**Management of HCV infection in pregnant and postpartum women with opioid use disorder: The potential of an integrated medical home model**

**Phase IV Trial of Sofosbuvir/Velpatasvir Fixed Dose Combination in Postpartum Women with Chronic Hepatitis C Virus Infection**

**Protocol version 8.0**

**Funding Agencies: Gilead Sciences**

**NCT03057847**

## Contents

## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine tranaminase |
| AST | Aspartate transaminase |
| CBC | Complete blood count |
| CMP | Comprehensive metabolic profile |
| 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 |
| Hep A total Ab | Hepatitis A total antibody |
| HBcAb | Hepatitis B core antibody |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C Virus |
| HIV | Human immunodeficiency virus |
| INR | International normalized ratio |
| IoR | Investigator of Record |
| IRB | Institutional Review Board |
| ISR | Interim Study Review |
| mL | Milliliter |
| MWH | Magee-Womens Hospital |
| NIH | National Institutes of Health |
| OHRP | Office of Human Research Protections |
| OUD | Opioid Use Disorder |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PoR | Pharmacist of Record |
| PPM | Postpartum |
| PRC | Pregnancy Recovery Center |
| PTID | Participant identification number |
| QOL | Quality of life |
| RNA | Ribonucleic acid |
| SAE | Serious adverse event |
| SOF | Sofosbuvir |
| SOF/VEL FDC | Sofosbuvir/velpatasvir fixed-dose combination |
| SOP | Standard operating procedure(s) |
| SSP | Study-specific Procedures |
| SVR | Sustained virologic response |
| UPMC | University of Pittsburgh Medical Center |
| VEL | Velpatasvir |

## RESEARCH TEAM

*Principal Investigator*: **Elizabeth E. Krans, MD, Msc**
Department of Obstetrics, Gynecology, Reproductive Sciences, Magee-Womens Hospital
300 Halket Street
Pittsburgh PA 15213
Phone: 412-641-4222
Email: kransee@mail.magee.edu

*Co-investigator:* **Naudia Jonassaint, MD**
Thomas E. Starzl Transplantation Institute, UPMC Montefiore N758
3459 Fifth Avenue
Pittsburgh , PA 15213
Phone: 412-864-5458
Email: jonassaintnl@upmc.edu

*Co-investigator:* **Debra Bogen, MD**
Department of Pediatrics
Children's Hospital of Pittsburgh, 3414 Fifth Ave #1
Pittsburgh PA 15213
Phone: 412-692-5135
Email: bogendl@upmc.edu

*Co-investigator:* **Jennifer Kiser, PharmD**
Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado
12850 E. Montview Blvd. V20-4102
Aurora, CO 80045
Phone: 303-724-6132
Email: jennifer.Kiser@ucdenver.edu

*Co-investigator:* **Catherine Chappell, MD, MSc**
Magee-Womens Hospital of UPMC
300 Halket Street
Pittsburgh, PA 15213 USA
Phone: 412-641-1809
Email: chappellca@upmc.edu

*Study Coordinator:* **Hollis Laird, MPH**
Magee Womens Research Institute
3380 Boulevard of the Allies
Pittsburgh PA 15213
412-641-2248
Email: lairdh2@mwri.magee.edu

## SUMMARY

**Short Title:** Chronic Hepatitis C treatment with Sofosbuvir/Velpatasvir for postpartum women with OUD

**Clinical Phase:** Phase IV

| | |
|---|---|
| **IND Sponsor:** | Exempt |
| **Protocol Chair:** | Elizabeth Krans, MD, MSc |
| **Sample Size:** | 30 |
| **Study Population:** | Postpartum women, a) chronic hepatitis C infection, b) 18 years or older |
| **Study Site:** | Magee-Womens Hospital of UPMC, Pittsburgh, PA |
| **Study Design:** | Single-site, single-arm prospective study |
| **Study Duration:** | 2.5 years: 1 year for planned accrual + 1.5 year for postpartum follow-up |
| **Study Medication:** | Fixed-dose combination tablet of 400 mg of Sofosbuvir and 100 mg of Velpatasvir (SOF/VEL) |
| **Study Regimen:** | Participants will take SOF/VEL one tablet once daily starting within their first 12 months postpartum for 12 weeks total. |

**Primary Objective:**

- Evaluate the feasibility/acceptability of a combined, peripartum HCV and opioid maintenance treatment clinical protocol on adherence to HCV treatment regimens

**Primary Endpoint:**

- Treatment feasibility will be established through the successful recruitment and enrollment of participants, administration of sofosbuvir/velpatasvir in the postpartum period and ability to determine SVR at 3 months following treatment completion.
- Acceptability of sofosbuvir/velpatasvir will be evaluated by self-report of treatment side effects and barriers and facilitators to treatment adherence.
- Adherence to sofosbuvir/velpatasvir will be evaluated with medication diaries, an assessment of missed doses, pill counts and attendance at opioid maintenance treatment visits.

**Secondary Objectives:**

- To investigate SOF/VEL drug levels in breast milk.
- Evaluate the rate of IVDU recidivism, HCV reinfection and health related QOL in women with OUD during the first postpartum year.

**Secondary Endpoints:**

- Breast milk concentrations of SOF, the SOF metabolite GS-331007 and VEL
- Rates of IVDU recidivism
- HCV reinfection
- Patient centered outcomes such as health related QOL will be assessed at 6, 9 and 12 months following treatment completion

**Table 1: Study Visit Schedule**

| | Study Visit | Time Period* |
|---|---|---|
| V1 | Screening A | 6 weeks 0 days to 12 months PPM |
| V2 | Screening B | 6weeks 0 days to 12 months PPM |

| | | |
|---|---|---|
| V3 | Enrollment | 6 weeks 0 days to 12 months PPM |
| V4** | Treatment initiation | 1 day PPM – 12 months PPM |
| VPK1-5*** | Breastmilk PK visits | 2-10 days PPM |
| V5 | 2 week treatment follow-up | 14 days after treatment initiation |
| V6 | 4 week treatment follow up | 28 days after treatment initiation |
| V7 | 6 week treatment follow-up | 42 days after treatment initiation |
| V8 | 8 week treatment follow-up | 56 days after treatment initiation |
| V9 | 10 week treatment follow-up | 70 days after treatment initiation |
| V10 | End of Treatment Visit<br>12 weeks treatment follow-up | 84 days after treatment initiation |
| V11 | SVR Visit<br>3 months post-treatment follow-up | 6 months after treatment initiation |
| V12 | 9 months post-treatment follow-up | 12 months after treatment initiation |
| V13 | End of Study<br>15 months post-treatment follow up | 18 months after treatment initiation |

