Official Title: Newer Direct-Acting Anti-Viral Agents as Sole Therapy of Porphyria Cutanea Tarda in Subjects With Chronic Hepatitis C
NCT03118674
IRB-Approved Date: 5/5/2020

Rare Diseases Clinical Research Network

Porphyrias Consortium

Newer Direct-Acting Anti-Viral Agents as Sole Therapy of Porphyria Cutanea Tarda in Subjects with Chronic Hepatitis C

Study Chair:

Herbert L. Bonkovsky MD
Professor of Medicine, Molecular Medicine & Translational Science
Wake Forest School of Medicine
Medical Center Blvd
Winston-Salem, NC 27157
Phone: 336-713-7341
Fax: 336 713 7322
Email: hbonkovs@wakehealth.edu

Table of Contents

1. Protocol Synopsis

Interventional Synopsis

Protocol Number:	7210
Protocol Title:	**Newer Direct-Acting Anti-Viral Agents as Sole Therapy of Porphyria Cutanea Tarda in Subjects with Chronic Hepatitis C**
Study Chair:	Herbert L. Bonkovsky, MD
Statistician:	Inga Peter, PhD; Jessica Overbey, MS
Consortium:	Porphyrias Consortium
Activation Date:	04AUG2017
Current Status:	Enrolling
Sample Size:	49
Target Enrollment Period:	3 years
Study Design:	Interventional, one arm, open label non-inferiority
Primary Study Objective:	To assess whether Harvoni alone is an effective therapy of active PCT (measured as resolution of active PCT by 7 months) in patients with Chronic Hepatitis C (CHC).
Secondary Study Objective(s):	To assess time to resolution of active PCT after initiation of treatment with Harvoni; To assess time course of normalization of urinary porphyrin profiles; To assess cure of chronic hepatitis c
Study Population and Main Eligibility/ Exclusion Criteria:	**Inclusion Criteria:** 1. Willing and able to give informed consent 2. ≥18 years of age 3. Symptoms and signs consistent with PCT and well documented biochemical diagnosis (urinary total porphyrin excretion > 500 mcg/g creatinine with HPLC pattern typical of PCT—predominance of 8- and 7-carboxyl porphyrins [>50% of total]) 4. Clinical diagnosis of PCT established by a study PI 5. Chronic hepatitis C: HCV RNA positive and quantifiable in serum detected within 90 days of enrollment, and documented HCV genotypes 1,4, 5, or 6 for which Harvoni is an approved therapy. 6. Women of child-bearing potential must be willing to avoid pregnancy and use an accepted and effective contraceptive method during treatment. **Exclusion Criteria:** 1. Women who are pregnant or who are breast-feeding 2. Patients who have already started treatment of PCT with phlebotomy or low dose hydroxychloroquine or chloroquine, or who have been in such treatment in the past 30 days 3. Patients who have already started another treatment regimen for CHC, or who have taken such treatment in the past 30 days 4. HIV infection with CD4 counts at baseline less than 350/μL or with evidence of any active AIDS-defining illnesses 5. Ongoing active alcohol abuse, defined as a history of drinking more than 25 drinks of alcohol per week during most weeks in the prior 4 months (History of prior, but not current alcohol abuse will NOT be grounds for exclusion because we seek to treat subjects with PCT and CHC of the type typically seen in clinical practice)

	6. Any ongoing active IV drug use 7. Patients who are taking amiodarone or who have taken amiodarone within 60 days prior to enrollment 8. Patients who are taking, or within the prior 28 days have taken, rifampicin or St John's wort (*Hypericum perforatum*), both of which are P-gp inducers, which may significantly reduce the drug levels and therapeutic effects of Harvoni 9. Uncontrolled diabetes (Hgb A1c >9.5% within 60 days prior to enrollment) 10. Chronic hepatitis B 11. Autoimmune hepatic liver injury—autoimmune hepatitis, primary biliary cholangitis/sclerosing cholangitis or overlap syndrome 12. Alcoholic hepatitis 13. Other metabolic disorders of the liver, e.g. Alpha 1 antitrypsin deficiency with ZZ Pi type, Wilson's disease 14. Prior known or suspected drug-induced liver injury within 6 months of enrollment 15. Known or suspected hepatocellular carcinoma 16. On liver transplant list, or current MELD >12 17. History of liver transplant 18. Estimated GFR (creatinine clearance) <30 mL/min (per Sofosbuvir being cleared by the kidney) 19. Serum ALT or AST >10x upper limit of normal 20. Serum bilirubin >2 mg/dL (excluding patients with known or suspected Gilbert's syndrome) 21. Any other comorbid condition, which in the opinion of the investigator precludes participation 22. Incarcerated individuals
Treatment (if applicable)	
Agent-	Harvoni—ledipasvir, 90 mg + sofosbuvir, 400 mg
Dosage, schedule, route of administration-	1 tablet per day, oral, taken with or without food. 8 weeks for patients without cirrhosis, not previously treated with HCV GT1 and HCV RNA < 6 million IU/mL; 12 weeks for patients without cirrhosis; 24 weeks for patients with compensated cirrhosis.
Safety Issues-	The drug is well-tolerated and highly effective for cure of HCV
Primary Outcome Measures:	The primary endpoint will be resolution of active PCT, defined as normalization of plasma porphyrins (less than 0.9 mcg/dL) by 7 months after start of therapy.
Secondary Outcome Measures:	Time to resolution of active PCT, defined as cessation of any new blisters or bullae and normalization of plasma porphyrins. Complete resolution of skin manifestations is expected to occur later than normalization of plasma porphyrins, because it takes time for healing of the skin fragility that predisposes of blister formation to occur. Decrease of the sum of urinary uro- and hepta-carboxyl porphyrins to less than 100 mcg/g creatinine, and a normal urine porphyrin HPLC pattern. Cure of CHC, defined as no detectable HCV RNA at end of treatment (EOT) and persisting for at least 12 weeks after EOT.
Statistical Considerations (sample size and analysis plan):	The primary study hypothesis is that the proportion of patients whose PCT resolves by 7 months will be non-inferior to the performance goal of 50%. The non-inferiority margin will be set to 10%; a difference from the performance goal judged to be both

	clinically acceptable and well within the margin needed to assure that the performance of Harvoni is at established levels of benefit from conventional therapies. Thus, the null hypothesis tested by this study is H_0: $\pi \leq 0.40$, against the alternative hypothesis H_1: $\pi > 0.40$. Sample size requirements are based on an exact test of a binomial proportion. Assuming that the study drug has a true success probability of 58%, 49 patients yield 80% power to reject the null hypothesis at a one-sided significance level of 0.05.
Sponsors (federal, state, foundation and industry support):	Gilead Sciences; National Institutes of Health (NIH)

1.1 Overview

The purpose of this study is to learn whether Harvoni, a simple oral treatment for chronic hepatitis C infection, is effective for treatment of porphyria cutanea tarda (PCT).

