# RUSH UNIVERSITY MEDICAL CENTERSubject Information Sheet and Consent Form

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Study Title: Investigation of Ranibizumab for the Treatment of Persistent Diabetic Neovascularization as Assessed by Super Wide-Field Angiography (Optos)

Sponsor: Genentech, Inc.

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## INTRODUCTION

You are being invited to participate in a research study at Rush University Medical Center. This consent form provides you with information about the study so you can understand the possible risks and benefits of participating. The investigator and/or sub-investigators will answer any questions you may have about this study. Before deciding whether to participate, you

should read this form carefully and ask any questions you have regarding the information it contains. Once the study has been explained and you have had all of your questions answered to your satisfaction, you will be asked to sign this consent form if you wish to participate.

You are being invited to participate in this study because you have proliferative diabetic retinopathy that has previously been treated with panretinal photocoagulation, also called laser treatment. You still have active disease even though you have been treated.

Proliferative diabetic retinopathy occurs when there is not enough oxygen to the retina. Because of this, the retina produces substances that cause new blood vessels to grow. These blood vessels are not able to provide oxygen to the retina. They are fragile and can break and lead to scar formation. These blood vessels can then lead to vitreous hemorrhage (bleeding in the eye), retinal detachment (separation of the retina from the back surface of the eye), glaucoma (increased pressure in the eye), loss of vision and loss of the eye.

## PURPOSE OF THE STUDY

The purpose of this research study is to test a new drug for the treatment of proliferative diabetic retinopathy. This drug is approved by the U.S. Food and Drug Administration for treatment of wet (neovascular)

macular degeneration, but is not approved for the use in proliferative diabetic retinopathy. The drug is called ranibizumab. This drug is given by injection into the eye.

The drug being tested blocks a growth factor (a protein in the body which provides nutrition to other cells) that is thought to be involved in formation of abnormal blood vessels that are formed in proliferative diabetic retinopathy.

Your voluntary participation in this study may help determine if ranibizumab will stop the growth of the abnormal blood vessels and to see if it is safe and well tolerated.

There are two groups in the study; if you enroll in the study, you will be assigned to participate in only one group.

The first group (Group A) will enroll seven (7) subjects. Subjects enrolled in this part of the study will initially receive one dose of ranibizumab in a dose of 0.5 milligrams (mg) by injection into the eye. The second group (Group B) will have three (3) subjects. These subjects will receive additional laser (panretinal photocoagulation) up to 500 additional spots in one treatment session. Subjects will be entered into the study groups based on when they enroll in the study. The first two subjects (Subject A and Subject B) will be entered into Group A and receive ranibizumab, the third subject (Subject C) will be entered into Group B and receive panretinal photocoagulation and so forth.

A total of ten (10) subjects at one study center will take part in this study.

## RESPONSIBILITIES/EXPECTATIONS AND PROCEDURES

The duration of the study is 6 months.

### SCREENING

If you volunteer to participate in this study, you will be screened within 30 days before study entry to check if you are a suitable candidate for this study. The screening tests include the following:

- Eye Exam
    - The eye exam will include measurement of your visual acuity (the ability to read letters on the vision chart). You will also have a contrast sensitivity test, which tests how well you see different shades of gray. The doctor will also look at your pupils and eye movements. The structures inside the eye will be examined through a special microscope. The lens and back of your eye will also be examined after drops have been placed in your eyes to dilate (enlarge) your pupil. The pressure in your eye will be measured. The doctor will also study your retina with an ophthalmoscope (an instrument with a strong light and magnifying lens).

- A review of your medical history

- A review of any medications you are or have been taking
- Urine pregnancy test, if applicable
    - If you are a female of childbearing potential, you will need to take a urine pregnancy test. This test must have a negative result in order for you to be in the study. You must use an effective method of birth control for the duration of the study.