*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

***For a subset of participants, n=5

# KEY ROLES

## Protocol Identification

| | |
|---|---|
| Protocol Title: | Management of HCV infection in pregnant and postpartum women with OUD: the potential of an integrated medical home model |
| Short Title: | Chronic Hepatitis C treatment with Sofosbuvir/Velpatasvir for postpartum women with OUD |
| Date: | May 10, 2017 |

## Funders, Sponsor and Monitor Identification

**Funding Agency:** Gilead Sciences Investigator Initiated Studies Program

**Site Monitoring:** Elizabeth Krans, MD MSc

**Pharmaceutical Collaborator:** Gilead Sciences

# INTRODUCTION

## Background

Intravenous drug use (IVDU) is the leading cause of new Hepatitis C virus (HCV) infections and is widespread among pregnant women with OUD. HCV screening during pregnancy is recommended for women with risk factors for HCV exposure and provides a unique opportunity to identify the virus among high-risk women of reproductive age. HCV positivity in pregnant women with OUD ranges from 40-75% and over 28% are newly diagnosed with HCV during pregnancy. Pregnancy is a unique opportunity to engage HCV-infected women in efforts to improve their health and facilitate HCV treatment. However, less than 2% of HCV-infected pregnant patients initiate HCV treatment within one year following delivery.

## Rationale

Incorporating HCV treatment into opioid maintenance treatment program clinical protocols is an innovative health care delivery model that has been associated with improved HCV treatment uptake in non-pregnant, drug-using populations. This “medical home” approach would combine HCV and opioid maintenance treatment into one treatment regimen and incorporate the expertise of obstetricians, hepatologists, substance abuse treatment providers and pediatricians into one comprehensive clinical care model. We hypothesize that co-locating prenatal care, HCV treatment and substance abuse treatment services in the same clinical environment will significantly improve HCV treatment uptake and compliance as well as facilitate ongoing recovery from opioid addiction.

## SOF/VEL Fixed Dose Combination

### Description

The study medication is a fixed-dose combination tablet containing sofosbuvir and velpatasvir for oral administration. Sofosbuvir is a nucleotide analog HCV NS5B polymerase inhibitor and velpatasvir is an NS5A inhibitor.

Each tablet contains 400 mg sofosbuvir and 100 mg velpatasvir. 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.

Sofosbuvir: The IUPAC name for sofosbuvir is (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 C22H29FN3O9P and a molecular weight of 529.45. Sofosbuvir is a white to off-white crystalline solid with a solubility of at least 2 mg/mL across the pH range of 2–7.7 at 37 oC and is slightly soluble in water.

Velpatasvir: The IUPAC name for velpatasvir is Methyl {(1R)-2-[(2S,4S)-2-(5-{2-[(2S,5S)-1-{(2S)-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}-1H-imidazol-2-yl)-4-(methoxymethyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate. It has a molecular formula of C49H54N8O8 and a molecular weight of 883.0. Velpatasvir is practically insoluble (less than 0.1 mg/mL) above pH 5, slightly soluble (3.6 mg/mL) at pH 2, and soluble (greater than 36 mg/mL) at pH 1.2.

### Mechanism of Action

Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator. In a biochemical assay, GS-461203 inhibited the polymerase activity of the recombinant NS5B from HCV genotype 1b, 2a, 3a, and 4a with an IC50 value ranging from 0.36 to 3.3 micromolar. GS-461203 is neither an inhibitor of human DNA and RNA polymerases nor an inhibitor of mitochondrial RNA polymerase. Sofosbuvir has a very short half-life in plasma. SOF accounts for only ~4% of the drug related material circulating in plasma. The majority (>90%) of the drug-related material in plasma is in the form of GS-331007, an inactive metabolite of sofosbuvir.

Velpatasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Resistance selection in cell culture and cross-resistance studies indicate velpatasvir targets NS5A as its mode of action.

## Clinical Studies

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

Approximately 1035 participants have been enrolled in several multicenter, Phase 3 trials to assess the efficacy of treatment with SOF/VEL in patients with genotype 1, 2, 3, 4, 5 and 6 chronic hepatitis C virus infection.

**Table 2: Study ASTRAL-1: Virologic Outcomes by HCV Genotype in SOF/VEL Treated Subjects without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)**

| | EPCLUSA 12 Weeks (N=624) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (all GTs) (N=624) | GT-1 | | | GT-2 (N=104) | GT-4 (N=116) | GT-5 (N=35) | GT-6 (N=41) |
| | | GT-1a (N=210) | GT-1b (N=118) | Total (N=328) | | | | |
| SVR12 | 99% (618/624) | 98% (206/210) | 99% (117/118) | 98% (323/328) | 100% (104/104) | 100% (116/116) | 97% (34/35) | 100% (41/41) |
| Outcome for Subjects without SVR | | | | | | | | |
| On-Treatment Virologic Failure | 0/624 | 0/210 | 0/118 | 0/328 | 0/104 | 0/116 | 0/35 | 0/41 |
| Relapse[a] | <1% (2/623) | <1% (1/209) | 1% (1/118) | 1% (2/327) | 0/104 | 0/116 | 0/35 | 0/41 |
| Other[b] | 1% (4/624) | 1% (3/210) | 0/118 | 1% (3/328) | 0/104 | 0/116 | 3% (1/35) | 0/41 |

GT = genotype; no subjects in the placebo group achieved SVR12.

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at their last on-treatment assessment
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

**Table 3: Study ASTRAL-3: Virologic Outcomes in Subjects with Genotype 3 HCV without Cirrhosis or with Compensated Cirrhosis (12 Weeks After Treatment)**

| | EPCLUSA 12 Weeks (N=277) | SOF + RBV 24 Weeks (N=275) |
|---|---|---|
| SVR12 | 95% (264/277) | 80% (221/275) |
| | Treatment difference +14.8%; 95% confidence interval (+9.6% to +20.0%) | |
| Outcome for subjects without SVR | | |
| On-Treatment Virologic Failure | 0/277 | <1% (1/275) |
| Relapse[a] | 4% (11/276) | 14% (38/272) |
| Other[b] | 1% (2/277) | 5% (15/275) |

SOF = sofosbuvir; RBV = ribavirin.

a. The denominator for relapse is the number of subjects with HCV RNA <LLOQ at the last on-treatment assessment
b. Other includes subjects who did not achieve SVR and did not meet virologic failure criteria.

