Phase 1 Pharmacokinetic Trial of Sofosbuvir/Velpatasvir in Pregnant Women with Chronic Hepatitis C Virus Infection

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IND Sponsor: **Catherine Chappell, MD, MS**

Protocol Chair: **Catherine Chappell, MD, MS**

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Protocol Signature Page

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements 15 (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

_____ _____

Catherine Chappell, MD, MS — Date
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University of Pittsburgh
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Phase 1 Pharmacokinetic Trial of Sofosbuvir/Velpatasvir in Pregnant Women with Chronic Hepatitis C Virus Infection

LIST OF ABBREVIATIONS AND ACRONYMS

ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
DBS	Dried blood spot
DAIDS	Division of AIDS
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	Expedited adverse event
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
IDI	In-depth Interview
INR	International normalized ratio
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Interim Study Review
VEL	Velpatasvir
SOF/VEL	Sofosbuvir/Velpatasvir
mL	Milliliter
MWH	Magee-Womens Hospital
MWRI	Magee-Womens Research Institute
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PBMC	Peripheral Blood Mononuclear Cell
PK	Pharmacokinetic
PoR	Pharmacist of Record
PTID	Participant identification number
RNA	Ribonucleic acid
SAE	Serious adverse event
SOF	Sofosbuvir
SOP	Standard operating procedure(s)
SSP	Study-specific Procedures
UPMC	University of Pittsburgh Medical Center

Phase 1 Pharmacokinetic Trial of Sofosbuvir/Velpatasvir in Pregnant Women with Chronic Hepatitis C Virus Infection

PROTOCOL TEAM ROSTER

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Phase 1 Pharmacokinetic Trial of Velpatasvir/Sofosbuvir in Pregnant Women with Chronic Hepatitis C Virus Infection

PROTOCOL SUMMARY

Short Title:	Treatment of Chronic Hepatitis C during Pregnancy with Sofosbuvir/Velpatasvir
Clinical Phase:	Phase 1
IND Sponsor:	Catherine Chappell, MD, MS
Protocol Chair:	Catherine Chappell, MD, MS
Sample Size:	10 women and their infants (participants who do not complete treatment or report less than 85% adherence will be replaced)
Study Population:	Pregnant women diagnosed with chronic hepatitis C infection that are between the ages of 18 and 39 and are between 14 + 0 and 22 + 6 weeks of gestation at Screening and infants born to the enrolled participants
Study Site:	UPMC Magee-Womens Hospital, Pittsburgh, PA
Study Design:	Single-site, single-arm pharmacokinetic study
Study Duration:	Approximately 28 weeks per maternal participant and one year of infant follow up.
Study Medication:	Fixed-dose combination tablet of Sofosbuvir 400 mg and Velpatasvir 100 mg (SOF/VEL)
Study Regimen:	Participants will take SOF/VEL one tablet once daily starting between 23 + 0 and 25 + 6 weeks of gestation for 12 weeks total.
PK Sampling:	Systemic exposure of both VEL and SOF (SOF and inactive metabolite GS-331007) and intracellular SOF (GS-461203) will be assessed by intensive pharmacokinetic sampling at 3 time points: 1) 3 weeks $\pm$ 7 days after first dose (intensive); 2) 6 weeks $\pm$ 7 days after first dose (sparse); 2) 9 weeks $\pm$ 7 days after first dose (intensive).

Primary Objective:

- To compare the plasma pharmacokinetic (PK) parameters of SOF/VEL administered in pregnancy to available data from nonpregnant women.

Primary Endpoint:

- Systemic plasma exposures of both VEL and SOF (SOF and GS-331007) will be assessed:
  - 3 weeks ± 7 days after first dose (intensive);
  - 6 weeks ± 7 days after first dose (sparse);
  - 9 weeks ± 7 days after first dose (intensive).

Secondary Objectives:

- To compare the intracellular concentrations of SOF (GS-461203) to available data from nonpregnant women.

- To compare the protein binding (free-fraction) of VEL in pregnant women vs. available data in non-pregnant women.

- To determine the rate of sustained viral response (SVR12), defined by undetectable hepatitis C virus twelve weeks after completion of SOF/VEL treatment for 12 weeks during pregnancy.

- To evaluate the safety for the mother and for the neonate of hepatitis C treatment with SOF/VEL during pregnancy.

Secondary Endpoints:

- **Intracellular SOF (GS-461203) concentrations** will be assessed at:
  - 3 weeks ± 7 days after first dose;
  - 6 weeks ± 7 days after first dose;
  - 9 weeks ± 7 days after first dose.

- Free-fraction of VEL (protein binding) will be assessed at:
  - 3 weeks ± 7 days after first dose;
  - 9 weeks ± 7 days after first dose.

- **Sustained Viral Response (SVR12)**
    - HCV RNA viral load will be assessed at 12 weeks after completion of SOF/VEL treatment. An undetectable viral load will be considered a SVR12.

- **Maternal Safety**
    - Safety laboratory assessments of blood counts, creatinine, liver function, creatinine kinase and lipase will be measured at the PK1 and PK2 visits (approximately 3 weeks and 6 weeks after treatment initiation).
    - Pregnancy and delivery outcomes collected prospectively by participant interview and medical record review.

- **Neonate Safety**
    - Major malformations, defined as structural abnormalities with medical, surgical or cosmetic importance;
    - Weight, length, and head circumference at birth, 8 weeks, 6 months and 12 months;
    - HCV RNA viral load at birth (as available), 1 to 3 months, at 6 months and then again at 12 months only if negative viral loads are not documented at 1 to 3 and 6 months;
    - Neurodevelopmental assessments at 6 months and 12 months.

Exploratory Objectives:

- Describe the perspectives of pregnant women with chronic HCV infection screening for a trial of antenatal sofosbuvir/velpatasvir (SOF/VEL) therapy

Exploratory Endpoint:

- In depth interviews conducted before enrollment in screened participants and after completion of treatment in enrolled participants.

Table 1: Study Visit Schedule

	Maternal Study Visit	Target windows†
V1	Screening	14+0 to 22+6 weeks gestation (weeks + days)
V2*	Enrollment	23+0 to 25+6 weeks gestation (weeks + days)
V3	PK1: Intensive	3 weeks ± 7 days after first dose of SOF/VEL
V3a^	PK1a, 24hr sample	24 hours ± 2 hours
V4	PK2: Sparse	6 weeks ± 7 days after first dose of SOF/VEL
V5	PK3: Intensive	9 weeks ± 7 days after first dose of SOF/VEL
V5a^	PK3a, 24hr sample	24 hours ± 2 hours
V6	End of Treatment	Within 7 days of SOF/VEL completion
Del**	Delivery	
V7/iV1	Post treatment	12 weeks ± 4 days after completion of therapy
	Infant Study Visit	Infant Age
Del**	Delivery	Newborn
V7/iV1	Infant Visit 1	8 weeks ± 6 weeks†
iV2	Infant Visit 2	6 months ± 2 weeks†
iV3	Infant Visit 3	12 months ± 2 weeks†

†These are target windows. If the participant cannot be seen within these windows then it will not be considered a protocol deviation.
*Start SOF/VEL and continue for 12 weeks
**The Delivery Visit will occur during admission for participants delivering at Magee-Womens Hospital. 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). All participants, regardless of delivery location will undergo a chart review to obtain delivery outcomes/variables, as long as medical records can be obtained/reviewed.
^Study visit is scheduled 24 hours from dosing at previous visit (V3 and V5); the 24 hour study visit and associated procedures must occur prior to dosing that day (V3a and V5a)

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	**Phase 1 Pharmacokinetic Trial of Sofosbuvir/Velpatasvir in Pregnant Women with Chronic Hepatitis C Virus Infection**
Short Title:	Treatment of Chronic Hepatitis C during Pregnancy with Sofosbuvir/Velpatasvir

1.2 Funders, Sponsor and Monitor Identification

Funding Agencies:

NIH Building Interdisciplinary Research Careers in Women's Health in Pittsburgh

Gilead Sciences

National Institutes of Health Eunice Kennedy Shriver National Institute of Child Health & Human Development

Pennsylvania Department of Health

IND Sponsor: Catherine Chappell, MD MSc

Pharmaceutical Collaborator: Gilead Sciences

1.3 Laboratories

Clinical Laboratory:	UPMC Presbyterian Shadyside CPPUH UPMC Clinical Laboratory Building 3477 Euler Way Pittsburgh, PA 15213 USA
Pharmacokinetic Processing:	Magee-Womens Research Institute Laboratory of Dr. Sharon Hillier 204 Craft Ave, 5th floor Pittsburgh, PA 15213
Pharmacokinetic Assays:	University of Colorado Antiviral Pharmacology Laboratory 12850 E Montview Blvd, V20-C238 Aurora, CO 80045
HCV Resistance Testing:	Quest Diagnostics Incorporated 1901 Sulphur Spring Rd. Baltimore MD 21227

