CLINICAL STUDY PROTOCOL

Study Title:	A Registry for Subjects with Cirrhosis Who Achieve a Sustained Virologic Response Following Treatment with a Sofosbuvir-Based Regimen without Interferon for Chronic Hepatitis C Infection
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
IND Number:	115268
EudraCT Number:	2014-001249-26
Indication:	Hepatitis C Virus Infection
Protocol ID:	GS-US-337-1431
Gilead Study Director/ Medical Monitor:	Name: PPD Telephone: PPD Mobile: PPD Fax: PPD Email: PPD
Protocol Version/Date:	Original: 08 July 2014 Amendment 1: 17 October 2014 Amendment 2: 17 August 2015 Amendment 3: 01 June 2017

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PROTOCOL SYNOPSIS
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404, USA

Study Title:	A Registry for Subjects with Cirrhosis Who Achieve a Sustained Virologic Response Following Treatment with a Sofosbuvir-Based Regimen without Interferon for Chronic Hepatitis C Infection
IND Number:	115268
EudraCT Number:	2014-001249-26
Study Centers:	Gilead will select which treatment protocols and sites will be included in this SVR Cirrhosis Registry study. All selected study centers must have at least one subject with cirrhosis who achieved a sustained virologic response (SVR) following treatment with a sofosbuvir (SOF)-based regimen without interferon (IFN) in a Gilead-sponsored hepatitis C (HCV) study, or after receiving an all-oral SOF-based regimen outside a clinical study at sites pre-selected by Gilead.
Objectives:	The primary objectives of this study are as follows: • To assess the durability of SVR; • To assess clinical progression or regression of liver disease, including the incidence of hepatocellular carcinoma (HCC) following SVR. The secondary objective of this study is as follows: • For subjects who received their SOF-based regimen in a Gilead parent protocol, to determine whether subsequent detection of HCV RNA in subjects who relapse following SVR represents the re-emergence of pre-existing virus, the development of resistance mutations, or re-infection. The exploratory objective of this study is as follows: • CCI [redacted].

Study Design:	This Registry will enroll cirrhotic subjects with or without decompensated liver disease who have achieved an SVR after receiving a SOF-based regimen without IFN while participating in a Gilead-sponsored HCV study or an all-oral SOF-based regimen outside a clinical study at sites pre-selected by Gilead. In order to manage the total study enrollment, Gilead Sciences, Inc. will determine which treatment protocols and sites to include in this SVR Cirrhosis Registry study. At its sole discretion, Gilead may at any time discontinue enrollment and/or early withdraw individual subjects from individual treatment protocols prior to study completion (upon written notice to the site) regardless of the progress or outcome of the protocol assessments performed. Once enrolled, subjects will be followed for 5 years. For subjects rolling over from a Gilead parent protocol, a Day 1 visit will be scheduled within approximately 60 weeks from a subject's projected SVR 24 visit in the treatment protocol, or subjects may enroll from the GS-US-248-0122 SVR registry study at any time with Sponsor approval. For subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, a Day 1 visit will be scheduled within approximately 2 years from the subject's SVR 12 date. Visits will occur at Day 1 and then every 24 weeks at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240.
Target Population:	Subjects with cirrhosis who have achieved an SVR after receiving a SOF-based regimen without IFN while participating in a Gilead-sponsored HCV study may be eligible to enroll in this Registry at activated sites. In addition, subjects with cirrhosis who have achieved SVR after an all-oral SOF-based regimen outside a clinical study may be eligible to enroll in this registry at sites pre-selected by Gilead.
Duration of Treatment:	This observational Registry will follow subjects for up to 5 years.

Diagnosis and Main Eligibility Criteria:

To be eligible for participation, a subject must:

1) Provide written informed consent;
2) Have either previously participated in a Gilead-sponsored HCV study and received a sofosbuvir-containing regimen without interferon; OR

   At pre-selected sites only, have received an all-oral SOF-based regimen outside a clinical study. These subjects must have documentation of the regimen, start and end of treatment dates (month and year), and of having achieved SVR12
3) Have achieved SVR either in a Gilead-sponsored study, as defined in the treatment protocol; OR, for subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, SVR will be defined as HCV RNA < LLOQ approximately 12 weeks following last dose of treatment.
4) Have liver cirrhosis, as defined in the treatment protocol, and have not had a liver transplant after receiving the SOF-containing regimen; OR

   Subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, will have had cirrhosis as diagnosed prior to initiation of HCV treatment.

