APPROVED
AS MODIFIED
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WIRB®

RESEARCH AND CONSENT FORM AND HIPAA AUTHORIZATION

TITLE: A Randomized Study to Evaluate the Safety and Efficacy of Adding Daclatasvir to the Combination of Sofosbuvir (SOF) and Ribavirin (RBV) for 16 Weeks Versus 24 Weeks in Cirrhotic Subjects with Chronic Hepatitis C Infection Genotype 3

PROTOCOL NO.: AI444284

SPONSOR: Tarek Hassanein, M.D.

INVESTIGATOR: Tarek I. Hassanein, MD
Suite 101
131 Orange Avenue
Coronado, California 92118
United States

STUDY-RELATED PHONE NUMBER(S): Tarek Hassanein, MD
619-522-0330 (24 hours)

Purpose of This Consent Form

This consent form is written to help you decide if you want to participate in a research study and take an experimental drug for your condition. An experimental drug is one that is not approved by the U.S. Food and Drug Administration (FDA). For you to receive this experimental drug, you must give your informed consent. Informed consent includes:

- Reading this consent form,
- Having your doctor or your doctor's staff explain the study and experimental drug to you, and
- Asking your doctor or your doctor's staff about anything that is not clear.

In addition:

- You may take home an unsigned copy of this consent form.
- You can think about it or talk to family or friends before you decide.

You should not sign this consent form until all your questions have been answered and you are satisfied with the answers.

Please read this consent form carefully. This form may contain words that you do not understand. Please ask the doctor or his staff to explain any words or procedures that you do not clearly understand.

Purpose and Description of the Study

You are being asked to participate in this research study because you have been diagnosed with hepatitis C infection (HCV) genotype 3 and cirrhosis (very severe scarring of the liver). You have either never received treatment for it or did, but your body did not respond to conventional therapy. You are now considering the use of Daclatasvir with sofosbuvir plus ribavirin. Sofosbuvir and ribavirin are FDA-approved drugs and the standard of care treatment. The standard duration of treatment with sofosbuvir and ribavirin for someone with HCV genotype 3 is 24 weeks. But Daclatasvir is experimental for your condition, and not all its risks or side effects are known.

You should be aware that:

- Some of the side effects may be life threatening.
- There is no promise that your condition will be helped.
- You do not have to take part in this study. Your decision about what to do must be made voluntarily. About 40 subjects are planned to complete the study.

Your doctor wants to see if Daclatasvir in combination with sofosbuvir and ribavirin is a superior treatment for chronic HCV infection than standard therapy of sofosbuvir and ribavirin alone. The study will also look at the safety of adding Daclatasvir to sofosbuvir and ribavirin.

Daclatasvir may not improve your chronic HCV. There is also the possibility that your chronic HCV may worsen.

More detailed information about Daclatasvir, sofosbuvir plus ribavirin follows. Please read it carefully.

Procedures for This Study

If you agree to take part in this study, no procedures will be done until you sign and date this consent form.

You will be randomized into one of two groups. This means that it will be randomly decided (by chance) if you will go into either Group A or Group B. You will have a 50/50 chance of being assigned to Group A or Group B:

- **Group A:** If you are in this group you will take Daclatasvir with sofosbuvir plus ribavirin for 16 weeks (4 months).

- **Group B:** If you are in this group you will take Daclatasvir with sofosbuvir plus ribavirin for 24 weeks (6 months).

Once you are randomized to a study, the study staff will tell you which group you were randomized to.

Once each day, you will take a 60 mg tablet of Daclatasvir (with or without food), a 400 mg tablet of sofosbuvir (with or without food), and twice each day you will take a 500-600 mg tablet of ribavirin (the exact dose will be determined according to standard of care). Ribavirin has to be taken with food (after eating). The duration of taking this combination will depend on which group you were randomized to.

Your doctor will see you every two weeks or more frequently until month 4 (if you are in Group A) or until month 6 (if you are in Group B). Regardless of which group you were in, the doctor will see you at weeks 4, 12 and week 24 after you finish your medications.

