Protocol:	Sponsor-Investigator Initiated CRI #15-05
Title:	Bridging Care to HCV Treatment Among Opioid Dependent Patients on Buprenorphine/naloxone Maintenance Therapy: A Pilot Study of Treating HCV with Epclusa at a Psychiatrist-staffed Outpatient Addiction Clinic
Protocol:	V7.0 September 13, 2017

NCT03235154

CLINICAL STUDY PROTOCOL --- CONFIDENTIAL

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Funder: Gilead Sciences, Inc.

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1 Protocol Synopsis

Sponsor:	Community Research Initiative of New England 529 Main Street Boston, MA 02129
Study Title:	Bridging Care to HCV Treatment Among Opioid Dependent Patients on Buprenorphine/naloxone Maintenance Therapy: A Pilot Study of Treating HCV with Epclusa at a Psychiatrist-staffed Outpatient Addiction Clinic
ClinicalTrials.gov Identifier:	NCT03235154
Study Design:	This is an open label, single center, pilot study to evaluate the efficacy, safety and tolerability of Epclusa treatment in naïve and treatment-experienced (including treatment intolerant) subjects with chronic HCV infection genotypes 1, 2, 3, 4, 5 and 6 in the context of a psychiatrist-staffed buprenorphine/naloxone clinic.
Study Centers:	One study center in North America.
Objectives:	
Primary Objective:	To assess the effectiveness, as measured by SVR12, of HCV treatment with Epclusa administered by a psychiatrist/licensed buprenorphine/naloxone provider during regularly scheduled visits to an outpatient addiction clinic for buprenorphine/naloxone replacement therapy and mental healthcare.
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 among subjects administered treatment in the context of visits to an outpatient addiction clinic for buprenorphine/naloxone replacement therapy and mental healthcare.
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 with Epclusa.
Number of Subjects:	20
Target Population:	Approximately 20 subjects with chronic HCV infection genotypes 1, 2, 3, 4, 5 or 6 will be enrolled.
Study Product:	Epclusa (sofosbuvir/velpatasvir) fixed dose combination tablets are pink, diamond-shaped, film-coated tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir. Subjects will take one tablet daily with or without food. Epclusa was approved by the FDA in 2016 for the treatment of adult patients with chronic hepatitis C infection genotypes 1, 2, 3, 4, 5, 6. It is recommended as first line therapy for treatment naïve and pegylated-ribavirin-experienced adults

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)

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)

2. Agreement to have weekly mentorship by telephone with Dr. Colson.
3. Provision of written informed consent addressing survey completion

Study Procedures /Frequency:

All study procedures will take place at the buprenorphine-naloxone clinic at OAS. Subjects will be seen approximately biweekly, in conjunction with their visits to the outpatient addiction clinic. Effectiveness of HCV treatment will be assessed at week 4 on treatment and at 4 and 12 weeks following completion of treatment by measuring HCV RNA using the Cobas® AmpliPrep/Cobas® TaqMan® HCV Test v 2.0.

Liver fibrosis will be assessed by Hepatitis C Virus (HCV) FibroSure® test collected at the screening visit as well as by FIB-4 index calculated from ALT, AST and platelet count collected at the screening visit. To the extent that the two tests differ, the higher fibrosis score will be used to guide therapy. Additional screening labs will include: ALT, AST, HgbA1C, indirect bilirubin, direct bilirubin, alkaline phosphatase, CBC with Platelet Count, basic metabolic panel with calculated GFR, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis B surface antigen, Hepatitis B quantitative DNA, HCV genotype (if not documented in the medical record), urine drug screen (for natural and synthetic opioids, cocaine, benzodiazepines, cannabinoids, barbiturates, and buprenorphine), and serum pregnancy test for women of childbearing potential).

All women of childbearing potential will be screened for pregnancy throughout study participation, and pregnancy prevention counseling will be offered to women of childbearing potential and all male participants. Urine drug screening will occur at every visit. Additional laboratory assessments may be conducted per standard of care for monitoring of health or adverse events, throughout the study. All laboratory assessments will be conducted as standard of care assessments.

At the screening visit, study participants will complete questionnaires assessing demographic characteristics. At baseline, week 4 on-treatment, end of treatment (or early termination), and 12 weeks after treatment, participants will complete quality of life questionnaires including the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), PROMIS v1.0 Emotional Distress – Depression Short Form 8a (PROMIS ED -Depression SF8a), and Short Form Health Survey (SF36).

Adherence to Epclusa will be monitored at each study treatment visit through pill counts and MEMSCap™ Medication Event Monitoring System smart packaging that records the date and time whenever the medication vial is opened.

Fully licensed psychiatrists who are also licensed buprenorphine/naloxone providers who work at the Cambridge Health Alliance's Outpatient Addiction Services will initiate and monitor Epclusa treatment with training and ongoing mentoring by Dr. Amy Colson, the Sponsor-Investigator. Initial training prior to enrolling subjects will address interpretation of HCV diagnostic tests, assessment of liver fibrosis, selection of patients for HCV treatment, administration/monitoring of Epclusa therapy, and post-therapy assessment of treatment effectiveness. The Sponsor-Investigator will conduct weekly telephone consultation and mentorship throughout the course of the study.

The psychiatrists' level of comfort with providing care for hepatitis C infection will be determined by a questionnaire administered before and at the completion of their training session and after 4 months of prescribing HCV therapy to study participants.

This study will be conducted in accordance with the guidelines of Good Clinical Practices (GCPs) including archiving of essential documents.

2 Glossary of Abbreviations and Definition of Terms

AE	adverse event
ALT	alanine aminotransferase (also SGPT)
AST	aspartate aminotransferase (also SGOT)
BID	twice a day
CD4	Cluster of differentiation 4
CI	Confidence Interval
CRF	case report form(s)
CRI	Community Research Initiative of New England
CSR	clinical study report
dL	Deciliter
DSPH	Drug Safety and Public Health
ECG	Electrocardiogram
eCRF	Electronic case report form(s)
EOT	End of Treatment
ET	Early Termination
EU	European Union
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	(United States) Food and Drug Administration
FDC	Fixed dose combination
FEV1	forced expiratory volume in one second
GCP	Good Clinical Practice (Guidelines)
GCSF	Granulocyte colony stimulating factor
GGT	gamma-glutamyl transferase
GSI	Gilead Sciences, Inc.
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HBV	Hepatitis B virus
HCV	Hepatitis C virus
ICH	International Conference on Harmonisation

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

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

3 INTRODUCTION

3.1 Background and Rationale

An estimated 3.2 million people in the United States are currently infected with hepatitis C virus (HCV). Since 1990, when the US introduced screening of the blood supply for HCV, injection drug use has been the primary mode of HCV transmission in the United States. It is widely recognized that addressing the HCV epidemic among people who inject drugs (PWID) depends on increasing access to: 1) clean injection equipment; 2) opioid substitution therapy (OST); 3) curative HCV treatment; and 4) assistance with comorbid psychiatric conditions and social issues (Robaeys, C et al, 2013).

Nevertheless, access to HCV treatment among current and former injection drug users is thought to be limited by several factors including: 1) insufficient number of infectious disease and gastroenterology providers and 2) provider and third-party payor concerns about adherence to medication and the risk of reinfection (Aspinall, EJ et al, 2013). Strategies to increase access among current and former injection drug users to direct acting antiviral drugs are urgently needed. The purpose of the current study is to assess the impact of co-treating chronic hepatitis C infection and opioid dependence within the context of an outpatient addiction clinic staffed by psychiatrists.

The partial μ-agonist, buprenorphine, is effective treatment for opioid dependence. Buprenorphine is typically co-formulated with naloxone and prescribed as buprenorphine/naloxone in a physician's office by providers who have undergone specialized training and licensure as proscribed by the Drug Abuse Treatment Act of 2000. Currently, there are more than 20,000 licensed buprenorphine/naloxone providers in the United States (Anson, 2013). Importantly, buprenorphine/naloxone patients are usually required to see their buprenorphine/naloxone providers for a new buprenorphine/naloxone prescription at least monthly, if not more frequently, and the adherence to these visits is extremely high. Moreover, buprenorphine/naloxone therapy is often prescribed through multidisciplinary clinics which are highly effective at retaining patients in care because comorbid psychiatric conditions and social problems are also addressed.

