with chronic hepatitis C infection genotypes 1-6 (AASLD and IDSA HCV Guidelines, October, 2016)

Duration of treatment: Subjects will be treated for 12 weeks.

Main Eligibility Criteria:

Inclusion Criteria for clinical subjects:
Subjects must meet all of the following inclusion criteria to be eligible for participation in this study.

1. Willing and able to provide written informed consent
2. Age ≥ 18 years
3. Confirmation of chronic HCV infection as documented by a positive HCV antibody test at least 6 months prior to the Baseline/Day 1 visit OR by patient report of infection for at least 6 months prior to the baseline/day 1 visit AND positive HCV RNA test at screening
4. HCV genotype 1, 2, 3, 4, 5 or 6
5. In stable remission from opioid use on buprenorphine/naloxone for at least 12 weeks
6. Within the following laboratory parameters as assessed at the screening visit:
    a. HCV RNA quantifiable
    b. Screening rhythm strip without bradycardia (heart rate > 60 or, if on beta blocker, > 55 BPM)
    c. ALT ≤ 10 x ULN
    d. AST ≤ 10 x ULN
    e. Direct bilirubin ≤ 1.5 x ULN
    f. Platelets > 60,000
    g. HbA1c ≤ 13%
    h. Creatinine clearance ≥ 30 mL/min, as calculated by the Cockcroft-Gault equation
    i. Albumin ≥ 3g/dL
    j. INR ≤ 1.5 x ULN or on an anticoagulant regimen affecting INR
7. Female subject is eligible to enter if it is confirmed that she is:
    a. Not pregnant or nursing
    b. Not of childbearing potential (i.e. s/p hysterectomy, oophorectomy or has medically documented ovarian failure, or are postmenopausal women > 50 years of age with cessation of menses for 12 months or greater)
    OR
    Of childbearing potential with a negative serum pregnancy test within 2 weeks of screening, a negative urine pregnancy test on Day 1, and a commitment to either abstain from intercourse or consistently use an acceptable method of birth control (Appendix 4)

IEC	independent ethics committee
IND	Investigational New Drug (Application)
INR	International Normalized Ratio of prothrombin time
IRB	institutional review board
IUD	intrauterine device
IU	international units
IV	Intravenous
Kg	Kilogram
L	Liter
LDL	low-density lipoprotein
LLN	lower limit of the normal range
LLOQ	Lower limit of quantification
LLT	Lower-Level Term
MCV	mean corpuscular volume or mean cell volume
Mg	Milligram
Mm	Millimeter
mL	Milliliter
Min	Minute
mmHg	millimeters mercury
P-gp	P-glycoprotein
PG	Pharmacogenomic
PO	by mouth
QD	once daily (use only in tablets)
PK	Pharmacokinetic
PT	preferred term or prothrombin time
RBC	red blood cell count
RNA	ribonucleic acid
RVR	rapid virologic response
SADR	Serious adverse drug reaction
SAE	serious adverse event

scheduled visits to an outpatient addiction clinic for buprenorphine/naloxone replacement therapy and mental healthcare.

4.2 Secondary Objectives:

- To assess the impact of HCV treatment on health-related quality of life among subjects on buprenorphine/naloxone therapy.
- To assess adherence to Epclusa therapy in subjects administered treatment in the context of visits to an outpatient addiction clinic for buprenorphine/naloxone replacement therapy and mental healthcare.

4.3 Exploratory Objective:

- To design and assess a curriculum and mentorship program to support psychiatrists with managing HCV infection. For the purpose of this study, the curriculum will be tailored to the management of HCV genotypes 1, 2, 3, 4, 5 and 6 and treatment with Epclusa.

5 STUDY DESIGN

5.1 Treatment Plan and Regimen

This is a single arm pilot study of administering HCV treatment at an outpatient addiction clinic staffed by psychiatrists at Cambridge Health Alliance. Approximately 20 subjects will be enrolled and treated with Epclusa tablet once daily for 12 weeks.

5.2 Subject Recruitment

Patients with HCV infection already engaged in addiction treatment at Cambridge Health Alliance will be identified by members of the study team and/or the psychiatrist-buprenorphine/naloxone providers and approached regarding participation. Importantly, HCV status will already be recorded in the medical record as all patients are routinely screened for hepatitis C infection upon entry into the OAS program.

Psychiatrist-buprenorphine/naloxone prescribers will be approached by study investigators to participate based on meeting the entry criteria as providers employed at the outpatient addiction clinic at Cambridge Health Alliance.

5.3 Visit Schedule

All study visits will take place at the outpatient addiction clinic at Cambridge Health Alliance. A study coordinator employed by Community Research Initiative will conduct the study visits in conjunction with the psychiatrist-buprenorphine/naloxone provider at Cambridge Health Alliance.

Subjects will complete all of the following visits: Screening, Baseline/Day 1, On-Treatment Visits approximately biweekly throughout treatment, and Post-Treatment Visits at Weeks 4 and 12 (from time of last dose of study drug.)