If you are eligible for study entry, you will be randomly assigned to one of the two groups in the study. Once enrolled you will have:

- A blood test that will measure your hemoglobin A1c (HbA1c). This is a test that determines your blood sugar level over the last three months. Approximately 3 teaspoons (15 mL) will be drawn during this visit.
- You will also have a physical examination and vital signs (heart rate, breathing rate, blood pressure, temperature) taken.

## TREATMENT PHASE

You will either be assigned to receive 0.5 milligrams (mg) of ranibizumab or additional panretinal photocoagulation (PRP). You will receive one injection of ranibizumab or one session of PRP consisting of up to 500 additional laser spots (Day 0).

*Initial Treatment Day (Day 0)*

When you first arrive, your visual acuity (the ability to read letters on the vision chart) will be measured and you will have contrast sensitivity vision testing. You will then receive eye drops to dilate (enlarge) your pupil. Similar to the eye exam you had when you were screened for the study, the doctor will look at your eyes. The pressure of your eyes will also be obtained.

You will have a fluorescein angiogram test at this visit using a machine called the Optomap *fa*. This is a picture test where dye is injected into a blood vessel in your arm through a needle. The needle is temporary and is removed after the dye is injected. This test will look at the blood vessels in your eyes. You will also have fundus photographs (pictures of the interior surface of the eye) at this visit, which will be with the same machine as the fluorescein angiogram. At this visit, you will also have Optical Coherence Tomography (referred to as OCT). This test uses a dim beam of light to measure the thickness of the retina. You will look into a machine at a pattern of flashing and rotating red and green lights, first with one eye and then the other.

Once all of these tests are complete, you will be able to receive the injection of ranibizumab or laser treatment.

To prepare for the injection, anesthetic (numbing) drops and antibiotic drops will be placed on the surface of the eye. An antiseptic solution will be used to reduce the chance of infection. The eye doctor may decide that you should also have an anesthetic injection under the surface of the eyeball. After the preparation is

complete, the ranibizumab will be injected into your study eye. Dr. MacCumber, Dr. Davis, Dr. Cohen, Dr. Merrill or Dr. Packo, using a fine needle and syringe, will perform all injections.

After the injection, you will remain in the eye clinic for about an hour. Tests will be performed on your eye to determine how well you count fingers, detect hand motion and see light, as well as how much pressure is within your eye. You will be given antibiotic eye drops to self-administer four times a day for three days post-injection.

Before beginning the laser treatment, anesthetic drops will be placed on the surface of the eye. The eye doctor may decide that you should also have an anesthetic injection behind the eye. A special contact lens is then placed on the eye during the treatment. You will sit with your chin and forehead resting against a frame during the treatment. The treatment usually takes anywhere from 10 to 30 minutes. We will ask you to keep your head and eye still during the actual treatment, but you will be able to take “breaks” to rest, if you need them. You will see bright flashes of light. You may experience slight discomfort, but there is usually no pain.

Two days after you are treated, you will receive a telephone safety check from the study coordinator. You will be asked to return 1 week after your initial treatment, and again 2, 3 and 4 weeks and 2, 3, 4 and 6 months after the treatment. You will have a full eye

exam at all visits, including having drops put in your eyes to test the eye pressure and to dilate (make the pupil large) the eyes.

This is a summary of what will happen at each visit:

1 week, 3 weeks, and 5 month visit:

- Vital signs
- Intraocular pressure (eye pressure)
- Full eye exam, including dilation
- Visual acuity
- Contrast sensitivity vision testing
- Color photographs of eyes

2 and 4 weeks, 2, 3, 4 and 6 month visit:

- Vital signs
- Intraocular pressure (eye pressure)
- Full eye exam, including dilation
- Visual acuity
- Contrast sensitivity vision testing
- Fluorescein angiography with Optomap FA
- Optical Coherence Tomography (OCT)
- Color photographs of eyes

Genentech will provide ranibizumab for the study and pay for any tests that are done.

