Protocol Title: A pilot study of moderate hyperbilirubinemia in type 1 diabetes mellitus

Principal Investigator: Josh Beckman, MD

Site Principal Investigator:

Description of Subject Population: Type 1 diabetes

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Why is this research study being done?

This research study is being done to identify a new way to protect people with type 1 diabetes from cardiovascular disease (heart and blood vessel disease). People with diabetes have high blood sugar, which harms the blood vessels. Preventing vascular (blood vessel) disease in people with type 1 diabetes is focused using insulin to keep blood sugar levels. However, people with diabetes still have a high risk of cardiovascular disease even when using insulin therapy. New means of preventing vascular disease in patients with type 1 diabetes are therefore needed.

In this study, we will give you atazanavir. Atazanavir is an FDA-approved medication used to treat patients with HIV infection, but atazanavir is <u>not</u> approved by the FDA to treat diabetes or cardiovascular disease. This research study is not about HIV, and taking atazanavir will not

affect your risk of HIV infection. We are using atazanavir because it causes bilirubin levels in your bloodstream to increase. Bilirubin is a normal product made when red blood cells break down. We are studying bilirubin because increasing bilirubin levels may be a new way to prevent vascular disease in people who have type 1 diabetes.

This is a pilot study. Pilot studies are done on a small group of subjects to learn if a larger study would be useful.

We are asking you to take part of this study because you have type 1 diabetes mellitus and are at risk of cardiovascular disease.

We plan to enroll 40 subjects in this study. Brigham and Women's Hospital is the only site for this study.

The National Institutes of Health National Institute of Diabetes, Digestive, and Kidney Disease is paying for this study to be done.

How long will I take part in this research study?

It will take you approximately 9 days to complete this study. We will ask you to make 3 study visits during this time.

What will happen in this research study?

Visit 1: Screening (1 hour)

This visit will take about 1 hour. You will read the consent form and ask any questions you would like. If you agree to participate you will sign the consent form, as will a physician from the study.

At this visit, we will:

- Ask about your medical history.
- Give you a physical exam, including height, weight, and blood pressure.A chance of pregnancy, you must use a form of birth control approved by the study doctor while you are taking part in the study. Approved forms of birth control include:
    - hormonal methods, such as birth control pills, patches, injections, the vaginal ring, or implants
    - barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)

- intrauterine device (IUD)
- abstinence (no sex)

If you are already using birth control, you must check with the study doctor or study staff to make sure it is okay to use during this study. The study drug may reduce the effectiveness of hormonal birth control and you may need to use another method. You need to start using birth control, or stay abstinent from sex, from the time you have your last period before your start taking the study drug until after the study is over to make sure you do not get pregnant while you are taking the study drug.

If you are taking proton pump inhibitors (PPIs) you will be asked to discontinue these 24 hours before beginning study drug. PPIs are drugs that help reduce gastric acid production (fluids that help digest food in the stomach). Examples of PPIs are: Losec, Prilosec, Prevacid, Inhibitol, Nexium, Kapidex, Protonix, Rabecid and AcipHex. If you cannot discontinue the PPI, you will not be able to participate in this study.

If you get pregnant during the study, you should notify the study doctor right away.

If you qualify for the study and would like to go forward, we will schedule you for Visit 2.

Visit 2: Day 1 (1 hour)

You must fast (have nothing to eat or drink) for at least 8 hours before this visit.

At this visit we will:

- Perform an ultrasound (pictures obtained by sound waves) to see how the brachial artery (the artery in your arm near the elbow) responds to certain tests. During the testing, we will ask you to lie quietly on your back on a portable bed, and the lights in the room will be dimmed. We will put a blood pressure cuff on the upper part of your arm. We will put a cool gel on your arm. An ultrasound probe that looks like a microphone will be used to scan back and forth over the arteries. Computer pictures of your arteries will be taken before and after inflating the blood pressure cuff for 5 minutes. We will measure the response of your artery to this temporary "blockage" (caused by inflation of the blood pressure cuff) of blood flow. Next, we will give you a small tablet of nitroglycerin, a medicine that causes blood vessels to dilate (expand). The tablet is placed under your tongue. We will take ultrasound pictures of your arteries again to see the effect of the nitroglycerin. This testing gives us information to compare with the same testing that we will do at the end of the study. It takes about 1 hour.

- Draw a blood sample to check things such as your liver function, sugar level, and the level of atazanavir in your blood. We will take an additional blood sample so we can analyze it in the future.

Taking the Study Drug
We will give you a supply of study drug to take home with you.

You will take the study drug atazanavir by mouth twice a day for the entire study (4 days). The study drug should be taken with food. It is important for you to follow our instructions about how to take the study drug. Bring any unused study drug with you to your final study visit (Visit 3).

If you are having side effects from taking the study drug, the study doctor may tell you to stop taking the study drug right away. The study doctor might take you out of the study if you have side effects. The study drug may raise your blood sugar. High blood sugar may make you feel drowsy, thirsty, or confused. It can also make you beathe faster or flush (red in the face or on other areas of your skin). We ask that you closely monitor your blood sugar and if you feel any of the symptoms listed above, please contact the study doctor right away.

Your Study Drug Diary

We will give you a study diary to fill out at home each day. You will write down the time you take the study drug, how much study drug you take, and whether you have any side effects. Bring this diary with you to each study visit, so we can track your progress.

Visit 3: Day 4 (1 hour)

You must be fasting for at least 8 hours before this visit.