Screening assessments will be completed within 28 days of the Baseline/Day 1 Visit. The screening window may be extended to 42 days prior to Day 1 for subjects with in extenuating circumstances, if approved by Medical Monitor.

The assessments performed at each visit are described in Sections 8.2 and 8.3.

5.4 HCV Virologic Response-Based Treatment Stopping Criteria

Treatment will be stopped if there is a less than 1 log10 decline in HCV RNA after 4 weeks of therapy.

Confirmation should be performed as soon as possible and must occur no later than 2 weeks after an initial observation indicating virologic failure. All subjects who terminate treatment early will complete the Early Termination (ET) Visit, Week 4 and Week 12 Post-Treatment Visits.

5.5 Treatment Discontinuation Criteria

The Medical Monitor should be consulted prior to subject discontinuation when medically feasible. Study drug must be discontinued in the following instances:

- Unacceptable toxicity, as defined in Section 9 of the protocol, or toxicity that, in the judgment of the Sponsor-Investigator or Sub-Investigator(s), compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy of female subject
- HCV efficacy failure as defined in Section 5.3
- Significant protocol violation
- Subject request to discontinue for any reason; it is important to determine and document whether the withdrawal of consent is primarily due to an adverse event (AE), lack of efficacy, or other reason
- Discontinuation of the study at the request of CRI, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

If a subject meets discontinuation criteria during treatment, an Early Termination Visit will be required (Section 8.2.4). Early Termination Visits should be scheduled as soon as possible following discontinuation of treatment. Subjects that discontinue treatment early are still required to complete Post-Treatment Weeks 4, and 12 Visits.

6 SUBJECT POPULATION

6.1 Number of Subjects and Subject Selection

Approximately 20 subjects with chronic HCV infection will be enrolled, including individuals who have compensated cirrhosis and who have been previously treated with pegylated-interferon and ribavirin ± an HCV protease inhibitor. Due to the limited resources available for this proof of concept pilot study, only English-speaking participants will be considered for enrollment.

6.2 Inclusion Criteria for clinical subjects

1. Willing and able to provide written informed consent
2. Age ≥ 18 years
3. Confirmation of chronic HCV infection as documented by a positive HCV antibody test at least 6 months prior to the Baseline/Day 1 visit OR by patient report of infection for at least 6 months prior to the baseline/day 1 visit AND positive HCV RNA test at screening
4. HCV genotype 1, 2, 3, 4, 5 or 6
5. In stable remission from opioid use on buprenorphine/naloxone for at least 12 weeks

If a subject discontinues treatment early for any reason then the following assessments for the Early Termination (ET) Visit must be performed:

- Assessment of AEs and concomitant medications
- Subject completes Quality of Life Surveys (FACIT-F, PROMIS ED -Depression SF8a, SF36)
- Obtain blood samples (Reference Study Procedures Table Appendix 2)
- Obtain urine samples (Reference Study Procedures Table Appendix 2)
- Pregnancy testing for women of childbearing potential only (Reference Study Procedures Table Appendix 2)
- Pregnancy Prevention Counseling
- Assess compliance with study drug dosing regimen including pill count
- Download MEMSCap™ Adherence Data

8.4 Post-Treatment Assessments

All subjects must complete the Post-Treatment visits 4 and 12 weeks following the last dose of study drug.

8.4.1 Post-Treatment Week 4 and 12 (+/- 5 days)

The following procedures/assessments are to be completed:

- Assessment of AEs
- Pregnancy testing for women of childbearing potential only at the Post-Treatment Week 4 visit only (Reference Study Procedures Table Appendix 2)
- Obtain blood samples (Reference Study Procedures Table Appendix 2)
- Additionally, at post treatment week 12 visit only, subject will complete Quality of Life Surveys FACIT-F, PROMIS ED -Depression SF8a, SF36)

Subjects with a HCV RNA > LLOQ at the Post-Treatment Week 12 Visit will return for confirmatory HCV RNA, preferably within 2 weeks.

8.5 Unscheduled Visit

A subject should attend an unscheduled visit if requested by the Sponsor-Investigator or Sub-Investigator(s). The assessments are at the requestor's discretion, and will at a minimum collect AE and concomitant medication information.

8.6 Assessments for Premature Discontinuation from Study Dosing

If a subject discontinues study drug dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures. If this is not possible or acceptable to the subject or Sponsor-Investigator, the subject may be withdrawn from the study.

8.7 Procedures and Specifications

8.7.1 Clinical Laboratory Analytes

- Blood Collection
    - All required laboratory blood assessments will be conducted as described in Appendix 2, and per the discretion of the Sponsor-Investigator or Sub-Investigator(s). Additional assessments may be conducted per standard of care at the enrolling site and per the discretion of the Sponsor-Investigator or Sub-Investigator(s).

- Urine Collection
    - Urine assessments for drug screening and pregnancy (in WOCBP) will be conducted as described in Appendix 2. Additional assessments may be conducted per standard of care at the enrolling site and per the discretion of the Sponsor-Investigator or Sub-Investigator(s).

