

SUBJECT CONSENT

I have been asked to participate in a research study entitled "FIALURIDINE (FLAU): Pharmacokinetic/Pharmacodynamic Dosing Regimen Study in Patients With Compensated Chronic Hepatitis B" under the supervision of Dr. David Paar and associates at The University of Texas Medical Branch at Galveston. I understand that The University of Texas Medical Branch is one of two centers in the United States where this study is being conducted.

PURPOSE OF STUDY

My doctor has explained to me that I have chronic hepatitis B. The purpose of this study is to determine whether two different doses of FLAU given at different intervals for 90 days are effective in reducing or eliminating the hepatitis B virus.

Fialuridine (LY303256, FLAU) is a new investigational anti-hepatitis B drug. My part in this study will last 17 to 29 months and will include 14 to 16 visits to my doctor. Approximately 35 other people will also be in this study. I will be followed for two years after I stop taking the medication if I benefit from the study drug or for one year after I stop taking the medication if tests do not show sufficient improvement.

QUALIFICATIONS:

I must have a pregnancy test prior to enrollment if I am a female of childbearing potential. My doctor has told me that I cannot be in this study or I may be discontinued after enrollment if I am or have any of the following:

- Pregnant;
- Breastfeeding an infant;
- Concurrent viral infection(s) (AIDS/HIV, hepatitis C, hepatitis D);
- Low blood count tests;
- Had antiviral, immunologic, or other investigational drug therapy within the last six months;
- Advanced cirrhosis on liver biopsy or significant liver disease other than hepatitis B;
- Any liver function tests that do not meet entry requirements;
- Abnormal kidney function;
- Abused alcohol or drugs within the preceding 6 months;
- Any significant underlying disease which, in the opinion of my doctor, could interfere with his determining the response of therapy;

STUDY PROCEDURE

I understand that while I am in this study I will not be allowed to take any immunologic therapy (e.g., corticosteroids or Imuran® (azathioprine), or other investigational drug therapy or antiviral (e.g., Intron® A (interferon-alpha-2β), acyclovir) not used in the study. Only FLAU, a drug being investigated for treating patients with the hepatitis B virus will be given to me in this study. I will be assigned to one of six drug treatment groups. The medication is a syrup that I will take by mouth as instructed by my physician (at least one hour before eating or at least two hours after

eating) for the 90 days of treatment. My doctor will tell me how much syrup I should take. I will measure each dose amount of syrup with a syringe given to me with the study medication bottle(s).

I understand that my doctor has examined me to determine that my chronic hepatitis is the type that meets the entry requirements to enroll in this study. Approximately one week before I begin treatment, I will have a liver biopsy if I have not had a liver biopsy within the past six months and adequate tissue is available for analysis. I may have to remain at the hospital for approximately one day for this procedure at no cost to myself. Also my blood will be drawn for analysis. One of the blood tests will verify that I am not infected with the human immunodeficiency virus (HIV), which can cause AIDS. My doctor has explained the risks and benefits of the test for AIDS. Other blood tests will verify that I am not infected with the hepatitis C or D virus. Based on the results of my liver biopsy, I will have my study admission visit approximately seven days later. I will not eat after midnight until my admission visit the next morning. At or before the admission visit, chest x-rays, an ECG, my medical history, and current assessment of my symptoms will be obtained. In addition, if I am a female that can have children, I must have a negative pregnancy test (urine test) before I may be enrolled in the study. Prior to receiving my first dose of study drug, my blood will again be drawn for analysis and I will provide a urine specimen. I will receive the first dose of study drug at the doctor's office, and blood will be drawn immediately before the dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 hours after the dose. In addition, I may have additional blood drawn at 12 and 24 hours after the dose depending on the treatment group to which I am assigned. Follow-up evaluations (laboratory and/or clinical) will be performed on Days 7, 14, 21, 28, Month 2, and Month 3. On Days 7, 14, and 21 my blood will be drawn right before my morning dose. I will take this dose at the doctor's office. The night before these visits, I will not eat after midnight until my visit the next morning. In addition, on Day 21, my blood will be drawn at the same times as on Day 1.

The Day 28, Month 2 and Month 3 visits will involve a physical examination, current assessment of my symptoms, blood test and a urine test, until I finish taking my study medication. I will then have a visit to the doctor's office every 3 months. One year after I have completed study drug therapy, I will have a liver biopsy; if my lab tests show that I have not benefited from the study drug, my physician will instruct me on when my next visit will be. Blood draws for each visit will require approximately 2-4 tablespoonfuls (30-60 ml) of blood. All evaluations and laboratory tests for this study will be free of charge.

I understand that during my dosing period, I will bring my study medication bottle(s) with any remaining syrup still in them to the doctor's office and give it to the person designated by the doctor for recording and collecting or reissuing.

If I am a female of childbearing potential, I understand that I should use adequate birth control (such as oral contraceptives, diaphragms with contraceptive jelly, cervical caps with contraceptive jelly, condoms with contraceptive foam, intrauterine devices (IUDs), Norplant®, or abstinence). If I am a male, my partner and I should use similar methods of birth control.

I also understand that my physician, or Eli Lilly and Company may stop my participation in the study at any time without my agreement. The FDA may also stop the study for safety reasons at any time without my agreement. If I stop being in the study, I understand that further treatment of my infection, if needed, will be discussed with me by my physician.

BENEFITS

I understand that because I have chronic hepatitis B, an infection for which the new drug is being considered as therapy, I may benefit medically from being a part of this study; however, I may receive no benefit at all. If I do not receive personal benefit, society as a whole will have benefited from my participation as the questions of whether this is a useful drug will have been answered.