2 INTRODUCTION

2.1 Chronic Hepatitis C Infection in Pregnancy

A rising prevalence of 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[1] and has resulted in a dramatic rise in prevalence of HCV among pregnant women[2]. From 2006 to 2012 the rate of HCV among young people increased by 364% in states hardest hit by the opioid epidemic such as Kentucky, Tennessee, Pennsylvania and West Virginia[3]. Chronic HCV leads to liver disease and cirrhosis[4] and is the leading cause of mortality from a nationally notifiable infection (NNI) in the US, surpassing all 60 other NNIs combined[5]. Infants born to women with HCV have a 4-7% risk of perinatal HCV infection[6], and are at increased risk for congenital anomalies, low birth weight, and neonatal intensive unit (NICU) care[2,7,8]. HCV-exposed infants also have a greater risk of adverse neurologic outcomes, including cephalohematoma, fetal distress, feeding difficulties, intraventricular hemorrhage, and neonatal seizure[9] although these finds could be confounded by comorbid 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[10-12]. Sustained virologic response (SVR12) is defined as the absence of detectable HCV RNA in the serum at least 12 weeks after ending therapy. SVR12 has been shown to be a durable predictor of HCV cure when HCV RNA is collected for five years or more[13,14]. Patients cured of HCV experience significant health benefits including decreased liver inflammation, slowed and reversed progression of liver fibrosis and cirrhosis[15]. Additionally, SVR is associated with a 70% reduction in the risk of hepatocellular carcinoma and a 90% reduction in the risk of liver-related mortality and liver transplantation[16]. Furthermore, treatment of persons who use injection drugs can prevent community transmission of HCV, so called “treatment as prevention[17].” For these reasons, the Infectious Disease Society of America (IDSA) treatment guidelines recommend that *all HCV-infected persons* be treated[18]. Despite these recommendations, 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 to eliminate 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[19]. 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 HCV transmission[20]. Although avoidance of certain obstetric procedures, such as amniotomy and invasive fetal monitoring, may decrease perinatal HCV transmission, evidence is lacking[21,22]. Thus, effective 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. 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]. 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[24]. 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[25]. *Thus, pregnancy may be the ideal period for enhanced HCV treatment adherence and engagement.*

Addressing the knowledge gap: pharmacokinetic and safety studies of new antivirals in pregnancy. Significant physiologic changes occur during pregnancy that effect drug absorption, distribution, metabolism and excretion, resulting in PK changes which may have clinical consequences[26]. For example, increased renal clearance of drugs could result in suboptimal concentrations with standard dosing for renally cleared drugs, leading to antiviral resistance or decreased efficacy[27]. To illustrate this, some antiretroviral medications, such as atazanavir and lopinavir, require dose changes during pregnancy to achieve therapeutic drug concentrations in the late second or third trimesters[27]. Plasma protein concentrations including alpha-1 acid glycoprotein and albumin decrease in pregnancy, potentially influencing free drug concentrations; therefore, to comprehensively evaluate the impact of these physiologic changes in pregnancy for highly protein bound drugs, assessment of both total and free drug concentrations is critical.

Preliminary data: Our Phase 1 trial of ledipasvir/sofosbuvir (LDV/SOF) treatment in pregnancy has promising preliminary results. Between June 2017 and October 2018, 9 pregnant women between 23-24 weeks' gestation with chronic genotype 1 HCV 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, 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[28]. Of 29 women screened, 20 were excluded due to genotype 2 or 3 infection (n=10), ongoing illicit drug use (n=4), declining participation (n=3), intention to deliver off-site (n=2), and an APRI score of >1 (n=1). All 9 women enrolled were white, with a median age of 31 years. Our published data documented that 93% of pregnant women having HCV at our institution are white[29]. Eight women were HCV infected due to intravenous drug use (4 receiving opioid pharmacotherapy) 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[30]. There were no significant differences found between the PK parameters at each gestational age timepoint.

Although there are significant physiologic differences between pregnant and non-pregnant women, there are minimal differences between the second and third trimesters of pregnancy[31]. For example, the glomerular filtration rate is increased 37% in the second trimester and 40% in the third trimester[32]. Therefore, PK parameters were averaged across the three visits and compared between participants and non-pregnant women from regulatory trials of LDV/SOF. The geometric mean ratios and corresponding 90% confidence intervals are shown in Table 1. *Similar LDV and SOF, but lower GS-331007 exposures were observed between pregnant and non-pregnant women. All nine participants (100%) were cured. There were no adverse events related to LDV/SOF greater than grade 2. One-year follow-up of infants is on-going, and all remain HCV negative.*

Table 1: Sofosbuvir, GS-331007, and Ledipasvir Exposure in HCV-Infected Pregnant women Compared to Non-Pregnant Women

PK Parameter Mean (%CV)		HCV-infected Pregnant Women (N=8)**	HCV-infected Non-Pregnant Women (N=43)***	%GMR (90%CI)
SOF	AUC_{tau} (hr*ng/mL)	1840 (15.2)	2210 (49.9)	92.0 (78.8, 107)
	C_{max} (ng/mL)	1290 (29.3)	1640 (47.8)	89.0 (68.6, 115)
GS-331007	AUC_{tau} (hr*ng/mL)	8930 (12.1)	14800 (29.6)	62.3 (56.4, 68.7)
	C_{max} (ng/mL)	706 (15.0)	1130 (25.9)	63.7 (57.3, 70.8)
LDV	AUC_{tau} (hr*ng/mL)	10500 (34.4)	12100 (46.0)	90.3 (69.6, 117)
	C_{max} (ng/mL)	580 (36.2)	644 (41.9)	91.8 (71.2, 118)
	C_{tau} (ng/mL)	343 (37.6)	433 (54.9)	84.9 (64.0, 113)

*All data are presented to 3 significant digits. Abbreviations: AUCtau, area under the concentration-time curve of the dosing interval; Cmax, maximum measured concentration, Ctau, concentration at the end of the dosing interval; CI, confidence interval; CV, coefficient of variation; GMR, geometric mean ratio.
**Average of individual participant PK parameters from all 3 PK visits were used. 1 participant was excluded from the analysis for suspected dosing errors prior to PK visits.
*** Non-pregnant women from LDV/SOF Phase 2/3 studies with intensive PK assessments.

In this first study of HCV treatment during pregnancy, LDV/SOF was safe and effective with similar LDV and SOF PK exposure in pregnancy. Lower inactive metabolite (GS-331007) exposure is likely due to increased glomerular filtration rate during pregnancy. The results from the completed study support the safety of LDV/SOF which provides additional safety data supporting the use of SOF/VEL in the proposed study. Further, this pilot study demonstrated that it is feasible to enroll and treat HCV infected pregnant women, but a pan genotypic regimen is needed. Because the PK did not differ by gestation, the proposed study will limit intensive PK sampling to a single gestational age as to not overly burden the participants, but sparse sampling will occur at other time points during treatment. Although no differences in SOF levels were detected when comparing pregnant women to historical nonpregnant controls, the inactive metabolite of SOF (GS-331007) was reduced over 30% suggesting that additional data are needed to confirm that no change in the active metabolite of SOF occurs. Compared with LDV, VEL is more highly reliant on the cytochrome P450 enzyme 3A (CYP3A). CYP3A is upregulated in pregnancy, so there is a potential for a greater effect of pregnancy on VEL.

VEL bioavailability is estimated to be 30-50% based on animal studies and is not influenced by food intake. Notably, VEL requires an acidic environment for absorption. VEL is >99.5% protein bound, is hepatically metabolized by cytochrome P450 enzymes (CYP3A4, CYP2B6, and CYP2C8). VEL is primarily eliminated via biliary excretion, resulting in a plasma half-life of 15 hours[33,34]. The bioavailability of SOF is >80% and a high fat meal increases SOF exposure by 67-91%. SOF is 61-65% plasma protein bound, 14% is hepatically metabolized by phosphorylation, and 80% is renally excreted. As a prodrug, SOF half-life is 0.4 hours, while GS-331007 is 27 hours. SOF is administered as a phosphoramidate prodrug of the uridine nucleotide analogue GS-331007 monophosphate[35]. SOF is hydrolyzed by cathepsin A and/or carboxyesterase 1 and then phosphorylated by cellular kinases to the triphosphate moiety (GS-461203)[35,36]. GS-461203 is the active form of SOF. GS-461203 then is dephosphorylated to GS-331007, which is the inactive SOF metabolite that is most readily measured in the plasma.

The physiologic changes of pregnancy and the possible PK effects on SOF and VEL are shown in Table 1.

Table 1. Possible Impact of Pregnancy on VEL and SOF PK

	Physiologic Alteration in Pregnancy	VEL	SOF	Comment
Absorption	Increased gastric pH	↓	--	Acid reducing agents decrease VEL levels
	Nausea and vomiting	↓	↓	Decreased absorption of both VEL and SOF
	Slowed gastrointestinal motility	--	--	Decreased Cmax and increased Tmax
Distribution	Volume expansion	--	--	VEL and SOF are only slightly soluble in water
	Reduced protein binding	↑	--	Increased free fraction of VEL (highly bound)
Metabolism	Hormone-mediated enzyme alterations	↓	?	Upregulation of CYP3A, no data on SOF enzymes
Excretion	Cholestasis due to estrogen	↑	--	Reduced biliary excretion of VEL
	Increased renal blood flow	--	↓	Increased excretion of SOF

Given that the magnitude of each physiologic change is hard to predict, the overall systemic VEL and SOF exposure cannot be assumed. Further, the plasma concentrations of SOF and GS-331007 may not reflect the intracellular concentrations of the active SOF metabolite (GS-461230). To address this knowledge gap, we will conduct a thorough PK evaluation of VEL and SOF, including protein binding and the measurement of the intracellular GS-461230 concentrations to offer insights into the physiologic processes altering the PK of these drugs in pregnancy and to determine whether dose adjustment is needed.

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[34].

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 100 mg Velpatasvir and 400 mg sofosbuvir. 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

Velpatasvir inhibits the HCV NS5A protein and sofosbuvir inhibits HCV NS5B RNA-dependent RNA polymerase, which are essential for viral replication. 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 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, and 0.130 respectively. Sofosbuvir similarly 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. SOF/VEL has potent activity against HCV genotype 1, 2, 3, 4, 5, and 6[34].