**Safety**

The adverse reactions data for SOF/VEL in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, without cirrhosis or with compensated cirrhosis, who received SOF/VEL for 12 weeks. SOF/VEL was studied in placebo- and active-controlled trials. The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received SOF/VEL for 12 weeks. The most common adverse reactions (adverse events assessed as causally related by the investigator and at least 10%) were headache and fatigue in subjects treated with SOF/VEL for 12 weeks.

Adverse reactions, all grades, observed in greater than or equal to 5% of subjects 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 who experienced these adverse reactions, 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 subjects treated with placebo compared to subjects treated with SOF/VEL (asthenia: 3% versus 5% for the placebo and SOF/VEL groups, respectively). The adverse reactions observed in subjects 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 subjects treated with SOF/VEL in ASTRAL-3.

### Rationale for Study Design

Incorporating HCV treatment into opioid maintenance treatment program clinical protocols is an innovative health care delivery model that has been associated with improved HCV treatment uptake in non-pregnant, drug-using populations. This “medical home” approach would combine HCV and opioid maintenance treatment into one treatment regimen and incorporate the expertise of obstetricians, hepatologists, substance abuse treatment providers and pediatricians into one comprehensive clinical care model.

## OBJECTIVES

### Primary Objective

1. To evaluate the feasibility/acceptability of a combined, peripartum HCV and opioid maintenance treatment program on adherence to HCV treatment regimens.

### Secondary Objectives

1. To investigate SOF/VEL drug levels in breast milk.
2. Evaluate the rate of IVDU recidivism, HCV reinfection and health related QOL in women with OUD during the first postpartum year.

## STUDY DESIGN

### Identification of Study Design

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

### Summary of Major Endpoints

**Primary Endpoints:**

- **Treatment Feasibility**
  - Successful recruitment and enrollment of participants
  - Administration of SOF/VEL in the postpartum period
  - Ability to determine SVR at 3 months following treatment
- **Acceptability**
  - Self-report of treatment side effects
  - Self-report of barriers and facilitators to treatment adherence
- **Adherence**
  - Medication diaries
  - Assessment of missed doses

- Pill counts
- Attendance at opioid maintenance treatment visits

**Secondary Endpoints:**

- Breast milk concentrations of SOF, GS-331007, and VEL
- Rates of IVDU recidivism
- HCV reinfection
- Patient centered outcomes such as health related QOL will be assessed at 6, 9 and 12 months following treatment completion
- Pregnancy and delivery outcomes collected prospectively by chart review and participant interview

## Description of Study Population

The study population will include 30 pregnant and postpartum women between the ages of 18-39 year old (inclusive) at screening who are chronically infected with Hepatitis C virus, as described in Sections 5.2 and 5.3.

## Time to Complete Accrual

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

## Expected Duration of Participation

The expected duration for maternal and infant participants is approximately 18 months after SVR Assessment, not including the screening window. Maternal study data will be collected from the participant and/or her medical records through the End of Study Visit (15 month post-treatment visit, V14). Infant study data will be collected from his/her medical record after End of Study Visit (15 month post-treatment visit, V14).

# STUDY POPULATION

## 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.

### Recruitment

HCV-infected pregnant or postpartum women will be recruited from the outpatient obstetrical clinics at Magee-Womens Hospital (MWH) of UPMC. There are over 10,000 deliveries at MWH per year and it is estimated that approximately 1% of women who deliver are infected with HCV. Recruitment will be primarily targeted from the MWH Pregnancy Recovery Center, which was established in 2014 to provide concurrent treatment for OUD with prenatal care, which has an estimated retention rate of 90% for weekly opiate substitution and prenatal visits. There are approximately 120 pregnant women with OUD who receive prenatal care at the Pregnancy Recovery Center per year. The prevalence of HCV infection in this Center is approximately 60%. Recruitment materials will be approved by the University of Pittsburgh Institutional Review Board prior to use.

### 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.

## 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 enrollment visit and the screening visit or if there is concern by the study investigators that the participant might not remain eligible, the screening laboratories can be repeated prior to enrollment.

1) Age 18 or older
2) Able and willing to provide written informed consent to be screened for and take part in the study procedures
3) Able and willing to provide adequate contact information
4) Chronic HCV, genotype 1 (1a, 1b), 2 (2a, 2b), 3, 4, 5, 6 infection, defined as a HCV antibody and detectable HCV RNA viral load at screening
5) Pregnancy at 6 + 0 to gestation to 12 months PPM at screening B
6) Documented negative Hepatitis B testing within 3 months prior to enrollment
7) Negative HIV testing within 3 months prior to enrollment or documented immunity to Hepatitis B as a result of vaccination
8) Per participant report at screening and enrollment, agrees not to participate in other research studies involving drugs or medical devices for the duration of study participation
9) Plans to deliver at Magee-Womens Hospital of UPMC (if being recruited during pregnancy)
10) Willing to obtain a Nexplanon, IUD, or Depo Provera shot for treatment duration (12 weeks) or has a planned tubal ligation

## 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 a sofosbuvir based regimen
    b. Use of any medications contraindicated with concurrent use of sofosbuvir/velpatasvir according to the EPCLUSA package insert[1]
    c. Plans to relocate away from the study site area in the next 18 months
    d. Current sexual partner is known to be infected with HIV or Hepatitis B virus
    e. History of decompensated cirrhosis (history of variceal bleed, ascites or hepatic encephalopathy)
2) Reports participating in any other research study involving drugs or medical devices within 60 days or less prior to enrollment
3) Breastfeeding or feeding infant expressed breastmilk at the time of treatment initiation (Women who participate in the breastmilk PK portion of the study (n=5) will express breastmilk exclusively for participation in the research study)
4) Any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease (other than Hepatitis C)
5) Has any of the following laboratory abnormalities:
    a. Aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than 10 times the upper limited of normal at screening
    b. Hemoglobin less than 10 g/dL immediately prior to treatment initiation
    c. Platelet count less than 90,000 per $mm^3$ immediately prior to treatment initiation
    d. International normalized ratio (INR) > 1.5
    e. GFR < 40

6) 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.