Study Procedures/ Frequency:	Assessments will include a limited physical exam and a liver disease assessment; quality of life surveys will be completed at each visit. Endoscopy to evaluate for varices will be performed at Day 1 and Week 240. At sites with a Fibroscan®, transient elastography will be performed at Day 1 and every 48 weeks through Week 240. CCI [redacted] At each visit, subjects will have blood drawn for plasma HCV RNA quantification, viral sequencing, chemistry, hematology, coagulation, α-fetoprotein, lipid panel, HOMA-IR, hemoglobin A1C, FibroTest®, ELF (Enhanced Liver Fibrosis) panel, and LOXL2. At Day 1, Week 96, and Week 240/Early Termination (as applicable), CCI [redacted] Model for End-Stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores will be calculated at each visit. CCI [redacted] If HCV RNA is detected, a repeat blood sample will be drawn for confirmation. If HCV RNA > LLOQ is confirmed the subject will be withdrawn from the Registry. Viral sequence analysis may be performed on available blood samples. Adverse events determined to be related to a study procedures occurring during the course of this Registry study will be followed and documented in accordance with this protocol.
Test Product, Dose, and Mode of Administration:	No test product will be administered in this Registry.
Reference Therapy, Dose, and Mode of Administration:	None.
Criteria for Evaluation:	This is an observational Registry to follow the incidence of signs, symptoms, and laboratory abnormalities, as well as radiographic and histologic changes, reflective of liver disease pathophysiology.

Statistical Methods:	Data from this Registry study will be summarized descriptively. Statistical hypothesis testing will not be conducted. All continuous variables will be summarized using an 8-number descriptive summary (n, mean, standard deviation, and median, Q1, Q3, minimum, maximum) by visit. All categorical variables will be summarized by number and percentage of subjects in each categorical definition. Safety data and adverse events, will be listed by subject and summarized using the number (proportion) of subjects with events or abnormalities for categorical data or using descriptive summary for continuous data.

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

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CRO	Contract (or clinical) research organization
CT	Computed Tomography
CTP	Child-Turcotte-Pugh
DSPH	Drug Safety and Public Health
eCRF	Electronic case report form(s)
EC	European Commission
ELF	Enhanced liver fibrosis
ET	Early termination (visit)
EU	European Union
EudraCT	European clinical trials database
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practice (Guidelines)
GGT	Gamma-glutamyl transpeptidase
GSI	Gilead Sciences, Inc.
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High density lipids
HLT	High level term
HLGT	High level group term
HRQoL	Health Related Quality of Life (surveys)
IB	Investigator's brochure
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IFN	Interferon
IL28B	IL28B gene
IND	Investigational New Drug (Application)
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
LDL	Low density lipids
LLT	Low level term
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease

mL	Milliliter
MRI	Magnetic resonance imaging
N	Number
OAV	Oral antiviral
PI	Principal investigator
PT	Prothrombin time or Preferred term
Q1, Q3	Quartiles 1 and 3
RNA	Ribonucleic acid
SADR	Serious Adverse Drug Reaction
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SGOT	Aspartate aminotransferase
SGPT	Alanine aminotransferase
SOC	System Organ Class or Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
TBD	To be determined
USA	United States

1. INTRODUCTION

1.1. Background

Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide {Ghany et al 2009}. The total HCV-infected population in the United States is estimated to be over 3 million people, with the vast majority infected with genotype 1 {Kershenobich et al 2011}. Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection. Consequences of chronic infection include cirrhosis and hepatocellular carcinoma (HCC). The annual rate of progression to cirrhosis in chronic HCV infected patients with advanced fibrosis is ~10%. Approximately 1 to 4% of patients per year with established cirrhosis will progress to hepatocellular carcinoma {Degos et al 2000}, {Dienstag et al 2011}, {Nishiguchi et al 1995}, {Serfaty et al 1998}. Given the asymptomatic nature of early infection, the slow progression to chronic liver disease, and the lack of adequate screening in at risk individuals, it is expected that the prevalence of subjects diagnosed with HCV-related complications will peak over the next 2 decades {Hoofnagle et al 2006}, {World Health Organization (WHO) 2000}, {El-Serag 2004}, {Davis et al 2003}. Complications of chronic hepatitis C account for the majority of liver transplants in the United States {Brown 2005}. In 2007 alone, it is estimated that over 15,000 people in the United States died from HCV-related complications. HCV now surpasses human immunodeficiency virus (HIV) as a cause of death in the United States {Ly et al 2012}.