The beneficial impact of co-treating opioid dependence and an infectious illness has been demonstrated in the case of HIV infection. Altice and colleagues conducted an observational study of HIV-infected opioid-dependent patients who were offered OST with buprenorphine/naloxone at 10 different HIV clinics. Subjects initiating buprenorphine/naloxone were more likely to initiate or remain on antiretroviral therapy (Altice, 2011).

The Extension for Community Healthcare Outcomes (ECHO) program has demonstrated that with proper training and mentorship, primary care providers with no prior experience in managing HCV are able to treat the disease effectively. The ECHO project employed video conferencing technology to provide specialist run didactic sessions and consultation to primary care physicians in rural areas and prisons of New Mexico. Between 2004 and 2008, 146 treatment-naïve subjects were treated at the HCV clinic at UNM, and 261 treatment naïve subjects were treated at ECHO sites. Sustained virologic response rates were similar at the academic medical center clinic and ECHO sites (57.5% at UNM HCV clinic versus 58.2% at ECHO sites, $P = .89$). At the UNM HCV clinic, 13.7% of patients had serious adverse events, as did 6.9% of those treated at ECHO sites (Arora et al, 2011).

Since the publication of the ECHO study, the treatment of HCV has become considerably less complicated due to the widespread availability of safe, highly effective single tablet regimens, such as Epclusa. We believe that treatment of HCV is now well within the grasp of physicians and other healthcare providers without training in internal or family medicine. We propose a single arm pilot study

of HCV treatment with Epclusa at an outpatient addiction clinic in Somerville, Massachusetts staffed by psychiatrists.

We hypothesize that:

- With proper training and mentorship, psychiatrists who are also licensed buprenorphine/naloxone providers will be able to effectively assess liver health and treat chronic hepatitis C infection with Epclusa
- Patients with chronic hepatitis C infection on buprenorphine/naloxone maintenance therapy who are treated for HCV by a psychiatrist during regularly scheduled visits to an addiction clinic will have high rates of
    - adherence to HCV treatment
    - SVR 12

Given that subjects will receive standard of care evaluation and treatment for their chronic hepatitis C infection, we believe that study participation poses minimal 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.

3.2 Epclusa

Epclusa is a two-drug fixed-dose combination product that contains 100 mg of velpatasvir and 400 mg of sofosbuvir in a single tablet. The recommended dosage of Epclusa is one tablet taken orally once daily with or without food for 12 weeks. Velpatasvir is a pangenotypic HCV NS5A inhibitor and sofosbuvir is a pangenotypic nucleotide inhibitor of HCV NS5B RNA-dependent RNA polymerase.

Epclusa was approved by the FDA in 2016 for the treatment of adult patients with chronic hepatitis C infection genotypes 1, 2, 3, 4, 5, and 6. It is recommended as first line therapy for treatment naïve and pegylated-ribavirin-experienced adults with chronic hepatitis C infection genotypes 1-6 (AASLD and IDSA HCV Guidelines, October, 2016). Safety and tolerability data for Epclusa is based on data from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which enrolled a total of 1035 subjects who either did not have cirrhosis or who had compensated cirrhosis (Epclusa Package Insert).

Overall, 0.2% of subjects in the three studies discontinued Epclusa due to adverse events.

The most common adverse reactions (≥10%) during 12 weeks of treatment with Epclusa were headache and fatigue.

ASTRAL-1 was a randomized placebo-controlled trial which enrolled 740 subjects with genotypes 1, 2, 4, 5, and 6 chronic HCV. Nineteen percent of these subjects had compensated cirrhosis and 32% were treatment experienced. The table below lists adverse reactions (adverse events assessed as causally related by the Investigator, all grades) observed in ≥5% of subjects in ASTRAL-1. The majority of adverse reactions were of severity grade 1. Importantly, each of these reactions occurred at a similar frequency or more frequently in the control arm, with the exception of asthenia which occurred in 5% subjects on Epclusa and 3% of subjects on placebo.

Reaction	Frequency in ASTRAL-1
Headache	22%
Fatigue	15%
Nausea	9%
Asthenia	5%
Insomnia	5%

Co-administration of amiodarone with Epclusa is not recommended because post-marketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is co-administered with sofosbuvir.

The concomitant use of Epclusa with P-gp inducers and/or moderate to potent CYP2B6, CYP2C8, and CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of velpatasvir and/or sofosbuvir and may lead to a reduced therapeutic effect of EPCLUSA. Therefore, the use of Epclusa with P-gp inducers and moderate to potent CYP2B6, CYP2C8, and CYP3A4 is not recommended.

Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of velpatasvir. Epclusa and antacid administration must be separated by at least 4 hours. H-2 receptor antagonists may be administered simultaneously with or 12 hours apart from Epclusa at a dose that does not exceed famotidine 20 mg BID. Co-administration of Epclusa and proton pump inhibitors is not recommended. However, if it is medically necessary to administer Epclusa and a proton pump inhibitor, Epclusa should be taken with food 4 hours before omeprazole at a dose which does not exceed 20 mg.

Epclusa interacts with several medications commonly used by our target population. Efavirenz and tipranavir/r should not be co-administered with Epclusa because these HIV medications decrease velpatasvir and/or sofosbuvir levels. Renal function should be monitored in patients taking tenofovir DF with Epclusa. Epclusa increases levels of the HMG-CoA reductase inhibitors, rosuvastatin and atorvastatin. Patients on atorvastatin and rosuvastatin should be monitored closely for evidence of myopathy; and the dose of rosuvastatin should not exceed 10 mg and the dose of atorvastatin should not exceed 20 mg.

Epclusa should not be administered in conjunction with the following medications:

- Proton pump inhibitors (other than omeprazole 20 mg as above)
- Amiodarone
- Digoxin
- Topotecan
- Carbamazepine
- Phenytoin
- Phenobarbital
- Oxcarbazepine
- Rifabutin
- Rifampin
- Rifapentine
- Efavirenz
- Tipranavir/ritonavir

- St. John's Wort
- Sofosbuvir as a single agent

The efficacy of Epclusa in treatment naïve and treatment experienced (with pegylated interferon and RBV ± Protease inhibitor) non-cirrhotics and compensated cirrhotics was evaluated in three Phase 3 trials of 1035 subjects with genotypes 1, 2, 3, 4, 5 and 6.

ASTRAL-1: Randomized placebo controlled trial of Epclusa for 12 weeks in subjects with genotypes 1, 2, 4, 5, 6
ASTRAL-2: Randomized controlled open label trial of Epclusa for 12 weeks compared with SOF/RBV for 12 weeks in subjects with genotype 2
ASTRAL-3: Randomized controlled open label trial of Epclusa for 12 weeks compared with SOF/RBV for 24 weeks in subjects with genotype 3

Week 12 sustained virologic response (SVR-12) rates for subjects treated in ASTRAL-1 with Epclusa for 12 weeks are shown in the table below

ASTRAL-1 Virologic Outcomes

Genotype (n)	SVR-12
1a (210)	98%
1b (118)	99%
2 (104)	100%
4 (116)	100%
5 (35)	97%
6 (41)	100%

Week 12 sustained virologic response (SVR-12) rates for genotype 3 subjects treated in ASTRAL-3 with Epclusa for 12 weeks or SOF/RBV for 24 weeks are shown in the table.

ASTRAL-3 Virologic Outcomes

	SVR 12 for Epclusa for 12 weeks		SVR 12 for SOF/RBV for 24 weeks	
Treatment class	Naive	Experienced	Naïve	Experienced
Without cirrhosis	98%	94%	90%	71%
With Compensated Cirrhosis	93%	89%	73%	58%

3.3 Buprenorphine/naloxone

Buprenorphine/naloxone is used to treat opioid dependence. It is a combination of two medications, buprenorphine and naloxone, in a 4:1 ratio.

Buprenorphine is a partial agonist at the μ-opioid receptor with a high affinity and slow dissociation from these receptors. In individuals undergoing withdrawal from full opioid agonists, such as heroin, buprenorphine ameliorates withdrawal symptoms by partially activating the μ-opioid receptors.

