INSTITUTE: National Institute of Diabetes and Digestive and Kidney Diseases

STUDY NUMBER: 15-DK-0143 PRINCIPAL INVESTIGATOR: Marc Ghany, M.D.

STUDY TITLE: Investigation Of Viral Kinetics, Interferon Stimulated Genes (ISGs) and mirRNA Among Subjects Infected With Different Hepatitis C Virus Genotypes During Therapy With Sofosbuvir and GS-5816

Continuing Review Approved by the IRB on 07/25/17
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

PURPOSE OF THE STUDY

Why is this research being done?

Chronic hepatitis C is a disease caused by a virus (known as the hepatitis C virus) that infects the liver. Over time, inflammation caused by the viral infection may cause scarring (fibrosis) of the liver and cirrhosis, which affects the way your liver functions. In time, if the virus is not treated, some infected people may develop liver cancer and/or need a liver transplant. Current treatments for chronic hepatitis C require the use of drugs that specifically block the production of new virus inside the liver. However, these drugs must be combined with interferon or ribavirin. Interferon has numerous side effects that make it difficult to tolerate and must be given by injection. Ribavirin also has side effects such as lowering your blood count or causing a rash. Interferon works by boosting your immune system and helping the liver cell

to make proteins that can eliminate the hepatitis C virus. It does not directly kill the virus. We do not know exactly how ribavirin works. In contrast, the new class of drugs developed to treat hepatitis C act by directly blocking important enzymes that the virus needs for its lifecycle –so called direct acting antiviral drugs. Different combinations of these drugs are very effective at suppressing the virus without the need for interferon and ribavirin, a so-called interferon free regimen. The advantages of these new drugs are higher efficacy, shorter courses of treatment and fewer side effects. These new drugs work better in some persons than others. As someone with chronic hepatitis C who has either never been treated or previously treated and failed to clear the hepatitis C virus, you are being invited to participate in this research study. The primary aim of this study is to learn more about why these new drugs being developed for treatment of hepatitis C sometimes fail to work. Sometimes the drugs don't work because people take them incorrectly or because the virus becomes resistant to the action of the drugs. Alternatively, the body's immune system may be important for helping the drugs to clear the virus from the liver. We believe the immune response to the virus in persons who fail treatment is different from those who clear the virus successfully. In order to understand this better we plan to compare immune responses of your liver cells to treatment in patients who fail and those who respond to treatment. Two liver biopsies are needed so we can compare the difference between how your liver cells are working before the treatment and then with the treatment. This will help us to understand what role the immune system plays with clearance of the hepatitis C virus and if so, which part of the immune system plays this role. Please be aware that the medicines being used in this study were approved by the Food and Drug Administration (FDA) in May 2016 so participation in this study is now an alternative to standard clinical care. Please also consider that the second liver biopsy is purely for research purposes and is not medically necessary. The second biopsy will provide research information that we will need to achieve the scientific goals of this study. Please consider carefully whether you will be willing to undergo the second biopsy before deciding to participate in the study. Another aim is to determine if these new drugs are safe and how well they work in persons with different strains of the virus.

As part of this study, we plan to monitor changes to your cholesterol levels before, during and after treatment to understand how cholesterol levels change as your body recovers from hepatitis C infection. Typically, persons with chronic hepatitis C have lower cholesterol levels compared to a person without hepatitis C infection because the hepatitis C virus uses some of the cholesterol produced by the liver to make new copies of itself. Therefore, it is possible that after you clear the hepatitis C virus from your blood, your cholesterol levels will increase. In this study we are planning to measure this change in greater detail by also studying the particles that carry cholesterol in your blood to and from the liver. These particles are called lipoproteins. High cholesterol and high lipoprotein levels in blood may increase your risk for heart disease and stroke. Therefore, understanding what happens to cholesterol and lipoprotein levels after clearance of hepatitis C virus could have important implications for your health. We will inform you of the results of this study and advise you if you need to follow up with your primary healthcare provider.

Who is being asked to take part in this research study?

Subjects with chronic hepatitis C genotypes 1, 2, 3 and 4 infection who were either never treated or treated previously with any interferon regimen with or without ribavirin and failed to eliminate the hepatitis C virus will be eligible to participate.

Who is conducting the research study?

The research will be conducted by The Liver Diseases Branch of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). The NIH is providing the funding for this study. Gilead Sciences, the manufacturer of sofosbuvir and GS-5816, will provide the study medications and perform resistance testing on coded samples from subjects whose viral level increases while on the study drugs or in whom the virus returns after the treatment is stopped.

How many people will take part in the research study?

Approximately 140 adult men and women will participate in this research study.

Study Population

This study includes patients who are at least 18 years of age and who are known to be infected with hepatitis C virus genotypes 1-4 and who have either never been treated or treated previously with an interferon regimen with or without ribavirin and failed to clear the virus.

There are several reasons you may be not be able to participate in this study and may include one or more of the following:

- If you are infected with HBV or HIV, you will not be able to participate in this study. You will be tested to see if you are infected with hepatitis B virus (HBV) or with human immunodeficiency virus (HIV), the virus that causes AIDS. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HBV and HIV infection, and the importance of informing your partners at possible risk because of your HBV or HIV infection.

- If you have history of severe psychiatric disorders like schizophrenia, bi-polar, mania, or others, you are not eligible to participate in this study.

- If you are currently taking certain drugs which are sometimes abused, you may not be able to participate in this study.

- If you are currently pregnant or become pregnant during the study, you are not eligible to participate in this study.

- If you are a sexually active man and your partner is pregnant at the time of your pre-treatment assessment, you are not eligible to participate in this study.

- You will not be eligible to participate in this study if you are a sexually active woman of childbearing potential and you are unwilling or unable to use two acceptable methods to avoid pregnancy (e.g. a male condom and an intrauterine device) beginning at screening, for the duration of the treatment phase and after the treatment phase for 3 months.

- You will not be eligible to participate in this study if you are sexually active man whose female partner is a woman of childbearing potential and you are unwilling or unable to use a condom while your partner uses a second birth control method to avoid pregnancy. Two effective methods of contraception must be used (e.g. a male condom and an intrauterine device) beginning at screening, for the duration of the treatment phase and after the treatment phase for 3 months.