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 hepatitis C virus infection, 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 EPCLUSA compared with 12 weeks of placebo in participants with genotype 1, 2, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis[37]. ASTRAL-2 was a randomized, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 12 weeks of treatment with SOF with ribavirin in subjects with genotype 2 HCV infection[38]. ASTRAL-3 was a randomized, open-label trial that evaluated 12 weeks of treatment with EPCLUSA compared with 24 weeks of treatment with SOF with ribavirin in subjects with genotype 3 HCV infection[38]. Approximately 40% (over 400) of the participants in these trials were women. There were no on-treatment virologic failures reported, however 13 (1%) participants experience virologic failure after treatment or relapse, most commonly among participants with genotype 3 infection. Another 12 (5%) participants failed to achieve SVR due to non-adherence, due to 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	N Total	N SVR12	Rate of SVR12	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 within the setting of Phase 3 clinical trials. Overall, SOF/VEL was well tolerated by patients with chronic HCV infection (N=1035) with only 2 participants permanently discontining treatment due to adverse events was 0.2%. The most common adverse reactions (adverse events assessed as causally related by the investigator and at least 10%) were headache and fatigue. Adverse reactions, all grades, observed in greater than or equal to 5% of participants receiving 12 weeks of treatment with SOF/VEL in ASTRAL-1 include headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving 12 weeks of treatment with 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 participants treated with placebo compared to participants treated with SOF/VEL (asthenia: 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 the ASTRAL-1 study, rash occurred in 2% of participants treated with SOF/VEL and in 1% of participants taking placebo. No serious adverse reactions of rash occurred and all rashes were mild or moderate in severity. In the ASTRAL-1 study, depressed mood occurred in 1% of participants treated with SOF/VEL and was not reported by any placebo participants. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity[34].

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. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). We will exclude participants that are anti-HBc positive for this reason. Additionally, postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with a sofosbuvir-containing regimen. Additionally a fatal cardiac arrest occurred in a patient taking amiodarone that was co-administered with sofosbuvir. For this reason, we will exclude participants who are taking amiodarone[34].

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 for 12 weeks, respectively; and in 6% and 3% of participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively[34].

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 for 12 weeks, 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 those in humans at 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[34].

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 experience with SOF/VEL in pregnant women, although based on the animal model data submitted to the FDA 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. Also, there is reassuring data from our prior study of treatment with LDV/SOF. Unfortunately, LDV/SOF is not approved for treatment of HCV genotypes 2 and 3 and therefore a pan-genotypic regimen in pregnancy is needed. Before larger scale treatment studies can be undertaken, it will be necessary to assess whether the pharmacokinetics of the drugs are similar in pregnant and nonpregnant women, and whether treatment response is similar to that observed in nonpregnant women, given the higher viral loads observed during pregnancy. This study is designed to address those knowledge gaps. We propose a single-arm, single-center, open label Phase 1 study of a 12-week course of SOF/VEL in 10 HCV-infected pregnant women. Treatment will be initiated during the second trimester, reducing the risk of SOF/VEL exposure during organogenesis and ensuring treatment completion by delivery, minimizing the risk of perinatal transmission. Additionally, this will allow adequate time for treatment course completion by delivery.

The study will be completed in 10 or 11 visits (7 maternal visits, delivery visit and 3 infant visits) which should easily align with prenatal and postpartum visits (Table 1). We plan to screen patients between 14+0 and 22+6 weeks of gestation confirmed by ultrasound by the time of their Enrollment visit who are known to have chronic HCV infection. A HCV RNA level to confirm the patient is actively infected with HCV as well as an HCV genotype (when not already available within 3 months of screening visit) will be obtained. A full laboratory evaluation of liver function including CBC, PT/INR, hepatic panel, creatinine, creatinine kinase and lipase will be obtained, to evaluate for renal failure and decompensated cirrhosis. A Hepatitis B Virus (HBV) panel will be performed to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. 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 23+0 and 25+6 weeks' gestation and initiated on a 12 week course of SOF/VEL.

3 OBJECTIVES

3.1 Primary Objective

1. To compare the plasma pharmacokinetic (PK) parameters of SOF/VEL administered during pregnancy to those of nonpregnant women.

3.2 Secondary Objectives

1. To compare the intracellular concentrations of SOF (GS-461203) during pregnancy to available data from nonpregnant women.

2. To compare the protein binding (free fraction) of VEL in pregnant women to available data from nonpregnant women.

3. To determine the rate of sustained viral response (SVR12), defined by undetectable hepatitis C virus twelve weeks after completion of SOF/VEL treatment for 12 weeks during pregnancy.

4. To evaluate the safety for the mother and for the neonate of hepatitis C treatment with SOF/VEL during pregnancy.

3.3 Exploratory Objective

1. To describe the perspectives of pregnant women with chronic HCV infection screening for a trial of antenatal sofosbuvir/velpatasvir (SOF/VEL) therapy

4 STUDY DESIGN

4.1 Identification of Study Design

This is a single-site, open label, single-arm Phase 1 trial.

4.2 Summary of Major Endpoints

Primary Endpoint:

- **Systemic PK**
  - Systemic exposure of both VEL and SOF will be assessed at three time points:
    1) 3 weeks after treatment initiation (intensive sampling);
    2) 6 weeks after treatment initiation (sparse sampling);
    3) 9 weeks after treatment initiation (intensive sampling).

Secondary Endpoints:

- **Secondary PK endpoints:**
  - Intracellular concentrations of GS-461203 from dried blood spots and peripheral blood mononuclear cells (PBMCs) will be assessed at:
    - 3 weeks $\pm$ 7 days after first dose;
    - 6 weeks $\pm$ 7 days after first dose;
    - 9 weeks $\pm$ 7 days after first dose.

  - Free-fraction of VEL (protein-binding) will be assessed at:
    - 3 weeks $\pm$ 7 days after first dose;
    - 9 weeks $\pm$ 7 days after first dose.

- **Sustained Viral Response (SVR12)**

- HCV RNA viral load will be assessed at 12 weeks after SOF/VEL treatment completion. An undetectable viral load will be considered a SVR12.

- **Maternal Safety**
  - Safety laboratory assessments of blood counts, creatinine, liver function, creatinine kinase and lipase will be measured at the PK1 and PK2 visit (3 and 6 weeks after initiation of SOF/VEL).
  - Pregnancy and delivery outcomes collected prospectively by participant interview and medical record review.

- **Neonate Safety**
  - Major malformations, defined as structural abnormalities with medical, surgical or cosmetic importance
  - Weight, length, and head circumference at birth, 8 weeks, six months and 12 months
  - HCV RNA will be assessed at birth (as available), 1-3 months and 6 months, and then again at 12 months only if detectable viral loads are documented in either of the two previous viral load assessments
  - Neonatal development assessed at 6 months and 12 months

Exploratory Endpoint:

- In depth interviews conducted before enrollment in screened participants and after completion of treatment in enrolled participants

4.3 Description of Study Population

The study population will include 10 pregnant women between the ages of 18-39 years old (inclusive) at Screening who are chronically infected with Hepatitis C virus, genotype 1, 2, 3, 4, 5 or 6 (or any combination of genotypes), as described in Sections 5.2 and 5.3 and infants born to the enrolled participants

4.4 Time to Complete Accrual

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

4.5 Expected Duration of Participation

The expected duration for maternal participants is approximately 24 weeks, not including the screening window. Infants will be followed for at least a full year after birth; therefore mother-child pairs will be enrolled for approximately one year and 4

months. Maternal study data will be collected from the participant and/or her medical records through the Post Treatment Visit (V7). Maternal participants who have AEs at the Post Treatment Visit (V7) that are clinically significant or related to study product/participation and have not resolved or stabilized will be followed beyond V7 until a clinically acceptable resolution of the AE(s) is confirmed and documented. 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/stabilization of the AE(s) is confirmed and documented.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants.

5.1.1 Recruitment

There are over 10,000 deliveries at Magee-Womens Hospital (MWH) per year and it is estimated that approximately 1% of women who deliver are actively infected with HCV. HCV-infected pregnant women will be recruited from MWH and antenatal clinics, opiate substitution therapy clinics and recovery programs in Pittsburgh and surrounding areas.

Recruitment will be primarily targeted from the MWH Pregnancy Recovery Center, which was established in 2014 to provide concurrent treatment for opiate dependence (buprenorphine) with prenatal care, which has an estimated retention rate of 90% for weekly opiate substitution and prenatal visits. There are approximately 120 opiate addicted pregnant women who received prenatal care at the Pregnancy Recovery Center per year. The prevalence of HCV infection in this Center is approximately 60%. Recruitment will also be targeted at the Magee-Womens Hospital ambulatory clinic and associated clinics that deliver at Magee-Womens Hospital. In order to engage HCV-infected women in recovery, but not yet engaged in prenatal care, we may also recruit patients from local opiate substitution therapy clinics and recovery programs that treat pregnant women.

Recruitment may also include women who are not receiving care at Magee-Womens Hospital through referrals from health care providers. These women must be willing to travel to Pittsburgh to complete the study visits but may deliver at an outside hospital as information from delivery may be reviewed after obtaining a signed medical record release.

Recruitment materials will be approved by the University of Pittsburgh Institutional Review Board prior to use.

5.1.2 Retention

The importance of retention will be stressed to the participant at each visit as part of protocol adherence counseling. Once a participant is enrolled, the study staff will make every effort to retain the participants in follow-up to minimize possible bias associated with loss-to-follow-up. Any participant that discontinues the study before the PK3 visit is completed or reports missing more than 1 dose per week averaged over the duration of the study will be replaced by recruiting another participant into the study. We anticipate needing to replace no more than one participant.

