Drugs of the Future 2003, 28(6): 541-545

CCC: 0377-8282/2003

Ranibizumab

USAN

Treatment of Age-Related Macular Degeneration
Humanized Monoclonal Anti-VEGF Antibodiy
Angiogenesis Inhibitor

rhu-Fab VEG
rhuFab V2
Lucentis™

Immunoglobulin G_1, anti-(human vascular endothelial growth factor) Fab fragment (human-mouse monoclonal rhuFAB V2 γ_1-chain), disulfide with human-mouse monoclonal rhuFAB V2 light chain

CAS: 347396-82-1

EN: 283520

Abstract

Wet type or exudative age-related macular degeneration (AMD) is a complex and multifactorial disease which affects older individuals and is characterized by subretinal or choroidal neovascularization (CNV) evident under the retina and macula. These new, abnormal blood vessels may bleed or leak fluid, causing the macula to bulge and lift up which results in rapid and severe distortion or destruction of central vision. Overexpression of vascular endothelial growth factors (VEGFs) and their receptors has been found to be associated with increased microvascular permeability in the eye. Thus, antiangiogenic therapy using VEGF as a target may be a selective and effective treatment option for the wet form of AMD. Ranibizumab is the antigen-binding fragment of a recombinant humanized monoclonal antibody directed toward VEGF that can penetrate the internal limiting membrane to access the subretinal space. Ranibizumab was chosen for further development as a treatment for the wet form of AMD.

Introduction

Macular degeneration includes several disorders that all result in malfunction and death of the light sensing cells of the macula and consequent gradual decline and loss of central vision with no effects on peripheral vision. One type of macular degeneration is age-related macular degeneration (AMD) which affects older individuals. AMD is complex and multifactorial with both genetic (*e.g.*, the apolipoprotein E gene [APOE] and ABCR gene have been implicated) and environmental factors (*e.g.*, long-term exposure to ultraviolet light, cigarette smoking, alcohol consumption) thought to be involved in its pathogenesis. There are two types of AMD: dry or geographic atrophy AMD which is responsible for about 85-90% of all cases of macular degeneration and wet or exudative AMD which accounts for approximately 10% of all cases. During the normal aging process, there is formation of a small amount of drusen which is accumulations of amorphous, acellular debris within the basement membrane of the retinal pigment epithelium (RPE) that appears as yellow spots within the macula. In contrast, a large amount of drusen is significantly linked to the development of both types of AMD. In dry AMD, drusen forms under the macula causing this area of the retina to thin and dry out. The degree of central vision loss is related to the location and amount of retinal thinning. In the wet form of AMD, subretinal or choroidal neovascularization (CNV) is evident under the retina and macula. The new, abnormal blood vessel may bleed or leak fluid causing the macula to bulge and lift up. The result is rapid and severe distortion or destruction of central vision (1-9).

Early treatment for macular degeneration particularly the wet type of AMD is essential since the disease progresses rapidly and early treatment can prevent irreversible vision loss. To date, there is no treatment or cure for the dry type AMD. Laser coagulation to destroy newly formed blood vessels has been used for treatment of the wet form of AMD. However, it causes full thickness retinal damage and can lead to immediate loss of central vision in the case of subfoveal lesions. Thus, researchers have focused efforts on more selective and effective treatment methods to avoid damaging adjacent retinal tissue or to

L.A. Sorbera, P.A. Leeson, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Table I: Angiogenesis inhibitors in development for the treatment of wet AMD.

Drug Name	Source	Mechanism of Action	Status
Anecortave acetate	Alcon	Angiogenesis inhibitor	Phase III
Pegaptanib sodium	EyeTech/Pfizer	VEGFR inhibitor/Oligonucleotide	Phase III
Ranibizumab	Genentech	Humanized MAb/Anti-VEGF	Phase III
Squalamine	Genaera	VEGFR inhibitor	Phase I/II
AdPEDF	GenVec	Angiogenesis inhibitor	Phase I

inhibit growth factor-mediated neovascularization. Photodynamic therapy (PDT), including several photosensitizing drugs such as verteporfin, has been extensively studied. Verteporfin is the only approved drug for PDT to date showing efficacy in reducing the risk of moderate vision loss in patients with subfoveal classical CNV. However, many treatment sessions are required and the rate of recurrence is high (1, 10, 11).