- If you are a sexually active man whose female partner is a woman of childbearing potential then you must agree to inform your partner of the contraception requirements and pregnancy testing recommendations for this study or you are not eligible to participate.

Study Treatment

If you qualify for the study, you will receive the following treatment:

- Sofosbuvir at the dose of 400 mg
- GS-5816 at the dose of 100 mg
  In a fixed dose combination tablet once per day taken orally

The total length of treatment:
You will receive the study drugs for 12 weeks.

Duration of the Study

Your participation in this study will last up to 48 weeks.

Study visit	Purpose
Screening phase	To determine if you qualify to take part in the study
Admission for baseline liver biopsy	To assess how damaged your liver is and to obtain liver tissue for research and to start treatment
Admission to start treatment (within 12 weeks of screening). If additional evaluation is required, you may delay therapy up to 20 weeks from screening)	Only required if you declined to start therapy during the admission for first liver biopsy
Day 0 (First day of treatment), 6, 12 and 18 hours	Take first dose of study medications and monitor how quickly the virus is cleared from your blood
Days 1, 2 and 3. Discharge on day 3	Monitoring how quickly the virus is cleared from your blood
Week 1	Monitor how well the medications are working and assess side effects
Week 2	Monitor how well the medications are working and assess side effects
Week 3	Monitor how well the medications are working and assess side effects
Week 4 Admission for second liver biopsy	This is to obtain liver tissue for research purposes only
Week 8	Monitor how well the medications are working and assess side effects
Week 12 End of treatment	Stop treatment
Post-treatment week 2	To check if the treatment worked and to monitor for side effects
Post-treatment week 4	To check if the treatment worked and to monitor for side effects
Post-treatment week 8	To check if the treatment worked and to monitor for side effects
Post-treatment week 12	To check if the treatment worked and to monitor for side effects
Post-treatment week 24	To check if the treatment worked and to monitor for side effects

Note: Additional visits may be required if you develop a side effect or the medications stop working.

The study is made up of the following parts:

- Screening Phase: Includes at least one visit to your study doctor lasting approximately 2 to 3 hours. Your study doctor will draw some blood and do some tests or procedures to see if you meet the requirements for being in the study. You will also be asked to complete some questionnaires and discuss the study schedule. If you meet the requirements, you will have up to 12 weeks from the Screening visit to start the study treatment, unless additional testing is required. If additional testing is required, then you will have up to 20 weeks from the Screening visit to start study treatment.

- Admission for Liver Biopsy: Admission to the Clinical Center for ~1 1/2 days and includes an overnight stay. The purpose of the liver biopsy is to assess how much damage the virus has done to your liver and to obtain a small sample of liver tissue for research purposes. If you have undergone a liver biopsy within 12 weeks of your planned treatment start date AND liver tissue was saved in a special preservative (RNAlater) then you will not need to undergo the first biopsy. Please understand that if you recently had a liver biopsy, then the need to repeat a biopsy would be only to obtain liver tissue for research.

- Admission for Start of Treatment: Days 0-3 (1st four days of taking study drug) may be combined with the admission for liver biopsy or will require a separate admission to the Clinical Center.
    - Day 0 is the first day of the study treatment phase. If you meet all the requirements, blood will be drawn to measure your viral level and you will be asked to take the first dose of study drug in the Clinical Center. Additional blood draws will be performed at 6,12 and 18 hours to monitor your viral level.
    - You will have your blood drawn in the morning on days 1, 2 and 3 to monitor your viral level. If you desire, you may leave the Clinical Center on pass after your blood draw, returning in the evening. You will be discharged from the clinical center after the blood draw on day 3. Your doctor will provide you with the study drugs to take home before you are discharged. The study staff will provide you with a schedule for each clinic visit per the study plan. You will be given instructions on how to take the study drugs at home.

- Study Treatment Phase: 12 weeks of study drug treatment, including 6 visits lasting 1 to 2 hours each. The details of these visits are provided below.

- Admission for Liver Biopsy at Week 4: You will be admitted to the Clinical Center at treatment week 4 for a second liver biopsy. This visit will last ~1 ½ days and include an overnight stay. This second biopsy is purely for research purposes. (See page 6 under **What procedures will be performed for research purposes?** for a more detailed explanation of the planned research using the liver tissue.) If after starting the therapy you decide against undergoing the second biopsy, you will continue to receive sofosbuvir and GS-5816 treatment for the planned 12 week duration.

- Follow-Up Phase: You will be asked to return to the clinical center for outpatient visits for five visits over 24 weeks after your last dose of study drug. Each visit will last 1-2 hours and will occur at 2 weeks, 4 weeks, 8 weeks, 12 weeks and 24 weeks after you take your last dose of study drug.

All study visits will be conducted at the Liver Diseases Branch of the Clinical Center, NIH. The research staff will give you instructions where to report for the study visit appointments.

DESCRIPTION OF STUDY PROCEDURES

Before any study procedures are done, the study doctor and research staff will explain the study to you and ask you to read this consent form. They will answer any questions you may have about the study and what you are being asked to do. If you decide to participate you will be asked to sign this consent form and a copy will be given to you. You will then

be ready to begin the first part of the study called the screening visit. If you qualify for the study, you will be asked to come for additional visits as described below.

What procedures are considered experimental?
The experimental procedure in this study is combining two oral drugs sofosbuvir and GS-5816 in a fixed dose combination tablet for treatment of chronic hepatitis C. The approved treatment for hepatitis C genotypes 1 and 4 infection is the combination of peginterferon with ribavirin plus sofosbuvir or simeprevir for 12 or 24 weeks. The approved treatment for treatment of genotype 2 is the combination of sofosbuvir and ribavirin for 12 weeks. The approved treatment for treatment of genotype 3 is the combination of sofosbuvir and ribavirin for 24 weeks.

What procedures will be performed for research purposes?
A liver biopsy will be performed at week 4 of treatment. The study is trying to understand why some people fail to respond to the virus. It is not known if your immune system is important for helping the antiviral drugs to clear the virus from the liver. We believe that the immune system is important and the immune response to the virus in persons who fail treatment is different from those who clear the virus successfully. In order to understand this better we plan to compare the activity of genes associated with the immune response to the virus in the liver before and during treatment in persons who fail and patients who respond to treatment. This will help us to understand what role the immune system plays with clearance of the hepatitis C virus and if so, which part of the immune system plays this role. You may be asked to undergo a procedure called a lymphapheresis. This will be explained in a separate consent form.