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

The following procedures will be done at these visits:

- Physical exam
- Review of any side effects or problems
- Review of any medications, vitamins or herbal treatments you take
- Weight
- Blood pressure, heart rate, and temperature
- Blood samples (by a needle stick into a blood vessel in your arm). The blood will be tested to see if there are changes in your liver, muscles, kidney, blood cells and other body systems and for measurements of the hepatitis C virus as well as storage for future testing, which will include testing to see how your body has reacted to the study drug (no genetic testing of your DNA will be done). At the end of the treatment period, any HCV still present will be tested to see whether it developed resistance to the study drug compared with similar testing performed at the start of your study participation.
  You will be also tested for HIV (AIDS virus). State law requires that positive results for this test be reported to a local health agency.
- ECG (electrocardiogram) (Screening, week 16 [Group A only], week 24 [Group B only] and post study drug week 24). An ECG records the electrical activity of the heart.
- Blood or urine pregnancy test (women of childbearing potential only).

Your Responsibilities/Restrictions

- Tell your doctor all of the medications that you have been taking for at least 30 days before you take part in the study. This includes vitamins, minerals, and medications that do not require a doctor's prescription. Some medications are not allowed. Your doctor will discuss these with you in detail.
- Ask your doctor before you take any new medications.
- Attend all visits as scheduled.
- Only you should take the study drugs. Keep them out of the reach of children and away from people who may not be able to read or understand the labels.
- If you have sexual intercourse with a female who could get pregnant, you must use two effective methods of birth control during the study and for 7 months after your last dose of ribavirin. Please see the "Reproductive Risks" section for more information.
- If you are a woman who can get pregnant, you must use two effective methods of birth control during the study and for 7 months after your last dose of ribavirin. Please see the "Reproductive Risks" section for more information.

Risks or Discomforts

Your condition may or may not improve and could even get worse if you take part in this study. The doctor will monitor you for any signs of a new or unexpected side effect. Tell your doctor if you have a side effect or feel unwell. Contact your doctor immediately if you:

- have a side effect that concerns you, or
- are unable to perform your daily functions.

Drugs that affect hepatitis C virus may not completely stop the virus from increasing in your body. If the drugs that you are taking do not completely stop the virus from increasing, your hepatitis C virus may develop drug resistance. Drug resistance may affect the ability of Daclatasvir to lower the amount of hepatitis C in your body and may also affect your ability to respond to future drugs if they are similar to Daclatasvir.

Experimental Drug Daclatasvir and Sofosbuvir

Thus far, more than 6000 subjects have exposed to Daclatasvir in clinical trials. In general, Daclatasvir has been well tolerated. No Daclatasvir specific safety concerns have been identified.

In a study of Daclatasvir and sofosbuvir, 167 subjects with chronic hepatitis C genotype 1, and 44 subjects with chronic hepatitis C genotype 2 or 3 were given 12 weeks or 24 weeks combination treatment. An interim analysis was performed. The data showed the combination was generally well tolerated.

No side effects were directly attributable to Daclatasvir. The most common side effects reported with Daclatasvir in combination with other treatment such as interferon or others include

- headache,
- dizziness,
- nausea,
- diarrhea,
- fatigue,
- back pain,
- insomnia,
- abdominal pain, and
- flatulence.

In rare cases there have been reports that Daclatasvir when taken with sofosbuvir and amiodarone can cause arrhythmias (a problem with the rate or rhythm of the heartbeat) in particular severe bradycardia (slow heart rate). It is not known whether this resulted from the interaction of amiodarone with Daclatasvir, sofosbuvir or both. Therefore, amiodarone is one of the medications that you will not be allowed to use during this research study. The study doctor will discuss what options are available for you if you have been taking it or in case you need to take it.

Sofosbuvir

The most commonly reported side effects (20% or more of patients) of sofosbuvir in combination with ribavirin are fatigue and headache.

Other common side effects include:

- Nausea,
- Insomnia,
- Itching,
- Rash,
- Decreased appetite,
- Diarrhea,
- Increased bilirubin,
- Irritability

Ribavirin

The most serious side effect seen with ribavirin is anemia (a decrease in the number of red blood cells in the body that carry oxygen). This may cause tiredness and lack of energy. Anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and non-fatal heart attacks.

Ribavirin is usually taken with pegylated interferon (a once per week shot, which you will **not** receive during this study).

The most common side effects when taking RBV combined with pegylated interferon are flu-like symptoms consisting of:

- Body aches and pains
- Fever
- Chills
- Headache
- Overall feeling of sickness
- Rash

Other common side effects are: anxiety, mood changes, depression and irritability.

In general

It is not expected that you will have all of these side effects. In addition, other side effects may occur that are not listed here or were not seen before. Talk to your doctor for more information. Side effects are usually temporary and can often be treated. However, it is very important that you report all side effects to the study staff, as it is possible that these side effects could be serious or fatal.