# STUDY MEDICATION

## Regimen

Each participant will take a 12 week course of SOF/VEL one tablet by mouth, once daily.

## Administration

Study medication will be dispensed in the immediate postpartum period in the quantities sufficient to have one dose per day until the next scheduled visit with 2 extra doses. Tablets will be packaged by the Investigational Pharmacist/Pharmacist of Record (PoR) in the pharmacy at Magee-Womens Hospital. Participants will be given a medication administration log to assist them with keeping track of when they took their doses. The medication administration log will include 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, they should take the dose as soon as it is remembered, but only one dose per day. Participants will be instructed to take their medication in the morning 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 taking to another daily activity, etc. Participants will be instructed to bring any unused medication to their next visit. Participants will be instructed to call the study staff immediately if they run out of medication or if they lose their study medication. In this case, all possible efforts will be made to get the participant study medication as soon as possible.

## Supply and Accountability

### Supply

Gilead Sciences will manufacture the study medication under Good Manufacturing Practices (GMP) and will package, label and ship all of the study medication directly to the PoR at Magee-Womens Hospital.

### Storage and Dispensing

SOF/VEL should be stored at room temperature below 30°C within the main pharmacy at Magee-Womens Hospital[1]. The PoR 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 until the next study visit with two 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 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.

### Accountability

The PoR will maintain complete accountability records of all study SOF/VEL FDC received and dispensed. All unused study medications will be returned to Gilead Sciences after the study is complete.

### 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, alternate arrangements will be made 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.

## 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 and over-the-counter preparations including vitamins will be recorded on forms for concomitant medications. Participants will be prohibited from using nutritional supplements, herbal preparations and medications contraindicated for concomitant use with Sofosbuvir and Velpatasvir as described in the package insert. Each reported medication will be reviewed to ensure the participant is not using prohibited medications 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.

# 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.

## Pre-screening

With IRB approval, study staff will pre-screen records to identify potential participants by evaluating minimum criteria (i.e. age, gestational age, Hepatitis C status). Clinic staff will be informed of the study and will be asked to provide an IRB-approved 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 if interested. 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 ads and flyers may also be used (i.e. hung throughout the hospital; displayed on electronic boards; emailed to providers or appropriate support or community groups).

## Visit 1- Screening A (V1)

Screening Visit A can take place anytime with the screening window. 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. All participants will meet with hepatology who will ultimately determine whether to initiate hepatitis C treatment in the immediate postpartum period and participants will be encouraged to discuss participation in the study with hepatology. For participants who subsequently do not meet the eligibility criteria, screening 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 enrollment visit and the screening visit or if there is concern by the study investigators that the participant might not remain eligible, the screening laboratories can be repeated prior to enrollment.

**Table 4: Screening Visit A (V1)**

| Visit 1- Screening Visit A | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review and obtain written informed consent for screening<br>• Sign appropriate medical record releases (i.e. to obtain records from the Pregnancy Recovery Center; outside records as necessary)<br>• Collect contact information<br>• Screening Questionnaire<br>• Assess eligibility<br>• Provide reimbursement for screening visit<br>• Schedule next visit |
| **Clinical** | • Collect medical history & review medical/prenatal records including documentation of chronic Hepatitis C, Opioid Use Disorder and gestational age/dating |
| **Laboratory** | • Collect blood<br>– HCV antibody*<br>– HCV RNA*<br>– HBsAg*<br>– HIV* |

*If not already available in the medical record 6 months prior to Screening A visit or not anticipated to be obtained by their primary health care provider prior to enrollment

## Visit 2- Screening B (V2)

The following procedures will occur at the Screening B visit. Screening Visit B can take place anytime with the screening window. All patients who meet basic eligibility criteria [chronic HCV, OUD, HIV negative, appropriate GA] will meet with Hepatology, who will conduct a full medical history and physical exam and ultimately determine if the patient is eligible to participate in the study. Participants will also complete the baseline assessment at this visit.

**Table 5: Screening Visit B (V2)**

| Visit 2- Screening Visit B | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review written informed consent for screening<br>• Review/update locator information<br>• Overview of study procedures/treatment regimen if participant chooses to enroll<br>• Schedule next visit (Enrollment visit with hepatology) if appropriate<br>• Complete Baseline Questionnaire |
| **Clinical** | • Collect medical history & review medical/prenatal records including documentation of chronic Hepatitis C and gestational age/dating<br>• Review of concomitant medications<br>• |
| **Laboratory**** | Collect blood<br>– HCV genotype*<br>– HepBcAb*<br>– HepBsAb*<br>– HepB DNA (only if surface antigen and core Ab positive)*<br>– HepA total antibody*<br>– PT/INR<br>– CMP* |

*If not already available in the medical record 6 months prior to Screening B visit or not anticipated to be obtained by their primary health care provider prior to enrollment

** Please note, if treatment initiation (V4) is occurring within 3 months of Screening B (V2), treatment initiation labs can be drawn at V2

## Enrollment (V3)

The following procedures will occur at the Enrollment visit (V3). The Enrollment Visit may occur between 6+0 weeks gestational age and 12 months postpartum. During the enrollment visit the participant will meet with the hepatologist, and sign the informed consent form.