8.7.1.1 Management of Positive Urine Drug Screening Assessment

In the event that a study subject has a positive urine drug screen the subject will be managed according to the judgment of the Sub-Investigator. Interventions may include increased frequency of study visits, additional remote monitoring and support, and enhanced supplemental services for substance use prevention.

8.7.2 Medical History

Selected medical history will be collected by subject self-report and available medical records, including:

- risk factor for HCV
- estimated duration of HCV infection
- prior assessments of fibrosis
- HCV genotype if known
- prior HCV treatment
- comorbid liver diseases including hemochromatosis, autoimmune hepatitis, alpha-1-antitrypsin deficiency, obesity
- history of hepatic decompensation including variceal bleed, ascites, and encephalopathy
- clinically significant, active in the last year and ongoing conditions at time of enrollment

8.7.3 Quality of Life Surveys

- Quality of life surveys included in this study are Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), PROMIS Short Form v1.0 - ED-Depression 8a (PROMIS ED -Depression SF8a), Short Form Health Survey (SF36) which will be completed by subjects at Baseline/Day 1, on treatment week 4 visit, End of Treatment/Early Termination visits and post treatment week 12 visit. The subject should read and complete the surveys by himself/herself and write/mark answers directly onto the questionnaire.

8.7.4 Missed Visits

In the event that a subject misses a scheduled clinic visit, the study staff will telephone the subject within 24 hours of the missed visit. Another study visit will be scheduled for as soon as possible. The study staff will counsel subjects on how to continue study drug dosing from their back-up medication pack until the rescheduled visit, to ensure no missed doses.

8.7.5 Mentorship

Participating psychiatrists must consent to participate in the study. A consent form will be provided to the psychiatrist-buprenorphine/naloxone provider prior to the initial training session with ample time for the psychiatrists to read the consent and have their questions answered. They will be offered the opportunity to review the consent with study investigators by telephone or in face-to-face meetings with a study investigator or study team member. If they agree to consent, the signing of the consent will occur in the presence of a study team member, who will cosign the document. A copy of the signed consent will be provided to each psychiatrist-buprenorphine/naloxone prescriber. The original will be kept in a secure, locked study file at the CRI facility. Study consent procedures consistent with CRI SOP for informed consent will be followed (outlined in detail in section 8.1).

After consenting to participate, but prior to screening the first subject, the psychiatrists at the outpatient addiction clinic will undergo a training session with the Sponsor-Investigator which will address the management of HCV. The following topics will be addressed:

- Pathogenesis of HCV infection
- Goals of therapy/benefits of curing HCV
- Pre-treatment assessment, including diagnosis of cirrhosis
- Usage of Epclusa

The session will be based on the teaching slides in Appendix 6.

In addition, the Sponsor-Investigator will provide regularly scheduled weekly telephone support to the psychiatrists.

The psychiatrists' comfort level with providing care for patients with HCV infection will be determined by a questionnaire administered prior to the training session, after the training session, and after 4 months of actively treating subjects (Appendix 3). All responses to these questionnaires will be kept strictly confidential.

8.7.6 Location of Study Activities

This protocol is intended for study and implementation within the outpatient addiction clinic at Cambridge Health Alliance. The Community Research Initiative Sponsor-Investigator and study team will collaborate with the psychiatry team at the outpatient addiction clinic to implement the study and collect study data at the addiction clinic location on pre-specified days.

All procedures with study participants will take place at the outpatient addiction clinic and at a phlebotomy lab one flight downstairs from the addiction clinic. No study-related records or study drug will be stored at the outpatient addiction clinic. For each day session of study visits at the Sub-Investigator's clinic, study staff will transport documentation and study drug, on the day of the session, for only the subjects scheduled for visits that day. Study staff will bring blank source documentation worksheets, questionnaires, and informed consents as needed. Study staff will transport investigational drug securely to the clinic for the subjects scheduled, per CRI SOPs. Refer to section 7.4 for further detail on storage and transportation of study-related medication. Upon completion of source documentation worksheets, questionnaires, and ICFs, the study coordinator will immediately transport these study documents and returned study medication containers to the CRI office for secure storage.

To ensure maintenance of subject confidentiality, the following procedures with study records will be followed:

- Any documentation from the subject medical record that contains subject identifying information will be faxed from the clinic to Community Research Initiative via secure fax, for inclusion in the subject source document. These items will be certified copies of the original faxed documents.
- Informed consent documents must include patient names and signatures and in accordance with the regulations, must be original documents. These documents will be transported by the study coordinator directly from the clinic to Community Research Initiative for secure storage. They will be transported in a private vehicle (i.e. livery or privately owned automobile) in the direct possession of the study coordinator and in a securely locked carry-case.
- To maintain subject confidentiality, all other source documentation worksheets completed at study visits will not have patient names or identifying information. These documents will be

completed utilizing the unique 3 letter code and study specific numeric code number assigned upon screening and enrollment.

