ADDENDUM TO THE PARTICIPANT INFORMED CONSENT FORM

STUDY TITLE: A phase IIIb, multicenter, randomized, controlled study of the safety, tolerability and efficacy of intravitreal injections of 0.5mg ranibizumab given monthly compared to a Treat and Extend protocol in patients with wet age-related macular degeneration (T-REX)

PROTOCOL NO: T-REX/ML28513

STUDY DOCTOR: Charles C Wykoff, MD

STUDY SITE: Retina Consultants of Houston
6560 Fannin, Ste. 750
Houston, TX 77030

Retina Consultants of Houston, The Woodlands
Medical Arts Center II
17350 St. Luke's Way, Ste. 120
The Woodlands, TX 77384

Retina Consultants of Houston-Katy
23501 Cinco Ranch Blvd., Ste. G205
Katy, TX 77024

TELEPHONE: 713-524-3434

SPONSOR: Retina Consultants of Houston

You are being given this Addendum to the Participant Informed Consent Form because you are currently participating in the TREX AMD (ML28513) study. You previously signed a consent form that told you about the study. The purpose of this addendum is to give you new information about the study.

One tube (approximately 5 teaspoons) of blood will be collected during Week 104, Week 128, and Week 156 visits (or visits closest to those weeks). These blood samples may be used for analysis of biomarkers to evaluate the amount of the study drug in your blood, how fast the study drug levels rise and fall, and what effects this may have in your body function. When collected, these samples are de-identified and stored at Retina Consultants of Houston and will later be transferred and stored at Genentech for future analysis for up to 5 years. Genentech or a third party will perform the analysis of the blood samples. The results of the blood samples will not be shared with you.

Blood Draw Risks

There may be some discomfort when the blood sample is collected, and there is a small risk of bruising, infection, or inflammation at the site in which the needle is inserted.

Blood samples are optional in this study. If you are unwilling to consent to these procedures, you will still be able to participate in this study. Please **initial** below indicating your preference:

_____ **YES**, I DO agree to donate the optional blood samples to be used and stored for additional research related to my disease/condition

_____ **NO**, I DO NOT agree to donate the optional blood samples to be used and stored for additional research related to my disease/condition

If you have any questions about participation, please contact the study doctor at the telephone number listed above. All other text in the Participant Informed Consent Form remains unchanged.

You will receive a copy of this signed addendum consent form, which has 2 pages.

Printed Name of Participant	Signature	Date
Printed Name of Person Conducting Review of Consent	Signature	Date

---------- **Use the following only if applicable** ----------

If this consent form is read to the participant because he/she is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

Signature of Impartial Witness	Date

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE: A phase IIIb, multicenter, randomized, controlled study of the safety, tolerability and efficacy of intravitreal injections of 0.5mg ranibizumab given monthly compared to a Treat and Extend protocol in patients with wet age-related macular degeneration (T-REX)

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TELEPHONE: 713-524-3434

SPONSOR: Retina Consultants of Houston

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully. To be in a research study you must give your informed consent. "Informed consent" includes:

- Reading this consent form.
- Having the study doctor or staff explain the research study to you.
- Asking questions about anything that is not clear.

- Taking home an unsigned copy of this consent form. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later on and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve investigational drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food and Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are investigational.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed, then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done
- What will happen during the research
- What drug or device or procedures will be used
- Any possible benefits to you
- The possible risks to you
- The other medical procedures, drugs or devices that could be used instead of being in this research study
- How problems will be treated during the study and after the study is over

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

You are being asked to participate in this study because you have wet age-related macular degeneration.

Age-related macular degeneration, often called AMD or ARMD, is the leading cause of vision loss and blindness among Americans who are age 65 or older. Macular degeneration is diagnosed as either "dry" (non-neovascular) or "wet" (neovascular). In "wet" macular degeneration, new blood vessels grow beneath the retina and leak blood and fluid. This leakage causes permanent damage and scarring to the retina and creates blind spots in a person's central vision.

There is no current treatment that will completely restore vision lost to eye disease caused by macular degeneration. Lucentis® 0.5mg is a drug that has shown to preserve and improve remaining vision. Lucentis 0.5mg is an FDA-approved medication used for treating "wet" macular degeneration. It works by blocking proteins called vascular endothelial growth factor (VEGF), which stimulate the growth of new blood vessels in the body. Lucentis 0.5mg is given by injection into the eye (intravitreal injection).