Antiangiogenic therapy is another possible approach for the treatment of CNV in the wet type of AMD. Prevention or regression of CNV before photoreceptor are irreversibly damaged could be effective in preventing blindness related to the wet form of AMD. There are several antiangiogenic agents currently under development for the treatment of the wet form of AMD, as shown in Table I. A potential antiangiogenic target is vascular endothelial growth factor (VEGF), a peptide with mitogenic effects on vascular endothelial cells that was shown to be present in surgically excised human CNV and in the aqueous and vitreous humor of patients with retinal neovascular disorders such as diabetic retinopathy. Overexpression of VEGFs and their receptors (VEGFR-1, VEGFR-2 and VEGFR-3) correlates with increased micro-vascular permeability in the eye. Moreover, antibodies to VEGF have been shown to inhibit neovascularization in monkeys with experimental retinal ischemia and iris neovascularization. These results suggest that blocking the activity of VEGF may be an effective method for treating the wet form of AMD (1, 12-15).

Ranibizumab (rhuFab V2) is the antigen-binding fragment of a recombinant humanized monoclonal antibody directed toward VEGF. The Fab portion is composed of the nonbinding human sequence making the agent less antigenic in primates, and a high-affinity binding epitope derived from mouse that binds to the antigen. Ranibizumab is smaller than the full-length antibody, thus allowing for intravitreous injection and penetration of the internal limiting membrane to access the subretinal space. Ranibizumab was chosen for further development as an antiangiogenic agent for the treatment of the wet form of AMD.

Pharmacological Actions

An *in vitro* study using human isoforms of VEGF (VEGF165, VEGF121, VEGF110) demonstrated that ranibizumab bound to all 3 VEGF forms. In addition, the antibody dose-dependently inhibited VEGF165-, VEGF121- and VEGF110-stimulated proliferation of human umbilical vein endothelial cells (HUVEC; IC_{50} = 0.29 ± 0.07, 0.48 ± 0.08 and 0.27 ± 0.09 nM, respectively) (17).

Ranibizumab (up to 6000 ng/ml) was shown to dose-dependently inhibit VEGF-induced permeability in the Miles assay in which guinea pigs were administered concomitant intradermal dorsum injections of the antibody and VEGF165 (100 ng/ml) following an intracardiac injection of Evans Blue dye (18).

A 26-week study with an 8-week recovery period was conducted in cynomolgus monkeys to evaluate the toxicity of intravitreal ranibizumab injections (500, 1000 and 2000 μg/eye intravitreal every 21 days for 26 weeks). The first injection of ranibizumab resulted in substantial anterior chamber/vitreal cellular inflammatory response that resolved by 1 week postdosing; less inflammation was observed with the second and third injections regardless of the ranibizumab dose. However, with injections 4-14, inflammation increased in severity and persistence in a dose- and time-dependent manner; the inflammatory response decreased between dosing. Retinal perivascular sheathing was observed and lymphocytes, macrophages, neutrophils and sometimes eosinophils were detected in the retina, optic nerve, ciliary body and iris of the majority of eyes treated with ranibizumab. Serum antibodies to ranibizumab appeared to correlate with more severe inflammatory responses, suggesting that the inflammatory adverse events associated with ranibizumab treatment were due to an immune-mediated response by monkeys to the humanized antibody. Lesions decreased after drug withdrawal and few alterations in ophthalmic examinations as compared to baseline were noted during the follow-up period (20).

The safety and efficacy of ranibizumab (500 μg/eye intravitreal every 2 weeks starting 21 days before CNV induction in 1 eye and on days 42 and 56 in both eyes starting after CNV induction on day 21) in preventing laser coagulation-induced CNV was examined in a crossover study in cynomolgus monkeys. No significant toxicities were observed with treatment, including no ocular hemorrhages. However, within 24 h of the first injection, acute anterior chamber inflammation was seen; this inflammation resolved within 1 week and was less severe with subsequent injections. Significantly less CNV was observed in eyes pretreated with ranibizumab and less leakage was noted in treated eyes with established CNV (20).