1.2. Rationale for This Study

Chronic hepatitis C virus infection can cause chronic liver disease, cirrhosis, liver failure, hepatocellular carcinoma, transplant and/or death. The progression to cirrhosis is often clinically silent, and some patients are not known to have hepatitis C until they present with complications of end-stage liver disease or HCC. The features of decompensated cirrhosis include development of ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, hepatorenal syndrome and hepatic encephalopathy. In the U.S., deaths associated with chronic HCV are more likely to be caused from decompensated cirrhosis rather than HCC. Studies have estimated the 3, 5, and 10-year survival rates of compensated cirrhosis to be 96%, 91%, and 79%, respectively. {Chen et al 2006} The cumulative probability of an episode of clinical decompensation is 5% at 1 year, and increases to 30% at 10 years from the diagnosis of cirrhosis. {Chen et al 2006} Once decompensated cirrhosis occurs, the 5-year survival rate falls to 50%. {Chen et al 2006}

Attaining a sustained virologic response (SVR) after HCV treatment has been linked to a reduction in all-cause mortality, as well as liver related liver transplantation, hepatocellular cancer, and hepatic decompensation {van der Meer et al 2012}, {Morgan et al 2013}. To date, however, studies that link SVR with such clinical outcomes have been limited to subjects who attain an SVR after an interferon (IFN)-containing regimen. The goal of this study is to prospectively follow subjects with cirrhosis who have attained SVR after treatment with an IFN-free regimen. This study will evaluate the durability of SVR as well as the incidence rate of clinical events in those with cirrhosis.

1.3. Compliance

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

2. OBJECTIVES

The primary objectives of this study are:

- To assess the durability of SVR;
- To assess clinical progression or regression of liver disease, including the incidence of hepatocellular carcinoma (HCC) following SVR.

The secondary objective of this study is:

- For subjects who received their SOF-based regimen in a Gilead parent protocol, to determine whether subsequent detection of HCV RNA in subjects who relapse following SVR represents the re-emergence of pre-existing virus, the development of resistance mutations, or re-infection.

The exploratory objective of this study is:

- CCI [redacted]

3. STUDY DESIGN

3.1. Study Design

This Registry will enroll cirrhotic subjects with or without decompensated liver disease who have achieved an SVR after receiving a SOF-based regimen without IFN while participating in a Gilead-sponsored HCV study; or, at a subset of sites preselected by Gilead, who have previously received an all-oral SOF-based regimen outside a clinical study. For subjects enrolling from a Gilead parent protocol, the definitions of cirrhosis and of SVR are defined in the Gilead-sponsored treatment protocol.

Subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, will have had cirrhosis confirmed prior to initiation of HCV treatment.

In order to manage the total study enrollment, Gilead Sciences, Inc. will determine which treatment protocols and sites to include in this SVR Cirrhosis Registry study. At its sole discretion, Gilead may at any time discontinue enrollment and/or early withdraw individual subjects from individual treatment protocols prior to study completion (upon written notice to the site) regardless of the progress or outcome of the protocol assessments performed.

Once enrolled, subjects will be followed for up to 5 years. For subjects rolling over from a Gilead parent protocol, a Day 1 visit will be scheduled within approximately 60 weeks from a subject's projected SVR 24 visit in the treatment protocol, or subjects may enroll from the GS-US-248-0122 SVR registry study at any time with Sponsor approval. For subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, a Day 1 visit will be scheduled within approximately 2 years from the subject's SVR 12 date. Visits will occur at Day 1 and then every 24 weeks at Weeks 24, 48, 72, 96, 120, 144, 168, 192, 216 and 240.

3.2. Discontinuation Criteria

Registry participation will be discontinued in the following instances:

- Subjects who experience virologic relapse or re-infection defined as HCV RNA > LLOQ on two samples collected at least one week apart;
- Subjects who have a liver transplant;
- Subjects who request to discontinue for any reason; it is important to clearly determine and document the specific reason for withdrawal of consent;
- Discontinuation of the Registry and/or subjects at the request of Gilead, regulatory agency or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

If a subject meets withdrawal criteria or discontinues participation for any reason, the subject should complete an Early Termination visit.

4. SUBJECT POPULATION

4.1. Inclusion Criteria

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) Have either previously participated in a Gilead-sponsored HCV study and received a sofosbuvir-containing regimen without interferon; OR

   At pre-selected sites only, have received an all-oral SOF-based regimen outside a clinical study. These subjects must have documentation of the regimen, start and end of treatment dates (month and year), and of having achieved SVR12

3) Have achieved SVR either in a Gilead-sponsored study, as defined in the treatment protocol; OR for subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, SVR will be defined as HCV RNA < LLOQ approximately 12 weeks following last dose of treatment.

4) Have liver cirrhosis, as defined in the treatment protocol, and have not had a liver transplant after receiving a SOF-containing regimen; OR

   Subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, will have had cirrhosis as diagnosed prior to initiation of HCV treatment.

4.2. Exclusion Criteria

Subjects who meet *either* of the following exclusion criteria are not to be enrolled in this study.

1) Subject plans to initiate a new course of HCV therapy, including approved products and any investigational agents, during the course of this Registry;

2) History of clinically-significant illness or any other major medical disorder that may interfere with the subject follow-up, assessments or compliance with the protocol.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Investigational Medicinal Products

This is a long-term observational follow-up Registry. No investigational medicinal product will be administered.

