

CONFIDENTIAL

MEDICAL RECORD

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

INSTITUTE NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES

STUDY NUMBER 93-DK-31 PRINCIPAL INVESTIGATOR: Jay H. Hoofnagle, M.D.

STUDY TITLE: A Six-Month Course of FIAU for Chronic Hepatitis B

INTRODUCTION

We invite you (or your child) to take part in a research study at the National Institutes of Health. It is important that you read and understand several general principles that apply to all who take part in our studies: (a) taking part in the study is entirely voluntary; (b) personal benefit may not result from taking part in the study, but knowledge may be gained that will benefit others; (c) you may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled. The nature of the study, the risks, inconveniences, discomforts, and other pertinent information about the study are discussed below. You are urged to discuss any questions you have about this study with the staff members who explain it to you.

As a patient with chronic hepatitis B, you are invited to take part in this research study designed to test FIAU for its effect on your liver disease. FIAU is an antiviral medication whose full name is 1-2' deoxy-2' fluoro-1-beta-D-arabinofuranosyl-5-iodo-uracil. In a previous study, we found that FIAU inhibits the levels of hepatitis B virus in the blood of patients with chronic hepatitis B. In a small number of patients, this inhibition was strong enough to cause the hepatitis B virus to disappear completely; these patients had an improvement in their liver condition. In other patients, however, the treatment did not have a lasting effect, either because the medication was not strong enough or was not given for a long enough time. For these reasons, we are planning to treat patients for a longer period - for six months - to see if a prolonged course of FIAU will cause a permanent improvement in the hepatitis.

We are asking you to enter this study in which you will receive FIAU for a total of 24 weeks. At the beginning of the study you will undergo a medical evaluation and a liver biopsy if you have not had one in the previous year. You will then will be assigned to receive one of two doses of FIAU; these doses were found to be most effective and yet best tolerated in the original study. Both during and after treatment you will be monitored closely for any side effects or changes in your chronic hepatitis. You will be told about any significant findings from this study (whether positive or negative) regarding the effects of FIAU on chronic hepatitis, and you will be informed if any alternative treatment becomes available during the course of this study.

PATIENT IDENTIFICATION

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

• Adult Patient or • Parent, for Minor Patient

NIH-2514-1 (9-91)

MEDICAL RECORD

CONTINUATION SHEET for either:

NIH 2514-1, Consent to Participate In A Clinical Research Study

NIH 2514-2, Minor Patient's Assent to Participate In A Clinical Research Study

STUDY NUMBER: 93-DK-31 CONTINUATION: page 2 of 6 pagesNATURE OF STUDY

The study will last for one year. It is explained below:

(1) You will be seen in the outpatient clinic of the NIH Clinical Center where we will do a complete medical history and physical examination.

(2) You will have a series of laboratory studies to define your overall medical condition, the degree of liver disease, and level of hepatitis virus infection. These studies will include multiple blood tests and a urine analysis. One blood test that you will have is for antibody to the human immunodeficiency virus (anti-HIV), the cause of acquired immune deficiency syndrome (AIDS). You will be notified promptly of the results of the anti-HIV test. If you are found to have this antibody (anti-HIV), you will be expected to inform your sexual partner(s) that they may have been exposed to HIV. We will help you and your sexual partner(s) obtain information regarding the meaning of the test and ways to prevent spread of the infection. You will be retested for anti-HIV at the end of the study.

(3) If you are a woman, you will have a pregnancy test.

(4) You will have a nerve conduction studies to test your peripheral nerves in your arms and legs. In this test, the physician will hold a electrode probe against your skin that delivers a small electrical pulse of current. You will also have small metal electrodes taped onto the skin on your arms or legs which are attached to a computer which measures the response to the pulse. The pulse will cause a tingling sensation or a muscle twitch, which enables us to measure how well the nerve is working.

(5) If you have not had one within the previous year, you will undergo a liver biopsy. For the biopsy you will be admitted to the NIH Clinical Center for 1 to 2 days. The liver biopsy is to confirm that you have chronic hepatitis and to assess the degree of liver injury caused by the hepatitis. The liver biopsy will be described and you will be asked to sign a separate consent form at the time.