A description of all procedures performed at each visit appears below:

Screening

At this visit, you will discuss and have time to review this consent form in detail and you will have time to have all of your questions answered. You will be asked to give informed consent by signing and dating this form. In addition, you will be asked questions about your current and past health and any medications you are taking.

The following procedures will be done at the screening visit(s):

- A doctor will do a complete physical exam.
- Height and weight will be measured.
- Blood pressure, heart rate, respiratory rate, and temperature will be taken
- Fatigue questionnaire (Promise 7)
- Visual analogue scale to assess your symptoms- a measurement tool used to assess your symptoms during treatment. For a particular symptom for example fatigue, you will be asked to make a mark along a continuous line ranging from worse to best, indicating how you feel about that particular symptom.
- Fibroscan - ultrasound (a procedure that uses high frequency sound waves to create an image of part of the inside of the body) to measure the stiffness of your liver and determine if cirrhosis is present
- Ultrasound, CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) scan on your liver to rule out liver cancer if you have not had one in the last 6 months
- ECG (or "electrocardiogram," which is a recording of the electrical activity of your heart). You will be asked about what other medications you are taking and if you are experiencing any side effects
- Blood and urine samples for safety tests (to check how your liver, muscles, kidney, blood cells and other body systems are working)

In addition, your blood will be tested for:
  - HIV, the virus that causes AIDS.

- Hepatitis B virus, another virus that causes hepatitis
- Hepatitis C virus (the type and amount of virus in your blood)
- Blood glucose levels to assess how well the sugar in your blood is controlled
- Thyroid (a gland in your neck that makes hormones) function test
- Coagulation tests to measures the time your blood takes to clot
- Alfa feto protein a test to help determine if you have liver cancer
- Lipid profile to assess overall cholesterol along with "good" and "bad cholesterol levels
- Lipoprotein profile, to assess amount and size of particles of "good" and "bad" cholesterol
- Serum Insulin, the level of a hormone that controls that amount of sugar in your bloodstream
- Hemoglobin A1c, a test to estimate the average sugar level in your bloodstream for last 3 months.
- Serum pregnancy test, if you are a woman who could become pregnant
- IL28B genotype test to obtain information on the potential ability to respond to treatment
- Research serum sample

If you cannot perform or do not want to do any of these procedures, you should not agree to be in this study.

Your study doctor will look at the results of your Screening tests to see if you qualify for the study. If you qualify and would like to take part, you will be asked to return to begin the study treatment phase.

Admission for Liver Biopsy

Before you begin treatment, a liver biopsy will be performed to assess the severity of damage to your liver and to obtain a sample of liver tissue to measure activity of liver genes. You may begin therapy the day after the biopsy or schedule another date to begin treatment.

Study Treatment Phase

Treatment will last for 12 weeks. At scheduled times during the study treatment phase you will need to come to the hospital. You will have the following hospital visits during the study treatment phase:

Your scheduled On-treatment visits are Day 0, 6 hours, 12 hours, 18 hours, 24 hours, 48 hours and 72 hours and then end of Weeks 1, 2, 4, 8 and 12.

At each visit, you will be asked about how you are feeling. You will also be asked if you have taken any medicine including any non-prescription (over-the-counter) medications other than the study drug(s).

Day 0, 1, 2 and 3 (Day 0 is 1st day of taking study drug)
Day 0 is the first day of the study treatment phase. Your study doctor or the study staff will do the procedures listed above. In addition, the following procedures will be done:

- Review of the study entrance criteria to see if you are still able to participate
- A doctor will do a brief physical exam
- Symptom questionnaire
- Visual analogue scale
- Review concomitant medications for possible drug interactions
- Blood tests to see that you are still able to participate
- Virus level prior to starting therapy
- Blood for immunological studies

- Lipid profile
- Lipoprotein profile
- Serum Insulin
- Blood sample for storage
- Pregnancy test (day 0 only)
- Pregnancy prevention counselling

If you meet all the requirements, you will take the first dose of study drug(s) in the hospital. You will be discharged from hospital on Day 3. You will be given instructions on how to take the study drug(s) at home.

Weeks 1, 2, 3, 8 and 12 and early termination visits

You will come back to the Outpatient Clinic for each of your visits. The following procedures will occur at these study treatment phase visits:

- Blood pressure, heart rate, respiratory rate, and temperature will be taken
- Blood samples will be taken by a needle stick into a vein in your arm. During the entire study, approximately 875 mL or 60 tablespoons or just less than 2 pints of blood will be taken. This volume is consistent with NIH guidelines which specify that no more than approximately one pint may be drawn for research purposes in any 8 week period. The following tests will be performed:
    - The blood will be tested to see if there are changes in safety tests (which check how your liver, muscles, kidney, blood cells and other body systems are working) while you are in the study and any changes in the extent of cirrhosis of your liver
    - Blood samples to measure the amount of virus in your body
    - Various measurements of your immune system:

    - Your doctor may ask you to return to the hospital for additional blood sample(s) to confirm any results and you may be withdrawn from the study if the amount of hepatitis C virus in your blood increases past a certain level, or you do not clear the hepatitis C virus from your blood. You may have to stop treatment if you develop a complication of the study medications such as elevated liver enzymes or if you develop a rash. You will still be asked to return for the end of study treatment visit and/or a post treatment follow-up visit.

    - Test your blood sample to look for hepatitis C viral resistance (if the virus has become resistant to the study drug). This testing will show how the virus is structured and is also known as "viral sequencing." You will continue to have this sample taken at every visit. This testing is required for the study. Because there is limited information on the development of resistance by the hepatitis C virus to the study drugs, the blood samples will be stored indefinitely in order to allow the researchers to perform additional resistance testing on the virus once resistance to the drugs used in this study is better understood.

