Predicting Response of Vitreous Hemorrhage after Intravitreous Injection of Highly Purified Ovine Hyaluronidase (Vitrase) in Patients with Diabetes

Abbdish R. Bhavsar, Lisa R. Grillone, Timothy R. McNamara, James A. Gow, Alan M. Hochberg, and Ronald K. Pearson

PURPOSE. To develop a predictive model for patients with diabetes who are most likely to have vitreous hemorrhage clearing by 3 months after a single, intravitreous injection of highly purified, preservative-free, ovine hyaluronidase (Vitrase; ISTA Pharmaceuticals, Inc., Irvine, CA).

METHODS. Post hoc data analysis was performed on two randomized, double-masked, placebo-controlled, phase 3 clinical trials of a single intravitreous injection of Vitrase for severe vitreous hemorrhage. Vitreous hemorrhage density was scored using a 0 to 4 vitreous hemorrhage grading scale in 12 radial segments of the fundus (“clock hours”). Reduction in total hemorrhage point score (ΔTHPS) between baseline and 1 month after injection was analyzed as a predictor of vitreous hemorrhage outcome at 3 months.

RESULTS. A strong predictive model was demonstrated by receiver operating characteristic (ROC) curve analysis; area under the curve (AUC) = 0.845 (P < 0.0001). The ΔTHPS was higher in hyaluronidase-treated subjects than in saline-treated control subjects. Median ΔTHPS was 8.0 and 6.0 in subjects treated with 55 IU (68 USP) and 75 IU (93 USP) of hyaluronidase respectively, versus 2.0 in saline control subjects (P < 0.0001).

DISCUSSION. The ΔTHPS at 1 month provides quantitative guidance for predicting the outcome of a single intravitreous ovine hyaluronidase injection in patients with diabetes and severe vitreous hemorrhage (ClinicalTrials.gov numbers, NCT00198510 and NCT00198497). (Invest Ophthalmol Vis Sci. 2008;49: 4219–4225) DOI:10.1167/iovs.07-1602

Vitreous hemorrhage, as a potentially vision-threatening complication of diabetes mellitus and other clinical conditions, may affect as many as 20,000 individuals annually in the United States. In addition to direct visual impairment, persistent vitreous hemorrhage may obscure the development of vitreoretinal traction and fibrovascular epiretinal membranes. Thus, vitreous hemorrhage must be reduced and, if possible, eliminated to restore visual acuity and permit treatment of the underlying vitreoretinal disease. In patients with proliferative diabetic retinopathy, treatment is most frequently accomplished with panretinal laser photocoagulation (PRP). Traditionally, the initial management of vitreous hemorrhage has involved observation for 3 to 6 months, followed by a vitrectomy when the hemorrhage does not clear spontaneously. During the observation period, visual impairment may interfere with activities of daily living and may increase the risk of falls in elderly patients.

Currently, dense vitreous hemorrhage is typically managed by observation or vitrectomy, or occasionally by off-label intravitreous injection of ovine hyaluronidase. Although vitrectomy is relatively safe and visual recovery usually occurs over several days to weeks, there are some potential risks of the surgery. The decision to proceed to surgery has both social and economic ramifications that the patient may face, including absence from employment for at least a few days, the necessity of care from family members after surgery, and cost of the surgery.

Enzymatic vitreolysis and clearance of the hemorrhage has been investigated as a minimally invasive, conservative, and economical treatment for vitreous hemorrhage. However, at present, there is no Food and Drug Administration (FDA)-approved agent for vitreolysis. Vitrase (ovine hyaluronidase injection; ISTA Pharmaceuticals, Inc., Irvine, CA) is FDA approved and is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. In this report we discuss the non-FDA-approved use of Vitrase for the treatment of vitreous hemorrhage. Intravitreous ovine hyaluronidase can facilitate hemorrhage clearance by inducing liquefaction of the vitreous, which allows for red blood cell lysis and phagocytosis. The efficacy and safety of a single intravitreous injection of highly purified, preservative-free, ovine hyaluronidase have been demonstrated in two large, multinational, randomized, double-blind clinical trials.

From the 1Retina Center PA, Minneapolis, Minnesota; 2ISTA Pharmaceuticals, Inc., Irvine, California; and the 4ProSanoS Corporation, Harrisburg, Pennsylvania.

*Present affiliation: PharmaQuest Associates, LLC, Carlsbad, California.

5Study group participants are listed in the Appendix.


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Corresponding author: Abdish R. Bhavsar, Retina Center PA, Park Avenue Medical Office Building, 710 E 24th Street, #304, Minneapolis, MN 55404; bhavs001@umn.edu.

Reprints requested: ISTA Pharmaceuticals, Inc., 15295 Alton Parkway, Irvine, CA 92618.
masked, placebo-controlled, phase 3 clinical trials. Although the primary efficacy end point was not met in these trials, all the secondary efficacy end points were met.

In some subjects, there was a relatively rapid response to hyaluronidase treatment, with substantial vitreous hemorrhage clearance within 4 weeks. The remaining subjects include a combination of those in whom the hemorrhage cleared within 3 months, and those in whom it appeared to be unresponsive to hyaluronidase treatment. Without a clear predictive method of distinguishing the responders from the nonresponders, the management of these patients is challenging. The clinician faces a dilemma: continued observation or vitrectomy surgery given the potential risks and costs, particularly for the high-risk surgical candidate or uninsured patient.