(6) You will also have an abdominal ultrasound (an examination of the liver using sound waves), an electro-cardiogram (heart-tracing) and a chest X-ray. These tests also will only be done if you have not had them during the previous year.

(7) You will then be assigned to receive one of the two doses of FIAU that we are studying. The assignment will be made randomly by computer generated numbers.

(8) You will then begin taking FIAU. FIAU will be provided as a liquid which we will teach you to measure correctly. You will take FIAU three times a day for 6 months (24 weeks).

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NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A.: 06-25-07

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NIH 2514-1. Consent to Participate In A Clinical Research Study  
NIH 2514-2. Minor Patient's Assent to Participate In A Clinical Research Study

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(9) While taking FIAU, you will need to be seen weekly for two weeks and then monthly in the clinic. Blood will be drawn to monitor drug side effects, if any, and the effects of FIAU on the hepatitis.

(10) After you have been on FIAU for approximately three months, you will have the nerve conduction tests done again. This will be done in the clinic and takes about one hour. Also if you have any symptoms of nerve damage during this study, you will have these tests done once more.

(11) After the treatment is stopped, you will be seen in the clinic for brief visits with blood drawing every one to two months until 12 months after starting FIAU. At the 12 month point, you will have a thorough evaluation including a medical history, a physical examination, multiple blood tests and a urine test in the outpatient clinic. At that point, this study will be over, but you will be eligible to enter other studies of therapy for chronic hepatitis B or to be followed without treatment in the clinic.

(12) If you are capable of bearing or fathering children, you will have to practice an effective method of birth control (both men and women) for the 24 weeks of treatment and for two months thereafter. Chromosomal changes have been detected in mice given high doses of FIAU; the effect of this in humans is unknown. Similarly, the risks of FIAU to an unborn fetus or to developing sperm are not known. If you are pregnant, you cannot participate.

#### RISKS AND DISCOMFORTS

(1) The local pain or discomfort of having blood drawn. You may have as many as 20 blood drawings during the 12 months of this study. No more than 14 ounces (approximately 28 tablespoonfuls) of blood will be taken for research purposes during any six-week period. Drawing blood occasionally causes a bruise in the skin where the needlestick occurs. Rarely, fainting occurs after blood drawing.

(2) The pain and risks of liver biopsy. This procedure uses a needle that is passed through the skin into the liver to obtain a piece of liver about two inches long and 1/16 of an inch in diameter. About 20% of persons who undergo a liver biopsy experience pain in the side of body over the liver that usually last from a few minutes to several hours. This rarely requires pain medication and disappears within a day or two. A rare complication of liver biopsy is bleeding severe enough to require a blood transfusion or even surgery to sew up the tiny hole in the liver made by the biopsy, a complication which occurs less than one in 1,000 times. Very rarely, in less than one in 10,000 cases reported worldwide, death has occurred from bleeding after a liver biopsy.

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NIH-2514-2 (10-84)

P.A.: 09-25-0099

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 NIH 2514-1, Consent to Participate In A Clinical Research Study  
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(3) The risks and discomforts of having nerve conduction tests done before treatment and again after three months of treatment. In this test, small amounts of electrical current are given to you as a pulse through an electrode that is held against your skin. The pulse of electricity causes a tingling sensation or a muscle twitch, which may feel uncomfortable. However, this test is entirely safe and without serious side-effects. There is no electrical hazard such as electrocution and the nerves are not damaged by the test. Nerve conduction tests have been done on many patients who are receiving antiviral medications and are usually very easy to tolerate. We will stop the test if you request it, and you can refuse this part of this study and still receive FIAU.

(4) The risks and discomforts of taking FIAU for 24 weeks. FIAU is a new medication, and its side effects have not been completely described. In studies of persons taking FIAU for 4 weeks, it was very well tolerated. Some side effects that have been reported or could occur are:

(a) Fatigue, irritability, trouble sleeping (insomnia). These are mild and disappear when treatment is stopped.

(b) Nausea and upset stomach. These intestinal complaints are not common with the doses of FIAU that we will be using. They are usually mild and disappear quickly when treatment is stopped.

(c) Skin rashes. Rarely patients who take drugs similar to FIAU develop mild, red, itchy rashes that last a few days only.