**Table 6: Enrollment (V3)**

| Enrollment Visit- Visit 3 (V3) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Confirm eligibility<br>• Review/update locator information<br>• Review and obtain written informed consent for treatment<br>• ICF Comprehension Assessment<br>• Assign participant ID (PTID)<br>• Schedule next visit |
| **Clinical** | • Review/update medical history, review medical record, document pre-existing conditions<br>• Instruct participants to contact study staff when in labor/being admitted to MWH labor and delivery if appropriate<br>• Provide Screening test results<br>• Review of concomitant medications<br>• Consultation with hepatologist<br>• Physical exam |
| **Laboratory** | • None |

## Treatment Initiation (V4)

**The treatment initiation visit will occur in the immediate postpartum period (1-14 days postpartum) or within 12 months postpartum if breastfeeding. Please note, if treatment initiation (V4) is occurring within 3 months of Screening B (V2), treatment initiation labs can be drawn at V2. During the treatment initiation visit the participant will be given instructions on using and begin taking the study medication.Table 7: Treatment Initiation (V4)**

| Treatment Initiation Visit- Visit 4 (V4) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Confirm eligibility<br>• Review/update locator information<br>• Sign appropriate infant medical record releases<br>• Completed visit questionnaire<br>• Schedule next visit |
| **Behavioral** | • Provide counseling<br>  • Protocol adherence<br>  • Study medication use/adherence |
| **Clinical** | • Review/update medical history<br>• Review/update concomitant medications<br>• Provide contraceptive counseling<br>• Provide available test results<br>• Obtain urine pregnancy test |
| **Medications** | • Participants will receive study medication (supply enough for next visit plus 2 extra doses)<br>• Participants will receive instructions for medication use<br>• Participants will receive medication adherence log |
| **Laboratory** | • CMP*<br>• CBC*<br>• GGT*<br>• |

*If not already available in the medical record 3 months prior to Treatment Initiation Visit

## Breastmilk Pharmacokinetics Substudy

A subset of women (n=5) will participate in a sub-study to determine the quantity of drugs (SOF and VEL) transferred into breastmilk. Because the drug has not been studied in infants, all expressed milk will be maintained by the study. We ask each of the 5women to express 5 samples of breastmilk and have paired blood samples collected at their convenience. Samples will be obtained starting at least 6 hours after the first dose and no sooner than 6 hours from a previous sample. All samples will be obtained by day 10 postpartum. The time of prior SOF/VEL dosing will be carefully recorded as well as the time of the breastmilk and blood collection.

Participants will be instructed to take their daily dose at home as usual. This subsample of participants will be given a pill box (Wisepill) that tracks drug timing so that we have accurate time stamp for when the drug was taken. This is important for the PK study to ensure women were adherent with the medication and to track the time of prior doses in relation to milk and blood collection.

Women will be asked to only express milk when they are at Magee-Womens Hospital under the supervision of the study staff. Women will be asked to express until both breasts are soft and the milk expression rate slows. Because women will be pumping infrequently, their milk volume will diminish and by 10 days, will be of limited volume. Individual venipuncture(s) will be used to collect all plasma samples, and participants will be instructed on how to pump to obtain breastmilk samples.

Case report forms will be completed for each set of breastmilk and blood samples obtained. Two 5-mL breastmilk samples will be processed and stored. One 5-mL aliquot of whole intact milk will be transferred to a cyrovial and stored. The second 5-mL aliquot will be centrifuged, the lipid layer removed and transferred to a cryovial and the remaining fluid transferred to a separate cryovial. All three cryovials will be stored at -80°Celcius until shipment to the Colorado Antiviral Pharmacology Laboratory for analysis. 5-mL of blood will be

obtained in a K2 EDTA tube and centrifuged, the plasma transferred to a cryovial and stored at -80°Celcius until shipment to the Colorado Antiviral Pharmacology Laboratory.

SOF, the SOF metabolite GS-331007 and VEL will be measured in plasma and breastmilk using validated LC/MS-MS methods at the Colorado Antiviral Pharmacology Laboratory.

**Table 8: Breastmilk Pharmacokinetics Visits (PK1-5)**

| Breastmilk Pharmacokinetics Visits (PK1-5) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Visit questionnaire<br>• Provide reimbursement for study visit<br>• Record/update AEs<br>• Schedule next visit |
| **Behavioral** | • Adherence assessment<br>• Provide modified counseling<br>– Protocol adherence<br>– Study medication use/adherence |
| **Clinical** | • Administer timed dose of study medication<br>• Adherence assessment |
| **Laboratory** | • Collect blood (all visits)<br>• Collect breastmilk sample (all visits) |

## Follow up postpartum visits (Visits 5-9)

1) 2 week treatment follow-up (V5): 14 days after treatment initiation
2) 4 week treatment follow-up (V6): 28 days after treatment initiation
3) 6 week treatment follow-up (V7): 42 days after treatment initiation
4) 8 week treatment follow-up (V8): 56 days after treatment initiation 10 week treatment follow-up (V9): 70 days after treatment initiation

The follow up visits will be scheduled as **early** as possible within the window to allow for visits that require rescheduling.

**Table 9: Postpartum Follow-up Visits (V5-9)**

| Postpartum Follow-up Visits 5-9 (V5-9) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Visit questionnaire<br>• Record/update AEs<br>• Schedule next visit |
| **Behavioral** | • Provide modified counseling<br>– Protocol adherence<br>– Study medication use/adherence |
| **Clinical** | • Review/update medical history<br>• Review/update concomitant medications<br>• Provide study medication with sufficient supply until next visit with 3 additional doses<br>• Provide test results if available<br>• Obtain urine pregnancy test (V7 only) |

| | |
|---|---|
| **Laboratory*** | Varies by visit:<br>• Visit 6 (4 week postpartum follow up)<br>  ○ HCV RNA<br>  ○ CMP, CBC, GGT<br>• Visit 8 (8 week postpartum follow up)<br>  ○ CMP, CBC, GGT<br>• All other visits: None |

*If necessary, V6 labs can be drawn at V7 and V8 labs can be drawn at V9

## End of Treatment Visit (12 week treatment follow-up, V10)

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.

**Table 10: End of Treatment Visit**

| End of Treatment Visit (12 week postpartum follow-up, V10) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Visit Questionnaire<br>• Record/update AEs<br>• Schedule next visit |
| **Behavioral** | • Collect remaining study medication and medication administration log<br>• Conduct qualitative interview |
| **Clinical** | • Review/update medical history<br>• Review/update concomitant medications<br>• Consultation with hepatologist (only if HCV virus not cleared at 8w)<br>• Provide test results if available |
| **Laboratory** | • HCV RNA<br>• CMP, CBC, GGT |

## SVR Assessment (3 month post-treatment visit, V11)

The following procedures will occur at the 3 month post-treatment visit

**Table 11: SVR Assessment (V11)**

| SVR Assessment (3 month post-treatment visit, V11) | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Visit Questionnaire<br>• Record/update AEs<br>• Schedule next visit<br>• Conduct qualitative interview |
| **Clinical** | • Review/update medical history<br>• Provide test results if available<br>• Consultation with hepatologist (by phone) |
| **Laboratory** | • HCV RNA<br>• CMP, CBC, GGT |

## 9 month post-treatment visit (V12)

The following procedures will occur at the 9 month post-treatment visit (V13)

**Table 13: 9 month post-treatment visit (V12)**

| V13: 9 month post-treatment visit | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review/update locator information<br>• Review infant demographics/sign release(s) for medical records for infant (if necessary)<br>• Schedule next visit |
| **Clinical** | • Review/update medical history<br>• Provide available test results |
| **Laboratory** | • HCV RNA<br>• CMP, CBC, GGT |

## End of Study Visit (15 month post-treatment visit, V13)

The following procedures will occur at the End of Study visit (V14). If the participant is unable/unwilling to return to MWH, this visit may be conducted via phone and/or email.