- Three Health Related Quality of Life questionnaires. These forms ask questions about your health, activities and emotional well-being. You will be shown how to complete these forms. You will read the questions yourself and write/mark answers directly onto the questionnaire.
- Urine pregnancy test, if you are a woman who could get pregnant (weeks 8 and 12 only)

Week 4

A second liver biopsy will be performed for research purposes to measure activity of liver genes since starting treatment.

The same procedures outlined for weeks 1, 2, 3, 8 and 12 will also be obtained at week 4, including a urine pregnancy test if you are a women who could get pregnant.

At every visit you must bring all study drug(s) (including empty bottles) and all study material with you. The study staff will count how many pills you have taken. You will also be asked to complete a diary card to keep track of how much medication you have taken and when.

Your physician will give you a new bottle of study drug(s) to take home every 4 weeks. The study staff will instruct you when to return for your next visit per the study plan.

Early Termination Visit

- If you stop treatment early, you will need to have a special visit to return your study drug(s) and be checked by your doctor. All of your study drug bottles must be returned to your study doctor/staff at this time.

Follow-Up Phase

You will return to the outpatient clinic for follow-up visits starting 2 weeks after your last dose of study drug(s). These visits will check to see if any HCV can be found in your blood. The follow-up visits will be scheduled at 2 weeks, 4 weeks, 8 weeks and 12 weeks, after your last dose of study drug(s). Each visit will last about 1 to 2 hours.

The following procedures will occur at all of the follow-up visits:

- Blood pressure, heart rate, respiratory rate, and temperature will be taken.
- Weight
- Three Health Related Quality of Life surveys will be completed. You will read the questionnaire yourself and write/mark answers directly onto the questionnaire.
- Obtain blood samples to measure the amount of virus in your blood (your HCV RNA level)
- Asked about what other medications you are taking and ask if you are experiencing any side effects
- Obtain blood samples to see if there are changes in safety tests (which check how your liver, muscles, kidney, blood cells and other body systems are working) while you are in the study.
- Research blood

Week 24, Final study visit

The following procedures will occur at all of the follow-up visits:

- Blood pressure, heart rate, respiratory rate, and temperature will be taken.
- Weight
- Three Health Related Quality of Life surveys will be completed. You will read the questionnaire yourself and write/mark answers directly onto the questionnaire.
- Obtain blood samples to measure the amount of virus in your blood (your HCV RNA level)
- Asked about what other medications you are taking and ask if you are experiencing any side effects
- Obtain blood samples to see if there are changes in safety tests (which check how your liver, muscles, kidney, blood cells and other body systems are working) while you are in the study.
- Obtain blood samples to see the cholesterol changes in your body.
- Additional blood testing to measure levels of antibodies and autoantibodies in your blood, alfa feto protein (a test for liver cancer)
- Research blood

- A Fibroscan test to measure stiffness of your liver

After all the follow-up visits and procedures are completed, you will have completed this study.

If you do not clear the hepatitis C virus from your blood, researchers would be interested in following your HCV viral sequence (how the virus is structured) for up to 3 years.

If you clear the hepatitis C virus from your blood by the end of the study (24 week follow-up visit), we would be interested in following your HCV status for a minimum of 5 years after you stop taking study drug. You will be asked to sign a separate consent form for a different study to take part in long-term follow-up visits if this applies to you.

All the blood test results done at Liver Diseases Branch, Clinical Center, NIH will be shared with you.

Alternative Treatments

Your doctor can provide detailed information about HCV and the benefits of other treatments that are available to you. A decision regarding when to begin treatment for your HCV disease should be made after discussion between you and your health care provider. It is not always necessary to begin treatment immediately, depending on the status of your disease. You are encouraged to discuss treatment options with your doctor.

Sofosbuvir and simeprevir, sofosbuvir and ledipasvir, ombitasvir/paritaprevir/ritonavir with dasabuvir with or without ribavirin are new treatments that were recently approved by the United States Food and Drug Administration for the treatment of chronic hepatitis C genotype 1 infection. Patients who use these new treatments are more likely to achieve a sustained reduction of their HCV RNA level than patients who use pegylated interferon-α and ribavirin alone. In some cases, patients on these new treatments may be eligible for a shorter course of therapy than if treated with only peginterferon alfa and ribavirin. Sofosbuvir and ribavirin were recently approved by the United States Food and Drug Administration for the treatment of chronic hepatitis C genotypes 2 and 3 infection. The standard of care for chronic hepatitis C genotype 4 infection is peginterferon and ribavirin given for 24 or 48 weeks.

Your doctor can provide you with more information about the side effects associated with these new treatments, as well as the potential benefits. At this time, it is unknown whether the experimental therapy in this study is more or less effective or more or less safe than sofosbuvir plus peginterferon and ribavirin, simeprevir plus peginterferon and ribavirin.

Other studies evaluating other interferon-free regimens are being conducted by other investigators and pharmaceutical companies. It is possible that you might qualify for one of these studies. At this time, it is unknown whether other experimental therapies will be more or less effective or more or less safe than the experimental therapy used in this study.

Risks, Inconveniences and Discomforts

Your condition may or may not improve and could even get worse if you take part in this study. The study doctor and study staff will monitor you for any signs of new or unexpected side effects. Please tell your study doctor if you have a side effect or feel unwell while in this study. Contact your study doctor immediately if you experience a side effect that concerns you, or are unable to perform your daily functions. **You should contact your study doctor if you start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.**

The possible risks of participating in this research study include the blood draws, receiving the study drugs, and/or the liver biopsy and loss of confidentiality. Drugs that affect hepatitis C virus may not completely remove the virus from your body.

If that happens, your hepatitis C virus may develop drug resistance. Drug resistance may affect your ability to respond to future drugs if they are similar to sofosbuvir and GS-5816. As with any research study, there may be adverse events or side-effects that are currently unknown. It is possible that some of these unknown risks could be permanent, serious or life threatening.

A. Blood draw: The risks of blood drawing may rarely, in less than 1% of people (or less than 1 out of 100 people) lead to infection, fainting, or bleeding or may infrequently, in 1% to 10% of people (or 1 to 10 out of 100 people), lead to bruising, soreness, discomfort at the site of the blood draw, or lightheadedness. This may be reduced by applying pressure to the blood draw site or lying down.