The purpose of this research study is to determine if a treat-and-extend regimen of Lucentis 0.5mg (increasing the time between visits when your disease is stable and not getting worse) is safe and effective for research participants with "wet" macular degeneration verses monthly dosing. The treat-and-extend dosing of Lucentis 0.5mg is investigational, which means the dose regimen is different than what is approved by the FDA. Lucentis is usually given once every month.

HOW MANY PEOPLE WILL PARTICIPATE

Approximately 60 men and women at least 50 years of age will participate in this study.

DURATION

If you agree to take part in this study, your involvement will last up to 36 months. You may be seen every 4 – 12 weeks, depending on your assigned dosing schedule. Your visits will range from 1 – 4 hours in length.

PROCEDURES

If you are interested in participating in this study after it has been explained to you, you will be asked to sign this consent form. You will then be asked to come to the study center for a Screening Visit to see if you are eligible to participate in this study. You will sign this consent form at the very beginning of your screening visit before any study related procedures are performed.

Screening

During the Screening Visit, the following will be performed:

- You will be asked about your medical history and medications that you have taken or currently take.
- Your vitals signs (blood pressure and pulse) will be measured.
- Your demographic information will be recorded (race, age, etc.)
- If you are a women of childbearing potential, you will take a pregnancy test.
- Testing Your Eyesight: You will be asked to read letters on an eye chart, similar to the test you have when you go to the eye doctor for a routine check-up.
- Slit Lamp Examination: You will be given other eye drops to dilate your pupils so that the study doctor can examine your eye. The study doctor will use a special lens and a bright light to look at the back of your eye. Your vision may be more blurred than usual for a while after this test. If you were able to drive before this visit, you may not be able to do so for several hours afterward.
- Testing the Pressure inside Your Eyes: You will be given an eye drop to numb your eye. The front of your eye will be touched briefly with a test instrument to measure the pressure inside your eyes.
- Fluorescein Angiography: For this test, you will have a fluorescent dye (one that glows green when exposed to certain kinds of light) injected into your arm. The dye will travel through your blood to other parts of the body, including your eyes. Roughly 10 to 15 seconds after the dye is injected, the back of your eye will be photographed, and the pictures will show if the disease in the back of your eye has changed in any way.
- Fundus Photography: Pictures will be taken of the inside of your eye using a special lens and a camera with a very bright flash bulb.
- Optical Coherence Tomography: The OCT test uses a very thin laser beam to create a picture of the tissues at the back of your eye (the retina). You will see a brief flash of light during the test.
- Autofluorescence: The AF test takes special pictures of your eye to assess macular degeneration in your retina.

If the study doctor decides you meet the criteria to be in this study, you will be assigned by chance (like flipping a coin) to one of two groups:

Group A (Monthly) - Participants will receive intravitreal (direct injection into the eye) injections of 0.5 mg Lucentis administered every 28 days for 100 weeks. Starting at week 104 participants will be seen every 28 days and will receive intravitreal (direct injection into the eye) injections of 0.5 mg Lucentis as needed, based on presence of activity from wet AMD observed at the study visit.

Group B (TREX) - Participants will receive intravitreal injections of 0.5 mg Lucentis administered every 28 days for 3 months. The dosing schedule will continue monthly until there is no activity from wet AMD observed at the study visit. The interval between the visits will be lengthened by 1 – 2 weeks, as long as there is no activity seen at the study visit.

Starting at week 104, participants who have met the 12-week extension will be seen every 28 days and will receive intravitreal (direct injection into the eye) injections of 0.5 mg Lucentis as needed, based on presence of activity from wet AMD observed at the study visit.

Participants in Group B who have not met the 12-week interval will continue to have interval between visits lengthened by 1 – 2 weeks, as long as there is no activity seen at the study visit. If a participant meets a 12-week interval extension, he/she will switch to as-needed 0.5 mg Lucentis and be seen every 28 days.

You will receive study drug at every visit in Years 1 and 2. The longest interval between study injections will not exceed beyond 12 weeks in Years 1 and 2.

There is **NO** placeb used in this study. A placebo is a "fake" medication, which contains no active medicine to treat your condition.

You will receive your first injection of 0.5mg Lucentis into your study eye at the screening visit. Your vision will be checked after the injection of the study drug, your intraocular pressure will be checked, and then you will be allowed to go home. You will receive a phone call from the study staff 3 days after your first injection to check on any eye symptoms you may be experiencing.