**Table 14: End of Study visit (V13)**

| V14: End of Study Visit | |
|---|---|
| **Component** | **Procedures** |
| **Administrative and Regulatory** | • Review results of infant HCV testing/sign release(s) for medical records for infant (if necessary)<br>• |
| **Clinical** | • Review/update medical history<br>• Provide available test results |
| **Laboratory** | • None |

## 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. 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 will continue for safety except the following:

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

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

- Viral load as needed (i.e. participant withdraws, investigator opinion)

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

## 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.

## 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 and meeting study participants at their regular clinic visits in order to improve adherence the study medication. All options will be included in the informed consent document and will be tailored to the participant's needs. At the follow-up visits (V5-10) all remaining medication will be counted, recorded and returned to the pharmacy. Study participants will be given a medication administration log upon enrollment to assist in study medication adherence. Each log will have instructions on how and when to take the medication. We will recommend that participants take the study medication between 8:00am and 9:00am daily. If a participant forgets to take a dose, she should take the missed dose as soon as she remembers but should never take more than one tablet of SOF/VEL FDC per day. Directions on how to store the medication as well as what to do if the medication is lost or stolen will be included on the medication administration log. Participants will be asked to bring the medication administration log to the next study visit for review. Medication administration logs will be collected and a new log will be given with each bottle/refill of study medication.

## In Depth Interviews and Qualitative Analysis

At the End of Treatment visit (V10) and End of Study visit (V14) a trained interviewer will conduct an in depth qualitative interview about Hepatitis C infection, HCV transmission risk behaviors, and HCV treatment during the postpartum period. All interviews will be recorded and transcribed verbatim. The original recordings will be destroyed after transcription. Following transcription, the research team will develop a qualitative codebook using an editing approach to ensure that all relevant topics and themes are represented. Two trained qualitative coders will then be trained in the codebook. 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. Thematic analysis will then be completed using a constant comparative method.

## 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*

*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.

## Laboratory Evaluations

UPMC's Clinical Laboratory will be used for HCV treatment laboratory evaluations:

- Blood
    - HCV antibody
    - HCV RNA viral load
    - Hepatitis C genotype
    - HIV
    - HepBsAg, HepBcAb, HepBsAb
    - HepB DNA
    - HepA total Ab
    - CBC with differential and platelets
    - CMP
    - GGT

Colorado Antiviral Pharmacology Laboratory:

- PK blood testing
- Breastmilk

## 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 will be transported from the Clinical Research site to Magee-Womens Research Institute 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.

## 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 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.

# ASSESSMENT OF SAFETY

## Safety Monitoring

The Principal Investigator (PI, Dr. Krans) is responsible for continuous close safety monitoring of all study participants, and for notifying Gilead Sciences, and the IRB if unexpected and/or serious events occur. An independent physician safety monitor who is not otherwise involved in the study will be identified and 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.

## Clinical Data and Safety Review

The PI is responsible for the initial evaluation and reporting of safety information at the participant level and for alerting Gilead Sciences if unexpected concerns arise. Additional reviews may be conducted as dictated by the occurrence of certain events.

The PI and research team will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. The PI and the independent safety monitor will meet approximately every month to review clinical data reports. The content, format and frequency of the clinical data reports will be agreed upon by the independent safety monitor, Gilead Science and the research team in advance of study implementation. In addition to routine safety data reviews, the independent safety monitor and 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, 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.

## Adverse Events Definitions and Reporting Requirements

### 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. Since the women enrolled in this study will be receiving prenatal care at Magee-Womens Hospital the women 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. 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 until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to investigational medication, including gradable laboratory findings. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009).

### Serious Adverse Events

An SAE will be defined as an AE that:

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

### 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)

## Expedited Adverse Event Reporting Requirements

### Reporting Requirements for this Study

All adverse events will be reported to Gilead Sciences on a monthly basis. All serious adverse events will be reported to the University of Pittsburgh Institutional Review Board, the FDA and Gilead Sciences according to the University of Pittsburgh IRB's reporting guidelines.

### Grading Severity of Events

The most current Division of DAIDS 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/.

## Regulatory Requirements

Information on all reported 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.

## 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.

**Managing any potential emotional distress from participating in this study:**

From prior studies, we have established relationships with experts in the fields of mental health, social work, and intimate partner violence, and with their advice we have developed several strategies to minimize and manage potential emotional distress that may occur as a result of participating in our research study.

The research staff and investigators who will be conducting the research activities will be trained regarding how to handle any situations in which a patient reveals her desire to change her situation, asks for additional

advice or information regarding her alcohol or drug use, reveals other risks such as depression or suicidality, or discloses that she may be in grave danger.

Because problems with alcohol, drug, and persistent tobacco use in women are often associated with other issues such as mental illness and intimate partner violence (IPV), all research team members will receive training in identifying and dealing with crises associated with these other conditions.

In any of the above cases or in the case that participation in the study elicits any emotional distress, Magee-Womens Hospital social workers will be available at all times by pager. All of these social workers have received extensive training in behavioral health assessment/management, suicide intervention, and IPV and crisis management. Clinical investigators will also be available for consultation on difficult cases at all times by pager. The Women's Center and Shelter of Greater Pittsburgh's telephone hotline, supported 24 hours a day, will also be available. Although we recognize that contacting the social workers for intervention with our study participants constitutes an intervention that directly impacts the study results, our first priority is the safety and well-being of our participants. In these situations, we will first ensure the appropriate care of the participants and then account for the events when performing our analyses.