5.2 Inclusion Criteria

Women must meet all of 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 39 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

4) Chronic HCV (for at least 6 months prior to screening)by participant report

5) Detectable HCV RNA viral load at Screening

6) Desired pregnancy at 23 + 0 to 25 + 6 weeks' gestation at Enrollment with gestational dating confirmed by ultrasound

7) Singleton gestation with no known fetal abnormalities

8) Documented negative Hepatitis B testing for current infection (negative HBsAg test) or previous infection (negative anti-HB Core) performed at the screening visit

9) Negative HIV testing at the screening visit

10) Per participant report at Screening and Enrollment, agrees not to participate in other research studies involving investigational drugs or medical devices for the duration of study participation

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 treatment for Hepatitis C virus with sofosbuvir or a NS5A inhibitor
    b. Use of any medications contraindicated with concurrent use of velpatasvir or sofosbuvir according to the most current EPCLUSA package insert[34]
    c. Plans to relocate away from the study site area in the next 1 year and 4 months and unable/unwilling to return for study visits
    d. Current sexual partner is known to be infected with HIV or Hepatitis B virus
    e. History of cirrhosis documented or reported by previous liver biopsy or liver imaging tests

2) Reports participating in any other research study involving investigational drugs or medical devices within 60 days or less prior to Enrollment

3) Clinically significant and habitual non-therapeutic drug abuse, not including marijuana, as determined by Protocol Chair

4) At Screening or Enrollment, as determined by the Protocol Chair, any significant uncontrolled active or chronic cardiovascular, renal, liver (such as evidence of decompensated cirrhosis by ascites, encephalopathy, or variceal hemorrhage), hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease (other than Hepatitis C)

5) Has a high risk of preterm birth defined as a history of spontaneous preterm birth at less than 34 weeks of gestation or a shortened cervical length of less than 20 millimeters

6) Has any of the following laboratory abnormalities at Screening:
    a. Aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 10 times the upper limited of normal
    b. Hemoglobin less than 9 g/dL
    c. Platelet count less than 90,000 per mm^3
    d. International normalized ratio (INR) > 1.5

e. Creatinine greater than 1.4

7) Has any other condition that, in the opinion of the IoR/designee, would preclude 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 of SOF/VEL one tablet by mouth, once daily.

6.2 Administration

Study medication will be dispensed at Enrollment, PK1, PK2, and PK3 visits in the quantities sufficient to have one dose per day until the next scheduled visit with 3 extra doses. Tablets will be packaged by the Investigational Pharmacist/Pharmacist of Record (PoR)/designee in the pharmacy at Magee-Womens Hospital. Participants will be encouraged to use an IRB approved, secure mechanism to capture a photo/video of study medication administration to assist with keeping track of when participants took their doses. This process will document the date and time of study medication administration and can be submitted electronically anytime throughout study participation or can be reviewed at a study visit. Participants will also be given a paper log to record the time of their dose and will be asked to return the log at the next study visit. The timing of each dose will be reviewed by the research team at each visit. Any discrepancies will be noted.

Each participant 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. Participants will be instructed to take the medication each day at the same time, preferably early in the morning. SOF/VEL can be taken with or without food. Additionally, 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 bring any unused medication to the next visit and to specifically remember to bring the morning dose to the PK1 and PK3 Visits rather than take it at home. 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.

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 UPMC Magee Womens Hospital Pharmacy's PoR. Study medication will be repackaged and labeled prior to dispensation according to protocol guidelines.

6.3.2 Storage and Dispensing

SOF/VEL should be stored at room temperature below 30°C within the main pharmacy at Magee-Womens Hospital[34]. The PoR/designee will maintain documentation of temperature in the area where the study medication is stored. Study medications will be dispensed from the pharmacy in a small bottle containing a quantity sufficient until the next study visit with a bottle of three additional doses in the case of a lost dose or missed study visit. Study medications will be dispensed from the pharmacy only upon receipt of a written prescription and/or a signed study drug order form from an authorized prescriber. The study medication will be dispensed to the study staff, then subsequently provided directly to the study participant in the research clinic.

6.3.3 Accountability

The PoR/designee will maintain complete accountability records of all study SOF/VEL received and dispensed. All available unused study medications will be returned to Gilead Sciences or destroyed as instructed by Gilead after the study is complete.

6.3.4 Retrieval of Study Medication

The 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). Unused medication will be accounted for by the clinician, documented in the participant's research record and then returned to the PoR and accounted for per pharmacy policy.

6.4 Concomitant Medications

Enrolled study participants may use non-prohibited concomitant medications during study participation. All concomitant medications reported throughout the course of the study will be recorded on case report forms designated for that purpose. All prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations will be recorded on forms for concomitant medications. Participants who are using medications that are contraindicated for concomitant use with velpatasvir and sofosbuvir as described in the package insert will be excluded from participation.[39] Each reported concomitant medication will be reviewed to ensure the participant is not using prohibited medications (i.e. St. John's

wort, carbamazepine) 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, specific dosing instructions will be reviewed regarding correct timing of acid suppressing medication use according to the EPCLUSA package insert.

7 STUDY PROCEDURES

An overview of the study visit 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.

In the unlikely event of interruptions in study procedures (i.e. from severe weather or pandemics like COVID-19), study staff will refer to a written HIP2 Mitigation Plan for direction in handling study visits and procedures. The Mitigation Plan outlines tiers or severities of interruptions and provides guidance for continuation of research activities, namely ensuring participants can complete 12 weeks of study medication. The Mitigation Plan will be submitted to the IRB so they are aware of the plan for unexpected disruptions in this study.

7.1 Pre-screening

Study staff will pre-screen records to identify potential participants by evaluating minimum criteria (i.e. age, gestation age, Hepatitis C status). Healthcare providers will be told about the study and will be asked to provide an IRB approved ad/written material to potential participants or will assess interest. If the participant agrees, research staff can provide additional information by reviewing an IRB approved screening script, which will include a brief overview of the study and minimum eligibility questions. Women who are interested and qualify based on the screening script may schedule a Screening Visit. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to participant identifiers. Procedures and documentation will comply with the University of Pittsburgh IRB requirements. IRB approved materials (i.e. ads, flyers videos, and social media posts) may also be used (i.e. hung throughout the hospital; displayed on electronic boards; emailed to providers or appropriate support or community groups).

7.2 Visit 1- Screening (V1)

Screening can take place anytime within the screening gestational age window (14+0 to 22+6 weeks with gestational age being determined by available clinical information at the screening visit with confirmation of gestational age by ultrasound prior to enrollment). The gestational age must be confirmed by an ultrasound prior to enrollment. If an ultrasound has not been performed yet, then an ultrasound is

performed as part of routine obstetric care at 20 weeks' gestation and prior to enrollment. The study team will assist the participant in scheduling an ultrasound as part routine obstetric care prior to enrollment if the participant does not have one already. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent will be obtained before any screening procedures are initiated. Participants will be encouraged to speak with their primary care provider to determine whether to initiate hepatitis C treatment during pregnancy before deciding whether to participate in the study. Participants who do not meet the eligibility criteria during the screening process will be discontinued once ineligibility is determined. 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 there is concern by the study investigators, the screening laboratories can be repeated prior to enrollment.

Table 3: Screening Visit (V1)

Visit 1- Screening Visit	
Component	**Procedures**
Administrative and Regulatory	• 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; outside records as necessary) • Collect locator information • Collect demographic information • Visit Questionnaire • In-depth Interview (IDI)** • Assess eligibility • Provide reimbursement for study visit • Schedule next visit
Clinical	• Collect medical history & review and print medical/prenatal records including documentation of chronic Hepatitis C • Review and obtain documentation of previous liver biopsy or liver imaging, if applicable • Collect concomitant medications • Pre/post-test HIV counseling, as applicable • Perform full physical examination • Assess fetal heart tones • Confirm gestational dating (by available clinical information but must be confirmed by ultrasound prior to enrollment)

Laboratory	• Collect blood
	  • Complete blood count (CBC) with differential and platelets
	  • Creatinine
	  • HIV-1 serology
	  • Hepatitis B Virus testing (HBsAg, anti-HBc, Anti-HBs)
	  • Coagulation (PT/INR)
	  • HCV RNA viral load
	  • HCV genotype*
	  • Hepatic function panel (AST, ALT, albumin, total and direct bilirubin, and alkaline phosphatase)
	  • Lipase
	  • Creatinine kinase

* HCV genotype testing will be performed as needed. If a result from routine care testing is available from within the past 3 months prior to the screening visit then additional genotype testing does not need to be performed.

**May be performed at the screening visit or any time prior to enrollment

7.3 Visit 2- Enrollment (V2)

The following procedures will occur at the Enrollment visit (V2). 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 reimbursement for study visit • Schedule next visit

Behavioral	• Provide counseling
	  • Protocol adherence
	  • Study medication use/adherence

Clinical	• Review/update medical history • Review/update concomitant medications • Document pre-existing conditions • Perform full physical examination • Assess fetal heart tones • Provide Screening test results and perform post-test HIV counseling, as applicable
Medications	• Participants will receive study medication (supply enough until next visit plus a bottle with 3 extra doses) • Participants will receive instructions for daily use and for PK visits • Participants will receive medication adherence log and/or be instructed on use of photo/video capture of daily dosing
Laboratory	• Collect blood - HCV RNA viral load

7.4 Follow-up Visits

7.4.1 Visit 3 to 5 (PK 1, PK2 and PK3)

The PK1, PK2, and PK3 visits will occur 3, 6 and 9 weeks (+/- 7 days), respectively, after initiating SOF/VEL. The PK visits will be scheduled as **early** as possible within visit window to allow for visits that require rescheduling.