Study Visits

You will be asked to return to the study center at a minimum of every 4 weeks for the next 36 months, depending on your assigned dosing schedule. You will have many of the same exams you had during the Screening Visit which include:

- Eyesight testing (all visits)
- Slit Lamp Examination (all visits)
- Testing the pressure inside your eyes, before and after study drug injection (all visits)
- Autofluorescence Testing (all visits)
- Fluorescein Angiography at screening visit, Week 24, Week 52, Week 76, Week 104, Week 128, and Week 152
- Fundus photography, at screening visit, Week 24, Week 52, Week 76, Week 104, Week 128, and Week 152
- Optical Coherence Tomography (all visits)

You will receive an injection of Lucentis 0.5mg into your study eye at every visit in Year 1 and Year 2. Starting at Week 104 you may or may not receive a study drug injection at every visit, depending on your assigned dosing schedule. Your vision and pressure inside your eye will be checked after the injection of the study drug, and then you will be allowed to go home.

RISKS AND DISCOMFORTS

Possible common side effects associated with the use of Lucentis 0.5mg include the following:

- vision changes
- eye pain, redness, or irritation
- discharge or bleeding from the eye
- increased eye sensitivity to light
- swelling around your eye
- seeing "stars" or flashes of light, especially in your peripheral (side) vision
- pain or burning when you urinate
- sudden numbness or weakness, especially on one side of the body or
- sudden headache, confusion, problems with vision, speech, or balance

Other less serious side effects are more likely to occur, such as:

- itchy or watery eyes
- dry eyes
- blurred vision
- runny or stuffy nose, cough, sore throat

The FDA-approved label (drug information) for Lucentis 0.5mg includes information about a possible risk of arterial thromboembolic events (blood clots forming in blood vessels in the body, including the eye) associated with intravitreal injections of drugs like Lucentis 0.5mg. These blood clots can cause events such as heart attack or stroke (also known as arterial thromboembolic events). It is not known today if eye injections with medications like Lucentis 0.5mg carry an increased risk of these blood clots, but there is a potential risk. Blood clots may be life threatening. The package insert for the medication is available at your request.

Side effects other than those listed here may also occur. Talk to your study doctor about any side effect that seems unusual or that is especially bothersome.

Risks and possible discomforts you might experience from the study procedures include:

<u>Risks associated with injection procedures:</u>

The administration of the study drug, Lucentis in this study involves an injection into the eye, which is associated with some risk of damage to the eye and possible vision loss. Although previous studies involving injections into the eye have shown these complications rarely occur, it is important to know the possible risks associated with the procedure, which include:

- Bleeding in the outer tissue of the eye where the injection was performed (subconjunctival hemorrhage), which is very common. The injected area may also become red (conjunctival hyperemia).
- Bleeding in the eye (intraocular hemorrhage)
- Increased pressure inside your eye.
- Inflammation and pain in your eye (sterile endophthalmitis) which could harm your vision
- The needle could touch the lens of your eye and cause it to get cloudy, which would make it hard to see clearly (traumatic cataract)
- The needle could cause the retina or other layers at the back of the eye to tear or become detached from the eye and cause damage to your vision (retinal detachment or retinal pigment epithelium detachment or tear/hole). This type of detachment may need to be repaired surgically.
- Infection inside the eye (endophthalmitis). This type of infection requires prompt treatment with antibiotics and/or surgery. You may feel pain and could permanently lose your vision as a result of this infection. The chances of this type of infection are low.

Intraocular Pressure Test Risk

The instrument used to measure the pressure inside your eye could scratch the outside of your eye (cornea).

Fundus Photography Risks

During fundus photography you may experience some brief discomfort, and you may "see spots" for a few minutes after we take these pictures.

Fluorescein Angiography Risks

Fluorescein angiography risks may include:

- Bleeding and bruising around the needle stick
- Itching
- Rash
- Vomiting
- Heart attack (rare)
- Stroke (rare)
- Death (rare)
- Allergic Reaction Risk

Intraocular Pressure Risks

There is a remote chance of a corneal abrasion (scratch on the surface of the eye) from the procedure to measure the pressure inside your eye. In the event that you get a scratch on the surface of your eye, you need to tell the study doctor.