REIMBURSEMENT

I understand that I will receive \$15.00 per clinic visit at the time of the visit while participating in the study up to a maximum of \$300.00 for completion of the study. I understand that medical evaluations, laboratory tests, and study medications required by the study protocol will be provided free of charge.

POTENTIAL RISKS OF STUDY

I understand that there may be risks for me if I agree to be in this study. FIAU is a new investigational drug for chronic hepatitis B. Fifty-four patients with chronic hepatitis B have been treated with this medication for 14 to 28 days. In addition, 100 patients have been treated for up to eight weeks with FLAC, a similar drug that is converted into FIAU in humans. Both drugs appear to have similar side effects. These side effects include anemia (abnormally low number of red blood cells in the bloodstream), changes in laboratory tests that measure liver, kidney, and muscle function, stomach pain, nausea, vomiting, headache, fatigue, and muscle aches. These laboratory changes are expected to improve once the study drug is stopped. Changes in heart, muscle, sperm, and fetuses have been found in laboratory test animals given extremely high doses of FIAU and FLAC. Additionally, chromosomal changes have been detected in mice given high doses of FIAU. The effect of this in humans is unknown.

The major effects of liver biopsy are pain, fainting, bacteria in the blood, puncture of an internal organ (other than the liver), and bleeding. Local pain and discomfort at the liver biopsy site occurs in 1 out of 5 patients, is usually mild, and lasts 1 to 12 hours. Fainting and bacteria in the blood occur in 2% or less of the patients biopsied. Puncture of an internal organ other than the liver and internal bleeding are very rare.

In addition, I understand that blood samples will be obtained for laboratory measurement during the study. I will experience some minor discomfort when blood is being drawn from my vein. Bleeding, bruising, or infection may also occur at the needle site where blood samples are obtained. The amount of total blood withdrawn will be approximately 600 ml, or 20 ounces over the 2-year and 3-month period.

Drugs and procedures in this study may involve risks to me or an unborn child that are not yet known. I understand that I am to tell Dr. Paar at (409) 772-2222 immediately if I have any unusual health experience, injury, or bad effect.

The study medication must be taken only by me, and it should be kept out of the reach of children and other adults.

COMPENSATION FOR INJURY

I understand that if I am physically injured because of any substance given to me or procedure properly performed on me under the plan for this study, Eli Lilly and Company will reimburse me for the reasonable medical expenses for the treatment of that injury which are not covered by my own insurance or health care program. No other compensation is available from Eli Lilly and Company if any injury occurs. I understand, however, that I am not waiving any of my legal rights by participating in this study.

ALTERNATIVE THERAPIES

As an alternative to participation in this study, I understand that interferon is approved by the FDA for the treatment of chronic HBV infection. I understand that I could choose this drug rather than participate in this research study.

STATEMENTS

1. I understand that informed consent is required of all persons in this project.
2. The principal and alternative procedures, including the experimental procedures in this project, have been identified and explained to me in language that I can understand.
3. The risks and discomforts from the procedures have been explained to me.
4. The expected benefits from the procedures have been explained to me.
5. An offer has been made to answer any questions that I may have about these procedures. If I have any questions before, during or after this study, I may contact Dr. David Paar at (409) 772-2222.
6. I have been told that I may stop my participation in this project at any time without prejudice or jeopardizing my medical care at UTMB. All new findings developed during the course of this research which may influence my desire to continue to participate in this study will be provided to me as such information becomes available.
7. I have been told that The University of Texas Medical Branch at Galveston, like virtually all other universities in the United States, does not have a mechanism for compensation of the injured research subject. Therefore, I understand that I cannot look to any such mechanism to receive financial remuneration for any such injuries resulting from my participation in this project. If physical injury occurs as a direct result of this research, emergency treatment, which is available to the general public, will be available to me. Neither UTMB nor Dr. David Paar can assume financial responsibility or liability for the expense of such treatment.
8. If I have any questions regarding my rights as a patient participating in this study or research-related injury, I may contact Dr. E. Ray Stinson, Director of the Office of Sponsored Programs-Academic at (409) 772-3482.

9. I have a right to privacy, and all information that is obtained in connection with this study and that can be identified with me will remain confidential as far as possible within state and federal law. Information gained from this study that can be identified with me will be released to no one other than the investigators, my physician, Eli Lilly and Company (the sponsor), and the United States Food and Drug Administration, which through its regulatory powers, may inspect records involving research participants. The results of this study may be published in scientific journals without identifying me by name.

I voluntarily agree to participate as a subject in the above named project. I understand that by signing this document I am not waiving any of my legal rights. I have read or had read to me all pages of this consent form. The study and this consent form have been explained to me. My doctor has answered all of my questions to my satisfaction. I believe that I understand what will happen if I agree to be part of this study. I understand that the original copy of the document will be retained by Dr. Paar with the study records and that I will receive a signed copy of this form. A copy of the signed consent form will be sent to the sponsor.

March 15, 1993
Date

Signature of Subject

Subject Name (Printed)

I have witnessed the signing of this consent by the subject or patients or his or her parent or guardian whose signature appears hereon. I have been assured by that person that the signing of this consent has been done freely and voluntarily.

3-15-93
Date

David W. BSCN
Signature of Witness

Using language that is understandable and appropriate, I have discussed this project and the items listed above with the subject and/or his/her authorized representatives. I have offered to answer any questions and have fully answered such questions. I believe that the patient, subject, or legal representative fully understands my explanation and has freely given informed consent.

3/15/93
Date

David Paar, M.D.
Signature of Project Director or
his/her Representative

FS402-ann
2-8-93

Protocol: H3X-MC-PPPA
Investigator: David Paar, M.D.
Patient Number: 9082/21