Participants will be asked to return the day after V3 and V5 for a 24 hour $\pm$ 2 hour PK visit. These visits will be labeled as V3a and V5a. The participant will be counseled not to take their dose of study medication until after V3a and V5a procedures. In the event that the participant is unable to be seen in the window period (24 hours $\pm$ 2 hours), the visit and study procedures will still be completed as long as the participant has not taken their dose for the day. Assistance with transportation or overnight accommodations will be offered as necessary to attempt to increase compliance with these visits/window periods.

Table 5: Follow-up Visits (PK1, PK2, and PK3)

Follow-up Visits 3-5 (PK1, PK2, PK3)	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit questionnaire • Provide reimbursement for study visit • Record/update AEs • Schedule next visit as applicable

Behavioral	• Adherence assessment
	• Provide modified counseling
	  • Protocol adherence
	  • Instructing participants to contact study staff when in labor/being admitted to labor and delivery
	  • Study medication use/adherence

Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination • Assess fetal heart tones • Provide available test results (if applicable) • Administer timed dose of study medication (PK1 and PK3 only) • Provide study medication with sufficient supply until next visit with 3 additional doses • Participants will receive medication adherence log and/or be instructed on use of photo/video capture of daily dosing

Laboratory	• Collect blood (plasma, DBS and PBMCs)
	  • Intensive PK sampling (PK1, PK3)
	  • Protein binding assay (PK1, PK3)
	  • Sparse PK plasma sampling (PK2)
	PRIOR TO VISIT DOSING, if applicable:
	  • CBC with differential and platelets (PK1, PK2)
	  • Hepatic function panel (AST, ALT, albumin, total and direct bilirubin, alkaline phosphatase) (PK1, PK2)
	  • PT/INR (PK1, PK2)
	  • Creatinine (PK1, PK2)
	  • Lipase (PK1, PK2)
	  • Creatinine kinase (PK1, PK2)
	  • HCV RNA viral load
	  • HCV Resistance Testing*

*as indicated per protocol section 9.3

Table 5a: 24 hour PK visit (PK1a and PK3a)

Follow-up Visits 3a and 5a (PK1a and PK3a)	
Component	**Procedures**
Administrative and Regulatory	• Visit questionnaire • Provide reimbursement for study visit • Record/update AEs
Laboratory	• Collect blood • Sparse PK sampling

VEL and SOF PK Evaluation

For the PK1 and PK3 visits (intensive PK), participants will be instructed not to take their daily dose at home but rather to bring their dose of SOF/VEL to the visit for a timed administration. Alternately, a dose will be dispensed by the PoR/designee for

the PK visits. Participants will be instructed about dietary restrictions for these visits as outlined in section 7.6. Participants will have their first PK plasma drawn before the time of the dose of SOF/VEL. The dose at each PK visit will be timed and blood samples will be collected at each PK visit as follows (relative to the timed dose): pre-dose, 0.5, 1, 2, 3, 4, 5, 8, and 12. An intravenous catheter may be placed and used to obtained samples throughout the PK visits. A saline solution will be used at a slow drip to attempt to keep the vein patent. In the event that the catheter fails, participants may have another IV inserted or individual venipuncture(s) to attempt to collect all PK samples. If still in place, the catheter will be removed after the 12 hour time point. If a PK sample(s) cannot be obtained, then the participant will remain evaluable, if at least one sample is obtained at each PK visit. Participants will return the following day for the 24 hour PK time point, which will be obtained by a single venipuncture. The participant will be instructed to take their daily dose following the single blood sample collection. For further details, see section 7.6 Pharmacokinetics.

For the sparse PK visit (PK2), the time when the previous dose of SOF/VEL was taken will be recorded and a single PK sample will be collected. This draw can occur at any time during the PK2 visit window and at any time during the day.

7.4.2 End of Treatment Visit (V6)

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 collect and follow up on any adverse events. 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 • In-depth Interview (IDI)** • Provide reimbursement • Record/update AEs
Behavioral	• Protocol adherence counseling, including delivery visit instructions • Collect remaining study medication • Collect medication administration log
Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination • Provide available test results if available • Assess fetal heart tones (if applicable)
Laboratory	• HCV RNA viral load • HCV resistance testing*

*as clinically indicated
**May be performed at this visit or prior to post-treatment visit (V7)

7.4.3 Delivery Visit (in person visit or 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. The Delivery Visit will occur during admission for participants delivering at Magee-Womens Hospital and will include maternal and cord blood samples. The date of the Delivery Visit for participants who deliver at Magee 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. All participants, regardless of delivery location will undergo a medical record review, if medical records are available to obtain delivery outcomes/variables. A copy of the delivery records will be placed in the participant's research chart. In the event that the participant delivers prematurely at UPMC Magee-Womens Hospital and is still taking study medication, then procedures from previously scheduled visits (V2-V6) may be performed, excluding intensive PK sampling. Rather than intensive PK sampling, a single maternal blood sample will be taken as close to the time of delivery as possible and cord blood will be collected for SOF/VEL PK analysis.

Table 7: Delivery Visit

Delivery Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit Questionnaire • Provide reimbursement, as applicable • Record/update AEs • Schedule next visit
Behavioral	• Protocol adherence counseling • Study medication use/adherence (if still on study medication)
Clinical (Maternal)	• Review/update medical history • Review/update concomitant medications • Provide available test results if available • Perform modified physical examination (or obtain from medical record) • Dispense study medication, as applicable to complete 12 week course (if still on study medication)*
Clinical (Infant)	• Review medical history including pre-existing conditions • Review concomitant medications • Full physical examination (may be collected via chart review)
Medical Record Review for Delivery Outcomes^	• Type of pregnancy outcome • Gestational age at pregnancy outcome • 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, non-reassuring fetal status, chorioamnionitis) – Other complications not related to a delivery

Baseline Infant Information^**	• Sex • Weight • Length • Head circumference • Apgar scores
Laboratory***	• Maternal HCV RNA viral load • Cord blood collection for HCV RNA viral load • Cord blood collection for PK analysis (if still on study medication) • Maternal plasma sample for PK analysis (if still on study medication) • HCV Resistance Testing (if indicated)

*Unless participant intends to breastfeed, in which case study medication will be discontinued.
**All Baseline Infant Information may be extracted from the infant medical record as available.
***Laboratory tests performed as applicable for participants who deliver at Magee-Womens Hospital.
^This information may be obtained by chart review abstraction and/or through extraction by R3.

7.4.4 Post Treatment (V7) Visit

The following procedures will occur at the Post Treatment visit (V7), which should be scheduled 12 weeks ± 4 days from the last dose of study medication. The V7 visit can occur simultaneously with the 8 week Follow-up Visit for the infant (iV1). This is the last scheduled clinic visit for the maternal participant.

Table 8: Post Treatment (V7)

Visit 7 (V7) Post Treatment Visit	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Visit questionnaire • Provide reimbursement • Record/update AEs
Behavioral	• Protocol adherence counseling
Clinical	• Review/update medical history • Review/update concomitant medications • Perform modified physical examination • 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
	  • Lipase
	  • Creatinine kinase
	  • HCV RNA viral load
	  • HCV resistance testing *

*If HCV RNA is detectable, the participant would be asked to return to have HCV resistance testing done, and HCV resistance testing should be done if the participant is still on study medication at time of delivery and study medication was discontinued at the delivery visit because the participant was planning to breastfeed.

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 ± 2 weeks
iV3: 12 months ± 2 weeks

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 will be made as necessary.

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

Visit iV1, iV2, iV3 Infant Follow-Up Visits	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Review infant demographics (iV1) • Sign release(s) for medical records for infant • Provide reimbursement • Schedule next visit (iV1, iV2) • Record/update AE's • Document pre-existing conditions (iV1)
Clinical	• Review/update medical history*** • Review/update concomitant medications*** • Growth assessment including weight, length, and head circumference*** • Perform age appropriate physical examination • Developmental Exam^ (iV2 and iV3 only); discuss results with mother, routine healthcare provider if needed and provide referrals (i.e. early intervention) if necessary • Provide available test results as applicable (i.e. HCV RNA test)

Laboratory	• Collect infant blood
	  • HCV RNA (iV1, iV2, and as applicable at iV3)*
	  • HCV resistance testing (if HCV RNA is detectable)**

^To include an age appropriate developmental exam, Bayley Scales of Infant and Toddler Development, and a general developmental screening tool completed by parents, Ages and Stages Questionnaire (ASQ). These evaluations will be done/reviewed by a qualified individual.
*If HCV RNA is detectable at iV1 or iV2, the infant would also have an HCV RNA performed at iV3. If HCV RNA is non-detectable/negative at both iV1 and iV2, no additional samples are needed. If infant sample is unable to be collected at iV1 and/or iV2, a sample may be collected at iV3.
**If HCV RNA is detectable at iV1 or iV2, the infant would need to return to have HCV resistance testing.
***May be collected from the medical record as applicable

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

Participants will be permanently discontinued for significant laboratory abnormalities or adverse events as outlined in section 9.3 and 9.4 or if they choose to discontinue the study medication. If participants miss greater than one dose per week (averaged over the duration of the study) they may be discontinued at the discretion of the Protocol Chair/Principal Investigator. Participants who are permanently discontinued from the study will be instructed to return the study medication and study medication

log. All protocol-specified study procedures may 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 in which study medication use is permanently discontinued:

- Collection of blood for PK analysis (single time point)
- HCV resistance testing
- Viral load as needed (i.e. participant withdraws, investigator opinion)
- Medical history review
- Concomitant medication review
- Brief physical examination including vital signs, if indicated.

The participant will be asked to continue in the study and complete all remaining scheduled maternal and infant visits per protocol for safety.

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 deemed clinically indicated. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

7.6 Pharmacokinetics

All enrolled participants will undergo intensive serum PK specimen collection procedures at the PK1 and PK3 visits. These collections will occur at study visits as described in Table 9.