Community Research Initiative will maintain and store all essential documents and study medication for this study. All study data entry into the eCRF will occur at the CRI office by trained study staff. Ongoing regulatory filing, maintenance of essential documents and monitoring of study data will occur at the CRI office and be conducted by trained study staff.

9 ADVERSE EVENTS AND TOXICITY MANAGEMENT

Given that subjects will receive standard of care evaluation and treatment for their chronic hepatitis C infection, we believe that study participation poses minimal excess risk. Indeed, we believe that subjects will benefit from improved access to this important treatment which will be provided at a convenient location by a known physician under the guidance of an infectious disease physician with extensive experience treating HCV infection. Potential risks to study participation may include

1. Increased frequency of appointments at the outpatient addiction clinic for those who are usually seen less frequently than every 2 weeks.
2. Increased duration of the appointments at the outpatient addiction clinic for completion of study procedures.

9.1 Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

9.1.1 Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the Screening Visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

Clarification of Serious Adverse Events:

- Death is an outcome of an adverse event, and not an adverse event in itself. In reports of death due to "Disease Progression", where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drugs.
- All deaths, regardless of cause, must be reported for subjects on study and for deaths occurring within 30 days of the last study evaluation.
- "Occurring at any dose" does not imply that the subject is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject is at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AE's. If a complication prolongs hospitalization, it is an SAE.
- "Inpatient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms

NOTE: The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

9.3 Sponsor-Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur after the subject first consents to participate in the study (i.e., signing the informed consent) and throughout the duration of the study, including the protocol-required post-treatment follow-up period, will be reported to CRI as instructed. This also includes any SAEs resulting from protocol-associated procedures performed from screening onwards.

All AEs, regardless of cause or relationship, that occur from initiation of study drug until 4 weeks after last administration of study drug shall be reported to the CRF/eCRF database as instructed.

Any SAEs and deaths that occur after the Post-Treatment follow-up visit OR within 30 days of the last dose of study drug (whichever is longer), regardless of causality, shall also be reported.

All AEs should be followed up until resolution or until the adverse event is stable, if possible.

Investigators are not obligated to actively seek SAEs after the 30 day period. However, if the Investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of study drug, he/she should promptly document and report the event for further assessment by CRI study team.

CRI has requirements for expedited reporting of serious adverse events which meet specific requirements of worldwide regulatory authorities. The reporting period begins when a subject signs the informed consent, and ends 30 days after discontinuation of dosing or completion of the subject's participation in the study if the last scheduled visit occurs at a later time. CRI and WIRB (or local IRB if not using the central IRB) will be notified within 24 hours of the Sponsor-Investigator's knowledge of an event. The procedures for Investigators and study staff reporting all serious adverse events, regardless of causal relationship, are as follows:

- Study staff notify the CRI Medical Monitor and Principal Investigator via 617-502-1799.
- The study staff will complete the IRB Promptly Reportable Information Form and MedWatch 3500A. The Principal or Sub-Investigator must sign and date the form. If only limited information is available, follow up reports are required. If the Investigator believes that an SAE is not related to the investigational product but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the potential relationship should be specified in the narrative section of the SAE report. If an ongoing SAE changes in its intensity or relationship to the investigational product, a follow up SAE report will be filed within 24 hours of awareness. As follow-up information becomes available, it should be sent immediately using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. The original SAE form must be kept on file at the study site.
- Record the event on the AE eCRF
- For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents with subject personal identifying information redacted.
- Additional information may be requested to ensure the timely completion of accurate safety reports.

Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's eCRF and the event description section of the SAE form.

9.4 CRI Reporting Requirements

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.

If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms. The following information should be captured for all AEs: onset, duration, intensity, seriousness, relationship to study drug, action taken, and treatment required. If treatment for the event was administered, it should be recorded in the medical record. The Sponsor-Investigator must retain and notify the IRB with any additional information requested, notably for reported deaths of subjects.

In accordance with relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the Sponsor-Investigator will report all serious adverse events, including reports of pregnancies, overdose and cancer that may or may not be associated with an adverse event to the FDA via filing of a FDA MedWatch 3500A form.

Assessment of expectedness for SAEs will be determined using reference safety information specified in the Investigator's Brochure.

Gilead Sciences, Inc. will provide timeline notification of relevant SUSAR reports. The Sponsor-Investigator must ensure notification of all study staff of the contents of the SUSAR reports, and will notify the IRB/IEC of SUSAR reports in accordance with the IRB/IEC policy.

9.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to investigational medicinal product interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 9.1.1 and 9.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (i.e., anemia) not the laboratory result (i.e., decreased hemoglobin).

Severity should be recorded and graded according to the GSI Grading Scale for Severity of AEs and Laboratory Abnormalities (Appendix 4). For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

9.6 Subject Stopping Rules

The Medical Monitor should be consulted prior to dose discontinuation of Epclusa unless the Investigator believes that immediate action is warranted to ensure the continued safety of the subject.