Should your disease change during the course of the study, you will be notified by your doctor of other options that may be available to you, which may include panretinal photocoagulation. Treatment in the non-study eye for diabetic retinopathy is allowed during the

course of this study. Your doctor and you will decide on the best treatment options.

If you have any health-related problems, you should contact the study nurse or your doctor as soon as possible.

## POTENTIAL RISKS AND DISCOMFORTS

During your participation in this study, you are at risk for the side effects described below. You should discuss these with the study doctor. There may also be other side effects that we cannot predict. Other medicines may be given to lessen the side effects and discomfort. Many side effects go away shortly after you discontinue therapy, but in some cases, side effects can be serious, long lasting, or permanent.

## STUDY DRUG ADMINISTRATION

Ranibizumab has been studied in humans in previously completed clinical trials. The following side effects have been observed:

- Temporary redness of the injected eye
- Minor and self-resolving bleeding related to the injection procedure
- Dull pain in the injected eye
- Mild and temporary burning and stinging
- Vision disturbances, including decrease in vision
- Self-resolving bleeding inside the injected eye

- Infection inside and/or outside the treated eye (endophthalmitis)
- Mild and self-resolving inflammation on the inside of the eye
- Severe inflammation in the inside of the eye (uveitis)
- Blockage of the blood flow in the main vein inside the eye (central retinal vein occlusion)
- Temporary increase in the pressure inside the eye (intraocular pressure)
- Damage to the lens inside the eye
- A tear through the retinal tissue in the eye (retinal tear)
- A rip in the pigment cell layer that lies beneath and nourishes the retina (retinal pigment epithelial [RPE] tear)
- Inadequate response of the pupil to light entering the eye (afferent pupillary defect/Marcus-Gunn Pupil)

Some of the complications listed above may result in permanent loss of vision or loss of the eye.

If you have a history of glaucoma, you may be at more risk for experiencing increased pressure within your eye after an injection of any substance, including ranibizumab. To participate in this study, it must be shown that your glaucoma is well controlled with medication and that you take your medication as it has been prescribed by your doctor.

Tests have shown that low levels of ranibizumab can reach your blood after injection into the eye. The significance of this is not well understood. Therefore, the risk of having a side effect involving a body system other than the eye is unknown. However, you will be carefully monitored for signs of side effects. Examples of possible side effects involving the body as a whole may include slowed wound healing or a tendency for more frequent or prolonged bleeding, heart attack and stroke.

In recent clinical trials, side effects occurring in less than 5% of subjects who received ranibizumab included heart attack (both fatal and non-fatal) and stroke.

There is a chance that your vision may worsen. Worsened vision could be due to progression of your diabetes, to a side effect of ranibizumab injection, or for other reasons.

There is a chance that you will experience an allergic reaction to ranibizumab. Allergic reactions may be mild, such as skin rash or hives, to severe, such as breathing difficulties or shock. A severe allergic reaction would require immediate medical treatment and could result in permanent disability or death. An allergic reaction can also cause dry or itchy eye. It is not possible to predict in advance if any of these problems will develop, but if they do, you will be promptly treated.

As is true for any experimental drug, unknown and potentially serious or life-threatening side effects could occur with ranibizumab.

## INJECTION INTO THE EYE

Injecting any medication into the eye may result in increased pressure within the eye, inflammation, cataract formation, a feeling of a foreign body in the eye, bleeding within the eye, damage to the retina (such as a retinal detachment or tear), or damage to other eye structures.

It is possible that you may get an infection within your eye (endophthalmitis) as a result of injection into the eye. An infection in the eye may lead to vision loss or, in rare cases, loss of the eye. Antiseptic cleaning of the eye and administration of topical antibiotics are given to minimize the risk of infection.

There may be minor discomfort from injection of ranibizumab. The injections will be performed by a specialist and will be done using a small needle after receiving local numbing (anesthesia). Your doctor will treat your symptoms according to his or her judgment.

