PROTOCOL

STUDY TITLE:	Investigation of Ranibizumab for the Treatment of Persistent Diabetic Neovascularization as Assessed by Super Wide-Field Angiography (Optos)
STUDY DRUG	Recombinant humanized anti-VEGF monoclonal antibody fragment (rhuFab V2 [ranibizumab])
SPONSOR	Rush University Medical Center 1725 West Harrison, Suite 915, Chicago, IL 60612 Phone: 312-942-2117 Fax: 312-563-2607
IND:	
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DATE FINAL:	*28 DEC 06*

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IRB APPROVAL DATE: 8/15/07
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1. BACKGROUND

1.1 PATHOPHYSIOLOGY

Diabetes is a disease of abnormal blood glucose secondary to insufficient or deficient insulin. This excess glucose is converted into alcohols through the aldose reductase pathway in tissues, the retina in particular because of the high level of aldose reductase in retinal capillaries. These alcohols result in structural changes in the capillaries that weaken them. This leads to microaneurysms, hemorrhages, increased permeability, and eventual closure of the capillaries. This results in hypoxia that causes several changes in the vasculature of the retina, including venous dilatation and new vessel growth. Areas of ischemic retina produce vasoproliferative substances, like vascular endothelial growth factor (VEGF). This stimulates the growth of new blood vessels in the retina, leading to neovascularization and proliferative diabetic retinopathy. (Aiello et al. 1999, Davis 1994)

1.2 TREATMENT OF DIABETIC NEOVASCULARIZATION

The current treatment of diabetic peripheral neovascularization is with panretinal photocoagulation. Laser photocoagulation is used to place 1200 or more 500-μm burns, separated by one-half burn width. Treatment is divided into two or more sessions. (ETDRS Report 9. 1991)

1.3 RANIBIZUMAB AND DIABETIC NEOVASCULARIZATION

Vascular endothelial growth factor A (VEGF-A) has been implicated in the development of neovascularization in diabetes. Using ranibizumab, an anti-VEGF-A drug, would inhibit this production.

1.4 NONCLINICAL EXPERIENCE WITH RANIBIZUMAB

1.4.1 Nonclinical Pharmacokinetics

The pharmacokinetics of ranibizumab have been investigated in rabbits and cynomolgus monkeys following intravitreal and intravenous administration. In

both species, following intravitreal administration, ranibizumab was cleared from the vitreous humor with a half-life of 2–3 days. Following single intravitreal administration to cynomolgus monkeys, retinal concentrations of ranibizumab were approximately one-third of vitreous concentrations and declined in parallel with vitreous concentrations. Intravitreal injections of ranibizumab can lead to detectable antibodies in serum in rabbits and cynomolgus monkeys.

1.4.2 Nonclinical Toxicology

A series of nonclinical studies of ranibizumab administered by intravitreal injection to cynomolgus monkeys have been performed (details regarding study design and results can be found in the Investigator Brochure).

1.4.3 Stability Studies

The stability of ranibizumab alone and in combination with verteporfin was assessed in vitro. The combination of ranibizumab and verteporfin in a 5% glucose solution at concentrations of 500 μg/mL and 1.4 μg/mL, respectively, resulted in ranibizumab degradation and a decrease in ranibizumab capacity to bind VEGF. The ranibizumab degradation products have not been fully characterized. Although it is currently unknown if such degradation also occurs in vivo, sequential administration of verteporfin followed by ranibizumab with an intervening washout period will decrease the likelihood of loss of ranibizumab activity and degradation.

1.5 CLINICAL EXPERIENCE WITH RANIBIZUMAB

Ranibizumab has been or is being clinically evaluated in eight wet AMD studies (additional details regarding study design and results can be found in the Investigator Brochure).

1.5.1 Study FVF1770g

The first clinical trial with ranibizumab, Study FVF1770g was a Phase Ia study of the molecule given as a single intravitreal injection to subjects with neovascular AMD. The goals of the study were to investigate safety and tolerability and to define the maximally tolerated dose (MTD). The single intravitreal MTD was determined to be 0.5 mg (limited by ocular inflammation).

1.5.2 Study FVF2128g

The Phase I/II study FVF2128g was the first clinical trial of multiple-dose regimens of intravitreally-administered ranibizumab. Sixty-four subjects were enrolled in the study. Data show that ranibizumab was safe and potentially efficacious in subjects with subfoveal choroidal neovascularization due to AMD.

1.5.3 Study FVF2425g

Study FVF2425g was a Phase I, open-label, randomized study of three escalating multiple-dose regimens of intravitreally-administered ranibizumab. Data show that doses of ranibizumab up to 2 mg could be safely given as part of an escalating dose regimen to subjects with subfoveal choroidal neovascularization due to AMD.

1.5.4 Study FVF2428g

Study FVF2428g is an ongoing Phase I/II, single-masked, multicenter study of the safety, tolerability, and efficacy of multiple-dose intravitreal injections of ranibizumab in combination with verteporfin PDT in subjects with neovascular AMD.

Preliminary findings from Study FVF2428g suggest that administration of ranibizumab injections 7 days (±2 days) after treatment with verteporfin PDT in the same eye may result in a decrease in visual acuity of ≥30 letters due to temporary intraocular inflammation (uveitis).

1.5.5 Study FVF2508g

Study FVF2508g is an ongoing Phase I extension study designed to assess the safety and tolerability of multiple-dose intravitreal injections of ranibizumab administered monthly in subjects who have completed the treatment phase of a Genentech-sponsored Phase I study.

