

NEW ENGLAND MEDICAL CENTER HOSPITAL  
DEPARTMENT OF MEDICINE, DIVISION OF GASTROENTEROLOGY

**FIALURIDINE (FIAU): PHARMACOKINETIC/PHARMACODYNAMIC DOSING REGIMEN  
STUDY IN PATIENTS WITH COMPENSATED CHRONIC HEPATITIS B  
PROTOCOL HBX-MC-PPPA**

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PURPOSE OF STUDY:

You are invited to participate in a research study of a new investigational anti-hepatitis B drug, fialuridine (LY303256, FIAU). This drug has been used to treat chronic hepatitis B in 54 patients, for up to 28 days and has been well tolerated. However, it has had limited use in humans, and limited use for prolonged periods of time. Your part in this study will last 17 to 29 months and will include 14 to 16 visits to the doctor. Approximately 35 other people will also be in this study at this site and one other.

Your doctor has explained to you that you have chronic hepatitis B. The purpose of this study is to determine whether two different doses of FIAU given at different intervals for 90 days are effective in reducing or eliminating the hepatitis B virus. You will be followed for two years after you stop taking the medication if you benefit from the study drug or for 1 year after you stop taking the medication if tests do not show sufficient improvement.

FIAU is an oral (syrup) medication which is an antiviral medication acting to interrupt the virus's ability to reproduce itself. During this study you will not be allowed to take any immunologic therapy (e.g. corticosteroids or Imuran<sup>®</sup> (azathioprine)), other investigational drug therapy or antiviral (e.g. Intron<sup>®</sup> A (interferon alfa-2b), acyclovir) not used in the study. Only FIAU, a drug being investigated for treating patients with hepatitis B virus will be given to you in this study.

Two different total daily doses of FIAU will be studied. (1) 0.1mg/Kg body weight daily and 2) 0.25 mg/Kg body weight daily. In each of these two dose groups, there will be 3 subgroups - A) Patients who take all the daily dose ONCE A DAY; B) Patients who divide the total daily dose, taking it TWICE A DAY, and C) Patients who divide the total daily dose, taking it THREE TIMES A DAY. Thus there are 6 possible dose/time schedules. You will be assigned randomly (that is by chance) to one of these 6 treatment groups. You will be instructed in how and when to take your specific dose. It should be taken on an empty stomach, at least one hour before eating, or at least 2 hours after eating.

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Valid through 1/19/94

VIAD/HEPATITIS B  
Marshall M. Kaplan, MD

PROCEDURES TO BE FOLLOWED

You have previously been evaluated, and the results of your examination and laboratory values indicate that you have chronic hepatitis B, and you do meet all the entry requirements required to enroll in this study.

Approximately one week before beginning treatment, you will have a liver biopsy if you have not had a liver biopsy, that we can use, within the past year. A liver biopsy means that the skin on your right side will be numbed and a needle will be inserted to remove a small piece of liver tissue. You will be instructed in breathing techniques to make the procedure easier and safer. After the biopsy you will lie on your right side for several hours. You will have to remain at the hospital for approximately one day for this procedure. Also your blood will be drawn for analysis. One of the blood tests will verify that you are not infected with the human immunodeficiency virus (HIV), which can cause AIDS. A separate consent form will be signed permitting us to test you for HIV. Your doctor has explained the risks and benefits of the test for AIDS. Other blood tests will verify that you are not infected with hepatitis C or D virus. Based on the results of your liver biopsy, you will be enrolled in the study at a visit approximately seven days later. You will not eat after dinner on the day before your admission visit and will not have breakfast until after you are seen the next morning. At the admission visit, chest x-rays, a EKG, your medical history, and current assessment of your symptoms will be obtained. In addition, if you are a female capable of having children, you must have a negative pregnancy test (urine test) before you may be enrolled in the study. Prior to receiving your first dose of study drug, your blood will be drawn for analysis and you will provide a urine specimen. You will receive the first dose of study drug at the hospital 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, you may have additional blood drawn at 12 and 24 hours after the dose depending on the treatment group to which you are assigned. Follow-up evaluations (laboratory and/or clinical) will occur on Day 7, 14 and 21 of your treatment period. On Day 7 and Day 14, your blood will be drawn right before your morning dose. The night before these visits, you will not eat after dinner until your visit the next morning.

At your Day 21 visit, you will take your morning dose of study drug at the hospital and your blood will be drawn immediately before the dose and after the dose at the same intervals as your first visit. After you have taken one month of study drug therapy, you will begin monthly visits to the hospital. You will continue the monthly visits, which will involve a physical examination, current assessment of your symptoms, blood tests and a urine test, until you finish taking your study medication. You will then have a visit to the hospital every 3 months.

One year after you have completed study drug therapy, you will have a liver biopsy, if your lab tests show that you have benefitted from the drug and you will continue to see the physician every six months for a more year. If your lab tests show that you have not benefitted from the study drug, your physician will instruct you on when your next visit will be. Blood draws for each visit will require approximately 2-4 tablespoonsful (30-60 ml) of blood. All evaluations and laboratory tests for this study will be free of charge.

**PIAU/HEPATITIS B**  
 Marshall M. Kaplan, MD

During your dosing period, the first 3 months in the study, you will bring your study medication bottle(s) with any remaining syrup still in them to the hospital and give it to the person designated by the doctor for recording and collecting or reissuing drug. You will be given a flow sheet of your specific appointments, dates and instructions.