PCT is the most common form of porphyria in the USA and most other countries and regions of the world. There are two major types of PCT: acquired (type 1, which accounts for about 80% of cases) and inherited (type 2). The major risk factors for type 1 PCT are heavy alcohol use, iron overload, hepatitis C (HCV) or human immunodeficiency virus (HIV) infection, and ingestions of estrogens. Most patients with PCT, either type 1 or type 2, have one or more of these risk factors. In type 2 PCT, subjects have a partial deficiency, usually ~ 50% of normal, activity of the enzyme uroporphyrinogen decarboxylase (UROD), whereas, in type 1 PCT, the deficiency in UROD activity is limited to the liver, and it appears usually to be acquired and due to excess iron, alcohol, HCV, HIV, etc.

The time-honored treatment of first choice for either form of PCT has been iron reduction, usually carried out most quickly and efficiently by therapeutic phlebotomy. However, (hydroxy) chloroquine in low doses also is effective. There have been anecdotal reports of treatment of HCV infection with interferon with or without ribavirin being effective treatment. To date, however, there have been no prospective case series of such treatments, nor have there been comparisons of results with anti-viral treatments, compared with iron reduction or (hydroxyl) chloroquine.

With the recent development of newer and highly active and effective therapies for HCV infection, with fewer side-effects than were heretofore possible, we have felt that it now is time for a careful and formal study to assess whether these agents are effective treatments for PCT.

This is an open-label study with a non-inferiority design, to assess whether Harvoni is an effective treatment of PCT.

2. Specific Aims (Hypothesis and Objectives)

Aim: To assess whether Harvoni alone is an effective and durable therapy of active PCT in patients with CHC due to any genotype for which Harvoni is approved for treatment, currently genotypes 1, 4, 5, or 6. Genotype 1 HCV accounts for ~ 75% of chronic hepatitis C infections in the USA. Genotype 4 is common in Egypt; rare in the USA, but it does occur. Our goal is to be as inclusive as possible and to test effects of Harvoni treatment in real-world situations. We will test whether Harvoni treatment is non-inferior to previously published remission times of other standard treatments of PCT (low dose hydroxy chloroquine or phlebotomy therapy) (Singal et al, 2012).

Hypothesis: Treatment of PCT associated with CHC with Harvoni is as effective and as durable as published data on the current standard treatments of iron reduction by phlebotomies or low dose hydroxychloroquine.

3. Background:

CHC is a well-known risk factor for PCT. Other risk factors include hepatic iron overload, often related to mutations of *HFE* associated with hereditary hemochromatosis, excess alcohol use, estrogen therapy, and HIV infection (Bonkovsky et al, 1998, 2013; Egger et al, 2002; Besur et al, 2014).

The standard of care therapy for PCT has been iron reduction by therapeutic phlebotomy, which has been effective in nearly all subjects, regardless of underlying major risk factors (Besur et al, 2014; Bonkovsky et al, 1998, 2013). Based upon more recent results, low-dose therapy with 4-aminoquinolones, (chloroquine and/or hydroxychloroquine), also has become a standard therapy, as has a combination of iron reduction and one of these agents (Stölzel et al, 2009; Singal et al, 2012; Bonkovsky HL, unpublished). However, it has been found that decreases in measures of iron status following chloroquine therapy did not occur in subjects with *HFE* mutations and that C282Y +/+ subjects did not respond very well to chloroquine (Stölzel et al, 2003). In addition, the use of 4-aminoquinolones, as against phlebotomy therapy, may be associated with earlier recurrence of active PCT after a course of therapy than after a course of iron reduction and maintenance of an iron-reduced state (Stölzel et al, 2003, 2009; & Bonkovsky, unpublished observations). This led to the recommendation that, for those with *HFE*-linked hemochromatosis, therapeutic phlebotomy should remain the treatment of first choice (Stölzel et al, 2003).

During the past 20 years or so, there have been anecdotal reports of PCT resolving with successful anti-viral therapy of CHC, although there also have been reports of such therapy precipitating or worsening PCT (Bonkovsky et al, 2013). Because active cutaneous lesions of PCT are generally more symptomatic than CHC, which usually occurs with few, if any, symptoms until late in the course of advanced liver disease, and because typically PCT is successfully treated within about 6 to 7 months, either with iron reduction or one of the 4-aminoquinolones (Singal et al, 2012), the usual recommendation has been first to treat active PCT and thereafter to treat CHC. Until

recently, therapy of CHC has been longer (usually at least 48 weeks), less often successful and fraught with adverse effects, especially related to the use of interferon alpha, which has been the cornerstone of treatment. However, during the past few years, newer and more effective oral therapies for CHC, with far fewer and less severe side-effects have been approved by the US FDA, the EMA, and other regulatory agencies. In particular, sofosbuvir (Sovaldi) with interferon and ribavirin or with simeprevir (Olysio), and more recently, the combination of ledipasvir + sofosbuvir (Harvoni) (Gilead Sciences) have proven highly effective and to produce far fewer severe adverse effects than the earlier therapeutic regimens based upon interferon (usually in combination with ribavirin) (Syllabus of Post-Graduate Course and presentations at annual meeting of AASLD, Nov 7-11, 2014, Boston, MA). Other combinations of all oral, direct-acting antivirals have recently been approved (e.g., Viekira Pak, Abbvie; Mavyret, Abbvie; Zepatier, Merck) and/or are in late-stage clinical trials.

Because treatment for CHC is now highly successful within as short a time as 8-12 weeks and with few adverse effects, it is reasonable to consider this treatment first in patients with both CHC and PCT. However, experience is needed with a reasonable number of patients in order to validate this approach, and in particular to demonstrate that time to remission is as rapid and that remission of PCT is as durable following therapy with Harvoni as with phlebotomy or (hydroxy) chloroquine. Also, PCT is a heterogeneous, multifactorial disease, and it is important to ascertain whether other co-existing susceptibility factors influence response to a new treatment approach and durability of remission.

The Office of Rare Diseases (ORD) of the National Institutes of Health (NIH) established a Rare Diseases Clinical Research Network (RDCRN) in collaboration with other NIH Institutes and has funded several rare diseases clinical research consortia and one Data Management and Coordinating Center (DMCC). The Porphyrias Consortium was created as part of the RDCRN, to study the human porphyrias.