The efficacy and safety of intravitreal ranibiizumab in combination with i.v. verteporfin PDT on laser-induced CNV was examined in a study in cynomolgus monkeys. Animals were treated weekly, alternating ranibizumab or placebo with PDT and starting 2 weeks after induction of CNV. All of the eyes (11/11) treated with combination therapy had no leakage from CNV, an effect which was sustained during the 6-month follow-up. While 7/11 eyes treated with placebo injection and PDT had no leakage, 4 eyes had persistent leakage at 3 weeks. Results suggest that combination therapy with ranibizumab and verteporfin PDT is more effective in reducing angiographic leakage than PDT alone (21).

Pharmacokinetics

The serum disposition of ranibizumab administered as a single i.v. bolus was examined in mice (5 mg/kg), rabbits (0.25 or 0.5 mg/kg) and monkeys (1 or 10 mg/kg). Values for clearance, central volume of distribution (V_c) and steady-state volume of distribution (respectively) were: 10.4 ± 0.720 ml/kg/day, 49.4 ± 5.23 ml/kg and 169 ± 11.4 ml/kg in mice; 50.1 ± 4.27/33.3 ± 3.98 ml/kg/day, 50.5 ± 1.97/39 ± 4.51 ml/kg and 50.5 ± 1.97/55.4 ± 6.25 ml/kg in rabbits (at 0.25/0.5 mg/kg); and 10.4 ± 2.92/5.40 ± 2 ml/kg/day, 26.8 ± 5.06/24.7 ± 2.25 ml/kg and 36 ± 6.98/38.9 ± 1.46 ml/kg in monkeys (at 1/10 mg/kg) (22).

The vitreal pharmacokinetics of ranibizumab were determined in rabbits using fluorescein-labeled ranibizumab (100 μg labeled ranibizumab + 400 μg unlabeled ranibizumab). The terminal $t_{1/2}$ for labeled ranibizumab was 2.9 ± 0.75 days and a mean residence time of 4.2 ± 1 days was obtained. No ocular inflammation was detected with treatment (23).

The pharmacokinetics and retinal distribution of a single intravitreal dose of ranibizumab (25 or 625 μg/eye) were determined in rabbits. Administration of [^{125}I]-labeled ranibizumab (225 μCi; 625 μg/eye) revealed rapid and persistent distribution of the agent through all retinal layers including RPE at 1, 2 and 4 days postinjection. On day 1 postdosing, diffuse retinal distribution and focal localization of the antibody were observed in the ganglion layer. Clearance, $t_{1/2}$ and V_c values (at 25/625 μg/eye) were 0.257/0.129 ml/day, 2.40/2.89 days and 0.892/0.537 ml, respectively. It was concluded that ranibizumab diffuses rapidly throughout the retinal layers and is cleared relatively slowly from the eye (24).

Another study using rabbits reported the ocular pharmacokinetics of a single intravitreal dose (500 μg) of ranibizumab. Clearance was determined to be approximately 0.3 ml/day and V_c and $t_{1/2}$ values were 1.3 ml and 3 days, respectively (18).

The ocular pharmacokinetics of intravitreal ranibizumab (500 or 2000 μg/eye every 14 days for a total of 3 doses) were also determined in cynomolgus monkeys. Clearance, V_c and $t_{1/2}$ values for the two doses (500/2000 μg) were 0.69/0.85 ml/day, 2.1/3.0 ml and 2.18/2.50 days, respectively. Retinal concentrations were about one-third of vitreous concentrations and were found to decrease in parallel with the latter (25).

Clinical Studies

An open-label, nonrandomized, escalating dose, phase Ia study involving 27 subjects with neovascular AMD involving the fovea (median baseline acuity = 20/250) examined the safety of a single intravitreal injection of ranibizumab (50-2000 μg). The 500 μg dose was determined to be the maximum tolerated dose (MTD) since 2 subjects administered the 1000 μg dose experienced mild to moderate ocular inflammation. Injections were well tolerated and no serious ranibizumab-related adverse events were observed (26, 27).