1.5.6 Study FVF2587g

Study FVF2587g is an ongoing Phase III active treatment–controlled study designed to assess the efficacy and safety of intravitreal administered ranibizumab compared with verteporfin in subjects with angiographically determined, predominantly classic subfoveal neovascular AMD.

1.5.7 Study FVF2598g

Study FVF2598g is an ongoing Phase III study designed to assess the efficacy and safety of intravitreal injections of ranibizumab administered monthly compared with sham injections administered monthly in subjects with angiographically determined, minimally classic or occult subfoveal neovascular AMD.

1.5.8 Study FVF3192g

Study FVF3192g is an ongoing Phase IIIb study designed to assess the efficacy and safety of intravitreal injections of ranibizumab administered as three monthly injections followed by quarterly injections for a total duration of

24 months, in subjects with angiographically determined subfoveal neovascular AMD with or without classic CNV.

2. OBJECTIVES

2.1 Primary Objective

To compare the efficacy of ranibizumab versus additional panretinal photocoagulation on diabetic neovascularization that is persistent despite previous treatment with panretinal photocoagulation.

2.2 Secondary Objectives

To evaluate concomitant macular edema after intravitreal injection of ranibizumab in patients with persistent neovascularization.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, Phase I/II study of intravitreally-administered ranibizumab in subjects with persistent (greater than three months) diabetic neovascularization previously treated with panretinal photocoagulation (at least 1200 or more 500-μm burns).

Consented, enrolled subjects will either receive open-label intravitreal injections of 0.5-mg dose of ranibizumab or additional panretinal photocoagulation (up to 500 300-500μm laser spots) in a ratio of two-to-one (2:1) at the beginning of the study period. ETDRS best-corrected visual acuity, contrast sensitivity, and Optos color photography will be performed at enrollment, at weeks 1, 2, 3 and 4, and at months 2, 3, 4, 5 and 6. The subjects will undergo fluorescein angiography utilizing the Optomap FA (fluorescein angiography) system and optical coherence tomography (OCT) at enrollment, at weeks 2 and 4, and at months 2, 3, 4 and 6. The subjects will be followed for a 6-month period for stabilization, regression, or recurrence of

neovascularization. In addition, patients will be evaluated for occurrence of macular edema.

3.2 RATIONALE FOR STUDY DESIGN

The pathophysiology of neovascularization associated with proliferative diabetic retinopathy has been shown to be via production of VEGF-A by ischemic retinal tissue. VEGF-A is produced and can be found in the vitreous cavity where it then acts to promote neovascularization. Ranibizumab is an anti-VEGF-A drug that has been shown to bind and inhibit the action of VEGF-A. Since diabetic neovascularization is the result of VEGF-A in the vitreous cavity, intravitreal injection of ranibizumab would bind the VEGF-A produced by the ischemic retina and therefore prevent neovascularization.

3.3 OUTCOME MEASURES

3.3.1 Primary Outcome Measures

The primary efficacy outcome measures include:

- The percentage change of the area of the patient's neovascularization as measured in pixels by Optomap FA
- The percentage change of macular edema measured by retinal thickness by OCT

The primary safety and tolerability outcome measures are:

- Incidence and severity of ocular adverse events, as identified by ophthalmic examination
- Incidence and severity of other adverse events, as identified by physical examination, subject reporting, and changes in vital signs

- ### 3.3.2 Secondary Outcome Measures

The secondary outcome measures are:

- Mean change in Best Corrected Visual Acuity (BCVA), as assessed by the number of letters read correctly on the ETDRS eye chart at a starting test distance of 4 meters 3 and 6 months
- Percentage of patients gaining 3 or more lines of vision according to ETDRS eye chart testing
- Occurrence rate of proliferative diabetic complications including vitreous hemorrhage, iris neovascularization and tractional retinal detachment

3.4 SAFETY PLAN

The safety assessments to be conducted for this study are listed in Section 4.5 and Appendix A.

- Potential adverse events include but are not limited to local injection site reaction, subconjunctival hemorrhage, vitreous hemorrhage, retinal tear or detachment or endophthalmitis.
- If a patient has an occurrence of retinal tear or detachment or endophthalmitis:
    - The patient will not be included in the study
    - Treatment will be based on the event and at the discretion of the treating physician based on current accepted practice standards
    - Any necessary testing such as ultrasound or cultures will be performed as indicated by the specific event.
    - Any necessary procedures, such as vitreous tap and injection, laser for tears or surgical repair of detachments will be performed according to current practice standards

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with current U.S. Food and Drug Administration (FDA) Good Clinical Practices (GCPs), and local ethical and legal requirements.

4. MATERIALS AND METHODS

4.1 SUBJECTS

4.1.1 Subject Selection

Ten (10) subjects from one site in the United States will be enrolled. Eligible subjects will have provided informed consent. (See Appendix A, the study flow chart, for screening assessments.)

4.1.2 Inclusion Criteria

Subjects will be eligible if the following criteria are met:

- Ability to provide written informed consent and comply with study assessments for the full duration of the study
- Age $\geq$ 18 years
- Patient-related considerations

  Patients with Diabetes Mellitus (Type I or II) are eligible. HgA_{1c} will be evaluated at the beginning of the study, but this value will have no significance in inclusion or exclusion. Patients will not be pregnant at enrollment and must provide evidence of the use of two types of birth control while enrolled in the study. Patients will have no known sensitivity to ranibizumab or other anti-VEGF injections.

