Changes in Vision- and Health-Related Quality of Life in Patients with Diabetic Macular Edema Treated with Pegaptanib Sodium or Sham

Jane V. Loftus,1 Marla B. Sultan,2 and Andreas M. Pleil,3 for the Macugen 1013 Study Group4

PURPOSE. To compare vision function and self-reported quality of life (QoL) in patients with diabetic macular edema (DME) treated with intravitreal pegaptanib 0.3 mg or sham injection.

METHODS. This randomized (1:1), controlled, multicenter trial included subjects with DME (center-point thickness on OCT, ≥250 μm) and visual acuity (VA) ≤65 letters and ≥35 letters. In year 1, pegaptanib or sham was administered every 6 weeks with focal/grid photocoagulation at investigator discretion after week 18. Subjects received injections as often as every 6 weeks per pre-specified criteria in year 2. Primary efficacy endpoint: proportion gaining ≥10 letters of VA from baseline to week 54. Change in QoL from baseline to weeks 54 and 102 was assessed with the 25-item National Eye Institute–Visual Function Questionnaire (NEI-VFQ 25) and the EQ-5D.

RESULTS. One hundred thirty-three pegaptanib- and 127 sham-treated subjects were in the year 1 intent-to-treat population. From baseline to week 54, ≥10 letter gains seen in 49 (36.8%) pegaptanib- and 25 (19.7%) sham-treated subjects (odds ratio [95% CI]: 2.38 [1.32–4.30]; P = 0.0047). At 2 years, the VA trend favored pegaptanib. The NEI-VFQ 25 domains of Near Vision, Distance Vision, and Social Functioning (week 54) and Distance Vision, Social Functioning, Mental Health, and Composite Score (week 102) demonstrated clinically meaningful (≥5-point between-group difference) and statistically significant (P < 0.05) benefits favoring pegaptanib. No significant difference in the mean change in generic EQ-5D-weighted utility scores was seen.

CONCLUSIONS. The VA improvement from pegaptanib treatment versus sham is reflected by improved vision-related QoL as reported by the DME patient (ClinicalTrials.gov number, NCT00605280). (Invest Ophtalmol Vis Sci. 2011;52: 7498–7505) DOI:10.1167/iovs.11-7613

Diabetic macular edema (DME) is an ocular complication of type I and type II diabetes mellitus, with edema resulting from increased vasopermeability and leakage of fluid into the retinal tissue of the macula. If left untreated, the disease may result in vision loss and eventual blindness. Several studies have demonstrated that quality of life (QoL) among DME patients is greatly affected at all stages of disease, from preliminary symptoms to diagnosis to vision loss.1–4 Treatment of DME may improve vision-related QoL in these patients.5,5

The importance of identifying safe and effective treatments for DME that result in anatomic, functional, and QoL improvements is underscored by the rising prevalence of diabetes—estimated to affect more than 350 million individuals worldwide by 2030.6 Among adults with diabetes, approximately 1 in 10 experiences vision-threatening diabetic retinopathy; half (5.7% of all diabetics) go on to develop DME,7 a condition responsible for 4.8% of blindness worldwide.8 Until recently, laser photocoagulation has been the standard treatment for DME, but vascular endothelial growth factor inhibitors have produced impressive gains in visual acuity during up to 2 years of follow-up in treating this condition (Radhakrishnan R, et al. IOVS 2010;52:ARVO E-Abstract 5042).9–15 A recent study14 found intravitreal (IVT) injections of pegaptanib sodium 0.3 mg to be a well-tolerated and effective treatment for DME. The study demonstrated a statistically significant difference in favor of pegaptanib over sham injection in the proportion of subjects with ≥10 letters (or 2 lines) visual acuity (VA) improvement at week 54 (primary endpoint). Improvement of at least 10 letters from baseline to week 54 was achieved by 36.8% (49/133) of subjects treated with pegaptanib compared with 19.7% (25/127) of sham-treated subjects (odds ratio [95% CI]: 2.38 [1.32–4.30]; P = 0.0047). The clinical benefit of pegaptanib treatment for DME was further supported by statistically significant differences favoring pegaptanib with regard to several secondary endpoints (e.g., degree of retinopathy, use of focal/grid laser treatment).