5.2. Prohibited Concomitant Medications

Subjects will not receive any antiviral therapy for HCV infection while participating in this Registry. If a subject requires HCV antiviral therapy, they will be discontinued from the Registry. There are no other concomitant medications which would preclude subjects from participating in this Registry.

6. 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.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

6.1.1. Day 1 Assessments

For subjects enrolled from a Gilead parent protocol, a Day 1 visit will be scheduled within approximately 60 weeks from a subject's projected SVR 24 visit in the treatment protocol; or subjects may enroll from the GS-US-248-0122 SVR registry study at any time with Sponsor approval. For subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, a Day 1 visit will be scheduled within approximately 2 years from the subject's SVR 12 date.

Subjects will be asked to come in fasting for this visit. The following will be performed and documented at Day 1:

- Obtain written informed consent (may be obtained prior to Day 1)
  - CCI [redacted]
- Review eligibility criteria
- Complete Health Related Quality of Life (HRQoL) Surveys
- Conduct limited physical exam
- Collect information for liver disease assessment. For subjects who enrolled having received an all-oral SOF-based regimen outside a clinical study, the liver disease assessment at screening will include a medical history of clinical liver-associated events and the start and stop dates of their most recent occurrences.
- Obtain blood samples (For subjects enrolling from the GS-US-248-0122 study, blood samples do not need to be collected for both studies if the ET from GS-US-248-0122 and D 1 visit from GS-US-337-1431 are done on the same day)
- Perform endoscopy (+/- 6 months, no need to repeat if subject has available endoscopy results performed within 6 months prior to Day 1 as standard of care)
- Perform transient elastography (+ 4 weeks, at sites with a Fibroscan®)
- Record any serious adverse events or adverse events that are related to protocol-required procedures occurring after signing of the consent form

6.2. Follow-Up Assessments

Follow-up assessment visits will be scheduled based on the Day 1 visit date.

6.2.1. Weeks 24, 72, 120, 168, and 216 (+/- 4 weeks)

Subjects will be asked to come in fasting for these visits. The following procedures will be performed and documented:

- Complete Health Related Quality of Life (HRQoL) surveys
- Conduct limited physical exam
- Collect information for liver disease assessment
- Obtain blood samples (For subjects enrolling from the GS-US-248-0122 study, blood samples do not need to be collected for both studies if the ET from GS-US-248-0122 and D 1 visit from GS-US-337-1431 are done on the same day)
- Record any serious adverse events or adverse events that are related to protocol-required procedures

6.2.2. Weeks 48, 96, 144, and 192 (+/- 4 weeks)

Subjects will be asked to come in fasting for these visits. The following procedures will be performed and documented:

- Complete Health Related Quality of Life (HRQoL) Surveys
- Conduct limited physical exam
- Collect information for liver disease assessment
- Obtain blood samples (For subjects enrolling from the GS-US-248-0122 study, blood samples do not need to be collected for both studies if the ET from GS-US-248-0122 and D 1 visit from GS-US-337-1431 are done on the same day)
- Perform transient elastography (at sites with a Fibroscan®)
- Record any serious adverse events or adverse events that are related to protocol-required procedures

6.2.3. Week 240/ Study Completion (+/- 4 weeks)

Subjects will be asked to come in fasting for this visit. The following procedures will be performed and documented:

- Complete Health Related Quality of Life (HRQoL) surveys
- Conduct limited physical exam
- Collect information for liver disease assessment
- Obtain blood samples
- Perform transient elastography (at sites with a Fibroscan®)
- Perform endoscopy (within 6 months prior to Week 240, no need to repeat if subject has available endoscopy results performed as standard of care; refer to Section 6.3.6)
- CCI [redacted]
- Record any serious adverse events or adverse events that are related to protocol required procedures

6.2.4. Early Termination (ET) Visit

Subjects discontinuing the Registry for any reason should undergo the Early Termination (ET) visit. Subjects will be asked to come in fasting for this visit and the following procedures will be performed and documented:

- Complete Health Related Quality of Life (HRQoL) Surveys
- Conduct limited physical exam
- Collect information for liver disease assessment
- Obtain blood samples.
- Perform transient elastography (at sites with a Fibroscan®)
- Record any serious adverse events or adverse events that are related to protocol-required procedures

6.3. Procedures and Specifications

6.3.1. Clinical Laboratory

Blood Collection

The following clinical laboratory assessments will be performed at each visit. Subjects must be fasting at least 8 hours prior to each visit. If the subject does not arrive to clinic fasting, they may return anytime in the next 4 weeks to provide a fasting sample.