Due to a clinical or laboratory event, administration of all study drugs(s) may be discontinued. There is no option for Epclusa dose reduction. If Epclusa is stopped for toxicity, it must not be restarted Post-Treatment Weeks 4 and 12 Visits must also be scheduled.

Subjects who meet any of the following laboratory criteria must stop all study drug(s):

- Elevation of ALT and/or AST >5x Baseline/Day 1 or nadir, confirmed by immediate repeat testing

- Abnormal elevation of ALT >3x Baseline/Day 1 and total bilirubin >2 x ULN, confirmed by immediate repeat testing
- Elevation of ALT >15 x ULN, confirmed by immediate repeat testing
- Any Grade 3 or greater rash associated with constitutional symptoms
- Any Grade 4 adverse event or laboratory abnormality assessed as related to Epclusa

9.7 Special Situations Reports

9.7.1 Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose reports and pregnancy reports regardless of an associated AE. These also include reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure.

- A pregnancy report is used to report any pregnancy following maternal or paternal exposure to the medicinal product.
- Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.
- Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.
- Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.
- An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the Investigator has reason to suspect that the subject has taken the additional dose(s).
- Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

9.8 Reporting Special Situations

9.8.1 Instructions for Reporting Pregnancies

Any pregnancy of a woman participant or female partner of a male study participant should be immediately reported to the Medical Monitor and Sponsor-Investigator. All pregnancies will be reported to the IRB/IEC within 24 hours of notification, and followed-up through the end of the pregnancy. Pregnancy outcomes will be recorded and reported to the IRB/IEC.

The Sponsor-Investigator will collect information on all pregnancies that are identified after the subject first consents to participate in the study (i.e., signs the informed consent) and throughout the study, including the post study drug follow-up period.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) will be reported by the Sponsor-Investigator within 24

hours as an SAE to the IRB/IEC. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as an SAE to the IRB/IEC.

Furthermore, any SAE occurring as an adverse pregnancy outcome post study will be reported to the IRB/IEC.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome of the pregnancy, whether the end of the pregnancy occurs after the study has been completed or during study participation, will be recorded. Outcomes that meet the definition of reportable to the IRB/IEC and FDA will be reported by CRI.

Pregnancies of female partners of male study subjects exposed to the study drug will also be followed closely and relevant information will be collected. Monitoring of the partner will continue until the conclusion of the pregnancy. The outcome will be collected and may be reported to the IRB/IEC and FDA.

Refer to the study operations manual for pregnancy information collection and reporting instructions.

AEs and SAEs related to the pregnancy that affect the mother and/or the fetus will be reported via FDA MedWatch Form 3500a when the Sponsor-Investigator assesses the adverse even to be possibly associated with the study product used during pregnancy. Instances of reportable pregnancy related SAE/AEs include but are not limited to: fetal death, miscarriage, spontaneous abortion, fetal adverse reaction, congenital anomaly and defect.

Additional reporting of pregnancy and outcomes to the study drug manufacturer may also occur.

9.8.2 Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to the CRI Medical Monitor within 24 hours of becoming aware of the situation. These reports must consist of situations that involve study drug, but do not apply to concomitant medications. Except for situations that result in AEs, special situations involving concomitant medications will not be reported. Any inappropriate use of medications prohibited by this protocol should not be reported as “misuse,” but may be more appropriately documented as a protocol deviation.

Refer to the study operational manual for full instructions on the mechanism of special situation capture and collection.

Note: All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

In addition to reporting SAEs and special situations to the IRB/IEC and regulatory authorities per the applicable recommendations and regulations, the Sponsor-Investigator will notify Gilead Sciences, Inc. of all safety information, including SAEs and special situation reports within 15 days of awareness of the safety information and in accordance with applicable laws and regulations. All reports will be addressed to Gilead at the attention of:

Gilead Sciences, Inc.
Drug Safety & Public Health
333 Lakeside Dr.
Foster City, CA 94404
Fax: 650-522-5477

10.2 Analysis Conventions

10.2.1 Analysis Sets

10.2.1.1 Efficacy

The analysis set for antiviral activity analyses will be subjects who were enrolled into the study and received at least one dose of study drugs.

10.2.1.2 Safety

The primary analysis set for safety analyses will include subjects who received at least one dose of study drug.

Treatment-emergent data will be analyzed and defined as data collected from the first dose of study drug through the date of last dose of study drug plus 30 days.

10.3 Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. Other than the endpoints discussed below, values for missing data will not be imputed.

For the analysis of post-baseline categorical efficacy endpoints, if a data point is missing and is preceded and followed in time by values that are deemed successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure.

Any subject with missing data due to premature discontinuation of the study drug will be considered a failure at the date of premature discontinuation and all time points subsequent to the date of premature discontinuation if there are no observed values available. If no HCV RNA values are obtained after the last dose of study drug, the subject will be considered a treatment failure for the SVR endpoints.