- Disease-related considerations

  Patients will have diabetic neovascularization as seen on fluorescein angiography that was previously treated with full (at least 1200 laser burns) panretinal photocoagulation and that has persisted at least three months. There will be no evidence of ocular inflammation at enrollment. There is no restriction on patient's current medications or concomitant illnesses as long as there is no interference with patient follow-up.

- Other considerations

  Patients may not be enrolled in another clinical study or observational trial. There is no limitation on patient's institutional status as long as the patient is able to participate in follow-up.

4.1.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

- Pregnancy (positive pregnancy test)
- Uncontrolled glaucoma on three medicines or more to control intraocular pressure
- Prior enrollment in the study
- Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated
- Participation in another simultaneous medical investigation or trial

4.2 METHOD OF TREATMENT ASSIGNMENT

The enrolled subjects will be randomized into two groups, 0.5 mg injection of ranibizumab or additional panretinal photocoagulation (PRP), in a two-to-one ratio (2:1). Randomization will occur by alternating treatment groups in the above ratio, as patients are included in the study For example, Patient A and

Patient B will receive ranibizumab, Patient C will receive additional PRP, Patient D and Patient E will receive ranibizumab, etc. Therefore, seven (7) patients will receive ranibizumab and three (3) patients will receive additional PRP. There will be no masking of which treatment each patient receives.

4.3 STUDY TREATMENT

4.3.1 Formulation

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile, 3-mL stoppered glass vial. Each vial contains 0.5 mL of 10mg/mL (0.5-mg dose level) ranibizumab aqueous solution (pH 5.5) with histidine, trehalose, and polysorbate 20. The vial contains no preservative and is suitable for single use only.

For further details and molecule characterization, see the Investigator Brochure.

4.3.2 Dosage, Administration, and Storage

a. Dosage

0.5-mg of ranibizumab will be injected intravitreally at the patient's enrollment in the study for patients in the ranibizumab treatment group.

b. Administration

**See Appendix B for detailed pre-injection procedures.*

c. Storage

Upon receipt, study drug kits should be refrigerated at 2°C - 8°C (36°F - 46°F). DO NOT FREEZE. Do not use beyond the expiration date. Ranibizumab vials should remain refrigerated. Protect vials from direct sunlight.

VIALS ARE FOR SINGLE USE ONLY. Vials used for one subject may not be used for any other subject.

4.4 CONCOMITANT AND EXCLUDED THERAPIES

Subjects may continue to receive all medications and standard treatments administered for their conditions at the discretion of their treating physician.

4.5 STUDY ASSESSMENTS

4.5.1 Assessments during the Treatment Period

Enrollment

- Informed consent
- Demographic data
- Hemoglobin A1c
- Urine pregnancy test
- Physical examination and medical history
- Vital signs
- Intraocular pressure
- Slit-lamp exam
- Dilated binocular indirect ophthalmoscopy
- Ranibizumab treatment with finger count vision after injection OR Panretinal photocoagulation (up to 500 300-500μm laser spots)
- Telephone safety check (2 days after visit)
- SAE monitoring
- ETDRS BCVA at 4 meters
- Contrast sensitivity testing
- Optomap FA
- Optical Coherence Tomography
- Optos color photos

1 week, 3 weeks, and 5 months

- Vital signs

- Intraocular pressure
- Slit-lamp exam
- Dilated binocular indirect ophthalmoscopy
- SAE monitoring
- ETDRS BCVA at 4 meters
- Contrast sensitivity testing
- Optos color photos

2 and 4 weeks, 2, 3, 4 and 6 months

- Vital signs
- Intraocular pressure
- Slit-lamp exam
- Dilated binocular indirect ophthalmoscopy
- SAE monitoring
- ETDRS BCVA at 4 meters
- Contrast sensitivity testing
- Optomap FA
- Optical Coherence Tomography
- Optos color photos

4.5.2 Early Termination Assessments

Subjects who withdraw from the study prior to completion should return for an early termination evaluation 14 days (± 7 days) following the last injection/study visit for monitoring of all adverse events (serious and nonserious). The schedule of assessments for early termination is the same as that for the final visit.

4.6 SUBJECT DISCONTINUATION

Subjects have a right to withdraw from the study at any time.

The subject may be withdrawn from the study for any reasons: if it is in the best interest of the subject, intercurrent illness, adverse events, or worsening

condition. Rush University Medical Center may request the withdrawal of a subject because of protocol violations, administrative reasons, or any other valid and ethical reasons.

Subjects will be discontinued and receive standard additional panretinal photocoagulation for development of neovascular glaucoma (NVG).

Other reasons for subject discontinuation may include, but are not limited to, the following:

- Sensory rhegmatogenous retinal detachment or Stage 3 or 4 macular hole
- Investigator determination that it is not in the best interest of the subject to continue participation
- Pregnancy
- Verteporfin PDT treatment in the study eye
- Pegaptanib sodium injection treatment in either eye
- SAE
- Any other safety concerns

If a subject discontinues or is discontinued from the study, he or she will not be allowed to re-enter the study.

In the event of an adverse event in the study eye that is considered by the investigator to be severe in intensity, serious consideration should be given to discontinuing the subject from the study.