The safety and efficacy of multiple intravitreal injections of ranibizumab (300 μg escalated to 1 mg every 2 weeks over 6 weeks followed by 1 mg every 4 weeks over 16 weeks; 300 μg escalated to 2 mg every 2 weeks over 14 weeks followed by a 2-mg dose at week 16; or 300 μg escalated to 2 mg every 4 weeks over 16 weeks) were examined in a multicenter, randomized, dose-escalation, phase I study involving 21 patients with neovascular AMD with different CNV lesion types (occult CNV, minimally or predominantly classic CNV, classic CNV after PDT and CNV with RPE tears). Intravitreous injections were well tolerated. Mild inflammation was the most frequent adverse event; no significant ocular inflammation was observed even with escalation up to 2 mg. Of the 21 patients treated, 19 had stable (± 4 correct letters on the ETDRS visual acuity testing chart) or improved vision (> 5 letters) at week 20 and 11 patients gained at least 3 lines (15 letters). Stable and improved vision correlated with a reduction in fluorescein angiographic leakage and retinal thickness. Ranibizumab was effective for all CNV lesion types (28). These results are summarized in Table II.

Results from an ongoing, phase Ib/II, open-label, randomized controlled study involving 64 subjects with wet type AMD (minimally or predominantly classic CNV or active lesion following PDT), administered ranibizumab (300 or 500 μg every 28 days for 4-8 injections) or usual care, showed that treatment with the agent improved visual acuity even at 6 months. Treatment was well tolerated with only a few serious drug-related adverse events (*e.g.*, reversible inflammation) reported. Preliminary data show that patients treated with 300 μg ranibizumab had an improvement on day 98 in average visual acuity of 8.5 ± 3.3 letters (correct on ETDRS charts) from baseline and an additional improvement of 4.3 letters on day 210; a net overall improvement in these patients on day 210 was 12.8 ± 3.4 letters. Patients in the usual care group had a decrease in correct letters of 3.0 ± 5.6 at day 98 but improved by 10.3 letters to 7.3 ± 6.6 letters at day 210. Moreover, analysis using optical coherence tomography of 25 subjects given 300 μg showed a marked decrease in retinal thickness which

Table II: Clinical studies of ranibizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Macular degeneration	Randomized, double-blind, multicenter	Ranibizumab, 300 µg [up to 1000 µg] intravitreal 1x/2 wk x 6 wk → 1000 µg intravitreal 1x/4 wk x 10 wk (n=5) Ranibizumab, 300 µg [up to 2000 µg] intravitreal 1x/2 wk x 14 wk → 2000 µg intravitreal [at wk 16] (n=8) Ranibizumab 300 µg [up to 2000 µg] 1x/4 wk x 16 wk (n=8)	21	Ranibizumab was well tolerated and significantly improved or stabilized visual acuity in 19 out of 21 patients with age-related macular degeneration. This effect was associated with a reduction in both fluorescein angiographic leakage and retinal thickness	28
Macular degeneration	Randomized, open	Ranibizumab, 300 µg intravitreal 1 x 28 d x 4-8 Ranibizumab, 500 µg intravitreal 1 x 28 d x 4-8 Control (usal care)	64	Ranibizumab was well tolerated and effective in improving visual acuity in patients with neovascular age-related macular degeneration. After 210 days of treatment, the patients showed increases of 4.3 letters above the 8.5-letter improvement reported after 98 days of treatment	29, 30

were found to be correlated with improvements in visual acuity (29, 30) (see Table II).

Ranibizumab continues to undergo phase III development for the treatment of wet type AMD. Studies that are currently recruiting patients include a phase I/II, single-masked, randomized, open-label, multicenter, crossover trial in subjects with neovascular AMD to examine the safety and efficacy of intravitreal injections of ranibizumab in combination with verteporfin PDT; a phase III, multicenter, double-blind, placebo-controlled, parallel-group study to examine the efficacy and safety of ranibizumab in subjects with minimally classic or occult subfoveal neovascular AMD; and a phase III, randomized, double-masked, active-treatment controlled trial to compare the efficacy and safety of ranibizumab with verteporfin PDT in subjects with predominantly classic subfoveal neovascular AMD (31-34).

Source

Genentech, Inc. (US); licensed to Novartis Ophthalmics (CH).

References

1. Prous Science Drug R&D Backgrounders: *Macular degeneration (online publication).* Updated May 22, 2003.

2. Chopdar, A., Chakravarthy, U., Verma, D. *Age related macular degeneration.* BMJ - Br Med J 2003, 326: 485-8.

3. Dunaief, J.L., Dentchev, T., Ying, G.S., Milam, A.H. *The role of apoptosis in age-related macular degeneration.* Arch Ophthalmol 2002, 120: 1435-42.