As part of the pivotal trial of pegaptanib in DME, changes in QoL over 54 and 102 weeks were evaluated by using the condition-specific 25-item National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) and the EuroQol five-dimension (EQ-5D) health status measure. Results of those evaluations are presented herein.

METHODS

The overall study design and subject selection criteria have been described in detail elsewhere.14 The trial protocol was approved by the institutional review boards and/or independent ethics committees at each investigational center. The study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki, all International Conference on Harmonisation Good Clinical Practice guidelines, and the United States Health Insurance Portability and Accountability Act. Each subject provided written informed consent before enrolling in the study.

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In brief, the pivotal study was a multicenter, randomized, sham-controlled, double-masked, parallel-group, comparative trial, to confirm the safety and compare the efficacy of pegaptanib sodium 0.3 mg when given as IVT versus sham injections to adult patients with DME involving the center of the macula. In both arms of the trial, focal or grid laser could be performed at week 18 as per ETDRS criteria determined by the investigator, and subjects subsequently could receive focal or grid laser photocoagulation, provided that a minimum of 17 weeks had elapsed between treatments (maximum of three laser treatments per year). Subjects were excluded from the study in the presence of high-risk proliferative diabetic retinopathy not adequately treated, edema due to etiology other than DME, any abnormality that would be likely to confound assessment of VA improvement or preclude improvement with treatment, or uncontrolled diabetes or other underlying systemic diseases that would preclude the use of pegaptanib. Randomization to pegaptanib or sham (1:1) was stratified by site, HbA1C (<7.6% vs. ≥7.6%), blood pressure (systolic, <140 vs. ≥140 mm Hg; diastolic, <80 vs. ≥80 mm Hg), and baseline VA (<54 letters vs. ≥54 letters).

Pegaptanib or sham treatment was administered as often as every 6 weeks for up to 2 years. A total of nine injections were given in year 1; during year 2, patients could receive study treatment as often as every 6 weeks, as per protocol-specified criteria based on VA, clinical examination, optical coherence tomography, and physician discretion. Only one eye was treated in each subject (the study eye). If both eyes were eligible, investigators selected one eye for participation; the fellow eye was treated according to the standard of care. The IVT procedure was identical between the sham and comparator arm, with the difference lying only in the application of an empty barrel of a needleless syringe in the sham procedure designed to mimic the IVT injection. Full masking was implemented, with one physician responsible for the IVT procedure and a second one responsible for study assessments, including recording adverse events and determining the relatedness of adverse events. VA examiners at each site were masked to the patients’ treatment assignment.

Quality of Life

In general, an individual’s overall QoL reflects two dimensions: health-and non-health-related. Economics and the environment are typically non-health-related determinants of QoL, although they may affect health. Generic measures of health status are used to measure the general concept of health-related QoL, whereas disease-specific measures are useful in examining the impact of a particular condition and its treatment on the person’s perception of health. Herein, vision-related QoL was measured using the interview version of the NEI-VFQ 25, whereas the EQ-5D was used to assess general health status. In our discussion, the general term QoL is used to refer to both levels of assessment, recognizing that our measures did not include non-health-related components of environment or economics.