4.7 STUDY DISCONTINUATION

This study may be terminated by Rush University Medical Center at any time. Reasons for terminating the study may include the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Data recording is inaccurate or incomplete

4.8 STATISTICAL METHODS

4.8.1 Analysis of the Conduct of the Study

There is no formal sample size calculation in this pilot study. As this is a phase I/II study, a sample size of 10 patients is chosen, making sure that it is feasible financially to conduct the study and logistically to complete the study within 12 months. If and when the study is planned for a phase II randomized control trial, appropriate statistical analysis will be determined.

- ### 4.8.2 Safety Analyses

Any adverse events, laboratory assessments, physical examinations, vital signs, ocular examinations and measurements from all 10 subjects will be utilized to summarize safety data for this pilot study.

- ### 4.8.3 Efficacy Analyses

As this is a small pilot study, no formal statistical analyses are planned

a. Primary Endpoint

- The percentage change of the area measured in pixels of the patient's neovascularization as measured by Optomap FA fluorescein angiography
- The percentage change of macular edema measured by retinal thickness by OCT

b. Secondary Endpoints

- Mean change in Best Corrected Visual Acuity (BCVA), as assessed by the number of letters read correctly on the ETDRS eye chart at a starting test distance of 4 meters, at 3 and 6 months

- Percentage of patients gaining 3 or more lines of vision according to ETDRS eye chart testing
- Occurrence rate of proliferative diabetic complications including vitreous hemorrhage, iris neovascularization and tractional retinal detachment

4.8.4 Missing Data

Analyses of efficacy and safety will be based on available cases, without imputation for missing values.

4.8.5 Interim Analyses

No formal schedule of interim analyses is planned. Reports of adverse events from this extension study may be reviewed and summarized periodically while the study is ongoing to ensure the safety of subjects.

4.9 DATA QUALITY ASSURANCE

Accurate, consistent, and reliable data will be ensured through the use of standard practices and procedures.

5. ASSESSMENT OF SAFETY

The safety of ranibizumab will be assessed through the collection and analysis of any adverse events that occur during the study whether related to the study drug or not.

5.1 ADVERSE EVENTS

AEs that start on Day 0 through the last study visit will be recorded on the appropriate AE pages of the CRF. Subjects discontinuing early from the study should return for an early termination evaluation and will be contacted 7 days after their last injection or study visit to elicit for occurrence of adverse events (serious and nonserious).

For this protocol, an AE is any "on study" untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness) that occurs in a study subject, regardless of the suspected cause. "On study" refers to Day 0 through the last study visit.

Unchanged, chronic conditions are NOT AEs and should not be recorded on the AE pages of the CRF. An exacerbation or worsening of a chronic condition should be recorded as an AE.

Both serious and nonserious AEs should be graded on a three-point scale (mild, moderate, severe) and reported in detail on the appropriate AE page of the CRF.

The suggested definitions are as follows:

Mild: Discomfort noticed but no disruption of normal daily activity

Moderate: Discomfort sufficient to reduce or affect normal daily activity

Severe: Incapacitating with inability to work or perform normal daily activity

Using the following criteria, investigators also need to assess whether there is a reasonable possibility that study drug caused or contributed to the AE.

- Yes (possibly or probably)

  There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or

  There is a biologically plausible mechanism for study drug causing or contributing to the AE; and

  The AE may or may not be attributed to concurrent/underlying illness, other drugs, or procedures.

- No

  A clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration; and/or

  A causal relationship is considered biologically implausible.

5.2 BASELINE MEDICAL CONDITIONS

It is not necessary to complete an AE CRF page for chronic medical conditions present at enrollment that do not worsen in intensity or frequency during the trial. These medical conditions should be adequately documented on the appropriate page of the CRF (medical history and/or physical examination). However, medical conditions present at enrollment that worsen in intensity or frequency during the treatment or post-treatment periods and ongoing AEs that started during the previous study should be reported and recorded as AEs.

5.3 EVALUATIONS

Reviews of body systems will be performed.

Ophthalmologic evaluations will include slit lamp examination, dilated binocular indirect high-magnification ophthalmoscopy, measurements of BCVA and intraocular pressure, and finger-count testing. (See Section 4.5 for a detailed description of the study assessments.)

5.4 VITAL SIGNS

Pulse, blood pressure, respiration, and temperature will be measured at protocol-specified study visits (see Section 4.5).

5.5 PROCEDURES FOR RECORDING AND REPORTING ADVERSE EVENTS

5.5.1 Recording Adverse Events (see examples below)

To improve the quality and precision of acquired AE data, investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording AEs on the AE pages of the CRF. Do not use colloquialisms and/or abbreviations.

- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms on AE pages of the CRF (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, signs and symptoms that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs on the CRF (e.g., if congestive heart failure and severe headache are observed at the same time, each events should be recorded as an individual AE).

- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A "primary" AE, if clearly identifiable, generally represents the most accurate clinical term to record on AE pages of the CRF. If a primary serious AE (SAE) is recorded on an SAE CRF, events occurring secondary to the primary event should be described in the narrative description of the case.

For example:

Orthostatic hypotension	→	Fainting and fall to floor	→	Head trauma	→	Neck pain

The primary AE is orthostatic hypotension.