Naloxone is a potent opioid antagonist at the μ-opioid receptor and precipitates opioid withdrawal when administered parenterally in individuals physically dependent on full opioid agonists. Naloxone has limited sublingual absorption such that the inclusion of naloxone in buprenorphine/naloxone reduces the potential for parenteral abuse of buprenorphine (i.e. by crushing and dissolving tablets or dissolving film for intravenous injection).

Buprenorphine/naloxone is available as both a sublingual film and a tablet.

Buprenorphine/naloxone sublingual film is supplied as an orange rectangular sublingual film with a white printed logo in four dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg
- buprenorphine/naloxone 4 mg/1 mg
- buprenorphine/naloxone 8 mg/2 mg
- buprenorphine/naloxone 12 mg/3 mg

Buprenorphine/naloxone sublingual tablets are supplied in 2 dosage strengths:

- buprenorphine/naloxone 2 mg/0.5 mg
- buprenorphine/naloxone 8 mg/2 mg

Typical maintenance doses range from 8-16 mg of buprenorphine with 2 to 4 mg of naloxone.

The safety of buprenorphine/naloxone is supported by clinical trials of buprenorphine (Subutex) sublingual tablets and buprenorphine/naloxone sublingual tablets and buprenorphine/naloxone sublingual solution and buprenorphine/naloxone sublingual tablets. In total, safety data from clinical studies are available from over 3000 opioid-dependent subjects exposed to buprenorphine at doses in the range used in the treatment of opioid dependence. The most common side effects of buprenorphine/naloxone include dizziness, drowsiness, abdominal pain, nausea, constipation, headache, insomnia, hyperhidrosis, and flushing. The sublingual film product may also cause numbness, burning, tingling of the mouth.

Buprenorphine, particularly when taken by the IV route, in combination with benzodiazepines or other central nervous system (CNS) depressants (including alcohol), has been associated with significant respiratory depression and death. Many, but not all, post-marketing reports regarding coma and death associated with the concomitant use of buprenorphine and benzodiazepines involved misuse by self-injection. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other CNS depressant drugs.

3.4 Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

4 OBJECTIVES

4.1 Primary Objective:

- To assess the effectiveness, as measured by SVR-12, of HCV treatment with Epclusa administered by psychiatrist/licensed buprenorphine/naloxone providers during regularly

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

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

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)

6.4 Eligibility Criteria for Provider Participants

All licensed buprenorphine/naloxone providers who are also fully licensed 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)
2. Agreement to have weekly mentorship by telephone with Dr. Colson.
3. Provision of written informed consent addressing survey completion

Given his role on the study team, Dr. Zev Schuman-Olivier will not be eligible to participate in the provider survey.

7 MEDICINAL PRODUCT

7.1 Enrollment and Treatment

This is an open label study.

7.2 Description and Handling of Epclusa

7.2.1 Formulation

Epclusa (sofosbuvir/velpatasvir FDC) tablets are pink, diamond-shaped, film-coated tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir. The tablets are debossed with "GSI" on one side and "7916" on the other side. The Epclusa tablets contain the following inactive ingredients: copovidone, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

7.2.2 Packaging and Labeling

Epclusa tablets are packaged in standard 28-tablet medication vials compatible with the MEMSCap™ Medication Event Monitoring System that will be utilized as an adherence monitoring method in addition to traditional pill counts. The TrackCap® product features integrated microcircuits that records the date and time whenever the medication vial is opened. The electronic data collected in the medication event monitoring system will be downloaded into a designated, secured, limited access study computer for immediate review and later analysis. All Epclusa packaging will be labeled to meet all applicable requirements of the US Food and Drug Administration (FDA), Annex 13 of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2010) and/or other local regulations as applicable.

7.2.3 Storage and Handling

Epclusa 28-tablet medication vials will be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 degrees Celsius (77 degrees Fahrenheit); excursions are permitted between 15 and 30 degrees Celsius (59 to 86 degrees Fahrenheit).

All drug products will be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of the study drug and to ensure proper product identification, the drug product will not be stored in a fashion other than the blister package in which they are supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling Epclusa.

7.2.4 Dosage and Administration of Epclusa

One Epclusa tablet is to be administered once daily with or without food. Each subject will be given instructions to maintain approximately the same daily dosing interval between study drug doses.

For a missed dose of Epclusa, subjects will be instructed to take the missed dose of study drug as soon as possible within 12 hours of the missed dose. Subjects will also be cautioned never to double the next dose with a missed dose of study drug under any circumstances.

7.3 Prior and Concomitant Medications

Concomitant medications taken within 30 days prior to screening, up to and including 30 days after the last dose of study drug, need to be recorded in the source documents and case report form(s) (CRFs).

The following medications are prohibited during the screening period and for a minimum of 28 days prior to the Baseline/Day 1 Visit through the end of study:

- Proton pump inhibitors (other than omeprazole 20 mg as below)
- Amiodarone
- Digoxin
- Carbamazepine
- Phenytoin
- Phenobarbital
- Oxcarbazepine
- Rifabutin
- Rifampin
- Rifapentine
- Efavirenz

- Tipranavir/ritonavir
- Sofosbuvir as a single agent
- St. John's wort, echinacea, milk thistle
- Rosuvastatin at a dose exceeding 10 mg
- Atorvastatin at a dose exceeding 20 mg

The following medications will be used with caution during the study:

Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease the concentration of velpatasvir. Therefore, patient who are currently on acid lowering therapy including Antacids (Tums, Mylanta, Maalox, Rolaids etc.), Famotidine/Pepcid, Ranitidine/Zantac, Esomeprazole/Nexium, Omeprazole/Prilosec, Lansoprazole/Prevacid, Pantoprazole/Protonix and who must continue acid lowering therapy must agree to one of the three acid lowering treatment regimens.

- Tums as needed separated from Epclusa by at least 4 hours
- Zantac at a dose no higher than 150 mg once daily to be separated from Epclusa by 12 hours
- Omeprazole at a dose no higher than 20 mg once daily. For patients on omeprazole, Epclusa must be taken with food 4 hours prior to omeprazole dosing.

Renal function should be monitored in patients taking tenofovir DF with Epclusa.

Epclusa increases levels of the HMG-CoA reductase inhibitors, rosuvastatin and atorvastatin. Patients on atorvastatin and rosuvastatin should be monitored closely for evidence of myopathy. The dose of rosuvastatin should not exceed 10 mg and the dose of atorvastatin should not exceed 20 mg.

Medications for disease conditions excluded from the protocol (e.g., active cancer, transplantation) are not listed under this Concomitant Medication section and are disallowed in the study.

7.4 Monitoring Accountability and Study Drug Adherence for Epclusa

The Sponsor-Investigator is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgement of receipt of the shipment of study drug (quantity and condition), detailed inventory documentation, and detailed dispensation and excess medication return documentation

Epclusa will be stored at the CRI facility in accordance with CRI SOPs, in a temperature controlled, secure, limited-access location. Epclusa will be transported to the study conduct location, Cambridge Health Alliance, 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. If any study drug transported to the study location is not dispensed, it will be returned to secure storage at CRI in the same manner. Temperature of drug environment during transportation will be monitored and recorded. Any excursion from acceptable storage temperature will result in quarantine from the dispensable supply.

Subjects will be instructed to bring back all study drug original containers at every post-baseline study visit through the end of treatment.

Study drug will be reconciled using study drug pill count at every post-baseline visit by the Sponsor-Investigator, Sub-Investigator(s) or designee (i.e. study coordinator) in order to monitor the subject's adherence with the study drug regimen.

Epclusa accountability records will be maintained in order to:

- Record the date, subject number, subject initials, the study drug dispensed.
- Record the date, quantity of used and unused study drug for returned Epclusa, along with the initials of the person recording the information.

Adherence will be further monitored through MEMSCap™ Medication Event Monitoring System. The TrackCap® features integrated microcircuits that records the date and time whenever the medication vial is opened. The electronic data collected in the medication event monitoring system will be downloaded via a dedicated MEMs reader onto a designated, secured, limited access study computer for review during the study visit and for later analysis. At every post-baseline study visit the Investigator or designee will download the electronic adherence monitoring data and review with the participant, providing adherence counseling as needed.