4. Gottlieb, J.L. *Age-related macular degeneration.* JAMA - J Am Med Assoc 2002, 288: 2233-6.

5. Husain, D., Ambati, B., Adamis, A.P., Miller, J.W. *Mechanisms of age-related macular degeneration.* Ophthalmol Clin North Am 2002, 15: 87-91.

6. Hyman, L., Neborsky, R. *Risk factors for age-related macular degeneration: An update.* Curr Opin Ophthalmol 2002, 13: 171-5.

7. Klaver, C.C., Kliffen, M., van Duijn, C.M., Hofman, A., Cruts, M., Grobbee, D.E., van Broeckhoven, C., de Jong, P.T. *Genetic association of apolipoprotein E with age-related macular degeneration.* Am J Hum Genet 1998, 63: 200-6.

8. Simonelli, F., Margaglione, M., Testa, F., Cappucci, G., Manitto, M.P., Brancato, R., Rinaldi, E. *Apolipoprotein E polymorphisms in age-related macular degeneration in an Italian population.* Ophthalmic Res 2001, 33: 325-8.

9. Yates, J.R., Moore, A.T. *Genetic susceptibility to age related macular degeneration.* J Med Genet 2000, 37: 83-7.

10. *Treatment of age-related macular degeneration with photodynamic therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin. One-year results of 2 randomized clinical trials -TAP report. Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group.* Arch Ophthalmol 1999, 117: 1329-45.

11. Schmidt-Erfurth, U., Miller, J.W., Sickenberg, M. et al. *Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration. Results of retreatments in a phase 1 and 2 study.* Arch Ophthalmol 1999, 117: 1177-87.

12. Ferrara, N., Bunting, S. *Vascular endothelial growth factor, a specific regulator of angiogenesis.* Curr Opin Nephrol Hypertens 1996, 5: 35-44.

13. Kvanta, A., Algvere, P.V., Berglin, L., Seregard, S. *Subfoveal fibrovascular membranes in age-related macular degeneration express vascular endothelial growth factor.* Invest Ophthalmol Vis Sci 1996, 37: 1929-34.

14. Lopez, P.F., Sippy, B.D., Lambert, H.M., Thach, A.B., Hinton, D.R. *Transdifferentiated retinal pigment epithelial cells are immunoreactive for vascular endothelial growth factor in surgically excised age-related macular degeneration-related choroidal neovascular membranes.* Invest Ophthalmol Visual Sci 1996, 37: 855-68.

15. Aiello, L.P., Avery, R.L., Arrigg, P.G. et al. *Vascular endothelial growth factor in ocular fluid of patients with diabetic retinopathy and other retinal disorders.* New Engl J Med 1994, 331: 1480-7.

16. Adamis, A.P., Shima, D.T., Tolentino, M.J., Gragoudas, E.S., Ferrara, N., Folkman, J., D'Amore, P.A., Miller, J.W. *Inhibition of vascular endothelial growth factor prevents retinal ischemia associated iris neovascularization in a nonhuman primate.* Arch Ophthalmol 1996, 114: 66-71.

17. Lowe, J., Araujo, J., Palma, M., Wang, Y., Gaudreault, J., Yang, J., Yu, N., Fei, D. *RhuFab 2 inhibits VEGF-isoforms-stimulated HUVEC proliferation.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 1828.

18. Gaudreault, J., Reich, M., Arata, A., Rusit, J., Pelletier, N., Shiu, V. *Ocular pharmacokinetics and antipermeability effect of rhuFab V2 in animals.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 3942.

19. O'Neill, C.A., Miller, P.E., Christian, B.J., Beyer, J.C., Bentley, E., VerHoeve, J.N., Nork, T.M., Leedle, R.A., Dubielzig, R.R., Albert, D.M. *26-Week intravitreal injection toxicity study with rhuFab VEGF in cynomolgus monkeys with an 8-week recovery.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 3929.

20. Krzystolik, M.G., Afshari, M.A., Adamis, A.P., Gaudreault, J., Gragoudas, E.S., Michaud, N.A., Li, W., Connolly, E., O'Neill, C.A., Miller, J.W. *Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment.* Arch Ophthalmol 2002, 120: 338-46.

21. Gauthier, D., Husain, D., Kim, I.K., Ezra, E., Tsilimbaris, M.K., Connolly, E., Lane, A.M., Gragoudas, E.S., O'Neill, C.A., Miller, J.W. *Safety and efficacy of intravitreal injection of rhuFab VEGF in combination with verteporfin PDT on experimental choroidal neovascularization.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 566.

