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INSTITUTIONAL REVIEW BOARD
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Daniel J Rader
Dm-exp Th Adm
654 Brb ii/iii/6160/Med

Thursday, March 20, 2003

PRINCIPAL INVESTIGATOR	:	Daniel J Rader
TITLE	:	A Phase II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients with Homozgyous Familial Hypercholesterolemia (Protocol # UP 1001, dated 3/5/03)
SPONSORING AGENCY	:	Doris Duke Charitable Foundation
PROTOCOL #	:	707255

Dear Dr. Rader,

Noted below are documents, for the above-referenced protocol, that were reviewed by Nicholas A. Kefalides, M.D., Ph.D., Executive Chairman of the IRB, utilizing an expedited mechanism, and approved on 3/18/2003.

· A revised protocol, dated 3/5/03, changing the title to reflect a Phase II study only
· A corresponding revised consent form, version date 3/5/03

Thank you for your cooperation with the Office of Regulatory Affairs.

Sincerely,

for Joseph R. Sherwin, Ph.D.
Director of Regulatory Affairs

University of Pennsylvania

IRB APPROVAL DATE: 3-18-03
EXPIRATION DATE: 8-11-03

Principal Investigator:
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Center for Experimental Therapeutics
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(Ask for the Medical Resident on Call)

CONSENT TO PARTICIPATE AS A SUBJECT IN AN INVESTIGATIONAL STUDY

TITLE: A Phase II Open-Label, Dose-Escalation Study to Determine the Safety, Tolerability and Efficacy of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor BMS-201038 in Patients with Homozygous Familial Hypercholesterolemia
(Protocol # UP 1001)

Introduction

You are invited to participate in a research study that will last approximately 22 weeks. Before you give your consent to volunteer, please read the following information and ask as many questions as necessary to be sure that you understand what your participation would involve. Approximately 8 subjects will be participating in this study. This study is only being conducted at The University of Pennsylvania.

Purpose

The purpose of this study is to study the safety and effectiveness of a new cholesterol lowering medication called BMS-201038. We want to examine how BMS-201038, is handled by the body and its effects on lowering low density lipoprotein (LDL) cholesterol (known as "the bad cholesterol") in males and females with homozygous familial hypercholesterolemia (hoFH). HoFH is a condition that results in very high levels of LDL cholesterol, increasing risk of heart disease. BMS-201038 has been shown to lower LDL cholesterol by as much as 80% in healthy people with high cholesterol. This medication is an "investigational" drug, which means that the drug has not been approved by the U.S. Food and Drug Administration (FDA) or any other regulatory agency in the world. This drug has not been approved as a prescription or over-the-counter medication because it is still being studied for the treatment of high cholesterol. You are being asked to participate in this study because you have homozygous familial hypercholesterolemia. If you decide to participate, you will receive BMS-201038 in different doses over a period as long as 16 weeks.

Procedures

Your participation in this research study will last approximately 22 weeks and you will need to visit the General Clinical Research Center (GCRC) at the Hospital of the University of Pennsylvania approximately 15 times during the study.

Screening (Visit 1) The purpose of this visit is to explain the study to you and see if you meet the requirements to be in the study. Research staff will measure your blood pressure, heart rate, height, weight and waist circumference. A physician or Nurse Practitioner will ask you questions about your past medical history and current medications. This individual will also perform a physical exam. In

addition, an electrocardiogram (also known as an EKG) will be performed, which provides a tracing of your heart's activity. You will have a small amount of blood drawn (about 2 tablespoons) for safety and lipid (cholesterol and triglycerides) labs after a 12- hour fast (nothing to eat or drink except water 12 hours before your scheduled appointment). You will also be asked to provide a small urine sample for a simple urinalysis. If you are a female who is capable of becoming pregnant, a standard pregnancy test will also be performed on this urine sample.

You will meet with the dietitian at the GCRC to discuss the diet that must be followed starting the day of your screening visit until the end of the study. It is important for study volunteers to follow this diet. The medication works to lower cholesterol by stopping the action of a protein that is involved with absorbing fat from food and packaging cholesterol in the blood. Since this medication is expected to stop the action of this protein, fat that you eat would not be allowed to be absorbed and would cause extreme diarrhea. If you remove most of the fat from your diet, you should not have diarrhea. Therefore, the dietitian will instruct you on how to remove fat (except a small amount) from your diet. She will instruct you on how to provide a small amount so that you get enough fatty acids that are needed for normal processes in the body. The dietitian will design the diet so that you maintain your weight and get all of your nutrients. Because fat-soluble vitamins (vitamins A, D, E and K, nutrients needed to perform normal functions in the body), from food need fat to be absorbed, you will need to take a multivitamin every day. Research personnel will provide you with multi-vitamins starting at the screening visit. You will receive multi-vitamins at specific visits throughout the study. The dietitian will also instruct you on how to keep dietary records that describe food and beverages you consume on a particular day. You will be asked to do this periodically throughout the study.

Once all clinical data has been reviewed, research staff will contact you and let you know if you qualify for the study.

Baseline (Visit 2) If you qualify for the study, you will be asked to return to the GCRC in approximately 2 weeks after the screening visit for the baseline visit. The baseline visit will last approximately 1 hour. Research staff will ask you if your medications or medical history have changed since the screening visit. You will have an electrocardiogram performed to trace your heart's activity. You will have blood drawn (a little less than 2 ½ tablespoons) after a 12 hour fast (nothing to eat or drink except water) for safety and lipid (cholesterol and triglyceride) labs and labs relating to the use of the medication. The study physician or Nurse Practitioner will perform a brief physical exam. You will be asked to provide a urine sample for routine safety labs and a standard pregnancy test (females capable of becoming pregnant only). Research staff will measure your blood pressure, heart rate, and weight. You will be asked if you are having any problems with your diet. At this visit, you will be given BMS-201038 in the amount of 0.03 mg per kilogram of body weight per day for 4 weeks. You will need to take the medicine once a day with water in the morning. Please bring the study medication bottle(s) containing any remaining pills with you to every future visit.