Where appropriate, safety data for subjects that did not complete the study will be included in summary statistics.

10.4 Demographic Data and Baseline Characteristics

Demographic data will include sex, self-identified race, self-identified ethnicity, and age.

Baseline characteristic data will include HCV RNA level, calculated FIB-4 index, and Fibrosis Score on FibroSure®. Demographic and baseline characteristics will be summarized using descriptive statistics: means and standard deviations for continuous characteristics such as age and frequencies/percentages for categorical measures such as sex and race. HCV RNA level will be reported as the categories “below LLOQ” or “detectable.”

10.5 Primary Analysis

The primary efficacy endpoint is SVR-12 (HCV RNA < LLOQ 12 weeks after discontinuation of study treatment). The percent of patients achieving SVR-12 and its 95% confidence interval of SVR-12 will be reported.

10.6 Secondary Analysis

Adherence:

- Percentage of patients who miss 1-4% of doses, 5-9% of doses, and 10-20% of doses and > 20% of doses and the 95% confidence interval will be reported. The percentage of doses taken out of total doses prescribed will be reported with its 95% confidence interval.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin HIV POSITIVE **Adult and Pediatric ≥ 57 Days**	 8.5 to 10.0 g/dL 85 to 100 g/L	 7.5 to < 8.5 g/dL 75 to < 85 g/L	 6.5 to < 7.5 g/dL 65 to < 75 g/L	 < 6.5 g/dL < 65 g/L
HIV NEGATIVE **Adult and Pediatric ≥ 57 Days**	10.0 to 10.9 g/dL 100 to 109 g/L OR Any decrease from Baseline 2.5 to < 3.5 g/dL 25 to < 35 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L OR Any decrease from Baseline 3.5 to < 4.5 g/dL 35 to < 45 g/L	7.0 to < 9.0 g/dL 70 to < 90 g/L OR Any decrease from Baseline ≥ 4.5 g/dL ≥ 45 g/L	< 7.0 g/dL < 70 g/L
Infant, 36–56 Days (HIV POSITIVE OR NEGATIVE)	8.5 to 9.4 g/dL 85 to 94 g/L	7.0 to < 8.5 g/dL 70 to < 85 g/L	6.0 to < 7.0 g/dL 60 to < 70 g/L	< 6.0 g/dL < 60 g/L
Infant, 22–35 Days (HIV POSITIVE OR NEGATIVE)	9.5 to 10.5 g/dL 95 to 105 g/L	8.0 to < 9.5 g/dL 80 to < 95 g/L	7.0 to < 8.0 g/dL 70 to < 80 g/L	< 7.0 g/dL < 70 g/L
Infant, 1–21 Days (HIV POSITIVE OR NEGATIVE)	12.0 to 13.0 g/dL 120 to 130 g/L	10.0 to < 12.0 g/dL 100 to < 120 g/L	9.0 to < 10.0 g/dL 90 to < 100 g/L	< 9.0 g/dL < 90 g/L

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Absolute Neutrophil Count (ANC) **Adult and Pediatric, > 7 Days**	1000 to 1300/mm^3 1.00 to 1.30 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	500 to < 750/mm^3 0.50 to < 0.75 GI/L	< 500/mm^3 < 0.50 GI/L
Infant, 2 – ≤ 7 Days	1250 to 1500/mm^3 1.25 to 1.50 GI/L	1000 to < 1250/mm^3 1.00 to < 1.25 GI/L	750 to < 1000/mm^3 0.75 to < 1.00 GI/L	< 750/mm^3 < 0.75 GI/L
Infant, 1 Day	4000 to 5000/mm^3 4.00 to 5.00 GI/L	3000 to < 4000/mm^3 3.00 to < 4.00 GI/L	1500 to < 3000/mm^3 1.50 to < 3.00 GI/L	< 1500/mm^3 < 1.50 GI/L
Absolute CD4+ Count HIV NEGATIVE ONLY **Adult and Pediatric** **> 13 Years**	300 to 400/mm^3 300 to 400/µL	200 to < 300/mm^3 200 to < 300/µL	100 to < 200/mm^3 100 to < 200/µL	< 100/mm^3 < 100/µL
Absolute Lymphocyte Count HIV NEGATIVE ONLY **Adult and Pediatric** > **13 Years**	600 to 650/mm^3 0.60 to 0.65 GI/L	500 to < 600/mm^3 0.50 to < 0.60 GI/L	350 to < 500/mm^3 0.35 to < 0.50 GI/L	< 350/mm^3 < 0.35 GI/L
Platelets	100,000 to < 125,000/mm^3 100 to < 125 GI/L	50,000 to < 100,000/mm^3 50 to < 100 GI/L	25,000 to < 50,000/mm^3 25 to < 50 GI/L	< 25,000/mm^3 < 25 GI/L
WBCs	2000/mm^3 to 2500/mm^3 2.00 GI/L to 2.50 GI/L	1,500 to < 2,000/mm^3 1.50 to < 2.00 GI/L	1000 to < 1,500/mm^3 1.00 to < 1.50 GI/L	< 1000/mm^3 < 1.00 GI/L
Hypofibrinogenemia	100 to 200 mg/dL 1.00 to 2.00 g/L	75 to < 100 mg/dL 0.75 to < 1.00 g/L	50 to < 75 mg/dL 0.50 to < 0.75 g/L	< 50 mg/dL < 0.50 g/L

in addition to condom use by her male partner(s) from the date of screening until 30 days after the last dose of study drug