At this visit we will:

- Perform an ultrasound to see how the brachial artery responds to certain tests. During the testing, we will ask you to lie quietly on your back on a portable bed, and the lights in the room will be dimmed. We will put a blood pressure cuff on the upper part of your arm. We will put a cool gel on your arm. An ultrasound probe that looks like a microphone will be used to scan back and forth over the arteries. Computer pictures of your arteries will be taken before and after inflating the blood pressure cuff for 5 minutes. We will measure the response of your artery to this temporary "blockage" of blood flow. Next, we will give you a small dose of nitroglycerin, a medicine that causes blood vessels to dilate. The tablet is placed under your tongue. We will take ultrasound

pictures of your arteries again to see the effect of the nitroglycerin. This testing gives us information to compare the testing from the beginning of the study. It takes about 1 hour.

- Draw a blood sample to check things such as your liver function, your sugar level, and the level of atazanavir in your blood. We will also take an additional blood sample so we can analyze it in the future.
- Ask you about side effects or health problems since your last visit
- Collect any unused study drug.

Storage Of Blood Samples

A portion of your blood sample drawn at each visit will be frozen and stored. The stored blood will be used to study chemicals in your blood that may give us information about how severe your diabetes is at the end of the study. These stored blood samples may also be used to understand factors that may affect blood vessel function.

We will label all your samples with a coded study number instead of your name. The key to the code connects your name to your health information and samples. The study doctor will keep the key to the code in a password protected computer or locked file. Only the study doctor and our research team will have access to your stored samples.

If at any time you choose to stop taking part in the study and want to have your samples destroyed, contact the study doctor.

Stopping the Study Early

If you decide to stop taking part in the study for any reason, we will ask you to make a final study visit. You will need to return all unused study drug and your study diary at this visit. The final study visit will take about 30 minutes. At this visit, we will:

- Give you a physical exam
- Ask about any side effects or health problems since your last visit
- Draw a blood sample
- Collect any unused study drug
- Collect your Drug Diary

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug because you are having more than mild side effects
- Your blood sugar levels are not adequately controlled while taking the study drug

- You can't make the required study visits
- The sponsor decides to stop the study
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

What are the risks and possible discomforts from being in this research study?

Risks of taking atazanavir:

Common

- diarrhea within 2-3 days of starting study drug
- nausea within 2-3 days of starting study drug

Uncommon

- headache
- reversible jaundice (yellowing of the skin)

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor immediately. If you are having trouble breathing, call 911 immediately.

Risks of Blood draw:

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Risks of Ultrasound and Nitroglycerin:

During the ultrasound test, we will inflate a blood pressure cuff on your upper arm to a high pressure for 5 minutes. This may cause discomfort or aching, but it is not risky. The ultrasound test does not involve needles, and testing is done on the surface of the skin only.

We will give you a small dose of nitroglycerin to take during the ultrasound testing. Nitroglycerin may cause a temporary headache. Less than 1 in 100 people may develop low blood pressure, or have a fall in heart rate with low blood pressure and dizziness or fainting. Blood pressure and heart rate are checked many times throughout the study, and a doctor will be

present at all times. If the top number of your blood pressure at rest is lower than 100 mm Hg, we will not give you nitroglycerin.

Other risks:

Taking atazanavir may make your diabetes worse. We think this risk is very small because you will only be taking the study drug for a short time. You will need to closely monitor you blood sugar levels while on the study drug. If your blood sugar levels are not well controlled, you should stop the study drug immediately.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of atazanavir on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a period for the past 12 months or more, you will not need to have a pregnancy test. Also, you will not need to have a pregnancy test if you have had a hysterectomy (surgical removal of your uterus and/or ovaries). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are a female who is sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control for the entire study**.**

Acceptable birth control methods for use in this study are:

- hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Risks of Taking Atazanavir with Other Medications:

Atazanavir is not safe if it is taken with some other medications, including some antibiotics, anti-anxiety medications, cancer medications, and drugs such as: UroXatral, Rifadin, irinotecan (cancer drug), Halcion, Versed, ergot derivatives (migraine medication), Propulsid, St. John's Wort, Altocor, Zocor, Orap, Viagra, and Crixivan. For your own safety, tell the study doctor if you are taking any other drugs before the study starts.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Risks of HIV Testing

As part of this research study, we will test your blood for HIV (the virus that causes AIDS). For most studies, this means that results will become part of your hospital medical record. If these tests show that you have HIV, you cannot be in the study. We will refer you for medical care if we find out you have this infection. By law, healthcare providers must report positive test results for infectious diseases to public health authorities, including the Massachusetts Department of Public Health. These reports are required to identify you by name.

What are the possible benefits from being in this research study?

There are no direct benefits to you from being in this study.

If this study is successful, it may identify a new way of protecting people with diabetes from heart attack and stroke.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

It is possible that we will have to ask you to drop out before you finish the study. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

We will pay you for the time and effort required to be in this study.

We will pay you $200.00 for completing the study. You will be paid at the end of the study. You will receive payment for completing the study within 6 weeks of your final visit.

We will pay for your parking in the hospital garage during study visits. We will pay for the cost of your transportation up to $10 per visit.

What will I have to pay for if I take part in this research study?

Study funds will cover the costs of the study drugs and tests.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Josh Beckman, M.D., is the person in charge of this research study. You can call him at (617) 732-5500. Dr. Beckman is available M-F 9-5. He is also available 24/7 for emergencies. You can also call Reena L. Pande, M.D., at (617) 732-5500 available M-F 9-5 or 24/7 (for emergencies only) with questions about this research study.

If you have questions about the scheduling of appointments or study visits, call our research assistants at 617-732-6320.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 617-424-4100.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you

should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study
- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow. We share your health information only when we must, and we ask anyone who receives it from us to protect your privacy. However, once your information is shared outside Partners, we cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

_____ _____

Study Doctor or Person Obtaining Consent Date/Time

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject

Date/Time

Consent Form Version: June 8, 2012