To ensure consistent access to study drug, at baseline, a 28 day supply of medication will be dispensed along with a 28 day back-up supply. In the event that a subject misses a regularly scheduled visit, s/he will be contacted by study staff to reschedule as soon as possible, and will be counseled on use of the back-up medication supply if necessary (see Section 7.2.4). Accountability for the back-up supply will be monitored at each study visit, any doses taken recorded, and the back-up supply will then be redispensed to the subject.

8 STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows.

All study procedures will take place at the outpatient addiction clinic at Cambridge Health Alliance.

The Sponsor-Investigator must document any deviation from protocol procedures and notify the IRB, per the IRB's reporting requirements.

8.1 Informed Consent

Prior to any protocol required procedures as outlined in Section 8, informed consent must be obtained. Patients identified by study team investigators or participating psychiatrist-buprenorphine/naloxone prescribers will be approached to potentially participate in the study. They will be given a copy of the informed consent and provided the opportunity to meet with study staff as many times as they would like, to review the details of the study, and the consent document. They may also take it home and share it with friends, family and other medical providers, as they consider participation. Once the subject feels all their questions have been answered, and study staff have assessed that they comprehend the study information presented in the informed consent document, the consent will be signed by the study subject and cosigned by the study staff explaining the study. Study staff will ensure that the process was compliant with CRI SOP for obtaining consent and will ensure the following essential components of consent:

- Process was not coercive
- Consent obtained before protocol procedures initiated
- Information about the study including all available options was provided in a language understood by the subject

- Opportunity was given to the subject to consider all available options
- Questions and concerns were addressed
- Subject states comprehension of information
- Consent signed and dated by subject with first and last name using ink
- Consent signed and dated by coordinator using ink
- Copy of signed Informed Consent was given to the subject
- Copy of signed Informed Consent was filed in source documents

8.2 Screening Visit (Day -28 to Day 0)

Subjects will be screened within 28 days of the Baseline/Day 1 Visit to determine eligibility for participation in the study. The screening window may be extended to 42 days prior to Day 1 for subjects with extenuating circumstances if approved by the Medical Monitor.

The following will be performed and documented at screening:

- Obtain written informed consent
- Determine eligibility (Reference Sections 6.2 & 6.3)
- Obtain select medical history including risk factor(s) for HCV infection, estimated duration of HCV infection, prior assessments of fibrosis, HCV genotype if known, prior HCV treatment, comorbid liver diseases
- Obtain details of AEs related to screening procedures (Reference Section 9)
- Obtain details of concomitant medications
- Pregnancy prevention counseling
- Pregnancy testing for women of childbearing potential only (Reference Study Procedures Table Appendix 2)
- Obtain blood samples (Reference Study Procedures Table Appendix 2)
- Obtain urine samples (Reference Study Procedures Table Appendix 2)

A single retest of screening labs is permitted only if there is reason to believe the retest value will be within accepted parameters (i.e. if the initial value was either due to a sample processing error or due to an extenuating circumstance such as intercurrent infection).

Subjects meeting all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 Visit assessments and enrollment.

From the time of obtaining informed consent through the first administration of study drug, all serious adverse events (SAEs), as well as any non-serious adverse events related to protocol-mandated procedures, will be recorded on the adverse events case report form (eCRF). All other untoward medical occurrences observed during the screening period, including exacerbation or changes in medical history, are to be captured on the medical history CRF/eCRF.

See Section 9: Adverse Events and Toxicity Management for additional details.

8.3 Treatment Assessments

8.3.1 Baseline/Day 1 Visit

The following baseline tests and procedures must be completed prior to enrollment and dosing/dispensing:

- Confirm eligibility
- Assessment of AEs and concomitant medications
- Pregnancy Prevention Counseling
- Subject completes Quality of Life Surveys (FACIT-F, PROMIS ED -Depression SF8a, SF36)
- Obtain urine samples (Reference Study Procedures Table Appendix 2)
- Pregnancy testing for women of childbearing potential only (Reference Study Procedures Table Appendix 2)
- Dispense 4 week study drug supply and backup bottle with MEMScaps™
- Instruct the subject on the packaging, storage and administration of the study drug

8.3.2 Weeks 2, 4, 6, 8, 10 (+/-3 days)

The following procedures/assessments are to be completed:

- Assessment of AEs and concomitant medications
- 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
- Dispense study drug supply (weeks 4 and week 8, or as needed for emergency supply)
- Additionally, at week 4 visit only, subject will complete Quality of Life Surveys FACIT-F, PROMIS ED -Depression SF8a, SF36)

8.3.3 End of Treatment (+/-3 days)

The following procedures/assessments are to be completed at the end of Epclusa treatment (Week 12):

- Assessment of AEs and concomitant medications
- Subject completes Quality of Life Surveys (FACIT-F, PROMIS ED -Depression SF8a, SF36)
- 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

8.3.4 Early Termination Visit

The Sponsor-Investigator and other study staff (e.g., Medical Monitor, Sub-Investigator(s), and Clinical Project Manager) must be informed, as soon as possible, when a subject comes off treatment due to an AE.

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)

- 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.

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

Tel: 650-522-5114
E-mail: Safety_FC@Gilead.com

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.

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.

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.

Before implementation, the Sponsor-Investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

11.3 Informed Consent

The Sponsor-Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study -related procedures. The Sponsor-Investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC of local requirements.

11.4 Confidentiality

The Sponsor-Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form submitted to the Sponsor-Investigator or IRB/IEC. NOTE: The Sponsor-Investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The Sponsor-Investigator agrees that all confidential study information, including but not limited to the Investigator Brochure, this protocol, eCRF, the study drug, and any other study information, remain the sole and exclusive property of the Sponsor-Investigator during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law). The Sponsor-Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.5 Study Files and Retention of Records

The Sponsor-Investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

- Sponsor-Investigator's study file, and
- Subject clinical source documents.

The Sponsor-Investigator's study file will contain the protocol/amendments, CRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Original, signed informed consent form with documentation that the consent was signed prior to initiating any study procedures;

- Documentation that subject meets eligibility criteria, i.e. history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of study drug, including dates of dispensing and return;
- Record of all adverse events and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant, dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents will be retained by the Sponsor-Investigator until 2 years after the investigation is discontinued and regulatory authorities have been notified.

11.6 Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF will be completed within three days of the subject visit to enable the Sponsor-Investigator to perform central monitoring of safety data. Subsequent to data entry, a study monitor will perform source data verification for select data points in accordance with the monitoring plan within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the Sponsor-Investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal CRI staff, who routinely review the data for completeness, correctness, and consistency. A read-only archive copy of the case report form will be stored in accordance with the records retention requirements outlined in Section 11.5.

Study data will be collected and managed using REDCap electronic data capture tools hosted by Boston Computing Network (Harris et al. 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. It satisfies HIPAA-Security guidelines and is 21 CFR Part 11 capable, with compliance assured by the Community Research Initiative Information Technology Department and Boston Computing Network. Data will be exported from REDCap to the statistician for statistical analysis will be de-identified.

11.7 Investigational Medicinal Product Accountability and Return

All used and unused study drug supplies will be destroyed by the study monitor or designee in accordance to the Sponsor-Investigator standard operating procedures. The Sponsor-Investigator must maintain accurate records for all study drug destroyed. Records must show the identification and

quantity of each unit destroyed, the method of destruction, and the person who disposed of the study drug. Upon study completion, copies of the study drug accountability records must be filed at the site.

11.8 Protocol Compliance

The Sponsor-Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.9 Protocol Modifications

All protocol modifications will be submitted to the IRB/IEC in accordance with local requirements and receive documented IRB/IEC approval before modifications can be implemented.

11.10 Study Monitoring

In accordance with regulations and guidelines, the Sponsor-Investigator is responsible for assuring ongoing monitoring of the study. The designated study monitor will have direct access to the Sponsor-Investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor will have access to any subject records needed to verify the entries on the eCRF.