(d) Bone marrow suppression, or a decrease in the red and white blood cells and platelets in the blood. Drugs similar to FIAU may lower the number of red blood cells, making some patients mildly anemic, or lower the number of white blood cells, which make up your immune system, thereby making you more susceptible to infections. However, you are unlikely to develop a serious infection because we will stop treatment if the white blood cell count falls too low. Drugs like FIAU can also decrease the number of platelets, which are responsible for blood clotting. A low platelet count may make you more prone to bleeding, but this should not cause serious bleeding. The effects of FIAU on the bone marrow will be monitored closely, and the dose will be lowered if the white blood cell or platelet count decrease too much. All of the bone marrow side effects have been mild in the few patients who have been treated with FIAU and they resolved quickly when treatment was stopped.

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NIH-2514-2 (10-84)

P.A. 09-25-0094

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(e) Seizures. Some patients receiving very high doses of drugs similar to FIAU have developed seizures. These patients had AIDS and many serious problems, and the doses used were much higher than you will receive. It is still not clear whether the seizures were due to the treatment or to the underlying AIDS in these very ill patients.

(f) Pains and numbness in the arms and legs can occur with high doses of FIAU. This side effect is also seen with other antiviral medications and may be due to irritation of the nerves or the muscles of the arms and legs. These pains can be severe and last for weeks to months. In some cases, a permanent decrease in nerve function is found. In our studies of FIAU given for 4 weeks, two patients complained of numbness or pains in the legs. However, these symptoms appeared several months after treatment and both patients had other reasons for having a neuropathy, so that we are not sure that these symptoms were due to the FIAU treatment. Because of the potential of this side effect, we are testing low dose of FIAU and are monitoring patients with nerve conduction tests. If you develop leg or arm pains, we will stop the FIAU and treat you with pain medications.

If you develop a severe side effect such as nerve and muscle pains, seizures, large decreases in the blood cell counts, or extreme fatigue, we will stop the FIAU. In addition, if you are a woman and become pregnant, FIAU will be stopped.

### BENEFITS

The benefits of participating in this study are the following:

- (a) You will have a thorough medical evaluation of your condition.
- (b) Your chronic hepatitis B may improve as a result of treatment.

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CONTINUATION SHEET for either:

NIH-2514-1 (10-84)

NIH-2514-2 (10-84)

P.A. 06-25-0099

STUDY NUMBER. 93-DK-13

**OTHER PERTINENT INFORMATION**

1. **Confidentiality.** When results of a study such as this are reported in medical journals or at meetings, the identification of those taking part is withheld. Medical records of National Institutes of Health or Clinical Center patients are maintained according to current legal requirements, and are made available for review, as required by the Food and Drug Administration or other authorized users, only under the guidelines established by the Federal Privacy Act.
2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any physical injury resulting from your participation in research here. Neither the National Institutes of Health, Clinical Center nor the Federal government will provide long-term medical care or financial compensation for such injuries, except as may be provided through whatever remedies are normally available under law.
3. **Payments.** If you are a patient, you are not paid for taking part in National Institute of Health studies. Exceptions for volunteers will be guided by the National Institutes of Health or Clinical Center policies.
4. **Problems or Questions.** Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research, or with regard to any research-related injury, you should contact the principal investigator, Dr. Jay H. Hootnagle or these other staff members also involved in this study: Dr. Michael Fried, Dr. Adrian Di Bisceglie, Dr. Stephen Straus  
 Building 10, Room 9-C-103B, Telephone: (301) 402-3236  
 National Institutes of Health  
 Bethesda, Maryland 20205
5. **Consent Document.** It is suggested that you retain a copy of this document for your later reference and personal records.

**COMPLETE APPROPRIATE ITEM BELOW, A or B:**

**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 & Date Signed

**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) & Date Signed

\_\_\_\_\_  
(If Other Than Parent, Specify Relationship)

\_\_\_\_\_  
Signature of Investigator & Date Signed

\_\_\_\_\_  
Signature of Witness & Date Signed

**PATIENT IDENTIFICATION**

**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)**

• Adult Patient or      • Parent, for Minor Patient

NIH-2514-1 (9-91)

F A 08-25-0088

File in Section 4 Protocol Consent