The NEI-VFQ 25 is a vision-related QoL instrument designed to assess subjects’ perception of their visual function and QoL. The instrument consists of 11 vision-related domains (General Vision, Ocular Pain, Near Vision Activities, Distance Vision Activities, Social Functioning, Mental Health, Role Difficulty, Dependency, Driving, Color Vision, Peripheral Vision) and one General Health item. An overall Composite Score is calculated as the unweighted mean of the 11 vision-related domain scores. The individual items are scored on a 5-point Likert-like scale and include a response option, indicating that the particular activity is not attempted for reasons other than vision. The response for each item was recoded to a 0-to-100 scale, and then the mean of the items in each domain was used for domain-level comparisons. The mean of the domain scores was used to construct the composite score of the NEI-VFQ 25. For a complete description of the scoring methodology, please refer to http://www.nei.nih.gov/resources/visualfunction/manual_cm2000.pdf. The NEI-VFQ 25 has been psychometrically validated and used to track subject outcomes across several ocular diseases. In recent years, it has been used to assess vision-related QoL in patients with wet age-related macular degeneration (AMD) and was included in phase 3 trials evaluating pegaptanib and ranibizumab for wet AMD, with demonstrable improvements in vision-related QoL after treatment.

The EQ-5D, also a widely used and validated instrument, was used as a measure of health outcome. It is applicable to a wide range of health conditions and treatments, and it provides a simple descriptive profile and a single index value for health status. The first part of the EQ-5D contains five domains (mobility, self-care, performance of usual activities, pain or discomfort, and anxiety or depression), with each allowing three levels of response (1, no problem; 2, some problem; and 3, extreme problem). For example, the responses to the five domains could be 1, 1, 2, 2, 2. This response would then be mapped to a corresponding weighted index score, which is a health state utility measure based on the preference of a general population. In this study, the UK-derived utilities were used for convenience. The score 1, 1, 2, 2, 2 corresponds to an EQ-5D index score of 0.689. To put this into context, a score of 1 represents a perfect health state. The second part of the EQ-5D is a visual analog scale (VAS). In the present study, two VAS-related scores were calculated (i.e., a single index value score and a VAS area under the curve [AUC] score).

Both instruments were administered between the screening and baseline visit and then within 1 week before injections at weeks 18, 54, and 102 by personnel at an independent call center, except at the sites in India, where face-to-face interviews were conducted in the clinic before other activities, including the injection procedure. This variation in the protocol was necessary because there was a lack of available speakers of the required five Indian languages at the call center and difficulty in assuring telephone access for all subjects, as required by the methodology. The call center methodology is summarized in Figure 1 and will be described in detail in a separate publication. Validated translations of each questionnaire, adapted to enable call center staff to administer the instruments over the telephone, were used. All interviewers were trained and certified before participating in the study. All interviews were conducted in the preferred local language of the subject by an interviewer with the local language as his or her first language, whenever possible. To assist the patients with completing the QoL questionnaires, before randomization, they were supplied with brochures and interview guides.

Analyses

Changes in vision-related and health-related QoL endpoints were evaluated in an analysis of covariance (ANCOVA) model including main effects of treatment (based on randomization) and the stratification factors (i.e., by site and baseline HbA1C levels, systolic and diastolic blood pressures, and VA). The statistical approach used was the change from baseline difference at weeks 54 and 102 between the pegaptanib group and the sham group. Missing item values were imputed using the approach recommended by the instrument’s developers and, in the case of missing questionnaires, using the last-observation-carried-forward (LOCF) approach. Changes in QoL measures from baseline to weeks 54 and 102 were the primary focus of analyses.
RESULTS

Details of subject disposition and baseline characteristics have been published elsewhere. Of the 288 randomized subjects (pegaptanib, 145; sham, 143), 260 were included in the MITT1 population (pegaptanib, 133; sham, 127) and 207 in the MITT2 population (pegaptanib, 107; sham, 100). Treatment groups were similar at baseline with regard to demographic and ocular characteristics (Table 1).

NEI-VFQ 25

At baseline, NEI-VFQ 25 domain and composite scores were similar in the pegaptanib and sham groups in both the MITT1 and MITT2 populations (Tables 2, 3, respectively).