Follow-up Visits 3, 4, 6, 7, 9, 10, 12, 13 You will be asked to come back to the GCRC on the following days (+/- 3 days) from the baseline visit (when you first started taking the study medication): 7, 14, 35, 42, 63, 70, 91, and 98. You will have a brief physical exam performed by either the study physician or Nurse Practitioner. At these visits, research personnel will measure your heart rate, sitting blood pressure, and weight. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs and a standard pregnancy test (females capable of becoming pregnant only). Research personnel will collect your bottle of study medication and provide you with additional study medication.

Follow-up Visits 5, 8, 11, 14

You will be asked to come back to the GCRC on the following days (+/- 3 days) from the baseline visit (when you first started taking the study medication): 28, 56, 84, and 112. You will have a brief physical exam (a full physical exam will be performed at visit 14 only) performed by either the study physician or Nurse Practitioner. At these visits, research personnel will measure your heart rate, sitting blood pressure, and weight. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. In addition, research staff will ask you about potential problems with following the research diet. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs and a standard pregnancy test (females capable of becoming pregnant only). You will have an electrocardiogram performed to trace your heart's activity. Research personnel will collect your bottle of study medication and provide you with additional study medication. At visits 5, 8, and 11, you will increase the dosage of study medication. At visit 5, you will take 0.1 mg study medication per kilogram of body weight per day for 4 weeks. At visit 8, you will increase dosage to 0.3 mg study medication per kilogram of body weight for another 4 weeks and at visit 11, you will increase the dosage to 1.0 mg per kilogram of body weight per day for the final 4 weeks. If you experience any side effects with the medication, the study physician will talk to you about whether to decrease the dosage or discontinue the medication.

Final Visit (Visit 15)

You will come back to the GCRC 4 weeks after visit 14 for the last visit. At this visit, you will have a brief physical exam. Research personnel will measure heart rate, sitting blood pressure and weight. You will have an electrocardiogram performed to trace the activity of your heart. Research personnel will ask you if you have experienced any unusual symptoms since we last saw you or added, removed or changed any medications. You will have blood drawn after a 12 hour fast (nothing to eat or drink except water) for safety labs and labs related to lipids. You will be asked to provide a urine sample for routine safety labs. Research personnel will collect your bottle of study medication.

The total amount of blood you will have drawn during the entire 22 weeks is approximately 360 ml (1 ½ cups), which is less than the standard Red Cross blood donation (2 pints, which is equal to 2 cups).

Risks

There are some potential risks and discomforts that you may reasonably expect as part of the study. BMS-201038 was studied in healthy volunteers with high cholesterol and caused an increase in liver function tests in some subjects. Some subjects were also found to have some fat built up in their liver, which at very high levels, can cause liver failure (liver does not work properly). Symptoms of liver failure may include: confusion, jaundice (yellow-colored skin and eyes), itchiness, and/or bleeding internally which can cause death. Both liver function tests and levels of fat in the liver found in the study using the medication BMS-201038 were not at a dangerous level. There were no deaths or serious side effects that occurred in the study. Some subjects taking this medication also reported stomach pain, diarrhea, nausea, and fatigue (being tired). It is believed these results occurred because the amount of fat in the diet was not restricted. We believe that by following the low fat diet described in this consent form, there should not be significant symptoms of those described above.

As with any blood test, there may be some minor discomfort, minor bruising, and/or fainting associated with the drawing of blood. There is also a very small chance (less than 1%) of infection at the needle puncture site.

Risks Associated with Pregnancy and Breastfeeding
The medication you will be receiving in this study, BMS-201038, has not been tested in pregnant women, or women who are breastfeeding. Therefore, taking this medication could cause harm to unborn children, children who are breast feeding, or to the health of the female who is pregnant or breastfeeding. For this reason, if you are currently breastfeeding, pregnant, or thinking of becoming pregnant, you should NOT participate in this study. If you are capable of becoming pregnant, you will have a urine pregnancy test at every visit while you are taking the study medication.

Costs and Financial Risks
There will be no cost to you for any visits or procedures required by this study.

Benefits
No direct medical benefit is assured from your participation in this study. If this study shows a positive effect in lowering cholesterol with BMS-201038, volunteers may benefit. While there may be no therapeutic benefit to you in this study, your participation will provide new information about the use of BMS-201038 in patients with homozygous familial hypercholesterolemia.

Alternatives
The alternative to this study is not to participate. There are treatments (LDL apheresis) and medications that are used to lower cholesterol in patients with hoFH that are available through your physician.

Compensation
We will compensate you for reasonable travel and lodging expenses that you need to spend in order to take part in this study. In order to compensate you for your time and effort, you will receive $25 for completing visit 1 and $50 each for completing all remaining visits. Therefore, if you attend and complete all 15 visits, you will be paid $725.

Confidentiality
Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential, except as may be required by court order or by law. Authorized representatives of the University of Pennsylvania, as well as the Food and Drug Administration (FDA), may have access to and may copy, both your medical records and records from your participation in this study. This access is necessary to insure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this research, you will not be identified by name.

Significant New Findings
You will be told of any significant new knowledge that is obtained during the course of this research, which may affect your health and/or relate to your willingness to continue participation. To find out more about any aspect of this study, you may contact the persons whose name, address and telephone number appears below.

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