferon alpha-2b, alone or in combination with ribavirin. J Viral Hepat 2013;20:524-9.
16. Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-13.
17. Younossi ZM, Stepanova M, Henry L, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2014;12:1349-59 e13.
18. Zelenev A, Li J, Mazhnaya A, Basu S, Altice FL. Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study. Lancet Infect Dis 2018;18:215-24.
19. Recommendations for Testing, Managing and Treating Hepatitis C. Infectious Diseases Society of America and American Association for the Study of Liver Diseases. Accessed at: http://www.hcvguidelines.org/fullreport on August 10,2016.
20. Sprague J, Wisner KL, Bogen DL. Pharmacotherapy for depression and bipolar disorder during lactation: A framework to aid decision making. Semin Perinatol 2020:151224.

21. Ko SC, Fan L, Smith EA, Fenlon N, Koneru AK, Murphy TV. Estimated Annual Perinatal Hepatitis B Virus Infections in the United States, 2000-2009. J Pediatric Infect Dis Soc 2016;5:114-21.
22. Hughes BL, Page CM, Kuller JA. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol 2017;217:B2-B12.
23. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. Aids 2012;26:2039-52.
24. United States Preventative Task Force. Hepatitis C Virus Infection in Adolescents and Adults: Screening. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/hepatitis-c-screening#fullrecommendationstart Accessed: April 13, 2020.
25. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC Recommendations for Hepatitis C Screening Among Adults - United States, 2020. MMWR Recomm Rep 2020;69:1-17.
26. Krans EE, Zickmund SL, Rustgi VK, Park SY, Dunn SL, Schwarz EB. Screening and evaluation of hepatitis C virus infection in pregnant women on opioid maintenance therapy: A retrospective cohort study. Subst Abus 2016;37:88-95.
27. Laird HJ, Jonassaint NL, Chappell CA, Krans EE. Postpartum Treatment for Chronic Hepatitis C Virus Among Women in Medication-Assisted Treatment for Opioid Use Disorder: the Potential of an Integrated Medical Home Model. Poster presentation at the IDSOG Annual Meeting, August 2019.
28. Chappell CA, Scarsi KK, Kirby BJ, et al. Ledipasvir plus sofosbuvir in pregnant women with hepatitis C virus infection: a phase 1 pharmacokinetic study. Lancet Microbe 2020;1:e200-e8.
29. German P, Moorehead L, Pang P, Vimal M, Mathias A. Lack of a clinically important pharmacokinetic interaction between sofosbuvir or ledipasvir and hormonal oral contraceptives norgestimate/ethinyl estradiol in HCV-uninfected female subjects. J Clin Pharmacol 2014;54:1290-8.
30. Food and Drug Administration. Epclusa Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208341s000lbl.pdf. Accessed: January 15, 2019.
31. Feld JJ, Jacobson IM, Hezode C, et al. Sofosbuvir and Velpatasvir for HCV Genotype 1, 2, 4, 5, and 6 Infection. N Engl J Med 2015;373:2599-607.
32. Foster GR, Afdhal N, Roberts SK, et al. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. N Engl J Med 2015;373:2608-17.
33. Ahmed H, Abushouk AI, Attia A, et al. Safety and efficacy of sofosbuvir plus velpatasvir with or without ribavirin for chronic hepatitis C virus infection: A systematic review and meta-analysis. J Infect Public Health 2018;11:156-64.
34. Chappell CA, Hillier SL, Crowe D, Meyn LA, Bogen DL, Krans EE. Hepatitis C Virus Screening Among Children Exposed During Pregnancy. Pediatrics 2018;141.