8. All male study participants must agree to consistently and correctly use condoms with their female partner(s) of childbearing potential and such female partner(s) must agree to use an acceptable method of birth control (listed) from the date of screening until 90 days after the last dose of study drug
9. Male subjects must refrain from sperm donation from the date of screening until 90 days after the last dose of study drug
10. Subject must be in generally good health, with the exception of HCV, in the opinion of the Sponsor-Investigator or Sub-Investigator(s)
11. Subject must be able to comply with dosing instructions for study drug administration and able to complete the study visits, including all required post-treatment visits

Exclusion Criteria for clinical subjects:
Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1. Presence of decompensated cirrhosis as defined by encephalopathy, ascites, or a history of a variceal bleed
2. Prior treatment with direct acting antiviral hepatitis C medications
3. Positive urine drug toxicity test at screening (except for cannabinoids and prescribed medications)
4. Absence of buprenorphine in urine sample at screening
5. Currently pregnant or breastfeeding female
6. Detectable HIV RNA > 50 copies/ml (co-infected subjects with suppressed viral load ARE eligible for participation)
7. Use of any prohibited concomitant medication within 28 days prior to day 1
8. Chronic use of systemically administered immunosuppressive agents
9. Difficulty with blood collection or poor venous access
10. History of solid organ transplantation
11. Known significant allergy to sofosbuvir or velpatasvir
12. Current chronic liver disease of a non-HCV etiology (including hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency)
13. Active HBV infection defined as either a positive HBV surface antigen test or a positive test for HBV DNA. (Subjects who are positive for HBV core antibody but negative for Hepatitis B sAb, sAg, and DNA ARE eligible)

Eligibility Criteria for Provider Participants

All licensed buprenorphine/naloxone providers who are also licensed staff psychiatrists at the outpatient addiction clinic at Cambridge Health Alliance are eligible to participate in the study. Participation will require

1. Attendance at the teaching session on the evaluation and management of hepatitis C infection conducted by the Study Investigator, Dr. Amy Colson (see Appendix 6 for teaching curriculum)

SF36	Short Form Health Survey
SOF	Sofosbuvir
SOP	Standard operating procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained Virologic Response
SVR4	Sustained viral response 4 weeks after discontinuation of study treatment
SVR12	Sustained viral response 12 weeks after discontinuation of study treatment
SVR24	Sustained viral response 24 weeks after discontinuation of study treatment
ULN	upper limit of the normal range
US	United States
VEL	Velpatasvir
WBC	white blood cell count
WOCPB	women of childbearing potential

6. Within the following laboratory parameters as assessed at the screening visit:
    a. HCV RNA quantifiable
    b. Screening rhythm strip without bradycardia (heart rate > 60 or, if on beta blocker, > 55 BPM)
    c. ALT ≤ 10 x ULN
    d. AST ≤ 10 x ULN
    e. Direct bilirubin ≤ 1.5 x ULN
    f. Platelets > 60,000
    g. HbA1c ≤ 13%
    h. Creatinine clearance ≥ 30 mL/min, as calculated by the Cockcroft-Gault equation
    i. Albumin ≥ 3g/dL
    j. INR ≤ 1.5 x ULN or on an anticoagulant regimen affecting INR
7. Female subject is eligible to enter if it is confirmed that she is:
    a. Not pregnant or nursing
    b. Not of childbearing potential (i.e. s/p hysterectomy, oophorectomy or has medically documented ovarian failure, or are postmenopausal women > 50 years of age with cessation of menses for 12 months or greater)
    OR
    Of childbearing potential with a negative serum pregnancy test within 2 weeks of screening, a negative urine pregnancy test on Day 1, and a commitment to either abstain from intercourse or consistently use an acceptable method of birth control (Appendix 4) in addition to condom use by her male partner(s) from the date of screening until 30 days after the last dose of study drug
8. All male study participants must agree to consistently and correctly use condoms with their female partner(s) of childbearing potential and such female partner(s) must agree to use an acceptable method of birth control (listed) from the date of screening until 90 days after the last dose of study drug
9. Male subjects must refrain from sperm donation from the date of screening until 90 days after the last dose of study drug
10. Subject must be in generally good health, with the exception of HCV, in the opinion of the Sponsor-Investigator or Sub-Investigator(s)
11. Subject must be able to comply with dosing instructions for study drug administration and able to complete the study visits, including all required post-treatment visits

Subjects must meet all of the above inclusion criteria to be eligible for participation in this study.