B. Risks of the study drugs:

Sofosbuvir Common Adverse Events
The safety profile of sofosbuvir in patients is based on the combined safety data from 4 studies where it was given for 12-16 weeks. In these studies, sofosbuvir was given at 400 mg once a day, in combination with ribavirin to 664 patients and in combination with ribavirin and pegylated interferon alfa 2a to 327 patients.

In patients taking sofosbuvir with ribavirin for 12-16 weeks, the most commonly reported adverse drug reactions (≥10%) were fatigue (41%), trouble sleeping (18%), and irritability (10%).

In patients taking sofosbuvir with ribavirin for 12-24 weeks, the most commonly reported adverse drug reactions (≥10%) were:

- fatigue (24-38%)
- headache (20-30%)
- nausea (18-22%)
- trouble sleeping (4-16%)
- low red blood cell count (0-10%)
- decreased appetite (6-10%)
- fever (0-4%)
- rash (8-9%)
- chills (1-2%)
- decreases in the blood cells that fight infection (<1%)
- itchiness (8-27%)
- flu-like illness (3-6%)
- muscle pain (0-9%)
- irritability (1-10%)
- diarrhea (6-12%)

Most of these side effects were considered to be mild. These side effects overall were similar to those seen in subjects who took pegylated interferon and ribavirin without sofosbuvir. About one in sixty-five subjects taking sofosbuvir with ribavirin had to stop their study medications early because of side effects. Most of these side effects were believed to have been caused by ribavirin.

GS-5816 Common Adverse Events
GS-5816 has been given alone or with other investigational drugs to over 1000 HCV-infected patients.
The most common side effect reported (>10%) in about 800 subjects taking GS-5816 with other investigational drugs and ribavirin for at least 12 weeks were:

- Fatigue (Tiredness) (22%)
- Headache (20%)
- Nausea (12%)

- Diarrhoea (7%)
- Constipation (6%)
- Insomnia (Trouble sleeping) (6%)
- Nasopharyngitis (sore throat and stuffy nose) (5%)
- Rash (5%)

Most of these side effects were considered to be mild.

Rare, but serious:

- One subject who had a prior history of seizure disorder, received sofosbuvir and GS-5816 25 mg, for 8 weeks and experienced a seizure on post-treatment Day 1 and was hospitalized. The subject was discharged 7 days later. The investigator assessed the event as not related to study drug. The investigator suspected that the subject may have been noncompliant with seizure medication.

- One subject stopped sofosbuvir and GS-5816 25 mg after experiencing abdominal pain, palpitations, and dizziness on treatment Day 6. The subject discontinued study drugs on treatment Day 7. A physical exam and ECG were performed on treatment Day 7 and were both normal. The palpitations and dizziness resolved on post-treatment Day 2. The abdominal pain has not yet resolved. The investigator assessed the events as related to study drug.

- One subject administered sofosbuvir and GS-5816 25 mg + ribavirin, stopped the study drug due to elevated liver tests. On Day 71, the subject's ALT was found to have increased from the previous visit 2 weeks earlier from 95 U/L to 146 U/L (normal range 6 to 34 U/L) and aspartate aminotransferase (AST) from 73 U/L to 114 U/L (normal range 9 to 34 U/L). Local laboratory results performed several days later confirmed the ALT and AST elevations and the investigator stopped the study medications. The ALT and AST liver enzymes returned to normal within 30 days of stopping the study medications. This event was assessed as related to study drugs. If your ALT rises greater than 5 times your baseline value and is confirmed on repeat testing or if your ALT rises more than 3 times the upper limit your baseline value and your bilirubin increases above 2 mg/dL, your study medications will be stopped.

- One subject discontinued study drugs due to eczema and eye inflammation. This subject had an undisclosed recent history of allergic eyelid inflammation and eczema on the cheeks and right eyelid. The patient had only received study drug for 8 days. The investigator assessed the events as related to study drug.

- One death, due to suicide was reported after completing 12 weeks of treatment with sofosbuvir and GS-5816. The patient a 36-year-old male had an extensive psychiatric history that included bipolar disorder, depressive disorder, anxiety, and drug and alcohol abuse. The investigator assessed the event as not related to study drug, but precipitated by acute external events (impending re-incarceration) in the setting of underlying severe psychiatric disease.

- Asymptomatic elevations in creatine kinase (a muscle enzyme) and lipase (a pancreatic enzyme) have been observed in 1-2 percent (1-2 per 100) of subjects treated with sofosbuvir and ribavirin or sofosbuvir and GS-5816. In all cases, these elevations were transient and not associated with symptoms. If you develop elevations in your creatine kinase or lipase enzymes, you may be asked to return for additional visits until the lab tests improve. Your study doctor will determine whether it is safe for you to continue taking the study medications or whether you will have to stop.

Sofosbuvir/GS-5816

The safety profile for Sofosbuvir/GS-5816 combination is primarily based on extensive clinical experience with administration of Sofosbuvir and GS-5816, as single agents. There is limited safety data in healthy volunteers. The most common adverse event experienced was constipation. The most common adverse events related to Sofosbuvir/GS-5816 were headache (2 subjects) and diarrhea (1 subject).

C. Unknown risks: The possibility exists that complications and side effects which are unknown at this time could occur. You will be informed of any significant new findings that may develop with sofosbuvir and GS-5816 which may affect your willingness to continue participation in the study.

D. Allergic reactions: Occasionally, people have allergic reactions to medications. A severe allergic reaction can be life-threatening or fatal. Examples of an allergic reaction include: rash, shortness of breath, wheezing, sudden drop in blood pressure, swelling (around the mouth, throat, or eyes), fast pulse, and sweating. You should inform the study staff and seek medical assistance promptly if you develop symptoms of an allergic reaction.

E. Liver biopsy: A liver biopsy is a standard procedure used by liver specialists to assess the health of your liver. The procedure involves numbing the skin over the liver with a local anesthetic, followed by passing a needle through the skin into the liver and removing a small core of liver tissue. A specialist will examine the tissue carefully under the microscope. There may be some discomfort associated with the procedure. A more detailed explanation of the procedure will now be provided:

You will first undergo an ultrasound examination of your liver. This test will identify exactly where your liver is, its size, and where the needle should be placed to do the biopsy. The liver biopsy will be performed in your bed in the hospital room. We often will inject a sedative medication into an arm vein to make you drowsy and relaxed for the biopsy. This needle will be left in place for the biopsy and for an hour or two thereafter.