Dilating Drops Risks

The dilating drops may cause temporary sensitivity to light and blurred vision until the effects of the dilating eye drops wear off (usually about 3 – 4 hours but may last until the next day). You should protect your eyes with sunglasses in bright light while your pupils are dilated. If you do not bring a pair of sunglasses with you to the study visits, the study staff will provide you with a pair. You should not drive or engage in any hazardous activity until your vision returns to normal.

Allergic Reaction Risks

There is a risk of allergic reaction when receiving Lucentis 0.5mg. You may also have an allergic reaction to the dyes or eye drops used in some of the eye exam procedures or to the solutions used to prepare your eye for injection. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms or any other side effects, during the study.

Other Risks

Your condition may not get better or may get worse during this study.

There may be risks to you that are unknown at this time.

Reproductive Risks

Women who are pregnant or breast-feeding a child may not take part in this study. Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study. If you think that you have gotten pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study.

The drug used in this study may harm an unborn child. If you are a man taking part in this study, you MUST use a condom unless your partner has stopped having periods (due to menopause) or is surgically sterile. If you think that you have gotten a woman pregnant, you must tell the study doctor at once. If your partner gets pregnant during the study, you may be asked questions about the pregnancy and the baby.

NEW INFORMATION

You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your vision may stabilize or may improve while you are in this study; however, this cannot be promised. The results of this study may help people with "wet" age-related macular degeneration in the future.

ALTERNATIVE TREATMENT

You do not have to be in this study to be treated for your "wet" AMD. If you decide not to enter this study, there is other care available to you. There are currently four FDA-approved drugs for treatment of "wet" AMD. Three are injected into the eye: Eyelea® (aflibercept), Macugen® (pegaptanib injection) and Lucentis® (ranibizumab). A fourth FDA-approved treatment, PDT or Verteporfin photodynamic therapy (injection of a dye into the vein followed by laser treatment) may slow the progression of certain types of "wet" AMD. In addition, several investigational drugs are being tested for the treatment of "wet" AMD. The study doctor will discuss the risks and benefits of alternative treatments with you.

SOURCE OF FUNDING FOR THE STUDY

Genentech will pay for this research study.

COSTS

The sponsor, Retina Consultants of Houston, will provide the study drug, fellow eye drug, clinic visits, and tests related to the study at no charge during this study. Procedures that are done only for the study, such as extra lab tests, will not be billed to you or your insurance company.

You or your insurance company may be billed for any standard medical care given during this research study.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study (For example: Fellow eye injection procedure).

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

PAYMENT FOR PARTICIPATION

You will receive $9.00 for parking (if applicable) at the medical center office for each visit.

COMPENSATION FOR INJURY

If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor. The above statement does not waive your legal rights.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Taking part in this study is voluntary. You may decide not to take part or you may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest
- you get pregnant
- you do not later consent to any future changes that may be made in the study plan
- or for any other reason

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end-of-study procedures done.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will collect your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Information gathered for this research about:
  - Physical exams
  - Eye exams
  - Laboratory, x-ray, and other test results
- Records about any study drug you received

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

The sponsor of this research. "Sponsor" means any persons or companies that are:
- working for or with the sponsor, or
- owned by the sponsor

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries, and
- Sterling Institutional Review Board

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

May I review or copy my information?

Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. This permission will have no end date.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission.

QUESTIONS

Contact Charles C Wykoff, MD at 713-524-3434 for any of the following reasons:

- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury or a bad reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions regarding your rights as a research participant, or if you have questions, concerns, complaints about the research, would like information, or would like to offer input, you may contact the Sterling Institutional Review Board Regulatory Department, 6300 Powers Ferry Road, Suite 600-351, Atlanta, Georgia 30339 (mailing address) at telephone number 1-888-636-1062 (toll free).

Sterling IRB is a group of people who independently review research. Sterling IRB will not be able to answer some types of questions, such as questions about appointment times. You may contact Sterling IRB if you cannot reach the research team or if you want to talk to someone else.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my legal rights. I will receive a signed copy of this consent form, which has 13 pages.

CONSENT SIGNATURE:

_____
Participant Name

_____ _____
Signature of Participant Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

---------- **Use the following only if applicable** ----------

If this consent form is read to the participant because he/she is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject. The subject freely consented to be in the research study.

_____ _____
Signature of Impartial Witness Date

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.