Any participants who are in immediate danger, threaten suicide, or constitute any potential harm to others will be immediately referred to social workers or behavioral medicine experts who are on call for all hospital patients. The usual protocol for social work or behavioral medicine in our institution is to communicate and collaborate with the obstetric care providers. We will thus leave the decision to contact and inform the obstetric care providers of any relevant and ongoing behavioral health concerns to the social work or behavioral medicine experts.

# 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 if they feel that the risk of study medication continuation outweighs the benefits of study medication continuation. The physician investigators will document all permanent discontinuations on applicable CRFs.

## Grading System

AE severity grading is described in Section 8.3.1.

## Dose Modification Instructions

No dose modifications will be permitted in this study.

## General Criteria for Permanent Discontinuation of Study Medication

A participant will be permanently discontinued from medication use by the physician investigators for any of the following reasons, according the HCV treatment guidelines:

- 5-fold or greater increase in ALT or AST at the V1 or V2 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) V1 or V2 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
- HIV seroconversion occurs during the time of study medication use
- Participant is unable or unwilling to comply with required study procedures
- If the participant 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 investigators. 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.

## 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 investigators 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.

## 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 participant will be permanently discontinued from medication use by the physician investigators.

## 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 with 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

# STATISTICAL CONSIDERATIONS

## Overview and Summary of Design

This is a Phase IV, single-arm, open label pilot study of immediate postpartum treatment for chronic HCV infection in 30 HCV-infected women with Opioid Use Disorder with a 12-week course of SOF/VEL FDC.

## 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 delivery and 18 months postpartum. Study medication will be initiated in the immediate postpartum period (1-14 days after delivery). Infants will be enrolled upon delivery and their medical records will be reviewed at approximately 18 months of age.

### Primary Endpoints

- Treatment feasibility will be established through the successful recruitment and enrollment of participants, administration of sofosbuvir/velpatasvir in the postpartum period and ability to determine SVR at 3 months following treatment completion.
- Acceptability of sofosbuvir/velpatasvir will be evaluated by self-report of treatment side effects and barriers and facilitators to treatment adherence.
- Adherence to sofosbuvir/velpatasvir will be evaluated with medication diaries, an assessment of missed doses, pill counts and attendance at opioid maintenance treatment visits.

### Secondary Endpoints

- Breast milk concentrations of SOF, GS-331007, and VEL
- Rates of IVDU recidivism
- HCV reinfection
- Patient centered outcomes such as health related QOL will be assessed at 6, 9 and 12 months following treatment completion

## Sample Size

To evaluate the primary objective, we estimate a desired sample size of 30 participants. A subset of 5 participants will participate in the PK visits. Approximately 375 OD pregnant patients receive prenatal and postpartum care at MWH each year and approximately 50% are HCV infected. Anticipating a 75% enrollment rate, 30 HCV infected pregnant patients will be available for participation following a 12 month enrollment period.

## Participant Accrual and Retention

Pregnant and postpartum 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 to minimize possible bias associated with loss-to-follow-up. Participant contact information will be reviewed at each follow-up visit and participants will be asked to contact study staff if their contact information changes. If a participant cannot be contacted using her primary contact information, alternative contacts will be called in order to reach the participant. A maximum of 10% loss-to-follow-up will be targeted.

## Data Analysis

Validated survey instruments will be used to collect data on patient-centered outcomes such as HCV health related quality of life (QOL). Protocol-specific survey instruments will be used to record treatment side effects, medication diaries, an assessment of missed doses and pill counts. All responses to data collection materials will be transferred into a secure database. Preliminary statistical analyses will focus on data checks for

completeness and accuracy and address any issues with data quality. Descriptive summaries will include the mean and standard deviations (or medians and quartiles for skewed distributions) for continuous variables and frequencies and proportions for categorical variables. 95% confidence intervals for means and proportions will be calculated. To visually examine distributions, boxplots and histograms will be constructed for continuous variables. Poisson regression analyses will be conducted for rates of SVR following treatment. Logistic regression analysis will be used for the remaining dichotomous outcome variables (IVDU relapse, HCV reinfection). Outcomes will be summarized overall and by race, age, parity, income, and insurance. All analyses will be conducted using STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX).

**Analysis of SVR12**

Approximately 98% of patients treated with SOF/VEL for 12 weeks obtained an SVR12. Therefore, we estimate that at least 29 out of the 30 chronically HCV-infected postpartum women will have a SVR12 after treatment.

**Analysis of breastmilk pharmacokinetics**

Drug concentrations in breastmilk and plasma will be listed and summary statistics will be used to describe the derived PK parameters. Nonlinear mixed effects modeling will be used to determine the pharmacokinetics of SOF, GS-331007, and VEL in breastmilk and plasma. The ratio of milk to plasma will be reported.

**Analysis of Safety Endpoints**

Rates of abnormal safety laboratory assessments will be compared to those reported in the literature on historic controls. Statistical significance will be determined by chi-square test.

**Study Oversight**

No Data and Safety Monitoring Board oversight is planned for this study, however, a medical monitor will provide oversight for this study. The medical monitor will be an independent physician investigator from the University of Pittsburgh who has experience monitoring clinical trials among subjects with chronic HCV infection. 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 medical monitor may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

# DATA HANDLING AND RECORDKEEPING

## Data Management Responsibilities

Study Case Report Forms will be developed by the study team in conjunction with data management.

## 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. All physical source documents will be stored in the participant's study chart, labeled with the participant ID number in a locked file cabinet in a locked office in the Pregnancy Recovery Center. All interactions with patients should be tracked, including but not limited to: dates they were called enrolled, recruited and consented, dates they completed each survey, dates interviewed, interviewer, dates they were contacted (and method of contact) to completed all follow up assessments, dates they completed follow up assessments, any and all study payments using the Participant Tracking Database. This database is password-protected and will be backed up weekly

### Quality Control and Quality Assurance

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

## CLINICAL SITE MONITORING

As this is an investigator initiated study, monitoring will be performed by the 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 Office for Human Subject Research (ECO-HSR), Research Conduct and Compliance Office will also oversee study activities. The ECO-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 ECO-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 ECO-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.

## 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.

### 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.

## Study Coordination

Elizabeth Krans MD MSc is the study principal investigator. 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.