11.11 Study Auditing or Inspections

Representatives of regulatory authorities may conduct inspections or audits of the clinical study. If the Sponsor-Investigator is notified of an inspection by a regulatory authority the Sponsor-Investigator will notify the CRI Medical Monitor and Regulatory Sponsor staff immediately. The Sponsor-Investigator will make available all source documents and other records for this trial to appointed study monitors, to IRBs/IECs or to regulatory authority or health authority inspectors.

11.12 Study Discontinuation

The Sponsor-Investigator reserves the right to terminate the study at any time. Should this be necessary, discontinuation procedures will be arranged and the appropriate regulatory authority(ies), IRBs, and IECs will be notified. In terminating the study, the Sponsor-Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

11.13 Finance and Insurance

No funds have been set aside for payment of treatment of any injury or illness that occurs as a direct result in a subject's participation in this study. No funds have been appropriated for other associated losses such as lost wages, disability or discomfort related to an injury or illness as a result of a subject's participation in this study. In the event that a subject experiences an injury or illness as described above, they should be immediately referred to their primary care provider for treatment. The subject will be responsible for payment of cost of treatment.

11.14 Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor-Investigator will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The Sponsor-Investigator may communicate, orally present, or publish in scientific journals or other scholarly media.

12 References

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13 Appendices

Appendix 1	Investigator Signature Page
Appendix 2	Study Procedures Table
Appendix 3	Questionnaire to Determine Psychiatrist Sub-Investigator Comfort with HCV Management
Appendix 4	GSI Grading Scale
Appendix 5	Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations
Appendix 6	HCV Treatment Curriculum

Appendix 1: Investigator Signature Page

Bridging Care to HCV Treatment Among Opioid Dependent Patients on Buprenorphine/naloxone Maintenance Therapy: A Pilot Study of Treating HCV with Epclusa at a Psychiatrist-staffed Outpatient Addiction Clinic Clinic

September 13, 2017 V7.0

Investigator Statement

I have read the protocol, including all appendices, and I agree that it contains all necessary details or my staff to conduct this study as described. I will conduct his study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all study-related information. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I affirm that the protocol, GCP guidelines and applicable regulatory requirements will be followed.

I will not initiate any study activities until the IRB/IEC and other required regulatory approvals are obtained.

_____ _____

Principal Investigator Name (Printed) Signature

_____

Date

Appendix 2: Study Procedures Table

	Screening	Baseline	Biweekly Visits on Treatment[h]	Unscheduled Visit	EOT or early termination	Post-Treatment weeks 4 and 12
Clinical Assessments:						
Informed Consent	X					
Eligibility Review	X	X				
Medical History[a]	X					
Adverse Events	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	
Pregnancy Prevention Counseling for WOCBP	X	X	X	X	X	
Health Related QOL Surveys[b]		X	X (week 4 only)		X	X (post treatment week 12 only)
Drug Dispensing		X	X[i]			
Instruct the subject on the packaging, storage and administration of study drug		X				
Pill count			X	X	X	
Download MEMSCap™ adherence data			X	X	X	
Laboratory Assessments:[g]						
Hepatic Function Tests[c]	X		X[d]			
CBC with Platelet Count[c]	X					
BMP with eGFR	X					
HgbA1C	x					
HCV RNA[d]	X		X[d]			X
HCV genotype if not documented in medical record	X					
FibroSure®	X					
Hepatitis B surface antibody, core antibody, surface antigen	X					
Hepatitis B quantitative DNA PCR test	X		X[d]			
Urine drug screen	X	X	X		X	
Urine screen for buprenorphine	X	X	X		X	

	Screening	Baseline	Biweekly Visits on Treatment[h]	Unscheduled Visit	EOT or early termination	Post-Treatment weeks 4 and 12
Serum Pregnancy Test for WOCBP	X					
Urine Pregnancy Test for WOCBP		X	X		X (post treatment week 4 only)	
Internal Medicine Mentorship and Assessments:						
Psychiatrist Sub-Investigator Mentorship [e]	X	X	X	X	X	X
Psychiatrist Sub-Investigator Questionnaire [f]	X		X[f]			

[a] Select Medical History to include: risk factor(S) for HCV, estimated duration of HCV, prior assessments of fibrosis, HCV genotype if known, prior HCV treatment, comorbid liver diseases

[b] FACIT-F, PROMIS ED -Depression SF8a, SF36

[c] ALT, AST, and platelet count will be used to calculate FIB-4 Index

[d] HCV RNA, HBV DNA and HFT to be assessed at week 4 on treatment but not at other biweekly on treatment visits unless clinically indicated

[e] Detailed teaching session prior to screening

[f] Administered before and at the completion of the training session and after 4 months of prescribing of HCV therapy to study participants.

[g] Additional safety laboratory assessments may be assessed per the clinical judgement of the Sponsor-Investigator or Sub-Investigator.

[h] While the goal is for all visits to be within +/-3 days of the target visit date, study visits will be accepted outside of the window as required by the patient and the operational flow of the clinic.

[l] Study drug will be dispensed at the week 4 and week 8 study visits, and as needed at other visits for emergency resupply.

Appendix 3: Questionnaire to Determine the Participating Psychiatrists' Comfort with HCV Management

	Not at all comfortable	Somewhat comfortable	Comfortable	Very Comfortable
Counseling patients on natural history of HCV infection				
Counseling patients on benefits of treatment				
Assessing fibrosis and diagnosing cirrhosis				
Counseling patients on proper usage of Epclusa				
Counseling patients on drug interactions with Epclusa				
Counseling patients on efficacy of Epclusa				