4. Study Design and Methods

This will be a one arm, open-label non-inferiority study of Harvoni for treatment of PCT complicating chronic hepatitis C infection caused by HCV genotypes for which Harvoni is approved as therapy, compared to a performance goal of a 50% remission rate at 7 months. This performance goal is based on recently published results from our Consortium (Singal et al, 2012), in which the median time to remission for subjects treated either with phlebotomy or hydroxychloroquine was 7 months, and on expert consensus that if Harvoni demonstrates a median time to remission of 7 months, porphyrias experts would consider using Harvoni over phlebotomy or hydroxychloroquine as a first line of treatment for PCT patients with Hepatitis C. Our aim is to be as inclusive as possible, so that the results will be as generalizable as possible to regular clinical practice. Comparison of response rates, both for amelioration of PCT (the primary endpoint) and for cure of HCV infection (a secondary

endpoint) will be by comparison to recently published results from our Consortium (Singal et al, 2012) and elsewhere (results of recent trials of Harvoni for treatment of chronic hepatitis C).

Adult subjects, of either gender with well-established PCT, who also have CHC due to an HCV genotype 1, 4, 5, or 6, for which Harvoni is approved as therapy, will be invited to take part. PCT patients with CHC typically have additional susceptibility factors, such as alcohol use, estrogen exposure, smoking, *HFE* mutations, *UROD* mutations or HIV infection (Bonkovsky et al, 1998, 2013; Egger et al, 2002), and none of these will be reasons for exclusion. Subjects previously treated for PCT and/or HCV infection will be eligible, provided they meet the current criteria for inclusion and exclusion.

Assessment of Stage of Liver Disease:

Cirrhosis will be considered to be present according to the following two-tiered approach:

Stage 1—based upon historical data:

a. Any prior liver biopsy that was interpreted by a pathologist as showing definite or probable cirrhosis (Ishak fibrosis score of 5 or 6; or Metavir fibrosis score of 4); and/or
b. Hepatic elastography/Fibroscan value, performed within the prior three years, that showed liver stiffness > 12.5 kPa.

Stage 2—for subjects without historical data:

a. A liver biopsy performed on the subject that shows definite or probable cirrhosis (Ishak fibrosis score of 5 or 6; or Metavir fibrosis score of 4); and/or
b. Hepatic elastography/ Fibroscan, performed for screening purposes, that shows liver stiffness greater than 12.5 kPa; and/or
c. Hepatic imaging study (ultrasound, CT or MRI), performed within three months of enrollment that showed findings typical of cirrhosis, such as irregular, lobulated or nodular appearance of the liver, enlargement of the spleen, gastro-esophageal varices, ascites, or other evidence of portal hypertension; and/or
d. Physical examination that shows findings typical of cirrhosis, such as multiple spider angiomas, red palms, prominent venous pattern of the upper abdominal wall, palpable and firm or hard liver, often with increased prominence of the left lobe, when accompanied by a decreased platelet count (<140,000/μL) in peripheral blood.

As is standard practice, if subjects use alcohol, they will be strongly encouraged not to consume alcohol in any form, at least for the duration of the study and it's follow-up. They also will be asked to stop any use of estrogens; and those that smoke cigarettes will be advised to stop smoking. Adherence to these recommendations will be tracked by patient interviews. Continuing use of estrogens and/or smoking will NOT be grounds

for removal of subjects from the study. Subjects may have HIV infection, as long as their CD4 counts at baseline are greater than or equal to 350/μL and they do not have evidence of any active AIDS-defining illnesses.

4.1 Inclusion Criteria

1. Willing and able to give informed consent
2. ≥18 years of age
3. Symptoms and signs consistent with PCT and well documented biochemical diagnosis (urinary total porphyrin excretion > 500 mcg/g creatinine with HPLC pattern typical of PCT—predominance of 8- and 7-carboxyl porphyrins [>50% of total])
4. Clinical diagnosis of PCT established by a study PI
5. Chronic hepatitis C: HCV RNA positive and quantifiable in serum detected within 90 days of enrollment, and documented HCV genotype for which Harvoni is an approved therapy: genotype 1, 4, 5, or 6.
6. Women of child-bearing potential must be willing to avoid pregnancy and use an accepted and effective contraceptive method during treatment.

4.2 Exclusion Criteria

1. Women who are pregnant or who are breast-feeding
2. Patients who have already started treatment of PCT with phlebotomy or low dose hydroxychloroquine or chloroquine, or who have been in such treatment in the past 30 days
3. Patients who have already started another treatment regimen for CHC, or who have taken such treatment in the past 30 days
4. HIV infection with CD4 counts at baseline less than 350/μL or with evidence of any active AIDS-defining illnesses
5. Ongoing active alcohol abuse, defined as a history of drinking more than 25 drinks of alcohol per week during most weeks in the prior 4 months (History of prior, but not current alcohol abuse will NOT be grounds for exclusion because we seek to treat subjects with PCT and CHC of the type typically seen in clinical practice)
6. Any ongoing active IV drug use
7. Patients who are taking Amiodarone or who have taken Amiodarone within 60 days prior to enrollment
8. Patients who are taking, or within the prior 28 days have taken, rifampicin or St John's wort (*Hypericum perforatum*), both of which are P-gp inducers, which may significantly reduce the drug levels and therapeutic effects of Harvoni
9. Uncontrolled diabetes (Hgb A1c >9.5% within 60 days prior to enrollment)
10. Chronic hepatitis B
11. Autoimmune hepatic liver injury—autoimmune hepatitis, primary biliary cholangitis/sclerosing cholangitis or overlap syndrome
12. Alcoholic hepatitis

13. Other metabolic disorders of the liver, e.g. Alpha 1 antitrypsin deficiency with ZZ Pi type, Wilson's disease
14. Prior known or suspected drug-induced liver injury within 6 months of enrollment
15. Known or suspected hepatocellular carcinoma
16. On liver transplant list, or current MELD >12
17. History of liver transplant
18. Estimated GFR (creatinine clearance) <30 mL/min (per Sofosbuvir being cleared by the kidney)
19. Serum ALT or AST >10x upper limit of normal
20. Serum bilirubin >2 mg/dL (excluding patients with known or suspected Gilbert's syndrome)
21. Any other comorbid condition, which in the opinion of the investigator precludes participation
22. Incarcerated individuals

4.3 Recruitment of Participants

The methods of recruitment will be:

A. *Patients followed by any of the Investigators in the Porphyrias Consortium:* Each of the Investigators is a Porphyria specialist in a Porphyria Center, and provides clinical care to individuals suspected of and diagnosed with porphyria, providing diagnostic and follow-up evaluations, consultations, and/or treatment. For such patients who are likely to be eligible for the study, the Investigators will either discuss the study with the patient during a clinical visit or will contact the patient by telephone, email, or mail, as appropriate per Central IRB (CIRB) approval. Any efforts to contact and recruit patients and families will be with CIRB approval and adhere to standards for ethical conduct of research and be fully HIPAA compliant.