Allergic Reaction

Occasionally, people have allergic reactions (including life-threatening reactions) when taking a medication. Symptoms of a serious allergic reaction can include: rash, hives, itching and/or trouble breathing, closing of the throat, swelling of the lips, tongue, or face, and rarely, death. **Get emergency medical care immediately if you have any of these symptoms.** Stop taking your drug drugs and let your doctor know.

In general, allergic reactions to medicines are more likely to occur in people who already have allergies. If you are allergic to other drugs, foods, or things in the environment, such as dust or grass, or if you have asthma, let your doctor know.

Blood Draw Risks

Possible side effects from drawing blood include dizziness, redness and swelling of the vein, pain, bruising, or bleeding from the site of the needle puncture. Rarely, a clot or infection could occur that would require treatment. Some people feel faint or sick when blood is taken.

ECG Risks

An ECG is a painless test, but you might have redness, irritation, or a rash on the skin where the adhesive patches are placed.

Unknown Risks

Daclatasvir is an experimental drug and might have other side effects, which are not known at this time. Taking Daclatasvir in combination with sofosbuvir and ribavirin could also have unknown side effects. Any unknown side effects could be serious.

Do not drive, operate machinery, or do other activities requiring mental alertness until you know how the medication will affect you. Discuss all side effects with your doctor.

Reproductive Risks/Birth Control

The effects of Daclatasvir on the fetus (unborn child) are not known. You must protect yourself/your female partner(s) from becoming pregnant before, during, and after the study. If you have sexual intercourse, you must use effective methods of birth control as described below. Your doctor will need to document what type(s) of birth control you are using.

Ribavirin has been shown to cause significant birth defects in animals and may cause birth defects in humans. Ribavirin can persist in the body for as long as 6 months after it has been discontinued.

If you/your female partner can become pregnant, you and your partner must use two forms of birth control for the entire study and for a minimum of 7 months after you stop taking the drugs or longer as directed by your doctor. One birth control method must be a barrier method (such as a condom with spermicide). Your doctor will discuss other methods of birth control that may be used in combination with a barrier method.

Tell your doctor if your female partner gets pregnant during this study or for up to 7 months after you stop taking the drug(s). Your doctor will want to know about the pregnancy and its outcome. The outcome, including any premature termination, must be reported to Bristol-Myers Squibb, Inc. (the company that will provide Daclatasvir for this study).

New Information

You will be told about any new information that might change your decision to be in this study.

Possible Benefits

The study drugs might improve your condition. However, there is no guarantee of this. The information gained during this study may benefit patients with your condition in the future.

Payment for Participation

You will not be paid for being in this study.

Alternatives

Instead of being in this study, you could choose to receive/continue to receive standard care for your HCV. The current standard care for your condition is sofosbuvir and ribavirin for 24 weeks (as received by Group B) or pegylated interferon alfa-2a with ribavirin.

Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your condition.

Costs to You

Daclatasvir will be provided at no cost to you. Tests and procedures that are done only for the study will not be billed to you or your health insurance company.

You or your health insurance company will be billed for any standard medical care you are given during this study. These are costs that you would normally have if you were being treated for your disease with standard care. You or your health insurance will be responsible for providing you with sofosbuvir and ribavirin (standard of care treatment) according to the standard of care duration. The approximate cost of sofosbuvir and ribavirin for 24 weeks (6 months) for individuals with Hepatitis C genotype 3 is around $170,000.

You may wish to consult your health insurance company about its payment policy for standard treatment received during a research study.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

Confidentiality and Release of Medical Records

We will try to protect the confidentiality of information about you as much as possible. However, we cannot guarantee complete confidentiality because the following groups may be given access to your original and study medical records:

- U.S. Food and Drug Administration (FDA),
- the Department of Health and Human Services (DHHS),
- similar health agencies in other countries
- Western Institutional Review Board® (WIRB®)

These groups may confirm procedures or data without violating your confidentiality to the extent permitted by the applicable laws and regulations.

Results from this study may be published or presented at scientific meetings, but your identity will not be revealed.

By signing this consent form, you are authorizing access to your medical records.

Compensation for Study-Related Injury

If you are injured or become ill from the experimental drug, medical treatment will be provided to you. Contact your study doctor at the number on the first page of this document to find out where to go for treatment. You or your health insurance company will be billed for the cost of the treatment. Neither Bristol-Myers Squibb, Inc. nor the doctor plans to provide other compensation in the event of an injury.

This does not restrict your right to pursue a claim through the legal system. You do not give up any legal rights by signing this consent form.