6.3 Exclusion Criteria for clinical subjects

1. Presence of decompensated cirrhosis as defined by encephalopathy, ascites, or a history of a variceal bleed

- Medical/surgical admission for purpose other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative).

9.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 9.1.1 and 9.1.2 If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 9.5.

9.2 Assessment of Adverse Events and Serious Adverse Events

The Investigator or qualified Sub-Investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

9.2.1 Assessment of Causality for Study Drugs and Procedures

The Investigator or qualified Sub-Investigator is responsible for assessing the relationship to study drug treatment using clinical judgment and the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.
- Yes: The adverse event occurred as a result of protocol procedures, (e.g., venipuncture)

9.2.2 Assessment of Severity

The severity grading of AEs will be assessed as Grade 1, 2, 3, or 4 using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (Appendix 4).

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

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10 STATISTICAL CONSIDERATIONS

10.1 Analysis Objectives and Endpoints

10.1.1 Analysis Objectives

Primary Objective:

- To assess the effectiveness, as measured by SVR12, of HCV treatment with Epclusa administered by an internal medicine physician/licensed buprenorphine/naloxone provider during regularly scheduled office visits for buprenorphine/naloxone maintenance therapy.

Secondary Objectives:

- To assess the impact of HCV treatment on health-related quality of life among subjects on buprenorphine/naloxone therapy.
- To assess adherence to Epclusa Therapy in subjects administered treatment in the context of visits to a buprenorphine/naloxone clinic.

Exploratory Objective:

- To design and assess a curriculum and mentorship program to support internal medicine providers with managing HCV infection. The curriculum for the purpose of this study will be tailored to the management of HCV genotype 1 and treatment with Epclusa.

10.1.2 Primary Endpoint

The primary efficacy endpoint is rate of SVR-12 (HCV RNA <LLOQ 12 weeks after discontinuation of study treatment).

10.1.3 Secondary Endpoints

Secondary efficacy endpoints include the following:

- Adherence to Epclusa expressed as percentage of patients who miss 1-4% of doses, 5-9% of doses, 10-20% of doses and > 20% of doses
- Overall ratio of doses taken/doses prescribed in the study population
- Change in scores of QOL questionnaires

10.1.4 Safety Endpoints

The primary safety endpoint is any AE leading to permanent discontinuation of study drug(s).

10.1.5 Other Endpoints of Interest

The Internal Medicine Physician's change in comfort level with providing HCV care over course of study.

Quality of Life:

- Mean in QOL scores from baseline to EOT will be reported with its 95% confidence interval.

Safety Analysis

- All safety data collected on or after the first dose of study drug administration up to 30 days after the last dose of study drug will be summarized**. All AE's of each level severity will be reported with the number and percent who experienced them. The number and percent of patients who stopped the study because of SAE's will be reported, with the 95% confidence interval.**

10.7 Other Analyses

The Internal Medicine Physician's change in comfort level with providing HCV care over course of study will be reported descriptively, with a graph of the comfort level on each of six areas of counseling at each time point measured. In addition, a qualitative description of the Internal Medicine Physician's experience with the training will be reported.

11 SPONSOR-INVESTIGATOR RESPONSIBILITIES

11.1 Good Clinical Practice

The Sponsor-Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject.

The Sponsor-Investigator will ensure adherence to the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators", 21 CFR, part 50, and 21 CFR, part 56.

The Sponsor-Investigator and all applicable Sub-Investigators will comply with 21 CFR, Part 54, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the Sponsor-Investigator's (and any Sub-Investigator's) participation in the study. The Sponsor-Investigator and Sub-Investigator(s) agree to file any change in reportable interests during the study and for 1 year following completion of the study per CRI SOPs. Study completion is defined as the date when the last subject completes the protocol-defined activities.

11.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The Sponsor-Investigator will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The Sponsor-Investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the Sponsor-Investigator.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperfibrinogenemia	> ULN to 600 mg/dL > ULN to 6.0 g/L	> 600 mg/dL > 6.0 g/L	— —	— —
Fibrin Split Product	20 to 40 µg/mL 20 to 40 mg/L	> 40 to 50 µg/mL > 40 to 50 mg/L	> 50 to 60 µg/mL > 50 to 60 mg/L	> 60 µg/mL > 60 mg/L
Prothrombin Time (PT)	> 1.00 to 1.25 × ULN	> 1.25 to 1.50 × ULN	> 1.50 to 3.00 × ULN	> 3.00 × ULN
International Normalized Ratio of prothrombin time (INR)	1.1 to 1.5 x ULN	>1.5 to 2.0 x ULN	>2.0 to 3.0 x ULN	>3.0 x ULN
Activated Partial Thromboplastin Time (APTT)	> 1.00 to 1.66 × ULN	> 1.66 to 2.33 × ULN	> 2.33 to 3.00 × ULN	> 3.00 × ULN
Methemoglobin	5.0 to 10.0%	> 10.0 to 15.0%	> 15.0 to 20.0%	> 20.0%