B. *Referrals from the American Porphyria Foundation (APF) to the Porphyrias Consortium centers:* The APF is an advocacy group that provides education about porphyria to patients, their families, healthcare professionals, and the public and supports porphyria research. Their outreach program includes a website, as well as periodic newsletters and special announcements emailed and/or mailed to individuals who have registered with the APF with information about new developments in treatment, porphyria-related education opportunities, and research studies available through the Porphyrias Consortium. Information about research studies includes contact information for the studies if they are interested in obtaining additional information or participating. The focus will be on patients and physicians from the following specialties: gastroenterologists, hepatologists, infectious disease physicians, and dermatologists.

C. *Non-study Physician referrals:* Physicians providing clinical care to individuals suspected of or diagnosed with PCT who are not investigators in this study may refer patients who may be eligible for and express interest in the study to a Porphyrias Consortium center.

D. *Self-referrals:* Including family members of individuals diagnosed with PCT (proband) and other individuals who may have heard about the study from other subjects or prospective subjects. In the case of family members, initial contact with the family member will not be made by the study team. The proband will be asked to contact such family members, requesting that they contact the study coordinator or to register through the RDCRN-Porphyria Consortium if interested in obtaining additional information or participating.

This study is registered on clinicaltrials.gov (NCT 03118674).

In the case of patients followed by one of the Consortium Investigators, the physician/Investigator or study coordinator will either: (a) contact the patient by telephone, email or mail informing him/her of the study and requesting that he/she contact the study coordinator if interested in obtaining additional information or participating, or; (b) discuss the study in-person during a clinical visit; informed consent may be obtained at this time. In all other cases, prospective subjects are instructed to contact the study coordinator, either the Project Manager or a site-specific study coordinator, by telephone, email or mail if interested in obtaining additional information or participating.

All patients will be encouraged to simultaneously enroll in the Longitudinal Study of the Porphyrias (PC7201), however it will not be required for inclusion into this study.

4.4 Retention Strategies

Only a small number of specialists have the expertise to evaluate and treat individuals with PCT. Clinical relationships established by the investigators with patients who enroll in this study will provide a context for increased communication with patients and their primary physicians that can facilitate retention. Furthermore, this study will provide a number of beneficial services to the participants and their primary physicians that will enhance retention. These include providing Harvoni, periodic evaluations, repeat laboratory testing, and information on new research developments in the field. Coordinators and other personnel at each site will also work to maintain close contact with participants, including regular clinic visits, newsletters and communication by phone, email and web sites. Counseling services will be provided so that patients and families are made aware of the results of studies and their correct interpretation. There will be no charge for Harvoni, the physician services, or laboratory tests done as part of this study.

4.5 Data Elements

The following laboratory tests and procedures will be used as the primary data elements:

- Medical history
- Physical examination

- Photographs of areas with PCT skin lesions
- Spot plasma and urinary porphyrins (including HPLC), and urinary creatinine concentrations
- Alcohol Consumption Questionnaire will assess alcohol use
- Serum HCV RNA by PCR
- Anti-HCV antibodies
- Complete metabolic panel (CMP), which includes:
    - Liver chemistries (serum ALT, AST, total bilirubin, albumin, total protein)
    - Serum creatinine, sodium, potassium, chloride, carbon dioxide, calcium, BUN, glucose
- CBC with differential
- INR
- Serum iron and TIBC
- Serum ferritin

These will be completed per the 4.7 Schedule of Events Flow Chart. In addition there will be adverse events reviewed at each visit.

If liver biopsies and/or Fibroscans have been performed, as part of standard of care, results of these will be entered into the study data CRF's; however, no liver biopsies or Fibroscans will be required for inclusion.

4.6 Study Procedures

Screening and Enrollment:

Potential subjects will be invited to take part and to sign informed consent forms. All participating centers will obtain CIRB approval.

Data collected at baseline will include demographic and clinical information. The screening laboratory tests will be:

- Serum HCV RNA by PCR (obtained within 30 days of enrollment)
- Anti-HCV antibodies
- CMP
- CBC with differential
- INR (if not done within 4 months of screening date)
- PTT
- Hepatitis B surface antigen
- Hemoglobin (Hgb) A1c
- Antibodies to HIV (if not done within 4 months of screening date). Those found positive will undergo HIV RNA and CD4 counts, to assure immune competence. Subjects with known HIV infection, with CD4 counts > 350/μL, whether receiving anti-HIV therapy or not, will **not** be excluded unless they require continuation of drug(s) contraindicated in subjects to receive Harvoni

- Spot plasma total porphyrins
- Spot urine delta-aminolevulinic acid (ALA), porphobilinogen (PBG), total porphyrins (including HPLC), and creatinine concentrations
- UROD enzyme activity and mutation analysis, if not previously done
- Serum iron and TIBC
- Serum Ferritin
- *HFE* genetic testing for C282Y and H63D, if not previously done
- Documentation of PCT symptoms and photographs of affected regions (hands, forearms, etc.)
- Alcohol and Tobacco use questionnaires
- Urine pregnancy for females of child-bearing potential

At baseline/screening, following informed consent, a standard interview to assess history of past and current alcohol use. HCV genotype should be confirmed prior to the screening visit as standard of care. History of smoking and current smoking status will also be assessed by interview and results recorded in suitable case report forms (CRFs). All prescription or over-the-counter drugs, including herbals, botanicals, and 'supplements' currently being taken or taken within the two weeks prior to screening, will be recorded, to include name, daily dose, and approximate duration of therapy (estimated to nearest month and year). Particular inquiry will be made regarding any and all estrogen use, including phyto-estrogens, as may be found in herbals and dietary supplements, such as black cohosh. All subjects will be evaluated by a hepatologist (the site PI or a Co-I) at baseline for liver disease based on the criteria detailed above for inclusion/exclusion.

The investigator will review that the subject has the typical clinical features of PCT, specifically blistering cutaneous photosensitivity, milia, thickened sclerodermatous changes, and/or skin fragility. The diagnosis of PCT will be confirmed at screening from the urine and plasma total porphyrin results. The urinary total porphyrin excretion should be >800 mcg/g creatinine and the HPLC pattern typical of PCT, with a predominance of uro- and heptacarboxyl- porphyrins. The plasma porphyrin results should be >2.7 µg/dL with a predominance of uro- and heptacarboxyl- porphyrins, and a fluorescence emission peak at ~619 nm (with excitation at ~410 nm).