Hematology: Platelets

Chemistry: Alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), albumin, total bilirubin, direct bilirubin, Creatinine

Coagulation Test: INR, prothrombin time (PT)

Additional Tests:

- Alpha-fetoprotein (α-fetoprotein) level
- FibroTest®: alpha-2-macroglobulin, alpha-2-globulin (haptoglobin), apolipoprotein A1, GGT, and total bilirubin
- Enhanced Liver Fibrosis (ELF) panel: hyaluronic acid, amino-terminal propeptide of type III collagen, and TIMP-1
- Fasting lipid panel: low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol
- Hemoglobin A1C (HbA1c)
- HOMA-IR (fasting insulin x fasting glucose / 405)
- LOXL2 levels

Virological Tests: Plasma HCV RNA, and viral sequence analysis (if applicable)

Genetics Analysis: CCI [redacted]

6.3.2. HCV RNA Confirmation and Sequence Analysis

If at any time during the course of the registry a subject's HCV RNA result is > LLOQ, the subject will be asked to return for a confirmation sample to be drawn for determining virologic relapse or re-infection. Virologic relapse is defined as HCV RNA > LLOQ on two samples collected at least one week apart with the same virus present prior to treatment in the treatment

protocol. Re-infection is defined as HCV RNA > LLOQ on two samples collected at least one week apart with a different virus than that present prior to treatment in the treatment protocol. HCV sequencing will be performed if HCV RNA is sufficient. The specific HCV genes to be sequenced will be based on the specific oral antiviral (OAV) agent(s) administered to the subject in the Gilead-sponsored treatment protocol.

For subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study, HCV RNA results > LLOQ will be confirmed, as above; sequencing may be performed if appropriate, given available information.

6.3.3. Health Related Quality of Life Surveys

Quality of life surveys included in this study are Short Form-36 (SF-36), Chronic Liver Disease Questionnaire (CLDQ-HCV), and Work Productivity and Activity Impairment Questionnaire: Hepatitis C (WPAI: Hepatitis C) which will be completed by subjects and collected at each visit. Subjects should read the questionnaires and write/mark answers directly onto the paper questionnaires prior to any other study assessments. Sites will mail completed surveys with a transmittal sheet to a data entry vendor as directed.

6.3.4. Limited Physical Exam

The limited physical exam includes height (at Day 1 only) and weight measurements for calculation of BMI. Assessments for ascites and encephalopathy will be conducted at each visit for calculation of CTP score.

6.3.5. Liver Disease Assessment

Information will be collected at each visit for a liver disease assessment. Day 1 assessment will include determining whether any of the following have occurred since the last parent-protocol study visit prior to Day 1 for patients who achieved SVR in a Gilead-sponsored study or since the completion of the HCV therapy resulting in SVR prior to Day 1 for subjects who enroll after receiving an all-oral SOF-based regimen outside a clinical study. Assessment at all other study visits will include determining whether any of the following have occurred since the last study visit through Week 240 or early termination (unless otherwise specified). For subjects enrolled having received an all-oral SOF-based regimen outside a clinical study, the screening liver disease assessment will include the start and stop date of any clinical liver-associated events.

- Imaging of the liver performed as part of standard of care (eg, CT, MRI, or Ultrasound; results, if available)
- Liver biopsy or endoscopy to evaluate for varices (results, if available)
- Clinical liver-associated events including reports of hepatic encephalopathy, hepatocellular carcinoma, hepatorenal syndrome, hepatopulmonary syndrome, portopulmonary hypertension, hepatic hydrothorax, bleeding varices or spontaneous bacterial peritonitis
- Liver transplant (at any time prior to Day 1 and during the study)

6.3.6. Endoscopy

An endoscopy will be performed to evaluate for varices at Day 1 (+/- 6 months) and within 6 months prior to Week 240. There is no need to repeat if subject has available endoscopy results performed within 6 months prior to Day 1 or Week 240 as part of standard of care. The results of the endoscopy will be recorded into the clinical database.

6.3.7. Transient Elastography

A transient elastography will be performed to assess the liver at Day 1 (+ 4 weeks) and every 48 weeks (+/- 4 weeks) through Week 240 at sites with a Fibroscan®. The results of the scan will be recorded into the clinical database.

6.3.8. CCI [redacted]

CCI [redacted]

6.3.9. MELD Score and Child-Turcotte-Pugh Score

Model for End-Stage Liver Disease (MELD) Score and Child-Turcotte-Pugh (CTP) data will be calculated at each visit.

For the components of the MELD score and the components of the CTP score which are based on laboratory values, the data will be obtained from the central laboratory, and the scores will be calculated within the clinical database.

6.3.10. CCI [redacted]

CCI [redacted]

7. ADVERSE EVENTS MANAGEMENT

7.1. Adverse Events

This study is a long-term observational Registry in which no study medication will be administered. Adverse events related to the Gilead-sponsored treatment protocol will be followed in accordance with that protocol. Adverse events related to an all-oral SOF-based regimen used outside a clinical study should be reported as described in the locally approved product information utilizing the usual means for spontaneous reporting.