Table 9: SOF and VEL PK Sampling

Time since SOF/VEL*	Plasma Sample	Timed Meal	SOF/VEL PK sample (mL)	Protein Binding (mL)	PBMC/DBS sample (mL)	Total blood (mL)
predose	+		4	0	4	8
DOSING		+				
30 mins	+		4	0	0	4
1 hour	+		4	0	0	4
2 hours	+		4	6	0	10
3 hours	+		4	0	0	4
4 hours	+		4	0	0	4
5 hours	+		4	0	0	4
8 hours	+		4	0	0	4
12 hours	+		4	0	0	4
24 hours	+		4	0	0	4

*Time listed is the target time for PK sample. If a sample is collected prior to next scheduled PK sample it will not be considered a protocol deviation. Only missed samples will be considered protocol deviations.

Participants will be instructed to bring their daily dose of SOF/VEL to the visits requiring intensive PK sampling (PK1 and PK3 visits) for timed administration. If they do not bring their dose, then a dose of study medication can be dispensed from the pharmacy/PoR/designee. Intravenous catheters may be placed during intensive PK visits. A pre-dose sample will be collected. Study drug will be administered as close as possible to the participant's normal dose time if possible and within 5 minutes of completing and within 30 minutes of initiating a standardized moderate-fat-calorie breakfast (~600 calories and 25 to 30% fat) following an overnight fast (no food or liquids, except water, for at least 8 hours). Participants will be restricted from food intake until after collection of the 4 hour blood draw and restricted from water consumption 1 hour before and 2 hours after dosing, except for approximately 240 mL of water given with study drug and standardized meal. Whole blood will be collected into appropriate sized Vacutainer® Plus plastic sterile tube(s) with K_2EDTA (spray dried) additive. Immediately after collection, the collection tube will be inverted 8 to 10 times to allow mixing with the anticoagulant . Further processing instructions can be found in the Specimen Collection and Procedures Manual.

For the PK2 visit (sparse PK visit), a single 8mL blood sample (PK and PBMCs) will be drawn noting the time of the collection and the time at which the participant took their previous SOF/VEL dose.

7.7 Adherence Counseling and Assessment

Adherence counseling to the study protocol will be performed at each study visit. Additionally, investigators may use text messaging (daily or weekly), follow-up phone calls, email, and/or meeting study participants at their regular clinic visits in order to improve adherence to the study medication and procedures. All options will be included in the informed consent document and will be tailored to the participant's needs. At the follow-up visits (PK1, PK2, PK3 and End of Treatment Visit), all remaining medication will be counted, recorded and returned to the pharmacy. Study participants will be given a medication administration log and also may be instructed on the use of photo/video capture of study medication administration using an IRB approved and secure mechanism to assist in study medication adherence. Participants will take a photo/video of themselves when taking their study medication daily through an IRB approved mechanism and send the photo/video via text to the ID research designated study smart phone or the photos/videos may also be reviewed during study visits. The provided paper log will have instructions on how and when to take the medication. Research staff will recommend that participants take the study medication consistently at a time convenient for their schedule, preferably in the morning. 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. Directions on how to store the medication as well as what to do if the medication is lost or stolen will be given to the participant and included on the medication administration log as applicable. Participants will be asked to bring the medication

administration log to the next study visit for review. Medication administration logs will be collected at the next visit and a new log (as applicable) will be given with each bottle/refill of study medication. The completed logs will be compared to the photos/videos, as available. Adherence counseling will be performed at the following visits: enrollment, PK1, PK2, and PK3 (and at delivery if the participant has not completed the 12 weeks of study medication and is not breastfeeding).

7.8 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

- General appearance
- Weight
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Height^
- Abdomen*
- Head, Eye, Ear, Nose and Throat (HEENT) Examination*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*

^obtained at Screening Visit only
*may be omitted after the Enrollment Visit

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

7.9 Laboratory Evaluations

Local Laboratory (UPMC Clinical Laboratory)

- Blood
    - HIV serology
    - Hepatitis B Virus testing
        - HBsAg
        - Anti-HBc
        - Anti-HBs
    - PT/INR
    - Lipase
    - Creatine kinase
    - HCV RNA viral load: Maternal and Infant
    - Hepatitis C genotype (as required at screening)
    - CBC with differential and platelets
    - Creatinine
    - Hepatic function panel
        - AST
        - ALT
        - Albumin
        - Total and direct bilirubin
        - Alkaline phosphatase

Outside Laboratory

- Blood
    - Blood PK for SOF and VEL(University of Colorado)
    - Dried Blood Spots and Peripheral Blood Mononuclear Cells for intracellular concentrations of the active SOF metabolite (GS-461230) (University of Colorado)
    - Protein Binding Assay (University of Colorado)
    - HCV Resistance Testing (Quest Lab)

7.10 In Depth Interviews

At the screening visit and the end of treatment visit a trained interviewer from the Qual EASE team (CHRC Data Center, University of Pittsburgh) will conduct an in- depth interview about Hepatitis C infection, risks of perinatal transmission, concerns about treatment during pregnancy and drug research during pregnancy. The interviewer will use the HIP Script to conduct the interview. All interviews will be recorded and transcribed verbatim. The original recordings will be destroyed after transcription. The interview may be conducted at the visit or prior to the next visit via phone or a secure video conferencing system.

7.11 Specimen Collection and Processing

The study site will adhere to the standards of good clinical laboratory practice and standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens. Specimens for SOF/VEL PK analysis and protein binding

will be transported from the Clinical Research site to the Magee-Womens Research Institute Microbiology Laboratory for storage until they are shipped to the appropriate laboratory for processing and analysis. The samples will be shipped when arranged with the respective laboratories listed for PK analysis and protein binding.

7.12 Biohazard Containment

As the transmission of hepatitis C and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood medications, appropriate blood and secretion precautions will be employed by all personnel during blood draws and transport, shipping and handling of all specimens for this study as recommended by the CDC and National Institutes of Health (NIH). All biological specimens will be shipped using packaging mandated by Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be shipped according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Study investigators are responsible for continuous close safety monitoring of all study participants, and for notifying Gilead Sciences if unexpected and/or serious events occur. Two independent physician safety monitors, who are not otherwise involved in the study will review the safety data once per month or more frequently as needed throughout the period of study implementation, discuss study medication management, and address any potential safety concerns.

8.2 Clinical Data and Safety Review

The clinical research investigators are responsible for the initial evaluation and reporting of safety information at the participant level to the Protocol Chair. The Protocol Chair is responsible for alerting Gilead Sciences if unexpected concerns arise. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

The Reproductive Infectious Disease Data Management team will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. The clinical investigator and two independent safety monitors (one obstetrician and one pediatrician) will communicate approximately every month, as applicable to review clinical data reports. The content, format and frequency of the clinical data reports will be agreed upon by the independent safety monitors and the study investigators in advance of study implementation. In addition to the routine safety data reviews, the independent safety

monitors and the study investigators will convene 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 pregnancy, newborn medicine, infectious diseases, hepatology 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.

To assist in consistent and efficient concomitant medication recording for inpatient admissions (delivery and serious adverse event), the UPMC Health Record Research Request (R3) service may be used to extract concomitant medications administered during any inpatient admission for maternal and infant study participants. If utilized, the extracted data will be provided to the study team in a format agreed upon by R3 and data management. Additional data may be extracted by R3 and/or the MOMI database to assist in data capture (i.e. APGARS, obstetric age, pregnancy outcomes).

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.

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. Participants receiving prenatal care and/or delivering at Magee-Womens Hospital will be instructed to come to Magee-Womens Hospital if they experience any adverse events requiring evaluation. Participants will be seen by a physician investigator/study clinician. If the participant is not receiving care at Magee-Womens Hospital, then they will be instructed to seek medical care with their local primary care physician/obstetrical team. Participants may have an unscheduled visit with the physician investigator/study clinicians as necessary or desired. 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 obtained 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 physician investigator 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. Medication from hospital admissions may be extracted from the medical record using the UPMC Health Record Research Request (R3) service and/or MOMI database to ensure consistency and accuracy of reporting.

Some of the study participants will have opioid use disorder (OUD) and may be prescribed either methadone or buprenorphine as treatment. Infants who are exposed to these medications often experience neonatal opioid withdrawal syndrome (NOWS). Given that this is an expected outcome for this treatment, we will not report this as an AE. All opioid exposed infants in the UPMC hospital system have at minimum a 5-day observation period and those who require pharmacologic treatment for NOWS can remain in the hospital for up to a month (mean 14 days). A study pediatrician, will review all NOWS related hospitalization records to ensure that there are no hospital events that are outside the scope of standard NOWS findings, for example pneumonia, sepsis, and hypoglycemia.

Additionally, certain adverse events are expected as a consequence of labor and delivery. Prior to delivery, expected pregnancy findings, such as lower extremity edema, physiologic discharge of pregnancy, and pain from contractions as determined by a study clinician will not be considered adverse events. During the postpartum period, expected pregnancy findings such as lower extremity edema, abdominal pain from uterine cramping, incisional pain from a cesarean section, perineal pain after vaginal delivery, and vaginal bleeding as determined by a study clinician will not be considered adverse events. Expected symptoms may be further defined and reported accordingly in a protocol specific standard operating procedure (SOP) or guidance document.

AE severity will be graded per the most current DAIDS Table for Grading Adult and Pediatric Adverse Events.

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, except those that are expected such as hospitalization for neonatal opioid withdrawal syndrome.
- 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 physician investigator 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 agent(s)
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent(s)

8.4 Expedited 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. All serious adverse events that are considered unexpected and related to the study medication will be reported to the University of Pittsburgh Institutional Review Board, the FDA and Gilead Sciences according to their reporting guidelines.