At week 54, statistically and clinically significant differences from sham in change from baseline scores were observed in the pegaptanib group for the domains of Near Vision Activities, Distance Vision Activities, and Social Functioning (Table 2; MITT1). Other domains, including Driving (P = 0.055) and the Composite Score (P < 0.1) showed numeric but not statistically significant benefits in favor of pegaptanib. The between-group differences in change from baseline to week 54 least-squares (LS) mean NEI-VFQ 25 domain scores (pegaptanib–sham) are presented in Figure 2.

At week 102, the Composite Score and the domains of Distance Vision Activities, Social Functioning, and Mental Health showed statistically and clinically meaningful differences in favor of pegaptanib over sham (Table 3; MITT2). The main differences from year 1 to year 2 were that the between-treatment difference on the Near Vision Activities domain was no longer significant at year 2, but the difference on the Mental Health domain was significant at year 2. Between-group differences in changes in LS mean NEI-VFQ 25 scores at week 102 (pegaptanib – sham) are presented in Figure 3.
The NEI-VFQ 25 is a valid and reliable vision-specific QoL assessment tool. It has been used to measure vision-related QoL across several ocular diseases, including glaucoma, cataracts, AMD, and, to a lesser extent, DME. Although the characteristics of a particular eye disease may affect the NEI-VFQ 25 domains differently, there is a demonstrable impact on health-related or vision-related QoL. Standard objective clinical assessments that measure a patient’s distance VA may not capture these aspects of vision functioning; hence, it is important to assess patients’ perceptions of the effect of treatment on their functional ability.

In the present study, the relatively low mean baseline scores (relative to scores observed in other eye diseases) for the Near Vision Activities and Distance Vision Activities domains indicate that these DME patients have problems with the quality of vision (e.g., difficulty in reading newspapers or watching a film at the cinema). The low mean baseline scores for the Mental Health, Role Difficulty, and Dependency domains relative to scores found for individuals with other ocular conditions indicate that patients with DME may feel particularly isolated.

In the present study, the visual benefit of treatment with pegaptanib as measured by best-corrected VA in the study eye compared with treatment with sham was consistent with the benefit of treatment, as described by patients in terms of vision-related QoL. No domains of the NEI-VFQ 25 were designated a priori as primary domains, but clinically and significantly greater improvement among pegaptanib-treated patients compared with treatment with sham was consistent with the benefit of treatment, as described by patients in terms of vision-related QoL.

EQ-5D

Mean EQ-5D weighted index scores were similar at baseline in the MITT1 and MITT2 populations (Table 4). No between-treatment difference in change in weighted index scores from baseline to weeks 54 or 102 was statistically significant. Similarly, differences in changes in VAS and AUC scores were not statistically significant at either postbaseline time point.

### DISCUSSION

The NEI-VFQ 25 is a valid and reliable vision-specific QoL assessment tool. It has been used to measure vision-related QoL across several ocular diseases, including glaucoma, cataracts, AMD, and, to a lesser extent, DME. Although the characteristics of a particular eye disease may affect the NEI-VFQ 25 domains differently, there is a demonstrable impact on health-related or vision-related QoL. Standard objective clinical