- **5.5.2 Serious Adverse Events**

An AE occurring **at any dose** (including overdose) should be classified as **SERIOUS** if:

- It resulted in death (i.e., the AE caused or led to death).
- It was life threatening (i.e., the AE placed the subject at immediate risk of death; it does not apply to an AE that hypothetically might have caused death if it were more severe).
- It required or prolonged inpatient hospitalization (i.e., the AE required at least a 24-hour inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay; hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion).
- It was disabling (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- It resulted in a congenital anomaly/birth defect (i.e., an adverse outcome in a child or fetus of a subject exposed to the molecule or study drug prior to conception or during pregnancy).
- It does not meet any of the above serious criteria but may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

SAE Reporting

Investigators must report all SAEs to Genentech within 48 hours of observing or learning of the event. For initial SAE reports, investigators should record all case details that can be gathered within 48 hours on the SAE page of the CRF.

The completed SAE page and SAE Fax Cover Sheet should be faxed immediately upon completion to the Genentech Drug Safety at:

(650) 225-4682

or

(650) 225-5288

Relevant follow-up information should be submitted to Genentech as soon as it becomes available.

- **5.5.3 Special Reporting Situations**

a. Death

Death is an outcome of an event. The **event** that resulted in the death should be recorded and reported on the SAE pages of the CRF.

b. Hospitalizations for Surgical or Diagnostic Procedures

The **illness** leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

c. Pregnancy

5.5.4 Type And Duration Of Follow-Up After Adverse Events

All reported AEs should be followed until resolution or until the subject's participation in the study ends. Subjects who have an ongoing study drug–related SAE at study completion or at discontinuation from the study will be followed by the investigator or his or her designee until the event is resolved or determined to be irreversible, chronic, or stable by the investigator.

- **5.5.5 Regulatory Reporting Requirements for Principal Investigators Holding Their Own INDs**

Investigators conducting studies under their own INDs are responsible for expedited Safety Reports and IND Annual Reports to the FDA.

Expedited IND Safety Reports:

For this **Investigator Sponsored IND Study**, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32.

Events meeting the following criteria should be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

Fatal or Life-Threatening, Unexpected, Drug-related SAEs

The Investigator is required to notify the FDA of any **fatal or life-threatening** adverse event that is **unexpected** and assessed by the investigator to be **related** to the use of ranibizumab. Reports are to be telephoned or faxed to the FDA **within 7 calendar days** of the Investigator's knowledge of the event. Additionally, notify Genentech Medical Science Liaison by telephone **within 7** calendar days.

An **unexpected** adverse event is one that is not already described in the ranibizumab Investigator's Brochure (IB) This includes adverse events that have not been identified as life-threatening or causing a death as described in the IB, for example, elevated hepatic enzymes or hepatitis versus liver failure. This also includes unusual AEs not specifically described in the IB, for example, hemorrhage versus intraocular bleeding.

The 7-day telephone or fax report must be followed within 8 additional calendar days by a written IND safety report (MedWatch 3500A Form). Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. (See Appendix D for Analysis of Similar Events template). All safety reports previously filed to the IND concerning similar events should be analyzed. The significance of the new report in light of the previous, similar reports should be commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, the IRB, and all participating investigators within 15 calendar days of the

Investigator's knowledge of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA Fax Number for IND Safety Reports:

1 (800) 332-0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to:

Genentech Medical Science Liaison:

Name: Sara L. Butterworth, OD, FAAO
Tel: (319) 358-9770 or (319) 331-9795)
Fax: (319) 354-4751

AND:

Genentech Drug Safety at:

(650) 225-4682 or (650) 225-5288

AND:

Institutional Review Board:

Research and Clinical Trials Administration Office
Rush University Medical Center
1725 W. Harrison, Suite 439
Chicago, IL 60612
Phone: (312) 942-5498
Fax: (312) 942-2874

For questions related to Safety reporting, contact your Genentech Medical Science Liaison.

Serious, Unexpected, and Drug-related SAEs (not life-threatening or fatal)

A written IND Safety Report (described above) should also be produced for any unexpected SAE that is considered **related** to the use of ranibizumab but is **not life-threatening or fatal**. Investigators are required to notify the FDA, Genentech, the IRB, and all participating investigators by submitting the IND Safety Report within 15 days of the Investigator's knowledge of the event.

IND Annual Reports
All IND annual reports submitted to the FDA by the Investigator should be copied to Genentech. Copies of such reports should be mailed to:

Jim Nickas
Director of Drug Safety
Mailstop #84
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

- **5.5.5.1 MedWatch 3500A Reporting Guidelines: (See Appendix C for MedWatch form)**

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Identification of the primary event term
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- If a death occurred, autopsy results if available

MedWatch forms can be obtained on-line at www.fda.gov/medwatch or by calling the FDA at 1-800-332-1088.

- **Follow-up information:**

Additional information may be added to a previously submitted report by any of the following methods:

- Add to the original MedWatch 3500A report and submit it as follow-up
- Add documents and submit as follow-up with the original MedWatch 3500A form
- Summarize new information and fax it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted. (Patient identifiers are important so that new information is added to the correct initial report.)

Occasionally Genentech may contact the investigator for additional information, clarification, or current status of the subject for whom an adverse event was reported.

For questions regarding SAE reporting, you may contact the Genentech Medical Science Liaison.