At baseline, subjects who, within the prior 120 days, have not already had either hepatic elastography with Fibroscan or similar technique and/or had Fibrosure-HCV testing performed will undergo one of these measures. The decision of which test to perform will be at the discretion of the site PI's (similar testing will again be performed at the end of the study, as shown in the Schedule of Events).

All subjects found to be eligible will be invited to take part in the study. We anticipate that most subjects at baseline will not be undergoing treatment for PCT or CHC, but they may have done so in the past and have recurrence of active PCT with persistent or recurrent CHC. To be eligible, subjects previously treated for CHC must have ended such treatment at least 30 days prior to enrollment into this study.

Treatment and Follow-up Visits:
The therapy will be Harvoni at the usual dose (90 mg of ledipasvir and 400 mg of sofosbuvir) and duration for CHC therapy. One tablet taken daily for 8 weeks for patients without cirrhosis, not previously treated with HCV GT1 and HCV RNA < 6 million IU/mL; 12 or 24 weeks, duration to be determined based upon clinical features and prior treatment experience. 8 or 12 weeks for subjects with or without cirrhosis, not previously treated with anti-virals for CHC, and 24 weeks for subjects with cirrhosis who were previously treated with anti-virals for CHC without having achieved SVR. During the first year study visits will be monthly, and this includes the treatment period of either 12 or 24 weeks. To assess cure of HCV infection, repeated HCV RNA levels at 3, 6, and 12 months after end of Harvoni therapy will be done, as well as annually thereafter. Evaluation by a hepatologist at follow up visits will be as needed, determined by the screening lab test results and by clinical and lab findings at follow-up visits.

Lab measures to be checked monthly during therapy will include CBC, CMP, plasma total porphyrins, urinary total porphyrins (with HPLC), and levels of HCV RNA in serum by quantitative PCR (Section 4.7 Schedule of Events).
Porphyrin specific lab tests will be performed at the UTMB Porphyria Laboratory; all other labs will be performed at Covance Laboratories.

Subjects who have their treatment discontinued for any reason will continue to be followed until the end of the study, including longer-term follow up visits, unless they withdraw consent. If a subject becomes pregnant during the study Harvoni will be discontinued. The outcome of the pregnancy will not be followed as part of this study. Pregnancy during the study should be reported as an SAE.

Longer-Term Follow-up:
12 months after beginning treatment, subjects will be asked to return every four months for one year, with repeat of interval history and physical examination (especially to reassess the status of cutaneous lesions of PCT) and the above studies.

Every effort will be made to have all subjects return annually thereafter as part of the Longitudinal Study of the Porphyrias, for at least 5 years, to assess whether there has been relapse either of active PCT or HCV infection. This will be done by assessing history of skin symptoms and measuring plasma and urine porphyrins. All subjects will be strongly encouraged to return to a study center if they think they are experiencing recurrence of active PCT. If there has been relapse, subjects will be treated further as part of routine standard of care, and their clinical and biochemical features will continue to be recorded.

4.7 Schedule of Events

	Screening (-30 to -1 Days)	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 210	Day 240	Day 270	Day 300	Day 330	Day 360	Day 480	Day 600	Day 720
			(Window +/- 7 days)														
			M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M16	M20	M24
Consent	X																
Complete Medical History	X																
Interval Medical History		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X			X			X			X			X	X	X	X
Skin Assessment (including pictures)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Alcohol & Tobacco use questionnaires	X																
Adverse Event/SAE Review			Each visit														
Urine Pregnancy	X																
Anti-HCV antibodies	X																
PTT	X																
Hepatitis B Surface Antigen	X																
HIV-1/HIV-2 Antibodies	X																
Serum Ferritin	X																
Serum iron and TIBC	X																
Complete Metabolic Panel[$]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
INR**	X																
HbA1c	X																
Erythrocyte UROD enzyme activity*	X																
UROD mutation analysis*	X																
HFE genetic testing*	X																
Hematology with Differential[#]	X	X	X	X	X	[X]*	[X]*	X	X	X	X	X	X	X	X	X	X
HCV RNA	X	X				[X]*	[X]*	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Plasma Total Porphyrins	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spot Urine ALA, PBG, Total Porphyrins	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fibroscan (if available at institution)	X													X			X
Dispense Study Drug[€]		X	X	X	X	X	X	X									

[#] Hematology (complete blood count): white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, platelet count

[$] Comprehensive metabolic panel: sodium, potassium, chloride, carbon dioxide, calcium, BUN, creatinine, glucose, and liver panel, including total protein, albumin, total bilirubin (TBR), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP)

*If not previously done

**INR (if not done within 4 months of screening)

[€] Drug is only to be dispensed at months 2-6 if additional therapy is warranted

[X]* Samples at these time points will be obtained only in subjects with cirrhosis who 24 weeks of Harvoni therapy is indicated; [X] Samples at these time points will be obtained 3, 6, and 12 months after the end of Harvoni treatment, and annually till end of study or EOT

4.8 Investigational Product

All study drug will be stored and dispensed from individual centers' research pharmacies according to their standard operating procedures. Drug will only be dispensed after authorized by a site Investigator and to a member of the study team. All study drug will be provided to each site by Gilead Sciences, Inc. through communication with Wake Forest University School of Medicine.

Obtaining Study Drug: Once a potential participant is identified, the site will contact the project manager at Wake Forest University School of Medicine to have study drug sent to the research pharmacy at the site to be dispensed to the study team and the patient.

Dispensing, Dosage, and Accountability: All participants will receive treatment for either 8, 12, or 24 weeks depending upon the usual clinical criteria and recommendations that inform clinical treatment of HCV with Harvoni: We anticipate that, for most subjects, the duration of indicated treatment will be 12 weeks. For patients with cirrhosis, previously treated for HCV infection without response or with response followed by relapse, the duration of treatment will be 24 weeks. Study drug will be dispensed with 4 week supplies (28 tablets). It is recommended that 1 week of additional drug is provided, in case of the need for follow-up appointments to be rescheduled. New supplies of drug will not be provided to subjects until the previous supply has been accounted for by the site coordinator or investigational pharmacy and reconciled. Medication will only be provided at in person study visits, no medication will be mailed to subjects.

The dosage is one tablet of the combination of ledipasvir (90 mg) + sofosbuvir (400 mg) taken daily with or without food. Tablets should not be broken or chewed. No dose adjustments are recommended based upon considerations of age, mild or moderate renal impairment, or mild, moderate, or severe hepatic impairment.