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**Table 3. Mean Baseline and Week 102 NEI-VFQ 25 Scores and Difference in LS Mean Change from Baseline to Week 102 (MITT2 Population; LOCF)**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline Week 102</th>
<th>Baseline Week 102</th>
<th>LS Mean Difference (Range)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health</td>
<td>41.2</td>
<td>43.6</td>
<td>2.84 (–3.43 to 9.10)</td>
<td>0.372</td>
</tr>
<tr>
<td>General vision</td>
<td>54.9</td>
<td>61.2</td>
<td>0.79 (–4.58 to 6.16)</td>
<td>0.775</td>
</tr>
<tr>
<td>Ocular pain</td>
<td>76.1</td>
<td>85.4</td>
<td>4.58 (–2.01 to 11.17)</td>
<td>0.172</td>
</tr>
<tr>
<td>Near vision activities</td>
<td>57.5</td>
<td>63.0</td>
<td>2.24 (–3.98 to 8.86)</td>
<td>0.478</td>
</tr>
<tr>
<td>Distance vision activities</td>
<td>60.8</td>
<td>64.6</td>
<td>3.95 (3.64 to 16.27)</td>
<td>0.002</td>
</tr>
<tr>
<td>Social functioning</td>
<td>78.0</td>
<td>80.1</td>
<td>9.91 (3.65 to 16.18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mental health</td>
<td>55.0</td>
<td>64.7</td>
<td>7.17 (0.33 to 14.01)</td>
<td>0.040</td>
</tr>
<tr>
<td>Role difficulty</td>
<td>56.1</td>
<td>61.4</td>
<td>2.03 (–6.78 to 10.85)</td>
<td>0.650</td>
</tr>
<tr>
<td>Dependency</td>
<td>67.6</td>
<td>73.6</td>
<td>3.02 (–5.28 to 11.33)</td>
<td>0.473</td>
</tr>
<tr>
<td>Driving</td>
<td>50.4</td>
<td>51.8</td>
<td>3.75 (–3.22 to 10.73)</td>
<td>0.288</td>
</tr>
<tr>
<td>Color vision</td>
<td>86.9</td>
<td>85.1</td>
<td>0.36 (–7.74 to 7.91)</td>
<td>0.923</td>
</tr>
<tr>
<td>Peripheral vision</td>
<td>69.9</td>
<td>73.8</td>
<td>4.53 (–2.76 to 11.82)</td>
<td>0.223</td>
</tr>
<tr>
<td>Composite score</td>
<td>65.2</td>
<td>69.8</td>
<td>4.47 (0.26 to 8.68)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

**Figure 2.** Changes in least-squares means in NEI-VFQ 25 scores at week 54 (pegaptanib – sham). MITT1; LOCF. Pegaptanib, n = 133; sham, n = 127. †P < 0.05; ‡P < 0.01.

**Figure 3.** Changes in least-squares means in NEI-VFQ 25 scores at week 102 (pegaptanib – sham). MITT2; LOCF. Pegaptanib, n = 107; sham, n = 100. †P < 0.05; ‡P < 0.01.
they may have felt more control over what they can do and improvement in the patients' confidence in their own abilities; vision after pegaptanib treatment may be translated into an least in part, to the condition and treatment effect.18 For significant, the lack of significance may be attributable, at

was seen in the Near Vision Activities, Distance Vision Activities, and Social Functioning domains at week 54 and in Distance Vision Activities, Social Functioning, Mental Health, and the Composite Score at week 102. Patients' perceptions of improvement in Near Vision Activities and Distance Vision Activities reflect changes in activities of daily living (e.g., reading and shopping), an important QoL parameter. The significant improvement in Mental Health seen in pegaptanib- compared with sham-treated subjects at week 102 is meaningful because baseline scores revealed that DME patients such as the ones included in this study have a substantial degree of impairment compared with normal-sighted peers.34 Taken in aggregate, the statistically significant changes noted in several domains at week 54 and 102 demonstrate that improvement in vision after pegaptanib treatment may be translated into an improvement in the patients' confidence in their own abilities; they may have felt more control over what they can do and may have had reduced feelings of isolation.

Although clinically and statistically significant between-treatment differences were not reached in all domains at week 54, a positive numerical trend favoring pegaptanib was observed in the majority of the remaining domains, including the Composite Score, Mental Health, and General Vision. At week 102, all domains except Color Vision demonstrated a positive numerical trend in favor of pegaptanib-treated subjects. In domains where differences between the active treatment and sham groups were not statistically significant, the lack of significance may be attributable, at least in part, to the condition and treatment effect.18 For specific domains such as Peripheral Vision, significant differences in favor of active treatment with pegaptanib would be unexpected, since DME and treatment with pegaptanib have less impact on these vision characteristics than, for example, on distance vision and near vision. Not unexpectedly, the Driving domain had the additional complication of a smaller sample size, as many of the subjects either had never driven or had stopped driving for reasons other than vision. Comparisons between groups of subjects numbering less than 100 are generally considered insufficiently powered to detect a 5-point difference as significant.

was reported for ranibizumab compared with 5.1 points for pegaptanib.15 To our knowledge, no year 2 QoL data for DME patients treated with ranibizumab have been published.