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.

## Risk Benefit Statement

### Risks

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

It is also not known if SOF/VEL is present in human breast milk. If the participant intends to breast feed, she will not be eligible to enroll in this study.

There is a potential risk that the hepatitis virus may become resistant to SOF/VEL 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.

The following side effects have been associated with the use of oral SOF/VEL used daily for 12 weeks of duration in men and non-pregnant women. With the exception of asthenia, each of these adverse reactions occurred at a similar frequency or more frequently in subjects treated with placebo compared to subjects treated with SOF/VEL (asthenia: 3% versus 5% for the placebo and SOF/VEL groups, respectively).

| | Percentage of Participants N=624 |
|---|---|
| Headache | 22% |
| Fatigue | 15% |
| Nausea | 9% |
| Asthenia | 5% |
| Insomnia | 5% |

There are risks of alterations in laboratory values with the use of this medication. Previous studies have shown the following:

*Lipase Elevations:* In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with SOF/VEL and placebo for 12 weeks, respectively; and in 6% and 3% of subjects 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 10xULN were reported in 1% and 0% of subjects treated with SOF/VEL and placebo for 12 weeks, respectively; and in 2% and 1% of subjects 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 risks of confidentiality loss.

Participants will be asked to provide personal/protected health information (PHI). All attempts will be made to keep PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see PHI. All paper records will be kept in a locked file cabinet or maintained in a locked room at 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).

### Benefits

Participants may or may not benefit from being in this study. Participants may benefit from this study though the opportunity to receive treatment for their chronic HCV. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to evidence-based guidance for the treatment of chronic hepatitis C infection in the postpartum period in conjunction with opioid maintenance treatment.

## Informed Consent Process

Written informed consent will be obtained from each study participant prior to performing study procedures. 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 will 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 safety and efficacy profile of the study medication
- 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 potential social harms associated with study participation (and what to do if such harms are experienced)
- The benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

- Optional participation in the breastmilk PK portion of the study. Participants who wish to participate in the PK portion of the study will sign an additional informed consent form covering the procedures and potential risks and benefits of participating in this portion of the study.

## 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 Magee Medical Building. 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 separately from study records identified by code number following completion of the study. All local databases will be secured with password protected access systems. 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

## Special Populations

### Pregnant Women

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

### Children

Infant procedures will be conducted 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).

## Compensation

Pending IRB approval, 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 and additional incentives for making study appointments within the window period.

## 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.

## Access to HIV-related Care

### 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 will also have HIV screening as part of routine prenatal care at 28 weeks' gestation, and if clinically indicated during the study.

### Care for Participants Identified as HIV-Positive

Identified as HIV-Positive Prior to Enrollment

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).

Identified as HIV-Positive While on Study Medication

The participant will discontinue with the study medication and study procedures, and will be immediately referred to PACT.

### 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.

## 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 30 days prior to submission for their review and approval.

## APPENDIX

**APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS**

| | Screening A (V1) | Screening B (V2) | Enrollment (V3) | Treatment Initiation (V4) | Breastmilk PK Visits* | Treatment Follow Up (V5-9) | End of Treatment (V10) | Post treatment (V11) | 12 month follow up (V12) | End of Study (V13) |
|---|---|---|---|---|---|---|---|---|---|---|
| **ADMINISTRATIVE AND REGULATORY** | | | | | | | | | | |
| Informed consent(s) | X | | X | | X | | | | | |
| Assess informed consent comprehension | | | X | | | | | | | |
| Sign medical record releases | X | | | X | | | | | X | X |
| Assignment of PTID | | | X | | | | | | | |
| Collect/review locator information | X | X | X | X | X | X | X | X | X | X |
| Visit questionnaire | | X | | | | X | X | X | | X |
| Eligibility assessment | X | X | | | | | | | | |
| Eligibility confirmation | | X | X | X | | | | | | |
| Reimbursement | | | | | X | | | | | |
| Record/ update AEs | | | | | X | X | X | X | X | X |
| Schedule next visit | X | X | X | X | X | X | X | X | X | |
| **BEHAVIORAL** | | | | | | | | | | |
| Protocol adherence counseling | | X | X | X | X | X | X | X | X | |
| Contraception counseling | | | | X | | | | | | |
| Medication use/adherence counseling | | | | X | X | X | X | *** | | |
| Qualitative interview | | | | | | | X | | | X |
| **CLINICAL** | | | | | | | | | | |
| Review medical history and medical records, document findings | X | X | X | X | | X | X | X | X | X |
| Concomitant medications | X | X | X | X | | X | X | | | |
| Consult with hepatologist | | X | X | | | | *** | X | | |
| Physical examination (full or modified) | | X | X | | | | | | | |
| Provide available test results | | | X | X | | X | X | X | X | X |
| Administer timed medication dose | | | | | X | | | | | |
| **LABORATORY** | | | | | | | | | | |
| *Collect breastmilk* | | | | | X | | | | | |
| *Collect Blood* | | X | | X | X | X | X | X | X | |
| BloodHIV: HCV antibody | X** | | | | | | | | | |
| BloodHIV: HCV RNA viral load | X** | | | | | X (V6 or 7) | X | X | X | |
| BloodHIV: HCV Genotype | | X** | | | | | | | | |
| BloodHIV: HCV Resistance testing | | | | | | | *** | *** | | |
| BloodHIV: HepBsAg | X** | | | | | | | | | |
| BloodHIV: HepBcAb, HepBsAb | | X | | | | | | | | |
| BloodHIV: HepA total Ab | | X | | | | | | | | |
| BloodHIV: HIV | X* | | | | | | | | | |
| BloodHIV: CBC | | | | X* | | X (V6 or 7, | X | X | X | |
| CMP | | X | | X* | | X (V6 or 7, | X | X | X | |
| GGT | | | | X | | X (V6 or 7, | X | X | X | |
| PK sampling breastmilk and blood | | | | | X | | | | | |
| **STUDY MEDICATION** | | | | | | | | | | |
| Provision of Study Medication | | | | X | X | X | | | | |
| Collect Remaining Study Medication | | | | | | | X | | | |

*For a subset of participants, n=5 **If not collected as part of standard prenatal/postpartum care; can be collected at V2 if within 3 months of treatment initiation ***If clinically indicated