22. Hsei, V., Siguenza, P., Ralph, P., Baughmann, S., Gaudreault, J. *Preclinical pharmacokinetic comparison of two rhuMAb VEGF molecules.* Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

23. Gaudreault, J., Escandon, E., Maruoka, M., Reich, M., Li, D., Hsei, V. *Vitreal pharmacokinetics of rhuFab V2 in rabbits using a non-invasive method.* Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 2801.

24. Gaudreault, J., Webb, W., Van Hoy, M. et al. *Pharmacokinetics and retinal distribution of AMD rhuFab V2 after intravitreal administration in rabbits.* Annu Meet Am Assoc Pharm Sci (AAPS) (Nov 14-18, New Orleans) 1999, Abst.

25. Gaudreault, J., Fei, D., Suboc, P., Chan, P., Nelson, J., Lappin, P., Hartmangruber, M., Rusit, J., O'Neill, C., Hsei, V. *Ocular pharmacokinetics (PK) of rhuFab V2 following intravitreal (ITV) administration in cynomolgus monkeys.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

26. Blumenkranz, M., Rosenfeld, P.J., Miller, J.W., Haller, J., Fish, G., Lobes, L., Singerman, L., Greene, W.L., Reimann, J. *Safety of rhuFab V2, an anti-VEGF antibody fragment, as a single intravitreal injection in subjects with neovascular age-related macular degeneration.* Annu Meet Assoc Res Vision Ophthalmol (April 29-May 4, Fort Lauderdale) 2001, Abst.

27. McCluskey, E.R. *RhuFab V2, an antiangiogenic Fab antibody fragment that binds VEGF, is being investigated as an intravitreal injection in subjects with neovascular age-related macular degeneration.* 4th Int Symp Ocular Pharmacol Pharm (Feb 28-March 3, Seville) 2002, Addendum.

28. Rosenfeld, P.J., Villate, N., Feuer, W.J., Puliafito, C.A., McCluskey, E.R. *RhuFab V2 (anti-VEGF antibody fragment) in neovascular AMD: Safety, tolerability, and efficacy of multiple, escalating dose intravitreal injections.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 970.

29. Puliafito, C.A., McCluskey, E.R. *Optical coherence tomographic (OCT) findings following treatment of choroidal neovascularization with rhuFabV2.* 35th Annu Meet Retina Soc (Sept 28-Oct 2, San Francisco) 2002, Abst.

30. Heier, J.S., Sy, J.R., McCluskey, E.R. *RhuFab V2 in wet AMD - 6 month continued improvement following multiple intravitreal injections.* Annu Meet Assoc Res Vision Ophthalmol (May 4-9, Fort Lauderdale) 2003, Abst 972.

31. 2003 First Quarter Report. Genentech Web Site, April 2003.

32. *Safety & efficacy study of rhuFab V2 in combination with verteporfin for treatment of age-related macular degeneration.* ClinicalTrials.gov June 2, 2003.

33. *Efficacy and safety study of rhuFab V2 (ranibizumab) to treat age-related macular degeneration.* ClinicalTrials.gov June 2, 2003.

34. *Safety and efficacy study of rhuFAb V2 (ranibizumab) to treat age-related macular degeneration.* ClinicalTrials.gov June 2, 2003.

Additional References

Heier, J.S., Sy, J.P., McCluskey, E.R. *RhuFabV2 (anti-VEGF antibody) for treatment of exudative AMD.* 35th Annu Meet Retina Soc (Sept 28-Oct 2, San Francisco) 2002, Abst.

Husain, D., Kim, I., Gauthier, D. et al. *Safety and efficacy of intravitreal injection of rhuFab VEGF V2 in combination with verteporfin PDT on experimental choroidal neovascularization.* 35th Annu Meet Retina Soc (Sept 28-Oct 2, San Francisco) 2002, Abst.

Heier, J.S., Greene, W.L. *RhuFab V2 (an anti-VEGF antibody fragment) in neovascular AMD: Safety and tolerability of multiple intravitreal injections*. Annu Meet Assoc Res Vision Ophthalmol (May 5-10, Fort Lauderdale) 2002, Abst 2520.