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 other applicable government and regulatory authorities. The Protocol Chair will submit AE information in accordance with the requirements of the University of Pittsburgh IRB.

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 Gilead Sciences and to the University of Pittsburgh IRB.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study medication are outlined in this section. In general, the physician investigators will only discontinue study medication in consultation with the independent physician safety monitor(s) if they feel that the risk of study medication continuation outweighs the benefits of study medication continuation. The physician investigator(s) will document all permanent discontinuations 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 physician investigator(s) for any of the following reasons, according the HCV treatment guidelines[23]:

- 5-fold or greater increase in ALT or AST at the PK1 or PK2 visit compared to baseline result (Screening visit), confirmed by immediate repeat testing
- Any increase of ALT or AST of less than 5-fold from baseline (Screening visit) at the PK1 or PK2 visit that is accompanied by any weakness, nausea, vomiting, or jaundice
- 3-fold or greater increase in ALT or AST accompanied by bilirubin >2x the upper limit of normal, confirmed on immediate repeat testing
- Increase HCV RNA viral load by greater than 10-fold at PK2 visit (6-8 weeks after starting treatment)
- Participant is unable or unwilling to comply with required study procedures
- If the participant delivers prematurely (and is still on study medication) and desires to breastfeed
- Participant might be put at undue risk to their safety and well-being by continuing medication use, according to the judgment of the study investigator(s). The study investigators will consult with the independent safety physician prior to all study medication discontinuation instituted for this reason.

Any time a participant is permanently discontinued from study medication (prior to completion of the 12 week course of study medication), HCV resistance testing will be performed.

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 1.0, December 2004 (Clarification dated August 2009) regardless of relationship to study medication will continue study medication use.

Grade 3
For participants who develop a Grade 3 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) that is judged by the study investigators to be unrelated to study medication, the study medication will continue. The study medication must be permanently discontinued for participants who develop a Grade 3 AE judged by a physician investigator to be related to the study medication.

Grade 4
If a participant develops a Grade 4 AE as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009) and the AE is determined to be related to study medication, then study medication must be permanently discontinued.

Any time a participant is permanently discontinued from study medication (prior to completion of the 12 week course of study medication), HCV resistance testing will be performed.

9.5 HIV-1 Infection

Participants who are positive for HIV (known or positive at Screening) will not be eligible to participate. If HIV seroconversion occurs during the time of study medication use, the study medication will 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. Participants also may be withdrawn if Gilead Sciences, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Detailed reason 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 1, single-arm, open label study of treatment for chronic HCV infection during pregnancy in 10 HCV-infected pregnant women with a 12-week course of SOF/VEL.

10.2 Study Endpoints

Pregnant women meeting all of the criteria in section 5.2 and 5.3 will be enrolled into the study and followed prospectively through 12 weeks after the last dose of study medication. Infants will be enrolled upon delivery and followed prospectively through approximately one year of age.

10.2.1 Primary Endpoints: Maternal

The primary endpoints of the study are primary plasma PK parameters (specifically AUC_{tau}, C_{max}, and C_{min}) of VEL, SOF, and GS-331007 assessed at 3 weeks (+/- 7 days of medication initiation.

10.2.2 Secondary Endpoints: Maternal

The secondary endpoints of the study are:

1) Secondary plasma PK endpoints of VEL, SOF and GS-331007:
    a. Free-fraction of VEL, SOF and GS-331007
2) Secondary PK endpoints for intracellular SOF (GS-461203)
    a. Pre-dose GS-461203 concentrations from dried blood spots and peripheral blood mononuclear cells
3) Maternal sustained virologic response after 12 weeks of therapy (SVR12)
4) Adverse events including clinical and laboratory changes
5) Pregnancy outcomes including the following:
    a. delivery prior to 37 completed weeks of gestation
    b. stillbirth or intrauterine fetal demise
    c. intrapartum hemorrhage
    d. postpartum hemorrhage
    e. non-reassuring fetal status
    f. chorioamnionitis
    g. hypertensive disorders of pregnancy
    h. gestational diabetes
    i. intrauterine growth restriction

10.2.3 Exploratory Endpoints

The exploratory endpoint of the study is:

1.) In depth interviews conducted before enrollment in screened participants and after completion of treatment in enrolled participants.

Secondary Endpoints: Infant

Consistent with the secondary study objectives, the following secondary endpoint will be assessed for infants:

- Major malformations, defined as structural abnormalities with surgical, medical, or cosmetic importance.
- Weight, length, and head circumference at birth, 8 weeks, six months and 12 months.
- Neurodevelopmental assessments at 6 months and 12 months as measured by Bayley Scales of Infant and Toddler Development and Ages and Stages Questionnaire (ASQ).
- Perinatal HCV transmission assessed by presence of HCV RNA at 8 weeks, six months or 12 months.

10.3 Sample Size

To evaluate the primary objective, we estimate a desired sample size of 10 participants. In order to maintain our sample size, any participant who discontinues treatment during the 12-week treatment period will be replaced. Based on SOF/VEL prescribing information, we will have 87% power to detect a 50% decrease in VEL AUC and >99% power to detect a 2-fold increase. For power calculations we chose this degree of change in VEL AUC because the therapeutic range of SOF/VEL is quite wide and decreases in VEL AUC of up to 50% and increases of up to 2-fold are still associated with efficacy and have acceptable safety/tolerability, respectively. The FDA does not recommend co-administration of VEL with EFV because it decreases the VEL AUC by >50% [34]. Additionally, this sample size provides an estimated power of 0.82 to detect a 25% change in the AUC of the SOF, given the reported interpatient variability of 35.6% among female patients Power determinations were performed in SAS v. 9.4 (SAS, Cary, NC).

Any participant that discontinues the study before the PK3 visit is completed or if a participant reports missing more than 1 dose per week averaged over the duration of the study then they will be replaced by recruiting another participant into the study.

10.4 Participant Accrual and Retention

Pregnant and chronically HCV-infected women who meet the criteria outlined in Section 5 and are interested in participating, will be enrolled into this study. Once a participant is enrolled, the study staff will make every reasonable effort to retain her for the entire study period. Any participant lost to follow-up prior to Visit 7 will be replaced.

10.5 Data Analysis

10.5.1 Analysis of SOF and VEL concentrations

Between-group comparisons will evaluate changes in SOF and VEL PK parameters between the historical controls (nonpregnant women without severe renal disease or cirrhosis) compared to the 10 pregnant women. Area under the time concentration cure over a dosing interval (AUC_{tau}), maximum concentration (C_{max}), and minimum concentration (C_{min}) will be calculated, as applicable. The PK parameters (including the free-fraction of VEL and intracellular SOF concentrations) of the pregnant women will be compared to the historical control group by calculating the geometric mean ratios and 90%CIs. Drug concentrations will be summarized descriptively (mean, median, minimum, maximum, standard deviation) by study visit.

10.5.2 Analysis of SVR12

Outside of pregnancy, 99% of patients treated with SOF/VEL for 12 weeks obtained an SVR12. In this pilot study, we estimate that at least 9 out of the 10 chronically HCV-infected pregnant women will have a SVR12 after treatment. Participants who do not complete the treatment course or report low adherence will be excluded from the analysis.

10.5.3 Analysis of Safety Endpoints

Rates of abnormal safety laboratory assessments will be compared to those reported in the literature on historic controls and rates of adverse pregnancy outcomes will be compared to historic HCV-infected pregnant women who have delivered at our institution. Statistical significance will be determined by chi-square test.

Qualitative Analysis

Following transcription of the IDIs, the Qual EASE team will develop a qualitative codebook using an editing approach to ensure that all relevant topics and themes are represented. Two trained qualitative coders from Qual EASE will then be trained in the codebook. A primary coder will code all interviews in the pre- and post-treatment interview groups, and a secondary coder will code half of the interviews in the pre- and post-treatment interview groups. Coding will be completed using Atlas.ti software, which will help to determine the frequency and prevalence of the topics and themes which were discussed. Cohen's Kappa scores will be calculated to determine intercoder reliability.

10.5.4 Data and Safety Monitoring Plan

No Data and Safety Monitoring Board oversight is planned for this study, however a Study Steering Committee comprised by the Protocol Chair, a second physician

investigator from the University of Pittsburgh, a laboratory scientist from the University of Pittsburgh, the Data Management lead statistician and a representative from Gilead Sciences Clinical Research will provide oversight. Reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments will take place approximately every 3 months, and as needed. At the time of these reviews, or at any other time, the Study Steering Committee may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Two independent safety physicians experienced with monitoring of clinical trials among pregnant women will conduct interim safety reviews on a monthly basis or more frequently at the request of the Study Steering Committee.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study questionnaires will be developed by the study team in conjunction with data management.

11.2 Source Documents and Access to Source Data/Documents

The site will maintain source data/documents in accordance with current DAIDS policies. (http://rsc.tech-res.com/policiesandregulations/)

The study team will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations regarding testing investigational medications, the study investigator will maintain all study documentation for at least two years following the date of marketing approval for the study medications being tested for the indication in which they were studied. 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 US FDA is notified. For research involving children, records shall be retained at least until the pediatric subject reaches the age of 23.

Study records will be maintained on site for the entire period of study implementation.