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

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%

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to <LLN mEq/L 130 to <LLN mmol/L	125 to < 130 mEq/L 125 to < 130 mmol/L	121 to < 125 mEq/L 121 to < 125 mmol/L	< 121 mEq/L < 121 mmol/L
Hypernatremia	146 to 150 mEq/L 146 to 150 mmol/L	> 150 to 154 mEq/L > 150 to 154 mmol/L	> 154 to 159 mEq/L > 154 to 159 mmol/L	> 159 mEq/L > 159 mmol/L
Hypokalemia	3.0 to 3.4 mEq/L 3.0 to 3.4 mmol/L	2.5 to < 3.0 mEq/L 2.5 to < 3.0 mmol/L	2.0 to < 2.5 mEq/L 2.0 to < 2.5 mmol/L	< 2.0 mEq/L < 2.0 mmol/L
Hyperkalemia	5.6 to 6.0 mEq/L 5.6 to 6.0 mmol/L	> 6.0 to 6.5 mEq/L > 6.0 to 6.5 mmol/L	> 6.5 to 7.0 mEq/L > 6.5 to 7.0 mmol/L	> 7.0 mEq/L > 7.0 mmol/L
Hypoglycemia **Adult and Pediatric** **≥ 1 Month** **Infant, < 1 Month**	 55 to 64 mg/dL 3.03 to 3.58 mmol/L 50 to 54 mg/dL 2.8 to 3.0 mmol/L	 40 to < 55 mg/dL 2.20 to < 3.03 mmol/L 40 to < 50 mg/dL 2.2 to < 2.8 mmol/L	 30 to < 40 mg/dL 1.64 to < 2.20 mmol/L 30 to < 40 mg/dL 1.7 to < 2.2 mmol/L	 < 30 mg/dL < 1.64 mmol/L < 30 mg/dL < 1.7 mmol/L
Hyperglycemia, Nonfasting	116 to 160 mg/dL 6.42 to 8.91 mmol/L	> 160 to 250 mg/dL > 8.91 to 13.90 mmol/L	> 250 to 500 mg/dL > 13.90 to 27.79 mmol/L	> 500 mg/dL > 27.79 mmol/L
Hyperglycemia, Fasting	110 to 125 mg/dL 6.08 to 6.96 mmol/L	>125 to 250 mg/dL >6.96 to 13.90 mmol/L	>250 to 500 mg/dL >13.90 to 27.79 mmol/L	>500 mg/dL >27.79 mmol/L
Hypocalcemia (corrected for albumin if appropriate*) **Adult and Pediatric** **≥ 7 Days** **Infant, < 7 Days**	 7.8 to 8.4 mg/dL 1.94 to 2.10 mmol/L 6.5 to 7.5 mg/dL 1.61 to 1.88 mmol/L	 7.0 to < 7.8 mg/dL 1.74 to < 1.94 mmol/L 6.0 to < 6.5 mg/dL 1.49 to < 1.61 mmol/L	 6.1 to < 7.0 mg/dL 1.51 to < 1.74 mmol/L 5.5 to < 6.0 mg/dL 1.36 to < 1.49 mmol/L	 < 6.1 mg/dL < 1.51 mmol/L < 5.5 mg/dL < 1.36 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hypercalcemia (corrected for albumin if appropriate*) **Adult and Pediatric ≥ 7 Days** **Infant, < 7 Days**	>ULN to 11.5 mg/dL >ULN to 2.88 mmol/L 11.5 to 12.4 mg/dL 2.86 to 3.10 mmol/L	> 11.5 to 12.5 mg/dL > 2.88 to 3.13 mmol/L > 12.4 to 12.9 mg/dL > 3.10 to 3.23 mmol/L	> 12.5 to 13.5 mg/dL > 3.13 to 3.38 mmol/L > 12.9 to 13.5 mg/dL > 3.23 to 3.38 mmol/L	> 13.5 mg/dL > 3.38 mmol/L > 13.5 mg/dL > 3.38 mmol/L
Hypocalcemia (ionized)	3.0 mg/dL to < LLN 0.74 mmol/L to < LLN	2.5 to < 3.0 mg/dL 0.62 to < 0.74 mmol/L	2.0 to < 2.5 mg/dL 0.49 to < 0.62 mmol/L	< 2.0 mg/dL < 0.49 mmol/L
Hypercalcemia (ionized)	> ULN to 6.0 mg/dL > ULN to 1.50 mmol/L	> 6.0 to 6.5 mg/dL > 1.50 to 1.63 mmol/L	> 6.5 to 7.0 mg/dL > 1.63 to 1.75 mmol/L	> 7.0 mg/dL > 1.75 mmol/L
Hypomagnesemia	1.40 to <LLN mg/dL 1.2 to <LLN mEq/L 0.58 to <LLN mmol/L	1.04 to < 1.40 mg/dL 0.9 to < 1.2 mEq/L 0.43 to < 0.58 mmol/L	0.67 to < 1.04 mg/dL 0.6 to < 0.9 mEq/L 0.28 to < 0.43 mmol/L	< 0.67 mg/dL < 0.6 mEq/L < 0.28 mmol/L
Hypophosphatemia **Adult and Pediatric > 14 Years** **Pediatric 1 Year–14 Years** **Pediatric < 1 Year**	2.0 to < LLN mg/dL 0.63 to < LLN mmol/L 3.0 to 3.5 mg/dL 0.96 to 1.12 mmol/L 3.5 to 4.5 mg/dL 1.12 to 1.46 mmol/L	1.5 to < 2.0 mg/dL 0.47 to < 0.63 mmol/L 2.5 to < 3.0 mg/dL 0.80 to < 0.96 mmol/L 2.5 to < 3.5 mg/dL 0.80 to < 1.12 mmol/L	1.0 to < 1.5 mg/dL 0.31 to < 0.47 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L 1.5 to < 2.5 mg/dL 0.47 to < 0.80 mmol/L	< 1.0 mg/dL < 0.31 mmol/L < 1.5 mg/dL < 0.47 mmol/L < 1.5 mg/dL < 0.47 mmol/L

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyperbilirubinemia **Adult and Pediatric > 14 Days**	> 1.0 to 1.5 × ULN	> 1.5 to 2.5 × ULN	> 2.5 to 5.0 × ULN	> 5.0 × ULN
Infant, ≤ 14 Days (non-hemolytic)	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 to 30.0 mg/dL > 428 to 513 µmol/L	> 30.0 mg/dL > 513 µmol/L
Infant, ≤ 14 Days (hemolytic)	NA	NA	20.0 to 25.0 mg/dL 342 to 428 µmol/L	> 25.0 mg/dL > 428 µmol/L
Blood Urea Nitrogen	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Hyperuricemia	>ULN to 10.0 mg/dL >ULN to 597 µmol/L	> 10.0 to 12.0 mg/dL > 597 to 716 µmol/L	> 12.0 to 15.0 mg/dL > 716 to 895 µmol/L	> 15.0 mg/dL > 895 µmol/L
Hypouricemia	1.5 mg/dL to < LLN 87 µmol/L to < LLN	1.0 to < 1.5 mg/dL 57 to < 87 µmol/L	0.5 to < 1.0 mg/dL 27 to < 57 µmol/L	< 0.5 mg/dL < 27 µmol/L
Creatinine	> 1.50 to 2.00 mg/dL > 133 to 177 µmol/L	> 2.00 to 3.00 mg/dL > 177 to 265 µmol/L	> 3.00 to 6.00 mg/dL > 265 to 530 µmol/L	> 6.00 mg/dL > 530 µmol/L
Bicarbonate	16.0 mEq/L to < LLN 16.0 mmol/L to < LLN	11.0 to < 16.0 mEq/L 11.0 to < 16.0 mmol/L	8.0 to < 11.0 mEq/L 8.0 to < 11.0 mmol/L	< 8.0 mEq/L < 8.0 mmol/L
Triglycerides (Fasting)	NA	500 to 750 mg/dL 5.64–8.47 mmol/L	> 750 to 1200 mg/dL > 8.47–13.55 mmol/L	> 1200 mg/dL > 13.55 mmol/L
LDL (Fasting)	130 to 160 mg/dL 3.35 to 4.15 mmol/L	>160 to 190 mg/dL >4.15 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA

CHEMISTRY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Pediatric >2 to <18 years	110 to 130 mg/dL 2.84 to 3.37 mmol/L	>130 to 190 mg/dL >3.37 to 4.92 mmol/L	> 190 mg/dL >4.92 mmol/L	NA
Hypercholesterolemia (Fasting)	200 to 239 mg/dL 5.16 to 6.19 mmol/L	> 239 to 300 mg/dL > 6.19 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Pediatric < 18 Years	170 to 199 mg/dL 4.39 to 5.15 mmol/L	> 199 to 300 mg/dL > 5.15 to 7.77 mmol/L	> 300 mg/dL > 7.77 mmol/L	NA
Creatine Kinase	3.0 to < 6.0 × ULN	6.0 to < 10.0 × ULN	10.0 to < 20.0 × ULN	≥ 20.0 × ULN

* Calcium should be corrected for albumin if albumin is < 4.0 g/dL

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
AST (SGOT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
ALT (SGPT)	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
GGT	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Alkaline Phosphatase	1.25 to 2.50 × ULN	> 2.50 to 5.00 × ULN	> 5.00 to 10.00 × ULN	> 10.00 × ULN
Total Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Pancreatic Amylase	> 1.0 to 1.5 × ULN	> 1.5 to 2.0 × ULN	> 2.0 to 5.0 × ULN	> 5.0 × ULN
Lipase	> 1.0 to 1.5 × ULN	> 1.5 to 3.0 × ULN	> 3.0 to 5.0 × ULN	> 5.0 × ULN
Albumin	3.0 g/dL to < LLN 30 g/L to < LLN	2.0 to < 3.0 g/dL 20 to < 30 g/L	< 2.0 g/dL < 20 g/L	NA

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hematuria (Dipstick)	1+	2+	3-4+	NA
Hematuria (Quantitative) See Note below Females	>ULN - 10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Males	6-10 RBC/HPF	> 10-75 RBC/HPF	> 75 RBC/HPF	NA
Proteinuria (Dipstick)	1+	2–3+	4+	NA
Proteinuria, 24 Hour Collection **Adult and Pediatric ≥ 10 Years** **Pediatric > 3 Mo to < 10 Years**	200 to 999 mg/24 h 201 to 499 mg/m^2/24 h	>999 to 1999 mg/24 h >499 to 799 mg/m^2/24 h	>1999 to 3500 mg/24 h >799 to 1000 mg/m^2/24 h	> 3500 mg/24 h > 1000 mg/ m^2/24 h
Glycosuria (Dipstick)	1+	2-3+	4+	NA

Notes:

Toxicity grades for Quantitative and Dipstick Hematuria will be assigned by Covance Laboratory, however for other laboratories, toxicity grades will only be assigned to Dipstick Hematuria.