Voluntary Participation/Withdrawal

Your participation in this study is voluntary. You may decide not to take the experimental drug or you may freely withdraw from the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

In addition, your doctor may stop your participation in this study. This may happen without your consent at any time and for any reason, including any of the following reasons:

- your doctor determines it is in your best interest;
- you are not responding to the experimental drug;
- if you do not consent to continue in the study after being told of changes in the research that may affect you;
- you do not follow the study instructions; or
- Daclatasvir is no longer available to your doctor.

If you stop taking part in this study before the final visit, your doctor may ask you to have some final tests.

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

If You Have Questions

Contact Tarek Hassanein, MD, at 619-522-0330 (24 hours) for any of the following reasons:

- if you have any questions or concerns about being in this study,
- if you have a study-related injury or reaction to the drug(s), or
- if you have a complaint about the study.

If you have questions about your rights as a subject in this study or if you have questions, concerns, or complaints about the study, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite, 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study specific questions, such as questions about appointment times. However, you may contact WIRB if research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

Your Consent

- I have been told that this is a research study.
- I have been given enough time and information to decide to be in this study.
- I have had enough time to ask my doctor questions about this study. My questions so far have been answered to my satisfaction.
- I do not give up my legal rights by signing this consent form.
- I authorize access to my medical records the FDA, DHHS agencies, similar health agencies in other countries, and WIRB®.
- I have been told that I will receive a signed and dated copy of this consent form.

I agree to take part in this study.

_____

Signature of Patient **Date**

_____

Printed Name of Patient

I certify that the information provided was given in language that was understandable to the patient.

_____

Signature of Person Obtaining Consent **Date**

_____

Printed Name of Person Obtaining Consent

HIPAA AUTHORIZATION

The United States government has issued a privacy rule to protect the privacy rights of patients (Privacy Rule). This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your personal health information. The document you are reading, called an "Authorization," describes your rights and explains how your health information will be used and disclosed (shared).

As the sponsor, Tarek I. Hassanein, MD, will use and share personal health information about you. This is information about your health that also includes your name, address, telephone number, or other facts that could identify the health information as yours. This includes information in your medical record and information created or collected during the study. This information may include your medical history, physical exam, and laboratory test results including results of HIV (AIDS virus) testing. Some of these tests may have been done as part of your regular care. The doctor will use this information about you to complete this study.

In most cases, the doctor will use your initials and assign a code number to your information that is shared with the sponsor. The sponsor and its representatives may review or copy your personal health information at the study site. Regulatory authorities and Western Institutional Review Board® (WIRB®) may also review or copy your information to make sure that the study is done properly or for other purposes required by law.

By signing this Authorization, you allow the doctor to use your personal health information to carry out and evaluate this study. You also allow the study doctor to share your personal health information with

- the Western Institutional Review Board (WIRB),
- the U.S. Food and Drug Administration (FDA), and
- other regulatory agencies.

Your personal health information may be further shared by the groups above.

If shared by them, the information will no longer be covered by the Privacy Rule and may be disclosed without your permission. However, these groups are committed to keeping your personal health information as confidential as possible.

You have the right to see and get a copy of your records related to the study for as long as the doctor has this information. However, by signing this Authorization, you agree that you might not be able to review or receive some of your records related to the study until after it has been completed.

You may choose to withdraw this Authorization at any time, but you must notify the doctor in writing. Send your written withdrawal notice to the address below:

Tarek Hassanein, MD
Southern California Research Center
131 Orange Avenue, Suite 101
Coronado, California 92118

If you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes unless the information concerns a drug-related side effect. If a side effect occurs, your entire medical record may be reviewed. All information that has already been collected for study purposes and any new information about a side effect related to the study will be sent to the sponsor.

If you withdraw from the study but do not withdraw your Authorization, new personal health information may be collected until this study ends.

This Authorization will expire December 31, 2074, unless you withdraw it in writing before then. Your doctor will keep this Authorization for at least 6 years.

If you do not sign this Authorization, you cannot participate in this study or receive the experimental drug. Your decision to withdraw your Authorization or not to participate in the study will not involve any penalty or loss of access to treatment or other benefits to which you are entitled.

AUTHORIZATION

I authorize the release of my medical records and personal health information related to this study to the sponsor and its representatives, the Western Institutional Review Board (WIRB), the FDA, and other regulatory agencies as described above.

I have been told that I will receive a signed and dated copy of this Authorization for my records.

Signature of Patient	**Date**
Printed Name of Patient	
Signature of Person Obtaining Authorization	**Date**
Printed Name of Person Obtaining Authorization	