As a consequence, adverse event reporting in this Registry will be restricted to the following:

- Any adverse event occurring as a consequence of procedures required by this Registry protocol will be followed and documented in accordance with provisions outlined below.

For purposes of this Registry, an **adverse event** (AE) is any untoward medical occurrence in a clinical study subject associated with procedures required by this Registry protocol. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with procedures required by this Registry (e.g., hematoma following venipuncture).

An AE does not include the following for this Registry:

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and before Day 1 visit is not an AE.
- Any medical condition or clinically significant laboratory abnormality with an onset date after the consent form is signed that is related to the Gilead-sponsored treatment protocol or to an all-oral SOF-based regimen used outside a clinical study.

7.2. Serious Adverse Events

Any **serious adverse event** (SAE) occurring during the Gilead-sponsored treatment protocol will be followed, documented and reported under that treatment protocol. Similarly, any new SAEs occurring while the subject is participating in the Registry that are considered to be related to the study drugs administered or procedures in the treatment protocol will be followed, documented and reported under the Gilead-sponsored treatment protocol or as per locally approved product information. Any serious adverse event related to an all-oral SOF-based regimen used outside a clinical study should be reported as described in the locally approved product information utilizing the usual means for spontaneous reporting.

The only SAEs that will be reported under this Registry are events considered to be related to procedures required by the Registry protocol. A **serious adverse event** is defined as follows:

Any adverse event that results in any of the following outcomes:

- Death
- Life-threatening (the subject was at **immediate** 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 (excluding, for example, those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product. All pregnancy events will be followed to resolution/outcome in the Gilead-sponsored treatment protocol
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself.
- "Life-threatening" means that the subject was 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.
- "In-patient 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 relationship to study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following considerations:

- **No:** Evidence exists that the AE has an etiology other than the study procedure.
- **Yes:** The AE occurred as a result of protocol required procedures such as venipuncture.

7.3. Serious Adverse Event Reporting Requirements

7.3.1. All Serious Adverse Events

Gilead Sciences is required to expedite to worldwide regulatory authorities reports of SAEs, Serious Adverse Drug Reactions (SADRs) or Suspected Unexpected Serious Adverse Reactions (SUSARs) in line with relevant legislation, including the applicable US FDA Code of Federal Regulation, the European Commission Clinical Trials Directive (2001/20/EC); therefore, Gilead Sciences (or the CRO on the behalf of Gilead Sciences) must be notified immediately regarding the occurrence of any SAE or SADR that occurs after the subject consents to participate in the Registry, including SAEs/SADRs resulting from protocol-required procedures as defined in relevant legislation including 2001/20/EC, performed from Day 1 onwards. The procedure for reporting SAEs is as follows:

- All AEs and SAEs will be recorded in the electronic case report form (eCRF) database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead Drug Safety and Public Health (DSPH) within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, i.e., the eCRF database is not functioning, record the SAE on the paper serious adverse event reporting form and submit within 24 hours to:

Gilead Sciences DSPH:	Fax:	PPD
	E-mail:	PPD
Gilead Sciences Study Director / Medical Monitor:	Name:	PPD
	Telephone:	PPD
	Mobile:	PPD
	Fax:	PPD
	Email:	PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Gilead Sciences may request additional information from the investigator to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the event description section of the SAE form.

The investigator must take all therapeutic measures necessary for resolution of the SAE. Follow-up of SAEs will continue through the last day on the Registry and/or until a conclusive outcome (eg, resolved, resolved with sequelae, lost to follow-up, fatal) is achieved.

7.3.2. Investigator and Sponsor Reporting Requirements for SAEs

Any SAE deemed by the investigator to be related to a protocol-required procedure should be collected and reported throughout the Registry study and reported to Gilead Sciences DSPH using the SAE report form.

An SAE may qualify for reporting to regulatory authorities. All Investigators will receive a safety letter notifying them of relevant SUSAR reports. The Investigator should notify the IRB/IEC as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy.

In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead will notify worldwide regulatory authorities and the relevant Ethics Committees in concerned Member States of applicable SUSARs.

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

Lab abnormalities are usually not recorded as AEs or SAEs. Laboratory abnormalities will only be recorded as an AE/SAE if they are related to a protocol required procedure.

7.5. Procedures to be followed in the Event of Pregnancy

Procedures to be followed in the event of pregnancy occurring on the treatment protocol are detailed in the Gilead-sponsored treatment protocol. No additional pregnancy reporting requirements are included in this Registry protocol.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

Treatment regimen is defined in the Gilead-sponsored treatment protocol.