For the biopsy, you will lie on your back at the edge of the bed. The physician will clean the skin over the liver on the right side of your lower chest wall and place sterile drapes over the area. The doctor will then inject Xylocaine to numb the skin area where the biopsy is done. Xylocaine is the numbing medication that is most often used for minor surgical or dental procedures. The needlestick needed to inject the Xylocaine may be slightly uncomfortable. With the skin numbed, the doctor will place the liver biopsy needle into the skin in preparation for the biopsy. The doctor will then ask you to take a breath in and then blow it out completely and hold it out. You will be asked to practice this once or twice. Then when you have been prepared, and have exhaled completely, and are holding your breath, the doctor will do the biopsy by passing the biopsy needle rapidly into and out of the liver. The biopsy itself takes about one second. You may or may not feel it happen at all, but some people feel a slight sharp pain when the needle enters the liver.

More than 90 percent of the time, an adequate piece of liver is obtained with one attempt. However, sometimes the liver moves away when the biopsy is attempted, and at other times the piece of liver is too small. In these situations, additional attempts will be made to ensure that an adequate piece of tissue is obtained. For the second research biopsy no more than three passes will be tried. Furthermore, you can at any time refuse to have another attempt made.

After the biopsy, you will be asked to roll on your right side and lie on that side for two hours. This puts pressure on the site of the biopsy. During this time, you will have your blood pressure and pulse taken frequently, and the nurse will check on you regularly.

You will be asked to remain in bed for the rest of the day, but may be allowed to get up to go to the bathroom if you find it impossible to use a bed pan. Between 4 and 6 hours after the biopsy you will have a blood sample drawn to check your

red blood cell count; this is to make sure that there is no evidence of internal bleeding. The following morning you will be checked by the doctor, and if all is well you will be allowed to go home. You will be asked not to engage in heavy exercise or lifting for the next three days.

The following are the known complications of liver biopsy:

(a) Pain. About 20% of persons who undergo a liver biopsy experience pain in the side of body over the liver after the biopsy. This pain usually lasts from a few minutes to several hours and may require pain medication. In rare cases, the pain lasts a day or two.

(b) Fainting. Just as some people faint after giving blood, about 2% of persons pass out after a liver biopsy. Since you will be lying in bed, you are not going to fall down if you faint and this reaction is unlikely to cause you harm. Furthermore, we will give you a medication (atropine) to reverse the cause of fainting if it occurs. If you are the type of person who faints a lot, we can give you this medication before the biopsy to prevent you from fainting.

The other complications of liver biopsy are very rare.

(c) Infection. A rare complication of liver biopsy is infection that spreads to the rest of the body because the needle goes through skin that is not completely clean or sterile or goes through infected bile (as occurs in patients with gallstones sometimes). Antibiotics can treat such infections.

(d) Biopsy of another organ. In rare instances, the biopsy needle misses the liver and hits another internal organ, such as the lung, gallbladder, kidney, or intestine. This complication can be avoided by carefully selecting the site for the liver biopsy and using ultrasound to identify exactly where the liver is and the best position for the biopsy. Usually, the other organ is not damaged by the needle puncture; however, it is possible that surgery might be needed to repair the hole.

(e) The most important complication of liver biopsy is bleeding. A small amount of bleeding probably occurs in many patients after liver biopsy, but the amount of bleeding is usually too small to be detected or felt. Severe bleeding occurs in about one of every 1000 liver biopsies. Severe bleeding is most likely to occur in someone with cancer of the liver or with abnormal clotting studies, but bleeding can also occur in patients with mild forms of liver disease. Most cases of severe bleeding stop on their own with bed rest and observation for several days in the hospital. In rare instances, a blood transfusion or even surgery is needed to sew up the tiny hole in the liver made by the biopsy. Very rarely, in less than one in 10,000 cases, death has occurred from bleeding after a liver biopsy. Over 40 year period, liver specialists at the NIH have performed over 4,000 liver biopsies. Three deaths have occurred due to severe bleeding that could not be controlled- two patients had clotting problems and one had cancer that may have contributed to the inability to stop the bleeding. It is because of these possible side effects that you will be kept overnight in the Clinical Center after the liver biopsy with careful monitoring for any evidence of bleeding.

(f) The risks and discomforts of receiving the medications used during liver biopsy: Three medications are often used during a liver biopsy: Xylocaine to numb the skin, a sedative such as Versed (midazolam) to make you drowsy during the biopsy and atropine if you have a tendency to faint. All three medications are safe when given in the usual doses. In rare instances, they can induce allergic reactions which can be a skin rash, itching, wheezing, an asthma attack, or even anaphylaxis - or allergic shock. [If you have any allergies to medications, you should remind the doctors of these.] All of the allergic complications can and will be treated if they arise. Xylocaine, when given in high doses can also cause heart blockage, seizures, coma, or even death; but, in the doses given in this study it has no obvious effect on the heartbeat. Atropine can cause dryness of the eyes and mouth, difficulty focusing the eyesight, constipation and difficulty passing urine. All these side effects will disappear within a few hours. Versed or Midazolam which is used for sedation causes sleepiness and forgetfulness. In high doses, it can cause over-sedation with coma and depression of breathing and even death. This

medication is given in small amounts with careful monitoring of how deeply you are sedated. Medications and equipment are at hand during the liver biopsy to deal with the situation if you become too sedated and stop breathing normally. At the Liver Diseases Section, we have never had an emergency or serious reaction to these three medications during the years that they have been used in performing liver biopsies.

F. Viral Resistance

Treatment with drugs that directly inhibit the hepatitis C virus has been shown to lead to development of hepatitis C virus that is resistant to that drug and other drugs with the same type of action. These resistance mutations have been observed in the body as late as 4 to 5 years after treatment has ended. It is unknown whether having these resistance mutations might reduce the chance of treatment success with future drugs with the same type of action or with different types of action (such as protease inhibitors). It is possible that if you are treated with the drugs in this study and treatment doesn't work, you might have resistance mutations that would make future treatment less successful.