6.0 INVESTIGATOR REQUIREMENTS

6.1 STUDY INITIATION

Before the start of this study, the following documents must be on file with Rush University Medical Center or its appointed representative:

- FDA correspondence letter assigning an IND number or an IND waiver letter
- Original U.S. FDA Form 1572 (for all studies conducted under U.S. Investigational New Drug [IND] regulations), signed by the Principal Investigator
- The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local and national regulations.
- Current curricula vitae of the Principal Investigator
- Written documentation of IRB approval of protocol (identified by Rush University Medical Center, protocol number or title and date of approval) and informed consent document (identified by Rush University Medical Center protocol number or title and date of approval)
- A copy of the IRB-approved informed consent document
- Written documentation of IRB review and approval of any advertising materials to be used for study recruitment, if applicable
- The informed consent document and any advertising materials must also be reviewed and approved by the Rush University Medical Center Legal Department.

- Certified translations of IRB approval letters, pertinent correspondence, and approved informed consent document (when applicable)

- Current laboratory certification of the laboratory performing the analysis as well as current normal laboratory ranges for all laboratory tests.

6.2 STUDY COMPLETION

The following data and materials are required by Rush University Medical Center before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from screening through the end of the study follow-up period (if applicable)

- Case Report Forms properly completed by appropriate study personnel and signed and dated by the investigator (if applicable)

- Copies of protocol amendments and IRB approval/notification (if applicable)

- A summary of the study prepared by the Principal Investigator (will accept IRB summary close letter) (if applicable)

- All regulatory documents (e.g., curricula vitae for each Principal Investigator, U.S. FDA Form 1572)

6.3 INFORMED CONSENT

Informed consent documents will be provided to each subject.

The informed consent document must be signed and dated by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The following basic elements must be included:

- A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the patient's participation, a description of the procedures to be followed, and identification of any procedures or drug used for purposes which are experimental

- A description of any reasonably foreseeable risks or discomforts to the patients

- A description of any benefits to the patient or to others which may reasonably be expected from the research. A description that there may be no benefit from this research.

- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient

- A statement describing the extent, if any, to which confidentiality records identifying the patient will be maintained and that notes the possibility that the FDA and Rush University Medical Center and the drug manufacturer may inspect the records

- For research involving more than minimal risk, an explanation as to whether any compensation and any medical treatments are available should injury occur and, if so, what they consist of or where further information may be obtained

- An explanation of whom to contact for answers to pertinent questions about the research and research patient's rights, and whom to contact in the event of a research-related injury to the patient

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time

without penalty or loss of benefits to which the patient is otherwise entitled

6.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before the study is initiated. The study will be conducted in accordance with U.S. FDA, applicable national and local health authorities, and IRB/EC requirements.

The Principal Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB/EC must be updated at least once a year. The Principal Investigator must also keep the IRB/EC informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB/EC of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs or ECs may have other specific adverse event requirements that investigators are expected to adhere to. Investigators must immediately forward to their IRB/EC any written safety report or update provided by Rush University Medical Center (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.5 CASE REPORT FORMS

All CRFs should be filled out completely by appropriate personnel. The CRF should be reviewed, signed, and dated by the investigator.

All CRFs should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced CRF copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID ON THE ORIGINAL.

6.6 STUDY DRUG ACCOUNTABILITY

The Investigator is responsible for the control and distribution of study drug.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure.

6.7 DISCLOSURE OF DATA

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, the drug manufacturer and the IRB/EC for each study site, if appropriate.

6.8 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after the investigation is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

REFERENCES

Aiello LM, Cavallerano JD, Aiello LP, Bursell SE: Diabetic retinopathy. In: Guyer DR, Yannuzzi LA, Chang S, Shields JA, Green WR, eds. Retina Vitreous Macula. Vol 2. 1999:316-344.

Davis MD: Proliferative diabetic retinopathy. In: Ryan SJ, ed. Retina. Vol 2. 1994:1319-1360

Early photocoagulation for diabetic retinopathy. ETDRS report 9. Early Treatment Diabetic Retinopathy Study Research Group. Ophthalmology. 1991;98: 766-785

APPENDIX A: Study Flowchart

	Enrollment	1 week	2 weeks	3 weeks	4 weeks	2 months	3 months	4months	5 months	6 months	14 Days after withdrawal
Intormed consent	X										
Demographic data	X										
Hemoglobin A_{1C}	X										
Urine Pregnancy Test	X										
Physical examination and medical history	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp exam	X	X	X	X	X	X	X	X	X	X	X
Dilated binocular indirect ophthalmoscopy	X	X	X	X	X	X	X	X	X	X	X
Ranibizumab treatment	X*										
Finger count vision after injection	X										
Panretinal photocoagulation	X*										
Telephone Safety Check	X + 2 Days										
SAE monitoring	X	X	X	X	X	X	X	X	X	X	X
ETDRS BCVA at 4 meters	X	X	X	X	X	X	X	X	X	X	X
Contrast sensitivity testing	X	X	X	X	X	X	X	X	X	X	X
Optomap FA	X		X		X	X	X	X		X	X
Optical Coherence Tomography	X		X		X	X	X	X		X	X
Optos color photos	X	X	X	X	X	X	X	X	X	X	X

* Patients will be treated with either ranibizumab or PRP, depending upon randomization

APPENDIX B
Pre-Injection Procedures for All Subjects

The following procedures will be implemented to minimize the risk of potential adverse events associated with serial intravitreal injections (e.g., endophthalmitis). Aseptic technique will be observed by clinic staff involved in the injection tray assembly, anesthetic preparation, and study drug preparation and administration. In addition to the procedures outlined below, added safety measures in adherence to specific institutional policies associated with intravitreal injections will be observed.