8.1.1. Analysis Objectives

The primary objectives of this study are:

- To assess the durability of SVR;
- To assess clinical progression or regression of liver disease, including the incidence of hepatocellular carcinoma (HCC) following SVR

The secondary objective of this study is:

- For subjects who received their SOF-based regimen in a Gilead parent protocol, to determine whether subsequent detection of HCV RNA in subjects who relapse following SVR represents the re-emergence of pre-existing virus, the development of resistance mutations, or re-infection

The exploratory objective of this study is:

- CCI [redacted]

8.1.2. Primary Endpoints

The primary endpoints are:

- The proportion of subjects maintaining SVR at Week 240;
- The proportion of subjects who develop liver disease progression or regression, as assessed by clinical and laboratory parameters;
- The proportion of subjects who develop HCC through Week 240

8.1.3. Secondary Endpoints

The secondary endpoints will be assessed in subjects who received their SOF-based regimen in a Gilead parent protocol, as follows:

- The proportion of subjects with detectable HCV RNA due to re-emergence of pre-existing virus through Week 240;
- The proportion of subjects with detectable HCV resistance mutations through Week 240
- The proportion of subjects with detectable HCV RNA due to re-infection through Week 240

8.1.4. Other Endpoints of Interest

CCI [redacted]

[redacted]

[redacted]

8.2. Analysis Conventions

All individual subject data will be listed as measured. All statistical summaries and analyses will be performed using SAS® software (SAS Institute, Cary, North Carolina, USA).

8.2.1. Analysis Sets

8.2.1.1. Safety Analysis Set

The analysis set includes all enrolled subjects. Both the safety and efficacy analyses will be based on the safety analysis set.

8.3. Data Handling Conventions

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data will not be imputed.

All available data for subjects who do not complete the study will be included in data listings.

HCV RNA values below the LLOQ for the assay will be set to the lower limit minus 1 for calculation of summary statistics for the actual HCV RNA values and the change from baseline values by study visit. The reported values will be provided in the HCV RNA listing.

For selected analyses of early time point data, HCV RNA data (IU/mL) may be transformed to the logarithmic (base 10) scale ($\log_{10}$ IU/mL).

8.4. Interim Analyses

Interim analyses may be performed on an ad hoc basis.

8.5. Demographic Data and Baseline Characteristics

Demographic and baseline measurements will be summarized using standard descriptive methods.

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

Baseline characteristics data will include a summary of HCV RNA levels, liver function tests, platelets, coagulation test, α-fetoprotein, and HCV genotype and IL28B genotype, if known.

8.6. Efficacy Analysis

All continuous endpoints will be summarized using an 8-number descriptive summary (n, mean, standard deviation, median, Q1, Q3, minimum and maximum). All categorical endpoints will be summarized by the number and percent of subjects meeting the endpoint. Ninety-five percent confidence intervals will also be reported.

8.6.1. Primary Analysis

The proportion of subjects who maintain an SVR through Week 240 will be estimated using a Kaplan-Meier model, allowing for censored observations due to early discontinuation from the Registry.

The proportion of subjects who develop clinical progression or regression of liver disease through Week 240 will be estimated using a Kaplan-Meier model, allowing for censored observations due to early discontinuation from the Registry.

The proportion of subjects who develop HCC through Week 240 will be estimated using a Kaplan-Meier model, allowing for censored observations due to early discontinuation from the Registry.

8.6.2. Secondary Analyses

The proportion of subjects with detectable HCV RNA due to re-emergence of pre-existing virus through Week 240 will be summarized by number and percent of subjects by time point using the same model as in the primary analysis.

The proportion of subjects with detectable HCV resistance mutations through Week 240 will be summarized by number and percent of subjects by time point.

The proportion of subjects with detectable HCV RNA due to re-infection through Week 240 will be summarized by number and percent of subjects by time point.

Clinical laboratory test results related to liver disease progression or regression (ie, ALT, AST, bilirubin, albumin, platelets, PT and/or INR, and α-fetoprotein) will be listed by subject. Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results. Values falling outside of the relevant reference range will be flagged, as appropriate, in the data listings. Abnormalities in clinical laboratory test results will be summarized by enumeration of the number of subjects with values falling outside of the reference range by study day. Laboratory data will be descriptively summarized over time by study day and by the change from Baseline.

Clinical signs and symptoms related to liver disease progression or regression will be summarized by frequency and percent of subjects. Applicable clinical signs assessed include ascites, hepatic encephalopathy, varices, spontaneous bacterial peritonitis, HCC and transplant. In addition, Child-Turcotte-Pugh score will be included with the following categories, A (5-6), B (7-9), and C (10-15).

Descriptive summaries and listings will be provided for additional efficacy evaluations of the quality of life endpoints.

8.7. Safety Analysis

Analysis of safety measures will be descriptive and will include subjects in the Safety analysis set. Missing observations will be excluded from analysis of safety measures. All safety data collected on or after the date of enrollment through the remainder of the study will be summarized.

8.7.1. Extent of Exposure

This is a Registry study with no active treatment; hence, extent of exposure to study drug is not applicable.