With the exception of lipid tests, any graded laboratory test with a result that is between the LLN and ULN should be assigned Grade 0.

If the severity of a clinical AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac Arrhythmia (general) (By ECG or physical exam)	Asymptomatic AND No intervention indicated	Asymptomatic AND Non-urgent medical intervention indicated	Symptomatic, non-life-threatening AND Non-urgent medical intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated
Cardiac-ischemia/Infarction	NA	NA	Symptomatic ischemia (stable angina) OR Testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Hemorrhage (significant acute blood loss)	NA	Symptomatic AND No transfusion indicated	Symptomatic AND Transfusion of ≤ 2 units packed RBCs (for children ≤ 10 cc/kg) indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs indicated (for children ≤ 10 cc/kg) indicated
Hypertension (with repeat testing at same visit) **Pediatric ≤ 17 Years** (with repeat testing at same visit)	140–159 mmHg systolic OR 90–99 mmHg diastolic NA	> 159–179 mmHg systolic OR > 99–109 mmHg diastolic 91st–94th percentile adjusted for age, height, and gender (systolic and/or diastolic)	> 179 mmHg systolic OR > 109 mmHg diastolic ≥ 95th percentile adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences (eg, malignant hypertension) OR Hospitalization (other than ER visit) indicated Life-threatening consequences (eg, malignant hypertension) OR Hospitalization indicated (other than emergency room visit)
Hypotension	NA	Symptomatic, corrected with oral fluid replacement	Symptomatic, IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Pericardial Effusion	Asymptomatic, small effusion requiring no intervention	Asymptomatic, moderate or larger effusion requiring no intervention	Effusion with non-life-threatening physiologic consequences OR Effusion with nonurgent intervention indicated	Life-threatening consequences (eg, tamponade) OR Urgent intervention indicated

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged PR Interval	PR interval 0.21 to 0.25 sec	PR interval > 0.25 sec	Type II 2nd degree AV block OR Ventricular pause > 3.0 sec	Complete AV block
Pediatric ≤ 16 Years	1st degree AV block (PR > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	Asymptomatic, QTc interval 0.45 to 0.47 sec OR Increase interval < 0.03 sec above baseline	Asymptomatic, QTc interval 0.48 to 0.49 sec OR Increase in interval 0.03 to 0.05 sec above baseline	Asymptomatic, QTc interval ≥ 0.50 sec OR Increase in interval ≥ 0.06 sec above baseline	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Pediatric ≤ 16 Years	Asymptomatic, QTc interval 0.450 to 0.464 sec	Asymptomatic, QTc interval 0.465 to 0.479 sec	Asymptomatic, QTc interval ≥ 0.480 sec	Life-threatening consequences, eg, Torsade de pointes or other associated serious ventricular dysrhythmia
Thrombosis/Embolism	NA	Deep vein thrombosis AND No intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Deep vein thrombosis AND Intervention indicated (eg, anticoagulation, lysis filter, invasive procedure)	Embolic event (eg, pulmonary embolism, life-threatening thrombus)
Vasovagal Episode (associated with a procedure of any kind)	Present without loss of consciousness	Present with transient loss of consciousness	NA	NA
Ventricular Dysfunction (congestive heart failure, CHF)	NA	Asymptomatic diagnostic finding AND intervention indicated	New onset with symptoms OR Worsening symptomatic CHF	Life-threatening CHF

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Bronchospasm (acute)	FEV1 or peak flow reduced to 70% to 80%	FEV1 or peak flow 50% to 69%	FEV1 or peak flow 25% to 49%	Cyanosis OR FEV1 or peak flow < 25% OR Intubation
Dyspnea or Respiratory Distress	Dyspnea on exertion with no or minimal interference with usual social & functional activities	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities	Dyspnea at rest causing inability to perform usual social & functional activities	Respiratory failure with ventilatory support indicated
Pediatric < 14 Years	Wheezing OR minimal increase in respiratory rate for age	Nasal flaring OR Intercostal retractions OR Pulse oximetry 90% to 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilatory support indicated

OCULAR/VISUAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Uveitis	Asymptomatic but detectable on exam	Symptomatic anterior uveitis OR Medical intervention indicated	Posterior or pan-uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Visual Changes (from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alopecia	Thinning detectable by study participant or caregiver (for disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	NA
Cutaneous Reaction – Rash	Localized macular rash	Diffuse macular, maculopapular, or morbilliform rash OR Target lesions	Diffuse macular, maculopapular, or morbilliform rash with vesicles or limited number of bullae OR Superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Stevens-Johnson syndrome OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Toxic epidermal necrolysis (TEN)
Hyperpigmentation	Slight or localized	Marked or generalized	NA	NA
Hypopigmentation	Slight or localized	Marked or generalized	NA	NA
Pruritis (itching – no skin lesions) (See also Injection Site Reactions: Pruritis associated with injection)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]
Ascites	Asymptomatic	Symptomatic AND Intervention indicated (eg, diuretics or therapeutic paracentesis)	Symptomatic despite intervention	Life-threatening consequences
Cholecystitis	NA	Symptomatic AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (eg, sepsis or perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction)
Diarrhea **Adult and Pediatric ≥ 1 Year**	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline/24 hr	Persistent episodes of unformed to watery stools OR Increase of 4–6 stools over baseline per 24 hrs.	Bloody diarrhea OR Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (eg, hypotensive shock)
Pediatric < 1 Year	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Liquid stools resulting in severe dehydration with aggressive rehydration indicated OR Hypotensive shock

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Dysphagia-Odynophagia	Symptomatic but able to eat usual diet	Symptoms causing altered dietary intake without medical intervention indicated	Symptoms causing severely altered dietary intake with medical intervention indicated	Life-threatening reduction in oral intake
Mucositis/Stomatitis (clinical exam) See also Proctitis, Dysphagia-Odynophagia	Erythema of the mucosa	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Tissue necrosis OR Diffuse spontaneous mucosal bleeding OR Life-threatening consequences (eg, aspiration, choking)
Nausea	Transient (< 24 hours) or intermittent nausea with no or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24–48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Aggressive rehydration indicated (eg, IV fluids)	Life-threatening consequences (eg, hypotensive shock)
Pancreatitis	NA	Symptomatic AND Hospitalization not indicated (other than ER visit)	Symptomatic AND Hospitalization indicated (other than ER visit)	Life-threatening consequences (eg, sepsis, circulatory failure, hemorrhage)
Proctitis (functional-symptomatic) Also see Mucositis/ Stomatitis for Clinical Exam	Rectal discomfort AND No intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social/ functional activities OR Operative intervention indicated	Life-threatening consequences (eg, perforation)
Vomiting	Transient or intermittent vomiting with no or minimal interference with oral intake	Frequent episodes of vomiting with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated	Life-threatening consequences (eg, hypotensive shock)

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Alteration in Personality-Behavior or in Mood (eg, agitation, anxiety, depression, mania, psychosis)	Alteration causing no or minimal interference with usual social & functional activities	Alteration causing greater than minimal interference with usual social & functional activities	Alteration causing inability to perform usual social & functional activities	Behavior potentially harmful to self or others (eg, suicidal/homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions
Altered Mental Status For Dementia, see Cognitive and Behavioral/Attentional Disturbance (including dementia and ADD)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR obtundation, OR coma
Ataxia	Asymptomatic ataxia detectable on exam OR Minimal ataxia causing no or minimal interference with usual social & functional activities	Symptomatic ataxia causing greater than minimal interference with usual social & functional activities	Symptomatic ataxia causing inability to perform usual social & functional activities	Disabling ataxia causing inability to perform basic self-care functions
Cognitive and Behavioral/Attentional Disturbance (including dementia and Attention Deficit Disorder)	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full-time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
CNS Ischemia (acute)	NA	NA	Transient ischemic attack	Cerebral vascular accident (CVA, stroke) with neurological deficit