G. Risks to Reproduction, Unborn Babies and Nursing Infants

General Statement

You must not be pregnant or breastfeeding, and you should not become pregnant or breastfeed while you are taking the study treatments, and for 12 weeks after stopping treatment. You must use two methods of birth control to avoid pregnancy for the duration of this study and for 3 months after taking the study medication. You should immediately contact your study doctor if there is a change in your method to avoid pregnancy or if you start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.

It is unclear how long the investigational drugs, sofosbuvir and GS-5816 may last in the body's tissues, and the safety of this drug in women who are pregnant or nursing has not yet been established. If you are a woman who is pregnant or a female with the intent of becoming pregnant or a female who is currently nursing (breastfeeding) a child, you cannot be in this study. If you are a man whose partner is currently pregnant or wishing to become pregnant, you cannot be in this study.

You must protect yourself or your partner from becoming pregnant before, during, and after the study. Women, and men with female partners capable of becoming pregnant, must use two effective methods of birth control as described below. Your study doctor will need to document what type(s) of birth control you are using.

Women only:

Women who can get pregnant should not take study drug(s) unless they and their partner do not have intercourse ever or are using 2 methods of birth control for the duration of the study (starting 3 weeks prior to the Day 0 visit) and for a minimum of 3 months after last dose of study medications or longer as directed by your study doctor.

At least one method of birth control must be a condom used correctly by your male partner. Acceptable birth control methods (in addition to a male partner who correctly uses a condom) include:

- an intrauterine device (IUD) with a failure rate of <1% per year
- female barrier method: cervical cap or diaphragm with spermicidal agent
- tubal sterilization (having your tubes tied)
- hormone containing contraceptives

Women who can get pregnant must have a negative serum pregnancy test at screening and urine pregnancy test at the Day 0 visit, prior to taking the first dose of study medication. Pregnancy tests will be repeated every 4 weeks during the study treatment and post treatment phases.

You must tell your study doctor immediately if you become pregnant while in this study and for 12 weeks after stopping study drugs, or for as long as you have been directed by your study doctor to use contraception. The study doctor will tell you about the possible risks to your unborn child and options available to you.

In the event of a positive urine pregnancy result, you will be instructed to stop study drugs immediately and return to the study clinic as soon as possible for a serum (blood) pregnancy test. The pregnancy will be followed to its completion and the outcome, including any premature termination, must be reported to your doctor.

You should be counseled and monitored by your own doctor. As the risk to the unborn baby is unknown, it is recommended you seek medical supervision from your own doctor during the pregnancy and for the baby after it is born. Neither the study doctor nor the provider of the study medications (Gilead Sciences) will be responsible for providing routine medical care relating to the pregnancy.

Men only:

If you have a female partner who cannot become pregnant, you must still consistently and correctly use a condom.

If you have a female partner who can become pregnant, you and your partner must use <u>two</u> forms of birth control for the entire study and for a minimum of 12 weeks after the last dose of study medications or longer as directed by your study doctor. You must use a condom while your female partner uses 1 other method of birth control. Your study doctor will discuss with you other methods of birth control that can be used in combination with a condom.

If your female sex partner becomes pregnant while you are in the study or within 12 weeks after your last dose of study drug, the study drug may harm an unborn baby. If you have a female partner who becomes pregnant or suspects that she has become pregnant while you are in the study or within 12 weeks after your last dose of study drug, you will be required to notify your study doctor immediately. As the risk to your partner and unborn baby are not known, it is recommended for your partner to receive appropriate prenatal care. If you agree, your partner will be asked to release her medical information related to pregnancy. Your study doctor may need to disclose to your partner details of this study and your taking part in it. Neither the study doctor nor the manufacturer of the study medications (Gilead Sciences) will be responsible for the costs related to the pregnancy, delivery, or care of your child.

Male subjects must also agree not to donate sperm from the time you first take your first dose of study medication until 12 weeks after the last dose of study medications.

Please note: Hormonal birth control may be more effective when taken for at least 3 months. Even if you and your female partner use a medically proven birth control method, you could still cause your partner to become pregnant.

Please share this information with your partner.

Unforeseeable Risks

There may be unknown risks to you, your unborn baby or nursing infant if you are or become pregnant during this study or are breastfeeding during this study.

Risk of Embryo-Fetal Abnormalities Based on Laboratory & Animal Findings

While laboratory and animal studies have been conducted to determine possible risks, the results do not necessarily show what will happen when the drug is used in humans. Fertility and embryo-fetal development studies in rats indicate that doses of sofosbuvir and GS-5816 which were not harmful to the pregnant animal did not cause abnormalities to the fetus or embryo.

Human Pregnancy Outcomes

There is currently no available data on pregnancy outcomes with sofosbuvir and GS-5816.

Requirements for Pregnancy Testing

During this study you will have up to 7 pregnancy tests. Pregnancy will be determined on basis of a urine and / or blood sample. The pregnancy tests will be at the screening assessment, Day 0, treatment weeks 4, 8 and 12, and for post-treatment Weeks 4, 8, and 12. Women of child bearing potential must have a negative serum β-HCG at screening and a negative urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

Occurrence of Pregnancy or Suspected Pregnancy

If you become pregnant, suspect pregnancy or if you missed your period or it is late, or if you have a change in your usual menstrual cycle (e.g., heavier bleeding during your period or bleeding between periods), you should immediately contact your study doctor.

Discontinuation from the Study

Should you become pregnant during this study, you will have the investigational products discontinued and be referred for obstetric care. The NIH has not set aside any funds to pay for any aspects of obstetric, child or related care and does not plan to pay for them.

Pregnancy Reporting

In case of a pregnancy, your pregnancy and its outcome will be reported to Gilead Sciences, the manufacturer of the study medications.

H. Potential risks of a breach of confidentiality

Participation does involve the potential risks of a breach of confidentiality of the information and associated privacy of the participants. A breach of confidentiality could impact future insurability and employability. The risks will be minimized by 1) removing identifiers (names, social security numbers, medical record numbers) from stored samples; 2) limiting access to information linking codes assigned to samples by storing identifying information in a separate location; and 3) limiting access to information to study investigators at the Liver Diseases Branch, Clinical Center, NIH.