One limitation of studies of this type, when the vision endpoint is VA in the treated eye and the vision-related QoL endpoint is based on binocular “walking around” vision, is that the clinical benefit of treatment affects the treated eye alone. Unlike AMD for example, DME is more frequently a bilateral disease, but there is still some variability in the vision capability of the fellow eye. As such, the impact that treatment of a single eye may have on bilateral vision and subsequently on vision-related QoL can be complicated by the fact that the treated eye may be the better- or the worse-seeing eye. If it is the worse-seeing eye, even large improvements in VA may be difficult to translate to meaningful improvements in vision-related QoL in the 1- or 2-year time period covered in this study. Future analysis could include interrogating the QoL responses from the better-seeing eye after treatment and comparing the response to that obtained when the worse-seeing eye is treated. Perhaps future studies should consider bilateral visual acuity as an endpoint as well.

The mean EQ-5D baseline index score recorded for the DME population in this study was 0.748 compared to a baseline score of 0.778 for patients with type II diabetes.54 No significant difference in the mean change in EQ-5D weighted utility scores was seen at either time point between the pegaptanib- and sham-treated arms. Similarly, in a comparison of ranibizumab and laser in DME patients, none of the between-group differences from baseline in mean EQ-5D visual analog scores was statistically significant at any time point across 12 months.13 Detecting a change in utility score on the EQ-5D is based solely on changes in vision status; especially small changes in VA, is challenging, as the instrument is a generic measure that may not be sufficiently sensitive to detect changes in diabetic vision status. The absolute results from the General Health question of the NEI-VFQ 25 suggest a moderate amount of morbidity in both groups, but in the case of these diabetic patients, their general health condition was reasonably stable over time. This finding is not unexpected, given the nature of the condition and the mean age of the participants.

The quality of the data collected throughout the duration of the study was high; of the total number of randomized subjects in this trial, 96% of all questionnaires were completed. This high response rate is testament to the call center methodology that was implemented. All telephone interviews were con-
ducted by a trained interviewer, in the subject’s local language, using versions of the two QoL instruments adapted for telephone interviews. All responses from the subject were immediately entered into the call center database, and this systematic approach meant that respondents could not refuse to answer any of the questions. The face-to-face interviewer approach used in India may, in theory, have introduced more error; however, the metrics recorded there indicate that both data collection methods were reliable and robust. The 4% of data recorded as missing (in total) was attributable to staffing issues or miscommunication between the call center and the site.

**Conclusions**

This multicenter, randomized, sham-controlled, double-masked, parallel-group, comparative study is one of the first trials in DME patients to investigate the effect of treatment on QoL, hence greatly expanding the evidence base. The benefit demonstrated by vision improvement derived from treatment with pegaptanib 0.3 mg translated to vision-related QoL improvements after 54 and 102 weeks of treatment. At week 54, a statistically and clinically significant greater change from baseline was observed in the pegaptanib group for the NEI-VFQ 25 domains of Near Vision Activities, Distance Vision Activities, and Social Functioning. At week 102, statistically significant and clinically meaningful benefits favoring pegaptanib were demonstrated for the Composite Score and the domains of Distance Vision Activities, Social Functioning, and Mental Health. Stronger trends were observed at this time point, compared to week 54, for the majority of domains. Information concerning vision-related QoL benefits such as those demonstrated in the present study may be used by ophthalmologists to inform treatment choices and patient management decisions in patients with DME. Of note, the results suggest that the generic health status tool, the EQ-5D, may not be sensitive enough to detect relevant and meaningful changes in visual functioning. One should consider incorporating health status measures relevant to vision into clinical trials, to better understand the utility values of vision states. These findings suggest that the NEI-VFQ 25 may serve as a means of understanding the efficacy of treatment choice. A need for increased attention to the NEI-VFQ 25 may better serve patients who are in treatment for DME.