Injection of the numbing medication may lead to minor bleeding under the surface of your eyeball; the bleeding will usually stop on its own, and the surface of your eye should return to its usual appearance.

## BLEEDING ASSOCIATED WITH THE USE OF ANTICOAGULANT MEDICATION

The use of certain kinds of anticoagulant (blood-thinning) medications (for example, aspirin) is permitted during this study. However, these types of medication are known to increase the chance of

bleeding in the event of a wound or tissue injury and could possibly increase the chance of internal eye bleeding if you have eye inflammation because of receiving the study drug. The only prohibited anticoagulant is Coumadin.

## PANRETINAL PHOTOCOAGULATION

Complications from photocoagulation are very uncommon but they do occur. It is possible that you will be worse after photocoagulation than you are right now. Damage to the cornea, iris and retina have in rare instances been known to occur from photocoagulation. The results of this damage could be a worsening of vision, blindness and disease of the eye requiring prolonged treatment. It is possible that photocoagulation will make whatever disease is present in the eye develop more rapidly than it would without photocoagulation. It is also possible that whatever is present in the eye before photocoagulation will come back after the procedure is performed.

## BLOOD DRAW

For the HbA1c blood test, insertion of the needle into your skin may cause some pain, discomfort, and slight bruising. You also may faint or feel faint. You may develop an infection at the site where the needle goes in. Fainting, feeling faint, or developing an infection are not likely to happen. Less than 3 teaspoons (15 mL) of blood will be taken during a single visit for HbA1c testing.

## PREGNANCY RISKS

The effects of ranibizumab on a fetus are unknown and may be harmful; therefore, you should not become pregnant or father a child while in this study. To participate in this study, females who are capable of bearing children must agree to use an effective method of birth control (i.e., birth control pills, patches, intrauterine device (IUD), barrier method such as condoms or diaphragm with spermicide, hormone implants or surgical sterility) to prevent pregnancy and will be required to take a pregnancy test before entry into this study (during the screening phase). If you are pregnant, you cannot be in this study because of possible harm to the fetus. If at any time during the study you suspect that you have become pregnant, please notify the study doctor immediately. If after your participation in the study is over, you suspect that you have become pregnant within 90 days of the last administration of study drug, you should notify your doctor immediately. You can discontinue birth control ninety days after you complete your participation in the study. If you are a male and your partner becomes pregnant during the study, you should also notify the study doctor immediately.

You should not nurse (breast feed) a baby while in this study because ranibizumab may enter breast milk and possibly harm your child.

Males must also use birth control (i.e., condoms) while participating in this study.

## POSSIBLE BENEFITS

The study treatment may help preserve and/or improve your vision because it may help stop the growth of abnormal blood vessels responsible for your loss in vision. However, there is no guarantee that the treatment will be successful. No direct benefit can be promised to you as a result of your participation in this research study. Your participation in this study may lead to new treatments for persons who have proliferative diabetic retinopathy.

## ALTERNATIVES TO PARTICIPATION

If you decide not to participate in this study, your proliferative diabetic retinopathy will be treated in the routine manner. Your doctor will discuss your options with you. Your choice not to participate in this study will not affect your medical care in any way.

## NEW FINDINGS

Any significant new findings regarding ranibizumab that become known during the course of the research study that might reasonably affect your willingness to participate will be provided to you. You should discuss further options with the study doctors at that time.

## COST AND COMPENSATION

Genentech will pay for all study-related procedures/tests ***except*** for the cost of the eye exam at Visit One (baseline), 4 weeks, 3 months, and 6 months (end of study visit) as well as the cost of the OCT test at 4 weeks, 3 months and 6 months. You and/or your insurance company are responsible for the above mentioned exams/tests. Genentech will supply ranibizumab for Group A of the study. If you are assigned to Group B, you and/or your insurance company will be responsible for the costs associated with the panretinal photocoagulation.