At each study visit the participant will bring all study drug with him or her. The site coordinator will count and reconcile all study medication at each visit. At each visit the subject will return all previous study drug and empty bottles and receive a new 4 week supply. At the final treatment visit (8, 12, or 24 weeks, as may be appropriate), a new supply will not be issued.

Study Drug Destruction: Medication returned by subjects can be destroyed onsite per institutional SOP.

5.0 Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) and the Data Safety Monitoring Board (DSMB) before submission to CIRB for approval. Participant enrollment may only begin with CIRB approved consent forms.

This is an interventional study that meets the federal definition of moderate risk.

5.1 Study Oversight

The Study Chair has primary oversight responsibility of this clinical trial. The NIH appointed Data (Observational) Safety Monitoring Board (D/OSMB) has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The D/OSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance every 6 months. The D/OSMB makes recommendations to the NIH regarding the continuation status of the protocol.

Each site's Principal Investigator and his/her research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate reports- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the DMCC for DSMB review. Adverse events will be reviewed at each study visit by the research team. A separate report detailing protocol compliance will also be available from the DMCC for DSMB review. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

5.2 Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risks or information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study.

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at the National Cancer Institute.

5.3 Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

Drug Information for Harvoni

It was determined by the Food and Drug Administration that this study does not require an Investigational New Drug application.

Human Toxicity/ Adverse Events (adapted from package insert dated March 2015)
The safety assessment of HARVONI was based on pooled data from three Phase 3 clinical trials of subjects with genotype 1 chronic hepatitis C (CHC) with compensated liver disease (with and without cirrhosis) including 215, 539, and 326 subjects who received HARVONI for 8, 12 and 24 weeks, respectively.

The proportion of subjects who permanently discontinued treatment due to adverse events was 0%, <1%, and 1% for subjects receiving HARVONI for 8, 12, and 24 weeks, respectively.

The most common adverse reactions (≥10%) were fatigue and headache in subjects treated with 8, 12 or 24 weeks of HARVONI.

Table 2 lists adverse reactions (adverse events assessed as causally related by the investigator, all grades) observed in ≥5% of subjects receiving 8, 12, or 24 weeks treatment with HARVONI in clinical trials. The majority of adverse reactions presented in Table 2 occurred at severity of grade 1. The side-by-side tabulation is to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

Table 2 Adverse Reactions (All Grades) Reported in ≥5% of Subjects Receiving 8, 12, or 24 Weeks of Treatment with HARVONI

	HARVONI 8 weeks	HARVONI 12 weeks	HARVONI 24 weeks
	N=215	N=539	N=326
Fatigue	16%	13%	18%
Headache	11%	14%	17%
Nausea	6%	7%	9%
Diarrhea	4%	3%	7%
Insomnia	3%	5%	6%

Laboratory Abnormalities:
Bilirubin Elevations: Bilirubin elevations of greater than 1.5×ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.

Lipase Elevations: Transient, asymptomatic lipase elevations of greater than 3×ULN were observed in <1%, 2%, and 3% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively.

Creatine Kinase: creatine kinase was not assessed in Phase 3 trials of HARVONI. Isolated, asymptomatic creatine kinase elevations (Grade 3 or 4) have been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Study Procedures:
Venipuncture: The vein in which the needle has been inserted to draw blood may become sore and red. A temporary "black and blue mark" may develop, and rarely fainting may occur.

Safety Endpoints

Grade 3 or 4 toxicities: According to the scale of the World Health Organization. For liver tests, total serum bilirubin greater than 2.5 mg/dL or, if elevated at baseline, more than at 3-fold increase above the baseline level; serum ALT or AST or AP greater than 3 x ULN, or if elevated at baseline, > 3 x baseline level; INR > 2.0.

Worsening PCT symptoms: PCT is a rare disease and no standard disease severity scale exists. A standardized detailed skin assessment including pictures will be done at each time point in this study. If a subject experience significantly worsening symptoms in the opinion of the investigator that persist for 60 days, HCV therapy will be discontinued under the study and standard of care PCT treatment will be initiated. This length of time may be shortened depending on the severity of the subject's PCT symptoms. Any patient who experiences worsening PCT symptoms must be discussed by the site PI with the Study Chair prior to discontinuing Harvoni.

5.4 Reporting Timeline

- Within **24 hours** (of learning of the event), investigators will report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject

  -OR-
  - Is Unexpected/Unanticipated
- Investigators will report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs will be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Any SAE or Special Situations Reports (SSR) will also be reported to the Gilead Drug Safety and Public Health department within 15 days of learning of the event. Redacted SAE/SSR reports are preferred by email at the following contact information:

Gilead Sciences, Inc.
Drug Safety and Public Health
333 Lakeside Dr.
Foster City, CA 94404
Fax: 650 522 5477
Phone: 650 522 5114

Email: Safety FC@gilead.com

Local institutional reporting requirements to CIRB, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.5 RDCRN DMCC Adverse Event Monitoring Process

The DMCC will make adverse event reports available for review. Upon entry of a serious adverse event (SAE) into the DMCC database, the Study Chair, site PIs, the RDCRN D/OSMB medical review officer, and any additional agencies (if applicable-industry sponsor) will be notified immediately by email.

Serious adverse events: The NIH appointed Medical Review Officer (MRO) reviews the site investigator's report and determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO may request further information if necessary and possibly request changes to the protocol or consent form as a consequence of the adverse event. Any follow up reports or requested additional participant data will be entered into the DMCC Adverse Event Monitoring System by the reporting site and reviewed by the MRO. Completed AE reviews by the MRO will be sent to Study Chair, site PIs, and the appointed NIH officers.

If warranted, the MRO may request an ad hoc call with the DSMB to review the adverse event. All reported AE's will be reviewed during the regularly scheduled DSMB call. The DMCC Adverse Event Monitoring Process maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the system in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the MRO and RDCRN D/OSMB on an annual basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all adverse events (serious/not serious and expected, unexpected) for the DSMB, site investigators and CIRB.

5.6 Study Discontinuation

The NIH, RDCRN DSMB, and CIRB have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- The study objectives have been met
- The Study Chair / Study Investigators believe it is not safe for the study to continue
- The RDCRN DSMB suspends or closes the trial
- The NIH suspends or closes the trial
- The FDA suspends or closes the trial
- Gilead Sciences elects to suspend or close the trial

5.7 Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis. Every effort will be made to conduct a final study visit with the participants and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent by the participant
- Withdrawal by the investigator if early stopping rules have been met: If there are Grade 4 toxicities, such as severe bradycardia with syncope, Harvoni will be stopped. Subject's PCT symptoms worsen significantly (as specified in section 5.3)
- Withdrawal by the investigator for other reasons
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g. mental status change, large pleural effusion).