11.3 Quality Control and Quality Assurance

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

12 CLINICAL SITE MONITORING

As this is an investigator initiated IND study, monitoring will be performed by internal clinical study staff (i.e. QA/QC Reviewer), PoR, laboratory staff and local data management team. Internal reviews will include:

- Review informed consent forms, protocol procedures, and study documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including CFR Title 45 Part 46 and Title 21 Parts 50, 56, and 312
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study medications

The Education and Compliance Support for Human Subject Research (ECS-HSR), Office of Research Protections will also oversee study activities. The ECS-HSR has extensive experience in the auditing and monitoring of clinical investigations for compliance with GCP standards and IND commitments. To ensure appropriate institutional oversight of University-based IND applications, the ECS-HSR will periodically monitor the research oversight programs of IND Sponsors, which will include compliance of the Sponsor and Investigator with applicable FDA regulations, applicable University of Pittsburgh policies and the IRB-approved protocol and consent document. The frequency of these monitoring visits shall be determined by the ECS-HSR.

The study investigators also will allow inspection of all study-related documentation by authorized representatives of Gilead Sciences, FDA, OHRP, IRBs/ECs and other local and US 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. All eligibility criteria will be verified prior to initiation of investigational product. Recruitment will begin after receiving IRB approval and after the protocol has been submitted to the FDA. The study investigators will permit audits by the NIH, Gilead Sciences, the FDA, OHRP, IRB, and other local and US regulatory authorities or any of their appointed agents.

13.1 Institutional Review Boards

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

13.2 Study Coordination

Catherine Chappell, MD MSc holds the Investigational New Drug (IND) application for this study. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement (CTA) executed by the University of Pittsburgh and Gilead Sciences. Dr. Chappell will work closely with The University of Pittsburgh Office for Investigator-Sponsored IND and IDE Support (O3IS) who provides assistance to University researchers in order to ensure IND submission and notification requirements are met.

Close coordination between the study team is necessary to track recruitment, enrollment, retention, AEs and unanticipated problems and to address other issues that may arise in a timely manner. The study investigators and the independent safety physician will address issues related to study eligibility, AE management/reporting and unanticipated problems as needed to assure consistency. Rates of accrual, protocol adherence, retention, and AE incidence will be reported by data management and monitored closely by the team as well as the Study Steering Committee.

13.3 Risk Benefit Statement

13.3.1 Risks

<u>General/Maternal</u>

As with any research study, there may be adverse events or side effects 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 studies of SOF/VEL in pregnant women. However there has been one study of a similar medication ledipasvir/sofosbuvir in 9 pregnant women. There were no adverse events greater that grade 2 that were related ledipasvir/sofosbuvir. 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 response.

It is also not known if SOF/VEL is present in human breast milk. If the participant delivers while still on study medication and intends to breast feed, study medication will be discontinued and HCV resistance testing will be done at the next study visit.

There is a potential risk that the hepatitis 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 permanently discontinued treatment due to adverse events (0.2%). The most common adverse reactions (adverse events assessed as causally related by the investigator and at least 10%) were headache and fatigue. Adverse reactions, all grades, observed in greater than or equal to 5% of participants receiving 12 weeks of treatment with SOF/VEL 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 participants treated with placebo compared to participants treated with SOF/VEL (asthenia: 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 the ASTRAL-1 study, rash occurred in 2% of participants treated with SOF/VEL and in 1% of participants taking placebo. No serious adverse reactions of rash occured and all rashes were mild or moderate in severity. In the ASTRAL-1 study, depressed mood occurred in 1% of participants treated with SOF/VEL and was not reported by any placebo participants. No serious adverse reactions of depressed mood occured and all events were mild or moderate in severity.

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. Cases have been reported in patients who are HBsAg positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and anti-HBc positive). We will exclude participants that are anti-HBc positive for this reason. Additionally, postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with a sofosbuvir-containing regimen. Additionally, a fatal cardiac arrest occurred in a patient taking amiodarone that was co-administered with sofosbuvir. For this reason, we will exclude participants who are taking amiodarone.

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 for 12 weeks, respectively; and in 6% and 3% of participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively.

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 for 12 weeks, respectively; and in 2% and 1% of participants treated with SOF/VEL in ASTRAL-2 and ASTRAL-3, respectively.

There are known drug interactions with SOF/VEL and other prescription and non-prescription medications. A comprehensive list of medications will be obtained from participants including over-the-counter medications (i.e. antacids, St. John's wort) and compared to the package insert to assess any contraindication to participation or necessary alterations in dosing schedules with use of the study medication.

Phlebotomy or starting an IV may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Disclosure of HIV status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings.

Participation in clinical research includes the risk 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 Magee. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify participants by name. 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, the National Institute of Health (NIH) or its designee and the US Food and Drug Administration (FDA).

Technology assisted-directly observed therapy: There is a risk that people outside of the research team will see the directly observed dosing. The photo/video recording

of the dosing will be taken directly into the PittBox app and stored in this system for the research staff to access. . While the app is password protected, someone may access the information if they gain access to the password/app on the participant's personal device. Likewise, the telephone numbers for these communications could also be visible to third parties.

Fetus/infant:
There is not 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 and get to the fetus/unborn infant 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 side effects.

Obtaining blood samples from the infant may cause them to cry, cause bleeding, bruising or a clot and may be distressful to watch the infant have their 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 evidence-based guidance for the treatment of chronic hepatitis C infection in pregnancy and 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 IRB and utilizing an IRB approved mechanism. In obtaining and documenting informed consent, the study investigators will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Participants may be provided with a copy of the informed consent form if they chose.

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 unknown safety and proven efficacy of the study medications
- The importance of daily adherence to the study medication
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)

- The 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 extent possible. All study-related information will be stored securely at the clinical research unit. All participant information will be stored in locked areas with access limited to the clinical study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number (PTID) only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored electronically in the University of Pittsburgh REDCap system. Appropriate firewall and virus scanning software are installed and updated routinely by hospital support staff. Forms, lists, logbooks, appointment books, and any other listings that link participants' ID numbers (PTID) to identifying information will be stored in a separate, locked area with limited access. 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 US Federal Government, including the US FDA, the US OHRP and other local and US regulatory authorities
- Representatives of Gilead Sciences
- Study staff
- University of Pittsburgh IRB
- University of Pittsburgh Education and Compliance Office for Human Subject Research (ECO-HSR)

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 Magee-Womens Hospital or at iV1 visit if infant delivered outside of Magee-Womens 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 time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Reimbursement amounts will be specified in the informed consent form. Compensation may include parking/bus passes, assistance with transportation, and additional incentives for making study appointments within the window period. If needed and desired, compensation for overnight stay during the PK-1 and PK-3 visits may be provided to participants.

13.8 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV-1 identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

13.9 Access to HIV-related Care

13.9.1 HIV Counseling and Testing

HIV testing will be performed at Screening. HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine eligibility for participation. Counseling will be provided in accordance with standard HIV counseling policies and methods. Participants are expected to have HIV screening as part of routine prenatal care at 28 weeks' gestation, and if clinically indicated during the study.

13.9.2 Care for Participants Identified as HIV-Positive

<u>Identified as HIV-Positive Prior to Enrollment</u>
An individual who has been identified as infected with HIV-1 will not be eligible to participate and will be referred to the Pittsburgh AIDS Center for Treatment (PACT).

<u>Identified as HIV-Positive While on Study Medication</u>
The participant will continue with the study medication and study procedures, and will be immediately referred to PACT or another clinic/provider convenient for the patient.

13.10 Study Discontinuation

This study may be discontinued at any time by Gilead Sciences, the US FDA, the OHRP, other government or regulatory authorities, or the University of Pittsburgh IRB.

14 PUBLICATION POLICY

The University of Pittsburgh study investigators will be responsible for publication of the results of this study. The manuscript draft will be sent to Gilead Sciences approximately 30 days prior to submission for their review and approval.

15 APPENDICES

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

	SCR (V1)	ENR (V2)	PK1, PK2, PK3 (V3, V4, V5)	PK1a, PK2a (V3a, V5a)	End of Treatment (V6)	Delivery**	Post treatment (V7)
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	X
In-depth Interview	X				X		
Eligibility assessment	X						
Eligibility confirmation		X					
Reimbursement	X	X	X	X	X	X	X
Record/ update AEs			X	X	X	X	X
Schedule next visit	X	X	X			X	
BEHAVIORAL							
HIV pre- and post- test counseling	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(full)	X (modified)		X(modified)	+ (modified)	X (modified)
Assessment of 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	+						
HCV Resistance testing			*		*	*	*
HBV Testing	X						
CBC with diff and platelets	X		X (V3, V4)				X
Creatinine	X		X (V3, V4)				X
Hepatic Function Panel	X		X (V3, V4)				X
Lipase	X		X (V3, V4)				X
Creatinine kinase	X		X (V3, V4)				X
HIV serology	X						
PT/INR	X		X (V3, V4)				X
Intensive Plasma PK			X (V3, V5)				
Sparse Plasma PK			X (V4)	X		^	
DBS for intracellular SOF			X			^	
PBMC for intracellular SOF			X			^	
Protein Binding Assay			X (V3, V5)				
STUDY MEDICATION							
Provision of Study Medication		X	X			*	
Administer Timed dose of study medication			X (V3, V5)				
Review/collect of adherence tools		X	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 Magee or applicable procedures conducted by phone for participants who deliver at outside locations. For all participants, a chart review of the delivery records will be done as part of the Delivery Visit
^ If still on study medication at the time of delivery

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		
Reimbursement	X	X	X	X
Record/update AEs		X	X	X
Schedule next visit	X	X	X	
CLINICAL				
Medical history **	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
LABORATORY				
HCV RNA viral load	X	X	X	*
HCV Resistance testing		*	*	*
Sparse PK from cord blood	^			

*If indicated
**May be obtained from medical record as applicable
*** May be performed during hospital admission for infants born at Magee 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.
^ If mother on study drug at the time of delivery and delivers at Magee-Womens Hospital

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