**Acknowledgments**

The authors and their companies are especially indebted to the members of the Macugen 1013 Study Group for their dedicated efforts in conducting the study.

**References**


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**APPENDIX A**

The following investigators, data managers, and research coordinators participated in the study.

**Independent Data Management and Safety Monitoring Committee**

Alan Bird, Moorfields Eye Hospital (Chair), London, UK; Donald D’Amico, New York Presbyterian Hospital, New York, NY; Jay Herson, Westat, Inc., Rockville, MD; and Ronald Klein, University of Wisconsin (through October 2007), Madison, WI.

**Data Management and Statistics**

Axon CRO, sro, Prague, Czech Republic; Martin Wallisch.


Quintiles, Edinburgh, Scotland: Patricia Cameron, Marta Sawa, and Sharon Wallace.

**Fundus Photography Reading Center, University of Wisconsin, Madison, WI**

Michael Altaweel (Primary Investigator); Ronald Danis, Amitha Domalpally (Investigators); Sheri Alexander, Ellie Corkery, Michael Daywalt, Kristi Dohm, Ryan Endres, Anne Goulding, Michael Altaweel (Primary Investigator); Ronald Danis, Amitha Domalpally, Indianapolis, IN; Thomas A. Guillaumin, Medical College of Wisconsin, Milwaukee, WI; Dean Elliott and Tamer Mahmoud, Kresge Eye Institute, Detroit, MI; Thomas R. Friberg, University of Pittsburgh Eye and Ear Institute, Pittsburgh, PA; Charles A. Garcia, Charles A. Garcia & Associates, Houston, TX; Victor H. Gonzalez, Valley Retina Institute, McAllen, TX; Nicole Gross, Private Practice, New York, NY; Lawrence S. Halperin, Valley Retina Consultants, Fort Lauderdale, FL; Henry L. Hudson III, Retina Consultants, Tucson, AZ; Gregg Kokame, Retina Vitreous Consultants, Fort Lauderdale, FL; Henry L. Hudson III, Retina Consultants, Tucson, AZ; Eugene Lit, East Bay Retina Consultants, Inc., University of Wisconsin (through October 2007), Madison, WI.

Austria. Martina Krälering, Universitäts-Klinikum für Augenheilkunde, Innsbruck; and Michael Stür, Privatordination, Wein.

Brazil. Marcos Avila, Centro Brasileiro de Cirurgia de Olhos, UFESP (Universidade Federal de São Paulo), Sao Paulo; and Javo Lavinisky, Clinica Lavinsky Oftalmologia, Porto Alegre.

Canada. David Maberly, VHHSC/UBC (Vancouver Hospital and Health Sciences Centre/University of British Columbia) Eye Care Center, Vancouver, BC; and Sebastien Olivier, Pavillon Rosemont, Montreal, QC.

Czech Republic. Jaroslava Dusova, Fakultni nemocnice Hradec Kralove, Hradec Kralove; Jan Ernest, Ustredni vojenska nemocnice, Prague; Ivan Fiser, Cornea Lexum, Prague; Petr Kolar, Fakultni nemocnice Brno, Brno; and Jiří Rehak, Fakultní nemocnice Olomouc, Olomouc.

Denmark. Michael Larsen, University Hospital Glostrup, Glostrup.

France. Jean-Paul Berrod, CHU (Centre Hospitalier Universitaire) Hôpital Central, Nancy; Francois Devin, Centre d’Ophthalmologie Paradis Monticelli, Marseilles; Franoise Koenig-Supiot, Centre de Recherche en Ophthalmologie, Lyon; Pascale Massin, Groupe Hospitalier Lariboisiere Femand Widal, Paris; and Gisele Soubrane, Clinique Ophthalmologique Centre Hospitalier Universitaire de Creteil, Creteil.