Dr. Mathew MacCumber is being paid by the sponsor of the study, Genentech, to conduct this research study. This payment will be used to pay for the costs of the study which may include such things as tests, medications, etc. Also, a portion of the money will be given to Rush University Medical Center. One example of what this payment will cover would be the cost of rent for office space within the medical center.

## VOLUNTARY PARTICIPATION

Participation in this research study is voluntary. There is no penalty if you decide not to take part in this study. You will not be penalized if you decide to stop participating in this research study.

## RESEARCH RELATED INJURIES

If you are injured or become ill from the study drug being studied or the required study procedures, medical treatment is available. You and/or your insurance company will be responsible for the cost for any physical injury that specifically results from the study drug.

Rush University Medical Center does not have a program for financial compensation or other forms of compensation for injuries which you may incur as a result of participation in this study. No payments or compensation will be provided for lost income.

## TERMINATION/WITHDRAWAL

Your participation in this clinical study may be ended at any time for medical reasons or because Genentech finds it necessary to limit or terminate this clinical trial.

The doctor may decide to hold or stop the ranibizumab injections at any time during the study for safety reasons.

You may choose to withdraw from the study at any time without consequence to the medical care you will receive. You will continue to receive the medical care to which you were previously entitled before your participation in the study.

If during the course of the study you decide to withdraw from the study, or if your doctor or the Sponsor decides to withdraw you from the study, you will be asked to

complete a scheduled termination visit for safety reasons. During this visit you will complete the same examinations as the final clinic visit scheduled at the end of the 6-month period. As a subject in this research, your responsibilities include returning for scheduled study visits and informing your doctor of any health problems during the study. Should you miss more than two scheduled doses of study treatment in a year because of a side effect or other reason, serious consideration will be given by your doctor and Genentech to discontinue you from the study.

If you experience a side effect considered by your doctor to be possibly related to study drug, you will be asked to visit the clinic periodically, even after the study has ended, and until the event resolves or until your doctor assesses it as chronic or stable.

## CONFIDENTIALITY

Records of participation in this research study will be maintained and kept confidential as required by law. The data from this study will be used by the study sponsor, Genentech, Inc., and its designees to submit to the Food and Drug Administration (FDA) and other regulatory agencies so that they may assess the safety and effectiveness of the study drug. Strict confidentiality concerning your medical records will be maintained by your doctor, the study sponsor and its designees. Your personal records will not be released or revealed beyond the scope of the study without your permission.

If information from this study is presented publicly or published in a medical journal, you will not be identified by name, picture, or any other personally identifying information. Identification numbers instead of names will be used to identify study data.

The Rush Institutional Review Board (IRB) will have access to your files as they pertain to this research study. The IRB is a special committee that reviews human research to check that the rules and regulations are followed. Your identity will not be revealed on any report, publication, or at scientific meetings.

## QUESTIONS

Questions are encouraged. If there are any questions about this research study or if you suffer a research related injury, please contact Dr. Mathew MacCumber at 312-942-2117. Questions about the rights of research subjects may be addressed to the Rush Research and Clinical Trials Administration Office at 312-942-5498.

By signing below, you are consenting to participate in this research study. You have read the information given. You have had the opportunity to ask questions, which have been answered satisfactorily to you by the study personnel. You do not waive any of your legal rights by signing this consent document. You will be given a copy of the signed and dated consent form for your records. You are also aware that the investigator at my hospital will also retain a copy in his or her files.

You hereby give your consent to participate in this clinical trial. You also hereby authorize Rush to use and disclose your Authorized Health Information in the manner described in this Consent Form.

_____

Subject Name (print)

_____ _____

Subject Signature Date

_____

Name of person conducting informed consent discussion (print)

_____ _____

Signature of person conducting informed consent discussion Date

I observed the signing of this document.

_____

Witness Name (print)

_____ _____

Witness Signature Date