5.8 Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints; whether independent range and/or format limitations or 'relative' referential integrity limitations can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

5.9 Quality Control: Study Related Procedures

The standard laboratory measures will be performed at each Covance Central Laboratory. Porphyrin measurements will be performed in the CLIA certified laboratory of Dr. Karl Anderson, University of Texas Medical Branch, Galveston, TX (see Appendix I for processing instructions).

The investigational pharmacy at each site will be responsible for drug accountability while the investigators/coordinators will be responsible for compliance of the subjects. The Investigational Drug Service at Wake Forest University will serve as the coordinating pharmacy for this study.

6. Statistical Considerations

Primary endpoint: The primary endpoint is resolution of active PCT, defined as normalization of plasma porphyrins (less than 0.9 mcg/dL) by 7 months after the start of therapy. The primary hypothesis will be assessed by computing the exact (i.e., based on the binomial distribution) lower one-sided 95% confidence bound for the proportion of patients whose PCT resolves by 7 months. If this lower confidence bound exceeds 0.40 (the performance goal of 0.50 minus the non-inferiority margin of 0.10) then Harvoni will be declared non-inferior to the performance goal. Seven months has been chosen based upon recent results comparing iron reduction and hydroxychloroquine as therapy for PCT (Singal et al, 2012) and on the consensus of the investigators of the Porphyrias Consortium that a median time to resolution of 7 months would cause them to consider using Harvoni over phlebotomy or hydroxychloroquine as a first line of treatment for PCT patients with Hepatitis C.

Patients missing primary endpoint data are a potential problem in all clinical trials, with the potential for biased inference increasing with the amount of missing outcome data. We will report reasons for missing data, and examine the effect that any missing data might have on results via sensitivity analysis of augmented data sets (for example, best-case or worst-case scenarios). Patients missing the trial's primary endpoint will be included in the analysis by modern imputation methods for missing data.

If data are missing due to severity of illness, the patient will be counted as a treatment failure (i.e. resolution not achieved). Patients with missing primary outcome data not due to severity of illness will have their 7 month resolution status imputed via multiple imputation assuming that the data are missing at random (i.e. the missing nature of the variable is independent of the value of the variable given the observed data). The specific imputation model to be used will be determined prior to examination of any outcome data, but will include any measured plasma porphyrins from baseline to 6 months. Imputed data will be rounded to 0 (failure/resolution not achieved) or 1 (success/resolution achieved).

After the imputations are completed, all of the data (complete and imputed) will be combined and the analysis performed for each imputed-and-completed dataset. Rubin's method of multiple (i.e., repeated) imputation will be used to estimate treatment

effect. We propose to use 15 datasets (an odd number to allow use of one of the datasets to represent the median analytic result).

Secondary Endpoints:
Time to resolution of active PCT, defined as normalization of plasma porphyrins (less than 0.9 mcg/dL): The median time to resolution by this definition will be computed using Kaplan-Meier estimation and compared descriptively to the median time to resolution reported by standard therapies.

Time to resolution of active PCT, defined as cessation of any new blisters or bullae: Complete resolution of skin manifestations is expected to occur later than normalization of plasma porphyrins, because it takes time for healing of the skin fragility that predisposes of blister formation to occur. The median time to resolution by this definition will be computed using Kaplan-Meier estimation and compared descriptively to the median time to resolution reported by standard therapies.

Complete Biochemical remission of PCT: Complete biochemical remission of PCT will be measured as a decrease of the sum of urinary uro- and hepta-carboxyl porphyrins to less than 100 mcg/g creatinine, and a normal urine porphyrin HPLC pattern, defined as the total of highly carboxylated porphyrins (uro- and heptacarboxyl-porphyrins) being less than that of coproporphyrins, and absence of a fluorescence peak by fluorescence scanning. The proportion of patients who achieve complete biochemical remission by the end of study period will be computed and the median time to resolution by this definition will be computed using Kaplan-Meier estimation. Because of underlying liver disease and/or possible continuing alcohol use, total urinary porphyrins may remain elevated, due to increased coproporphyrins. We will explore whether and to what extent total urinary porphyrins may remain elevated, due to increased coproporphyrins descriptively in these subjects.

Cure of CHC: Cure of CHC will be defined as no detectable HCV RNA at end of treatment (EOT) and persisting for at least 12 weeks after EOT, now taken as usual definition of sustained virological response (SVR). The proportion of patients who achieve CHC cure will be reported.

Sample Size: The primary study hypothesis is that the proportion of patients whose PCT resolves by 7 months will be non-inferior to the performance goal of 50%. This performance goal is based on previously published data that reported a median time to resolution between 6-7 months for PCT patients undergoing treatment with iron reduction by therapeutic phlebotomies or hydroxychloroquine (Singal et al, 2012). The non-inferiority margin will be set to 10%; a difference from the performance goal judged to be both clinically acceptable and well within the margin needed to assure that the performance of Harvoni is at established levels of benefit from conventional therapies. Thus, the null hypothesis tested by this study is H0: $\pi \leq 0.40$, against the alternative hypothesis H1: $\pi > 0.40$.

Sample size requirements are based on an exact test of a binomial proportion. Assuming that the study drug has a true success probability of 58%, 49 subjects yield 80% power to reject the null hypothesis at a one-sided significance level of 0.05.

The null hypothesis would be rejected at the final analysis if 26 or more successes out of 49 subjects were observed (an observed success rate of 53.1%). The power of the test assuming a true success rate of 58% for Harvoni is 80.2%. Operating characteristics for the decision rule corresponding to the final analysis are given below (Table 3).

Table 3: Operating characteristics for the decision rule (Final analysis)

True Harvoni success rate (π)	Prob (26 or more successes|π, N=49)
0.40	0.0434
0.45	0.1609
0.50	0.3877
0.55	0.6627
0.60	0.8718
0.65	0.9695

7. Data Management

As much as possible, data quality is assessed at the data entry point using intelligent on-line forms via the DMCC. Data element constraints; whether independent range and/or format limitations or 'relative' referential integrity limitations can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency. In addition to those described above, we propose to build these checks into the initial tables and cross tabulations that should reveal any remaining data quality issues. The NIH Program Staff, the DMCC, and Porphyrias Consortium staff are responsible for assuring and monitoring data quality.

All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

7.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. CIRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. At time of enrollment, each subject is registered through the DMCC provided web-based registration system. A unique participant ID will be generated at the time of enrollment, which will allow for a common ID to link a participant to multiple studies. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second participant ID. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant.

7.2 Data Entry

Study data will be entered into an electronic data capture (EDC) system supported by the DMCC. The EDC system is hosted in a secure, cloud-based environment managed by the DMCC, and complies with all applicable guidelines to ensure patient confidentiality, data integrity, and reliability. All data management best practices including quality controls and data validation procedures will be applied to ensure the validity and accuracy of the clinical database.