Germany. Stefan Dithmar, Universitätsklinikum Heidelberg, Augenklinik, Heidelberg; Frank Holz, Universitäts-Augenklinik Bonn, Bonn; Antonia Joussen, Alexandra Lappas, Heinrich-Heine Universität Düsseldorf, Düsseldorf; Karl-Ulrich Bartz-Schmidt, Universitäts-Augenklinik Tübingen, Tübingen; Georg Spital, Augenarztpraxis am St. Franziskus-Hospital Münster, Münster; and Peter Wiedemann, Universitätsklinikum Leipzig, Klinik und Poliklinik für Augenheilkunde, Leipzig.

Greece. Ioannis Vergados, Atikion University Hospital, Athens.

India. Rajvardhan Azad, Dr. R. P. Centre for Ophthalmic Sciences, New Delhi; Subhadra Jalali, L. V. Prasad Eye Institute, Hyderabad; Praveen Murthy, Vittala International Institute of Ophthalmology, Bangalore; and Manish Naggal, Eye Research Center and Retina Foundation, Ahmedabad.

Italy. Francesco Bandello and Paolo Lanzetta, Clinica Oculistica Policlinico Universitario a Gestione, Udine; Rosangela Lattanzio, IRCCS (Istituto Ricerca e Cura a Carattere Scientifico) San Raffaele, Unità Operativa di Oculistica, Milano; and Ugo Menchini, Università degli Studi, Dipartimento di Scienze, Firenze.

The Netherlands. Jan Keunen, UMC St. Radboud University of Nijmegen, Nijmegen.

Portugal. Joao Figueira, AIBILI (Association for Innovation and Biomedical Research and Light and Image), Associação para Investigação, Coimbra.

Switzerland. Gian-Marco Sarra and Peter Trittibach, Inselspital Klinik und Poliklinik fur Augenheilkunde, Bern.

United Kingdom. Christopher Brand, Royal Hallamshire Hospital, Sheffield; and James Talks, Royal Victoria Infirmary, Newcastle on Tyne.

United States. Kenneth Carnevale, Ophthalmic Consultants of Long Island, Rockville Center, NY; Thomas A. Guillaumin, Indianapolis, IN; Thomas B. Connor, The Eye Institute/ Medical College of Wisconsin, Milwaukee, WI; Dean Elliott and Tamer Mahmoud, Kresge Eye Institute, Detroit, MI; Thomas R. Friberg, University of Pittsburgh Eye and Ear Institute, Pittsburgh, PA; Charles A. Garcia, Charles A. Garcia & Associates, Houston, TX; Victor H. Gonzalez, Valley Retina Institute, McAllen, TX; Nicole Gross, Private Practice, New York, NY; Lawrence S. Halperin, Valley Retina Consultants, Fort Lauderdale, FL; Henry L. Hudson III, Retina Consultants, Tucson, AZ; Gregg Kokame, Retinal Consultants of Hawaii, Aiea, HI; Eugene Lit, East Bay Retina Consultants, Inc., University of Wisconsin (through October 2007), Madison, WI.

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Oakland, CA; Dennis M. Marcus, South East Retina Center, Augusta, GA; Sunil Patel, Retina Research Institute of Texas, Abilene, TX; Peter Pavan, University of South Florida, Tampa, FL; Robert Rosa, Scott and White Memorial Hospital & Clinic, Temple, TX; Delia Sang, Ophthalmic Consultants of Boston, Inc, Boston, MA; Clive Sell, Associated Retina Consultants, Phoenix, AZ; Michael Singer, Medical Center Ophthalmology Associates, San Antonio, TX; Michael P. Varenhorst, Vitreo-Retinal Consultants & Surgeons, Wichita, KS; and John Wells, Palmetto Retina Center, Columbia, SC.