Benefits

Preliminary results of treatment with sofosbuvir and GS-5816 are promising and suggest that 90% or more of subjects receiving this regimen are cured of hepatitis C. Follow-up studies of patients with hepatitis C cured with other regimens

show that the rate of complications from hepatitis C such as variceal bleeding (bleeding from large veins in the food pipe), ascites (fluid in the abdomen) and liver cancer are substantially decreased compared to patients who are not cured.

There is no guarantee that you will receive personal benefit from taking part in this study. Sofosbuvir and GS-5816 may not improve your chronic hepatitis C. There is the possibility that your chronic hepatitis C may worsen. However, clinical research studies such as this are a way for doctors to determine if a drug is useful in fighting a disease. By taking part in this study, you may benefit if sofosbuvir and GS-5816 is effective in curing HCV. By you taking part in this study, it may benefit the community, scientists, and doctors who work with HCV by providing increased knowledge and information about the treatment of your disease. By taking part in this study, you will have close medical monitoring of your health condition by blood tests and other tests during clinic visits.

Knowing your cholesterol levels would help assess your risk for heart disease and stroke and may require additional medical intervention to lower this risk. Additionally, if you are already have high cholesterol and you are already on a cholesterol lowering medication, we would be able to tell you if you might need an increase in the medication. Your primary healthcare provider will be responsible for managing your cholesterol medication.

Compensation

You will not receive any compensation for participating in this study. Participation in this study will be free of charge. Neither you nor your insurance will be charged for research testing of your stored blood or liver samples. Sometimes, research results in findings or inventions that have value if they are made or sold. These findings or inventions may be patented or licensed, which could give a company the sole right to make and sell products or offer testing based on the discovery. There are no plans to offer you compensation for any present or future products, processes, and /or therapies developed as a result of this research.

Right of Withdrawal and Conditions for Early Withdrawal

You may tell us at any time that you no longer wish to participate in this study. You have the right to change your mind about allowing us to have access to your personal health information. If you choose to take away this permission you must inform the Principal Investigator in writing. Your withdrawal of this consent to participate will be effective immediately. Any information collected up to the time you choose to take away your permission will still be used. Deciding to no longer participate or withdrawing permission to access your personal health information will not result in any penalty or loss of benefits to you.

Discussion of New Findings with You

You will be promptly notified if any new significant information (either good or bad) develops during the conduct of this research study which may cause you to change your mind about continuing to participate. If new information is provided to you, your consent to continue participation in this study will be re-obtained. This does not apply to findings from the use of de-identified blood and liver samples in the future.

Study Termination

The study investigators and/or sponsor may terminate your participation in the study for various reasons. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.

- You do not follow instructions from the researchers.
- The study is suspended or canceled.

The study investigator and/or manufacturer of the study medications may also terminate this study for safety, scientific, or administrative reasons at any time.

Confidentiality

Your participation in this study will be kept confidential. No one other than the study personnel at the clinical center will be given your name, address, and other personal identifying information.

Representatives of the National Institutes of Health and Gilead may review your records at visits to the clinic. This is part of the ongoing monitoring of the study. In addition, representatives from the United States Food and Drug Administration (FDA) or the Institutional Review Board at this institution may review your study records, including your medical records.

Who will have access to identifiable information related to my participation in this research study?

In addition to all members of the research team at the Clinical Center, NIH the following individuals will, or may, have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the Clinical Center, NIDDK, NIH Institutional Review Board/Research Ethics Board (IRB/REB) may review your information to monitor the appropriate conduct of this research study. In unusual cases, the investigators may be required to release your information in response to an order from a court of law.

Authorized representatives of Gilead Sciences may view your study information. The purpose of providing this information is to monitor the accuracy and completeness of the research data.

Authorized representatives of Clinical Center, NIH or other affiliated health care providers may have access to your study information. This may be used for internal hospital operations and quality assurance.

You will receive a copy of this consent form. A copy will be placed in your hospital medical record so that any doctors who are treating you will know that you are participating in the study.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for a minimum of 7 years and for as long (indefinite) as it may take to complete this research study.

Research Use of Stored Samples and Data

Research blood samples will be initially stored at the Clinical Center, NIH. Some of the research blood samples may be sent to Gilead Sciences under code for resistance testing. These results will be shared with you.

The remaining research blood samples will be kept and maintained in locked freezers by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to be stored for future testing. Some clinical information about you will also

be stored in password-protected computers to help investigators interpret the results of tests done on the blood. Your blood samples and clinical information will be identified only by a code.

Liver biopsy samples obtained in this study will be read and stored at the Clinical Center, NIH. Results of the reading will be shared with you. A small piece of liver tissue will be saved to assess the gene response in the liver following receipt of treatment. If any liver tissue is remaining after this analysis is complete, it will be stored for future research. This material may help scientists develop new medical tests, treatments, and ways to prevent diseases.

Will my information for this study be used for any other studies?

Yes. If you choose to be in this study, other researchers may use your unidentifiable study information for studies of liver and non-liver diseases in the future.

May I have access to my medical information that results from my participation in this research study?

You are allowed to access medical information contained in your medical records, including information resulting from your participation in this research study. Any information from research laboratory tests obtained from use of banked blood and liver samples will not be placed in your medical records. By agreeing to participate in this study, you do not waive any right that you may have regarding access to and disclosure of your records. For further information on those rights, please contact Dr. Ghany (PI) at 301-496-1721.

Conflict of Interest

The National Institutes of Health reviews NIH employees at least yearly for conflicts of interest. The following link contains details on this process http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf. You may ask your research team for additional information or a copy of the Protocol Review Guide.

This protocol has investigator(s) who are not NIH employees. They are expected to comply with their Institution's conflict of interest policies.

Research Study Registry

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at anytime.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Marc Ghany M.D.; Building 10, Room 9B-16, Telephone: 301-496-1721. Other researchers you may call are: Elenita Rivera, RN at 301-435-6125, or the NIH operator 301-496-1211.

You may also call the Clinical Center Patient Representative at 301-496-2626.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JULY 25, 2017 THROUGH AUGUST 29, 2018.

Signature of Investigator _____ Date _____ Signature of Witness _____ Date _____

Print Name _____ Print Name _____