The following procedures (except where noted) will be conducted by the investigator. Subjects will have received antimicrobials (e.g. trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution) for self-administration four times daily for 3 days prior to treatment.

- The technician assembles the supplies and prepares a sterile field. Supplies include 10% povidone iodine swabs, sterile surgical gloves, 4×4 sterile pads, pack of sterile cotton-tipped applicators, eyelid speculum, sterile ophthalmic drape, 0.5% proparacaine hydrochloride, 5% povidone iodine ophthalmic solution, 1% lidocaine for injection, ophthalmic antimicrobial solution (e.g. trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution), and injection supplies.
- Instill 2 drops of 0.5% proparacaine hydrochloride into the study eye, followed by 2 drops of a broad-spectrum antimicrobial solution (e.g. trimethoprim-polymyxin B ophthalmic solution, ofloxacin ophthalmic solution, ophthalmic gatifloxacin solution, ophthalmic moxifloxacin solution).
- Disinfect the periocular skin and eyelid of the study eye in preparation for injection. Scrub the eyelid, lashes, and periorbital skin with 10% povidone iodine swabs, starting with the eyelid and lashes and continuing with the surrounding periocular skin. Make certain that the eyelid margins and lashes are swabbed, and proceed in a systematic fashion, from medial to temporal aspects.
- The investigator will glove, place sterile ophthalmic drape to isolate the field, and place the speculum underneath the eyelid of the study eye.
- Instill 2 drops of 5% povidone iodine ophthalmic solution in the study eye, making sure the drops cover the planned injection site on the conjunctiva.
- Wait 90 seconds.

- Saturate a sterile cotton-tipped applicator with 0.5% proparacaine hydrochloride drops and hold the swab against the planned intravitreal injection site for 10 seconds in preparation for the subconjunctival injection of 1% lidocaine hydrochloride ophthalmic solution for injection (without epinephrine).
- Use a sterile 4×4 pad in a single wipe to absorb excess liquid and to dry the periocular skin.

APPENDIX C: MedWatch Form FDA 3500A

Form Approved: OMB No. 0910-0291, Expires: 03/31/05
See OMB statement on reverse.

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For use by user-facilities, importers, distributors and manufacturers for MANDATORY reporting

Page ___ of ___

Mfr Report #

User/Importer Report #

FDA use Only

A. PATIENT INFORMATION

1. Patient Identifier	2. Age at Time of Event: or Date of Birth:	3. Sex	4. Weight
In confidence		☐ Female ☐ Male	___ lbs or ___ kgs

B. ADVERSE EVENT OR PRODUCT PROBLEM

1. ☐ Adverse Event and/or ☐ Product Problem (e.g., defects/malfunctions)

2. Outcomes Attributed to Adverse Event (Check all that apply)
- ☐ Death: ___ (mm/dd/yy)
- ☐ Life-threatening
- ☐ Hospitalization - initial or prolonged
- ☐ Disability
- ☐ Congenital Anomaly
- ☐ Required Intervention to Prevent Permanent Impairment/Damage
- ☐ Other: ___

3. Date of Event (mm/dd/year)

4. Date of This Report (mm/dd/year)

5. Describe Event or Problem

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatorenal dysfunction, etc.)

C. SUSPECT MEDICATION(S)

1. Name (Give labeled strength & manufacturer, if known)
#1
#2

2. Dose, Frequency & Route Used
#1
#2

3. Therapy Dates (if unknown, give duration)
#1
#2

4. Diagnosis for Use (Indication)
#1
#2

5. Lot # (If known)
#1
#2

7. Exp. Date (If known)
#1
#2

8. Event Abated After Use Stopped or Dose Reduced?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

9. NDC# (For product problems only)
_ _

8. Event Reappeared After Reintroduction?
#1 ☐ Yes ☐ No ☐ Doesn't Apply
#2 ☐ Yes ☐ No ☐ Doesn't Apply

10. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

D. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Type of Device

3. Manufacturer Name, City and State

4. Model #	Lot #	5. Operator of Device
Catalog #	Expiration Date (mm/dd/yy)	☐ Health Professional ☐ Lay User/Patient ☐ Other:
Serial #	Other #	

6. If Implanted, Give Date (mm/dd/yy)

7. If Explanted, Give Date (mm/dd/yy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
☐ Yes ☐ No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

10. Device Available for Evaluation? (Do not send to FDA)
☐ Yes ☐ No ☐ Returned to Manufacturer on: ___ (mm/dd/yy)

11. Concomitant Medical Products and Therapy Dates (Exclude treatment of event)

E. INITIAL REPORTER

1. Name and Address

Phone #

2. Health Professional?	3. Occupation	4. Initial Reporter Also Sent Report to FDA
☐ Yes ☐ No		☐ Yes ☐ No ☐ Unk.

PLEASE TYPE OR USE BLACK INK

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event.

FORM FDA 3500A (9/03)

Medication and Device Experience Report

(Continued)

Refer to guidelines for specific instructions.

Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA USE ONLY

Page ___ of ___

F. FOR USE BY USER FACILITY/IMPORTER *(Devices Only)*

1. Check One ☐ User Facility ☐ Importer
2. UF/Importer Report Number
3. User Facility or Importer Name/Address
4. Contact Person
5. Phone Number
6. Date User Facility or Importer Became Aware of Event *(mo/day/yr)*
7. Type of Report ☐ Initial ☐ Follow-up # ___
8. Date of This Report *(mo/day/yr)*
9. Approximate Age of Device
10. Event Problem Codes *(Refer to coding manual)* Patient Code ___ - ___ - ___ Device Code ___ - ___ - ___
11. Report Sent to FDA? ☐ Yes ___ *(mo/day/yr)* ☐ No
12. Location Where Event Occurred ☐ Hospital ☐ Outpatient Diagnostic Facility ☐ Home ☐ Ambulatory Surgical Facility ☐ Nursing Home ☐ Outpatient Treatment Facility ☐ Other: ___ *(Specify)*
13. Report Sent to Manufacturer? ☐ Yes ___ *(mo/day/yr)* ☐ No
14. Manufacturer Name/Address

G. ALL MANUFACTURERS

1. Contact Office - Name/Address *(and Manufacturing Site for Devices)*
2. Phone Number
3. Report Source *(Check all that apply)* ☐ Foreign ☐ Study ☐ Literature ☐ Consumer ☐ Health Professional ☐ User Facility ☐ Company Representative ☐ Distributor ☐ Other: ___
4. Date Received by Manufacturer *(mo/day/yr)*
5. (A)NDA # ___ IND # ___ PLA # ___ Pre-1938 ☐ Yes OTC Product ☐ Yes
6. If IND, Give Protocol #
7. Type of Report *(Check all that apply)* ☐ 5-day ☐ 15-day ☐ 10-day ☐ Periodic ☐ Initial ☐ Follow-up # ___
8. Adverse Event Term(s)
9. Manufacturer Report Number

H. DEVICE MANUFACTURERS ONLY

1. Type of Reportable Event ☐ Death ☐ Serious Injury ☐ Malfunction ☐ Other: ___
2. If Follow-up, What Type? ☐ Correction ☐ Additional Information ☐ Response to FDA Request ☐ Device Evaluation
3. Device Evaluated by Manufacturer? ☐ Not Returned to Manufacturer ☐ Yes ☐ Evaluation Summary Attached ☐ No *(Attach page to explain why not)* or provide code:
4. Device Manufacture Date *(mo/yr)*
5. Labeled for Single Use? ☐ Yes ☐ No
6. Evaluation Codes *(Refer to coding manual)* Method ___ - ___ - ___ - ___ Results ___ - ___ - ___ - ___ Conclusions ___ - ___ - ___ - ___
7. If Remedial Action Initiated, Check Type ☐ Recall ☐ Notification ☐ Repair ☐ Inspection ☐ Replace ☐ Patient Monitoring ☐ Relabeling ☐ Modification/ Adjustment ☐ Other: ___
8. Usage of Device ☐ Initial Use of Device ☐ Reuse ☐ Unknown
9. If action reported to FDA under 21 USC 360(j), list correction/ removal reporting number:
10. ☐ Additional Manufacturer Narrative and / or 11. ☐ Corrected Data

FORM FDA 3500A (9/03) (Back)

APPENDIX D

Analysis of Similar Events Template for IND Safety Reports

IND Safety Report

Case Summary

This section will be initiated by a research coordinator and may be modified by principal investigators if necessary. The case summary should describe the reported AE in detail, including a description of what happened and a summary of all relevant clinical information (e.g. medical status prior to the event, signs, symptoms, diagnoses, clinical course, treatment, outcome, etc.) The IND safety report should not identify the subject ID #, reporting investigator, or the site as this information may compromise the study blind.

PREVIOUS REPORTS

The information for this section comes from Principal Investigator and the search of similar events. This section should be written by the responsible principal investigator.

** Select one of the following two statements after reviewing the search of similar events results.*

Under IND _____(insert IND#), the following IND safety reports of similar AEs have been previously submitted:

MCN	Reported Event	Submission Date

Or

Under IND _____ (insert IND#), no IND safety reports of similar AEs have been submitted previously.

In addition to previously submitted IND safety reports of similar events, this section can also summarize pervious serious reports of the same/similar event that were considered unrelated to the investigational product at the time of the reporting. These events would remain blinded, unless a decision to unblind is made by an Independent Monitoring Committee for reasons of subject protection. The decision on what similar events to summarize in this section should be made after reviewing the similar events report generated by Clinical Data Management. If a safety signal is particularly worrisome (e.g., a study stopping type of event), a more extensive evaluation may be required.

Assessment of Relationship

After evaluation the new case report and reviewing any relevant previous reports of similar events, the PI selects one of the following boilerplate conclusion statements, if applicable. The PI may also craft an alternative conclusion

Based on review of available data, Rush University Medical Center believes there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE).

Additional information on risk factors and/or treatment of the AE may be provided if warranted.

Or

Based on review of available data, Rush University Medical Center does not believe that there is a reasonable possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE)

Explain if warranted. Do not speculate.

Or

Based on review of available data, Rush University Medical Center cannot establish or exclude the possibility of a cause-and-effect relationship between administration of _____(insert study drug name) and the occurrence of _____(insert AE)

Explain if warranted. Do not speculate

After review of the clinical details and investigator's comments pertaining to this AE, and based on experience to date, Rush University Medical Center does not believe that changes to the conduct of this clinical trial are warranted *This statement can be modified if changes to the conduct of the clinical trial are made*