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Developmental delay – **Pediatric □ 16 Years**	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated (other than ER visit) OR Headache with significant impairment of alertness or other neurologic function
Insomnia	NA	Difficulty sleeping causing greater than minimal interference with usual social/functional activities	Difficulty sleeping causing inability to perform usual social & functional activities	Disabling insomnia causing inability to perform basic self-care functions
Neuromuscular Weakness (including myopathy & neuropathy)	Asymptomatic with decreased strength on exam OR Minimal muscle weak-ness causing no or minimal interference with usual social & functional activities	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Seizure: (new onset)	NA	1 seizure	2–4 seizures	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure: (pre-existing) For Worsening of Existing Epilepsy the Grades Should Be Based on an Increase from Previous Level of Control to Any of These Levels	NA	Increased frequency of pre-existing seizures (non-repetitive) without change in seizure character OR infrequent breakthrough seizures while on stable meds in a previously controlled seizure disorder	Change in seizure character from baseline either in duration or quality (eg, severity or focality)	Seizures of any kind that are prolonged, repetitive (eg, status epilepticus), or difficult to control (eg, refractory epilepsy)
Seizure **– Pediatric □ 18 Years**	Seizure, generalized onset with or without secondary generalization, lasting < 5 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting 5–20 minutes with < 24 hours post ictal state	Seizure, generalized onset with or without secondary generalization, lasting > 20 minutes	Seizure, generalized onset with or without secondary generalization, requiring intubation and sedation
Syncope (not associated with a procedure)	NA	Present	NA	NA
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia See also Arthritis	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis See also Arthralgia	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Bone Mineral Loss	BMD t-score or z-score –2.5 to –1.0	BMD t-score or z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Pediatric < 21 Years	BMD z-score –2.5 to –1.0	BMD z-score < –2.5	Pathological fracture (including loss of vertebral height)	Pathologic fracture causing life-threatening consequences
Myalgia (non-injection site)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	Asymptomatic with radiographic findings AND No operative intervention indicated	Symptomatic bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Acute Systemic Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with medical intervention indicated OR Mild angioedema with no medical intervention indicated	Generalized urticaria OR Angioedema with medical intervention indicated OR Symptomatic mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Fatigue Malaise	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating fatigue/malaise symptoms causing inability to perform basic self-care functions
Fever (nonaxillary)	37.7°C to 38.6°C 99.8°F to 101.5°F	38.7°C to 39.3°C 101.6°F to 102.8°F	39.4°C to 40.5°C 102.9°F to 104.9°F	> 40.5°C > 104.9°F
Pain - Indicate Body Site See also Injection Site Pain, Headache, Arthralgia, and Myalgia	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization (other than ER visit) indicated
Unintentional Weight Loss	NA	5% to 9% loss in body weight from baseline	10% to 19% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated [eg, tube feeding or total parenteral nutrition]

INJECTION SITE REACTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Injection Site Pain (pain without touching) Or Tenderness (pain when area is touched)	Pain/tenderness causing no or minimal limitation of use of limb	Pain/tenderness limiting use of limb OR Pain/tenderness causing greater than minimal interference with usual social & functional activities	Pain/tenderness causing inability to perform usual social & functional activities	Pain/tenderness causing inability to perform basic self-care function OR Hospitalization (other than ER visit) indicated for management of pain/tenderness
Injection Site Reaction (Localized), > 15 Years **Pediatric ≤ 15 Years**	Erythema OR Induration of 5 × 5 cm to 9 × 9 cm (or 25–81 × cm^2) **Erythema OR Induration OR Edema present but ≤ 2.5 cm diameter**	Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm^2) **Erythema OR Induration OR Edema > 2.5 cm diameter but < 50% surface area of the extremity segment (eg, upper arm/thigh)**	Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage **Erythema OR Induration OR Edema involving ≥ 50% surface area of the extremity segment (eg, upper arm/thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage**	Necrosis (involving dermis and deeper tissue) **Necrosis (involving dermis and deeper tissue)**
Pruritus Associated with Injection See also Skin: Pruritus (itching—no skin lesions)	Itching localized to injection site AND Relieved spontaneously or with < 48 h treatment	Itching beyond the injection site but not generalized OR Itching localized to injection site requiring ≥ 48 h treatment	Generalized itching causing inability to perform usual social & functional activities	NA

ENDOCRINE/METABOLIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Lipodystrophy (eg, back of neck, breasts, abdomen)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious changes on casual visual inspection	NA
Diabetes Mellitus	NA	New onset without need to initiate medication OR Modification of current meds to regain glucose control	New onset with initiation of indicated med OR Diabetes uncontrolled despite treatment modification	Life-threatening consequences (eg, ketoacidosis, hyperosmolar non-ketotic coma)
Gynecomastia	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA
Hyperthyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, thyroid storm)
Hypothyroidism	Asymptomatic	Symptomatic causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (eg, myxedema coma)
Lipoatrophy (eg, fat loss from the face, extremities, buttocks)	Detectable by study participant or caregiver (for young children and disabled adults)	Detectable on physical exam by health care provider	Disfiguring OR Obvious on casual visual inspection	NA

GENITOURINARY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Intermenstrual Bleeding (IMB)	Spotting observed by participant OR Minimal blood observed during clinical or colposcopic exam	Intermenstrual bleeding not greater in duration or amount than usual menstrual cycle	Intermenstrual bleeding greater in duration or amount than usual menstrual cycle	Hemorrhage with life-threatening hypotension OR Operative intervention indicated
Urinary Tract obstruction (eg, stone)	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

INFECTION				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Infection (any other than HIV infection)	Localized, no systemic antiμbial treatment indicated AND Symptoms causing no or minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Systemic antiμbial treatment indicated AND Symptoms causing inability to perform usual social & functional activities OR Operative intervention (other than simple incision and drainage) indicated	Life-threatening consequences (eg, septic shock)

Basic Self-care Functions: Activities such as bathing, dressing, toileting, transfer/movement, continence, and feeding.

Usual Social & Functional Activities: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.

Appendix 5: Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Recommendations

Pregnancy and Contraception Requirements for Males and Females of Childbearing Potential

Non-clinical toxicity studies of Epclusa demonstrated no adverse effect on embryo-fetal development. However, there are no clinical studies of Epclusa in pregnant women. Please refer to the latest version of the Investigator's Brochure for additional information.

Definition of Female of Childbearing Potential and Contraceptive Requirements for Female Subjects (and their male partners)

Women >54 years of age with cessation for ≥12 months of previously occurring menses, or women of any age who have had a hysterectomy, have had both ovaries removed, or have had medically documented ovarian failure will be considered to be of non-childbearing potential.

Women who are ≤ 54 years of age (including those with amenorrhea of any duration) who have not had a hysterectomy, have not had both ovaries removed, and have not had medically documented ovarian failure will be considered to be of childbearing potential.

Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test on the Baseline/Day 1 visit prior to enrollment. They must also agree to one of the following from 3 weeks prior to Baseline/Day 1 until 30 days after last dose of study drug:

1) Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) is not permitted.

Or

2) Consistent and correct use of 1 of the following methods of birth control listed below in addition to a male partner who correctly uses a condom from the date of screening until 30 days after last dose of study drug:

    a) intrauterine device (IUD) with a failure rate of < 1% per year
    b) female barrier method: cervical cap or diaphragm with spermicidal agent (if locally available)
    c) tubal sterilization
    3) vasectomy in male partner
    a) hormone-containing contraceptive:
        i) implants of levonorgestrel
        ii) injectable progesterone
        iii) oral contraceptives (either combined or progesterone only)
        iv) contraceptive vaginal ring
        v) transdermal contraceptive patch

3. Contraceptive Requirements for Male Subjects (and their female partners)

All male study participants must agree to consistently and correctly use a condom, while their female partner agrees to use 1 of the methods of birth control listed above, from the date of screening until 90

days after administration of the last dose of study drug:

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of study drug.

4. Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the Investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for partners of male subjects) of last Epclusa dose. Subjects who become pregnant or who suspect that they are pregnant must report the information to the Investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the Investigator.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 9.8.

Appendix 6: HCV Treatment Curriculum