**RISKS AND POSSIBLE SIDE EFFECTS**

There may be risks for you if you agree to be in this study. PIAU is a new investigational drug taken for 14 to 28 days by 54 patients with chronic hepatitis B. An additional 100 patients have been treated for up to 8 weeks with a similar drug, PIAC that is turned into PIAU in humans. Both drugs appear to have similar side effects. These side effects are primarily nausea and fatigue but may include stomach pain, vomiting, headache, and muscle aches. Changes in laboratory tests that measure liver, kidney, and muscle function, and anemia have also occurred. These laboratory changes are expected to improve, once the study drug is stopped. In laboratory test animals given extremely high doses (much higher than in this study), changes in heart muscle with nonreversible toxicity, skeletal muscle, the formation and production of sperm, fetal development and kidney toxicity have been found. Additionally, chromosomal changes have been detected in mice given high doses of PIAU. The effect of this in humans is unknown. Because this drug may penetrate the skin and become incorporated into your genetic material, you should use caution in handling the medication and wash thoroughly with soap and water should it come in contact with your skin.

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 3 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 and bleeding are very rare.

In the event that your blood tests suggest damage to muscle, you may be asked to have a thigh muscle biopsy. This will be done under local anesthesia at no expense to you. This procedure may cause temporary discomfort at the biopsy site.

Some minor discomfort is caused when blood is drawn from my veins. Bleeding, bruising or infection may also occur at the site where blood samples are obtained.

In addition to these effects, other unpredictable bad effects due to the study drug or test procedures may occur.

If you should have an adverse effect any time during the study, you should tell your doctor immediately. Any new significant information developed during the course of this research which may change your wish to continue in this study will be provided to you and to the doctor.

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 Valid through 1/19/94

**YIAU/HEPATITIS B**  
Marshall M. Kaplan, MD

**FOR MEN AND WOMEN OF CHILDBEARING POTENTIAL:**

The medication used in this research study may involve risks to you or to an embryo or fetus if you are pregnant at any time during the study. If you are pregnant or should you intend to become pregnant, you should not be enrolled in this study. Males should also not father a child while in this study. If you choose to participate, you must use adequate birth control to prevent pregnancy during this study, while you are on study medication and for 3 months after the study medication has stopped (up to a total of 6 months). Adequate methods of contraception include birth control pills, diaphragms, or cervical caps, used with contraceptive jelly, condoms with contraceptive foam, IUD's (intrauterine devices), Norplant<sup>®</sup>, or abstinence. Should you become pregnant at any time during this time frame, you must immediately notify your physician, and your participation in the study will be terminated. A pregnancy test will be performed prior to your enrollment in the study.

**BENEFITS**

It is not known whether you will benefit from this study or not. Because you have chronic hepatitis B, an infection for which the new drug is being considered as therapy, you may medically benefit by the partial or complete healing of your infection. The study may also be of benefit to other patients with this type of infection in the future.

**OTHER TREATMENT**

As an alternative to participation in this study, you may be treated with interferon. You understand that you could choose this drug rather than participate in this research study. Therapy for chronic hepatitis B is limited. Only interferon-alpha-2B (Intron-A) is approved in the United States for the treatment of hepatitis B. You understand that you could choose this therapy rather than participate in this research study.

**COSTS**

While you are enrolled in the study, during the medication phase (90 days) and the follow up period (up to 2 years after medication) and during the one week pretreatment phase, all laboratory tests, hospital, outpatient clinic and physician charges will be provided to you at no cost. In addition all study medication will be provided to you at no cost to you or your insurance carrier.

**PHONE NUMBERS**

If you have any questions or problems during this study, you may call Dr. Marshall Kaplan at (617)-956-3877. Either he or an associate will be available to answer your questions. You may contact the GI Office of Clinical Trials at (617)-956-4332, either study nurse may also be of assistance. In the event of an emergency, call (617)-956-5114 and ask for the "GI Physician on Call" and explain to the physician that you are a part of this study.

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YIAU/HEPATITIS B  
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PARTICIPANT'S STATEMENT

I have read this consent form and have discussed with Dr. Marshall Kaplan or his representative the procedures described above. I have been given the opportunity to ask questions, which have been answered to my satisfaction. I understand that any questions that I might have will be answered verbally or, if I prefer, with a written statement.

I understand that I will be informed of any new findings developed during the course of this research study.

I understand that my participation is voluntary. I understand that I may refuse to participate in this study. I also understand that if, for any reason, I wish to discontinue my participation in this study at any time, I will be free to do so, and this will have no effect on my future care or treatment by my physicians or this hospital.

I understand that in the event I become ill or am injured as a result of my participation in this study, medical care will be provided to me. If I follow the directions of the doctors in charge of this study and I become ill or am injured because of the study drug or because of a properly performed study procedure, Eli Lilly and Company, the sponsor, will pay the medical expenses for the treatment of the injury or illness which are not covered by my medical insurance. I understand that no other compensation for such injury or illness other than for medical treatment will be provided.

If I have any questions concerning my rights as a research subject in this study, I may contact the Human Investigation Review Committee at (617)-956-7512.

I have been fully informed of the above-described study with its risks and benefits, and I hereby consent to the procedures set forth above. A copy of my signed consent will be reviewed by a representative of Eli Lilly and Company and I will receive a copy.

I understand that as a participant in this study my identity and my medical records and data relating to this research study will be kept confidential, except as required by law, and except for inspections by the U.S. Food and Drug Administration which regulates investigational drug studies, and the study sponsor.