8.7.2. Adverse Events

Clinical and laboratory adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term (PT), and Lower-Level Term (LLT) will be attached to the clinical database.

Events will be summarized by the date of onset for the event. An adverse event is defined as an event that begins or worsens on or after the date the ICF is signed through study completion or study discontinuation and is classified as related to study procedure.

Adverse events, including SAEs by the above definition, will be listed by subject. The frequency of subjects who experience adverse events will be summarized overall, by treatment regimen and by severity.

SAEs that do not meet the above definition will not be captured or summarized.

Data listings will be provided for subjects who discontinued the study due to an adverse event by the above definition.

8.7.3. Other Safety Evaluations

No other safety assessments are planned.

8.8. Pharmacokinetic Analysis

No pharmacokinetic analysis is planned.

8.9. Sample Size

Due to the observational nature of this study, no formal power or sample size calculations were used.

8.10. Additional Considerations

Any additional statistical analyses and/or method for this study will be described in the Statistical Analysis Plan (SAP).

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The 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 Harmonisation (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. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and Good Clinical Practice Directive 2005/28/EC.

The 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, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable subinvestigators will comply with 21 CFR, Part 54, 1998, 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 investigator's (and any subinvestigator's) participation in the study. The investigator and subinvestigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

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

The investigator (or sponsor as appropriate according to local regulations) 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 investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the 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.

9.1.3. Informed Consent

The 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

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 or local requirements. The consent form will inform subjects about sample retention, and their right to receive clinically relevant analysis results.

9.1.4. Confidentiality

The 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 or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a log showing codes, names, and addresses for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations.

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, CRF/eCRF, and any other study information, remain the sole and exclusive property of Gilead 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) without prior written consent from Gilead. The 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.

9.1.5. Study Files and Retention of Records

The investigator must 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: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, 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);
- Documentation that subject meets eligibility 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;
- Record of all adverse events related to study procedures (start and end date);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject enrolled, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. 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 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. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (eg, data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs or IECs, or to regulatory authority or health authority inspectors.

9.1.7. Protocol Compliance

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

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead 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.

After conclusion of the Registry and without prior written approval from Gilead Sciences, investigators in this Registry may communicate, orally present, or publish in scientific journals or other scholarly media ***only after the following conditions have been met:***

- the results of the Registry in their entirety have been publicly disclosed by or with the consent of Gilead Sciences in an abstract, manuscript, or presentation form; or,
- the Registry has been completed at all study sites for at least 2 years.

No such communication, presentation, or publication will include Gilead Sciences' confidential information (see Section 9.1.4).

The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for remote review of the eCRF at regular intervals to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them.

Ad hoc monitoring visits may occur on site, at which time the monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (remote or on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Registry for Subjects with Cirrhosis Who Achieve a Sustained Virologic Response Following Treatment with a Sofosbuvir-Based Regimen without Interferon for Chronic Hepatitis C Infection

GS-US-337-1431, Amendment 3, 01 June 2017

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD (Printed)
Study Director/Medical Monitor

PPD

Date

PPD

Signature

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this 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 information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed)

Signature

Date

Site Number

Appendix 2. Study Procedures Table

Clinical Assessments	Day 1	Study Week										
		24	48	72	96	120	144	168	192	216	240	ET
Informed Consent[a]	X											
Quality of Life Surveys	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Related to Procedures	X	X	X	X	X	X	X	X	X	X	X	X
Limited Physical Exam[b]	X	X	X	X	X	X	X	X	X	X	X	X
Liver Disease Assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X
Endoscopy	X									X		
Transient Elastography[d]	X		X		X		X		X		X	X
Liver Biopsy[e]											X	
Laboratory Assessments												
HCV RNA	X	X	X	X	X	X	X	X	X	X	X	X
Viral Sequencing[f]	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology (Platelets)	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Test (PT/INR)	X	X	X	X	X	X	X	X	X	X	X	X
Additional Tests[h]	X	X	X	X	X	X	X	X	X	X	X	X
HCV RNA Confirmation[i]	X											
CCI												

a Informed consent may be obtained prior to Day 1

b Assessment of ascites, encephalopathy, height (at Day 1) and weight; calculated scores include BMI, CTP and MELD

c Liver Disease Assessment: refer to protocol Section 6.3.5

d At sites with a Fibroscan® equipment

e CCI

f Plasma will be collected for possible viral sequencing or other virology studies if indicated.

g Includes ALT/SGPT, AST/SGOT, Albumin, Total bilirubin, Direct Bilirubin, Creatinine

h Includes α-fetoprotein level, FibroTest® , ELF panel, lipid panel, hemoglobin A1C, HOMA-IR and LOXL2

i Only in subjects with HCV RNA >LLOQ

j For subjects who consent