8. Human Subjects

8.1 GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.2 Benefits

Benefits of taking part include especially the opportunity for eligible subjects to receive Harvoni at no cost to them or their insurance carriers and to receive frequent and careful follow-up during and after this course of therapy. This is expected to lead to cure of HCV infection in the great majority of subjects. It may also lead to resolution of PCT.

The potential benefits of this protocol are felt by the investigators to outweigh the risks.

8.3 Risks

The potential risks of this study are:

1) Side effects of Harvoni: the most frequent side effects have been fatigue and headache, which have been of low severity.

2) Blood Draw: Needle insertion can cause pain and bruising at the site of insertion. Rarely fainting caused by a vasovagal response to the phlebotomy procedure may occur. Because the skin is penetrated by the needle, there is a low risk for infection at the venipuncture site. The amount of blood needed for each study visit (8mL tubes) is within approved safety limits. For any participant who has a medical condition that restricts their capacity to provide adequate sample volume, the number of tubes of blood obtained will be modified on an individual basis.

3) Loss of confidentiality: The risk of loss of confidentiality is low because as there are many safe guards in place. Conceivably, data including clinical and diagnostic information could be accidentally divulged. If such an event occurred, subjects might be at risk for discrimination by life or health insurance companies, by employers, and by adoption agencies. The Genetic Information Non-Discrimination Act (GINA) is a federal law that protects Americans from being treated unfairly because of differences in their DNA that may affect their health. This law prohibits genetic discrimination in the workplace and by health insurers. However, it provides no such protection for life insurance and disability insurance.

8.4 Written Informed Consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

8.5 Process of Consent

At each of the Porphyrias Consortium sites the principal investigator and/or study coordinator will identify subjects with PCT and HCV who are eligible for this study. The PI and/or coordinator will then approach the subject, either via a phone call or at a clinic visit, to fully describe the intent of the study and what the potential risks and benefits of participation in this study will be. The subject will have an opportunity to review the consent form and ask any questions of the study team, as well as discuss the study with

their primary care physician or others of their choosing, prior to signing the consent form.

8.6 Certificate of Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify the participant in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless the participant has consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if the participant consents to the disclosure, including for their medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research participants.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the U.S. Department of Health and Human Services and/or the National Institutes of Health, which is funding this project. The Certificate of Confidentiality does not prevent a participant from voluntarily releasing information about themselves or their involvement in this research. If a participant wants research information released to an insurer, medical care provider, or any other person not connected with the research, the participant must provide consent to allow the researchers to release it.

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person. The Certificate of Confidentiality will also not be used to prevent disclosure as required by federal, state, or local law, such as reports of child abuse and neglect, or harm to self or others.

9. References

1. Ahmad W, Ijaz B, Jawed FT. A comparison of four fibrosis indexes in chronic hepatitis C viral infection. Development of a new fibrosis-cirrhosis index (FCI). BMC Gastroent 2011; 11: 44-54.
2. Balwani M, Doheny D, Bishop DF, et al. Loss-of-function ferrochelatase and gain–of –function erythroid 5-aminolevulinate synthase mutations causing erythropoietic protoporphyria and X-linked protoporphyria in North American patients reveal novel mutation and a high prevalence of X-linked protoporphyria. Molec Medicine 2013; 19: 26-35. [PMID:23364466]
3. Besur S, Hou W, Schmeltzer P, Bonkovsky HL. Clinically important features of porphyrin and heme metabolism and the porphyrias. Metabolites 2014; 4: 977-1006. [PMID 25372274]
4. Bonkovsky HL, Poh-Fitzpatrick M, Pimstone N, et al. Porphyria cutanea tarda, hepatitis C, and *HFE* gene mutations in North America. Hepatology 1998; 27: 1661-1669. [PMID: 9620340]
5. Bonkovsky HL, Hou W, Li T, Guo J-T, Narang T, Thapar M. Porphyrin and heme metabolism and the porphyrias. In Wolkoff A, Lu S, and Omary B (Eds). Comprehensive Physiology, 2013; 3:365-401. [The American Physiological Society, Bethesda, MD, Wiley and Co] [PMID 23720291]
6. Bonkovsky HL, Maddukuri V, Yazici C, et al. Acute porphyrias in the USA: features of 108 subjects from porphyria consortium. American Jl of Medicine, 2014; 127: 1233-1241. [PMID: 25016127].
7. Egger NG, Goeger DE, Payne DA, et al. Porphyria cutanea tarda: multiplicity of risk factors including *HFE* mutations, hepatitis C, and inherited uropophyrinogen decarboxylase deficiency. Dig Dis Sci 2002; 47: 419-426. [PMID 17187403]
8. Fallatah HI. Noninvasive biomarkers of liver fibrosis: an overview. Adv Hepatol 2014; http://dx.doi.org. 10.1155/2014/357287.
9. Gilead Sciences, Approved package insert for Harvoni, revised 3/2015. http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf.
10. Singal A, Kormos-Hallberg C, Lee C, et al. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. Clin Gastroenterol Hepatol 2012; 10: 1402-1409. [PMID 22985607]
11. Stölzel U, Köstler E, Schuppan D, et al. Hemochromatosis (*HFE*) gene mutations in porphyria cutanea tarda. Arch Dermatol 2003; 139: 309-313. [PMID 12622622]

10. Appendices

I. Sample Processing Instructions

For Urine Porphyrin testing:

- Put 10 ml urine into a urine collection container with no preservatives. Label with the patient's name, date of birth, and date sample was taken, wrap immediately in aluminum foil, or place in amber bag, to protect from light, and freeze at -80^{0}C. If a -80^{0}C freezer is not available a -20^{0}C freezer is acceptable.

For Plasma Porphyrin testing:

- 5 ml blood drawn in sodium heparin (green-top) tube. Centrifuge and separate as follows:
- Transfer 1 ml plasma into two plastic (Eppendorf) tubes each. Label with the patient's name, date of birth, and date sample was taken, wrap immediately in aluminum foil, or place in amber bag, to protect from light, and freeze at -80^{0}C. If a -80^{0}C freezer is not available a -20^{0}C freezer is acceptable.

Samples should be shipped overnight on dry ice after each visit to the following:

Porphyria Lab
University of Texas Medical Branch
700 Harborside Drive, Ewing Hall 3.102
Galveston TX 77555-1109
**Write on shipping label "INSIDE DELIVERY ONLY"

Check with the Porphyria Laboratory before shipping to assure that samples are not delivered on holidays or weekends.