If a patient is treated with off-label ovine hyaluronidase, the goal is to achieve clearance of the vitreous hemorrhage. If the hemorrhage clears, the underlying disease can be treated. If the hemorrhage does not clear, then the retina surgeon must decide whether to continue observation for some period or to intervene with a vitrectomy. A predictive model to help guide the retina surgeon would be helpful in that circumstance. Such a model would allow patients to be treated with ovine hyaluronidase and then if the hemorrhage has not cleared within a month, a predictive model could be used to help predict whether the hemorrhage would be likely to clear by 3 months. If the model predicted a relatively high likelihood of clearance, then the patient would undergo continued observation. This approach may spare the patient unnecessary surgery. If the model predicted a relatively low likelihood of clearance, then vitrectomy surgery would be performed, potentially sparing the patient continued visual impairment and potential progression of the underlying disease for another 2 months.

Through a post hoc analysis of fundus examination data from the original phase 3 clinical trials, a simple and reliable scoring method was designed for distinguishing responders from nonresponders 1 month after a single intravitreal injection of ovine hyaluronidase. The method and potential implications for management of patients with diabetes and vitreous hemorrhage are described herein.

**RESEARCH DESIGN AND METHODS**

**Training Set and Validation Set**

To establish the applicability of results obtained in this retrospective analysis, the available subject data set was divided in half. One half, the training set, was used for the investigation and development of the predictive model. The other half, the validation set, was reserved until a final model was defined, and a decision threshold was chosen. The validation set was then passed through the predictive algorithm. The results reported were obtained from the validation set.

The two data sets were drawn from 856 subjects with diabetes who participated in the two phase 3 clinical trials of a single intravitreal injection of ovine hyaluronidase (Vitrase; ISTA Pharmaceuticals, Inc.) for the clearance of severe vitreous hemorrhage. Subjects who met the inclusion and exclusion criteria, including the absence of corneal or lenticular abnormalities that would preclude fundus observation along with vitreous hemorrhage, were sequentially assigned according to a computer-generated randomization list to a treatment group. The treatment groups included 7.5 IU (9.3 USP), 55 IU (68 USP), and 75 IU (93 USP). In consultation with the FDA, enrollment in the 7.5 IU group was terminated after 181 patients, because this dose was determined to be suboptimal. Data from this group are not included in this analysis.

Ophthalmic examinations were performed at baseline before intravitreous injection, at day 1, week 1, and months 1, 2, and 3 after intravitreous injection. Vitreous hemorrhage was scored at each assessment in the study eye in each of 12 angularly defined sections of the retinal fundus, corresponding to the 12 divisions of a clock face, as shown in Figure 1. Each section of the fundus was assigned a well-defined vitreous hemorrhage grading score ranging from 0 (no hemorrhage) to 4 (most severe hemorrhage). The 12 scores were summed to give a total hemorrhage point score (THPS) at each visit. The reduction in THPS between baseline and 1 month after intravitreous injection (ΔTHPS) was recorded. Note that this score is calculated as a "reduction" (THPS at baseline minus THPS at 1 month) rather than a "change" (THPS at 1 month minus THPS at baseline), to generate a positive number in most subjects.

The primary efficacy end point was defined by clearance of vitreous hemorrhage sufficient to see the underlying disease and to complete treatment, when indicated, by the month 3 visit. A subject was classified as having successful treatment if the vitreous hemorrhage in the study eye had sufficiently cleared for diagnosis of the underlying disease and if one of three predefined criteria were met within the month 3 visit window. One of the criteria was the completion of PRP for the underlying condition and at each clinical assessment. A notation was made in the case report form (CRF) as to whether PRP was initiated, ongoing, or successfully completed.

Data from the month 1 evaluation were used to predict the outcome in each subject at the end of month 3. Subjects for whom such a prediction would be irrelevant were eliminated from the receiver operating characteristic (ROC) curve analysis. Thus, subjects were excluded if the following events occurred before the month 1 visit: a serious adverse event, a vitrectomy or other ocular surgical procedure, and initiation or successful completion of PRP. A small number of subjects in whom ΔTHPS or outcome could not be determined due to missing data were eliminated. The remaining set of subjects was divided randomly into two halves: the training set and the validation set.

**Statistical Analysis**

A binary outcome classifier was assigned: 1, to designate a subject who had successful completion of PRP without vitrectomy at or before the month 3 visit (responder); 0, to designate a subject who did not have successful completion of PRP at or before the month 3 visit (nonre-
sponder). The $\Delta$THPS was evaluated as a predictor of this binary outcome. An algorithm known as a linear classifier was used. If the $\Delta$THPS exceeded a threshold value for a given subject, it was considered to be “positive,” predicting a favorable response to intravitreous ovine hyaluronidase treatment. If the $\Delta$THPS was less than or equal to the threshold, it was assessed as “negative,” predicting an unfavorable response. The selection of an appropriate threshold is discussed next.

The predictive value of $\Delta$THPS for the outcome was determined by using an ROC curve. The area under the curve (AUC) was calculated, and a z-score was used to compare the predictive value of $\Delta$THPS with that of a random classification with no predictive value (null hypothesis). Nonparametric density estimation was used to plot the distribution of $\Delta$THPS in subjects by treatment group, and the treatment groups were compared by using the Kruskal-Wallis test and pair-wise by the Wilcoxon rank sum test.

To evaluate the use of $\Delta$THPS for the classification of subjects, a threshold value for $\Delta$THPS which best separated responders from nonresponders was chosen. Two experienced clinicians were presented with a table, based on training set data, which listed the number of true positives, true negatives, false positives, and false negatives that would result from various thresholds from 0 to 48. The clinical consequences of each patient scenario—true positive, true negative, false positive, and false negative—were explained and discussed. The clinicians were then asked to reach an agreement on a threshold which, in their judgment, represented the best tradeoff between false positives and false negatives, given the clinical consequences of each. The same threshold value was then applied to data from the validation set. The outcomes were tallied for subjects above and below this threshold. All statistical analyses were performed with commercial software (S-Plus, ver. 7.0; Insightful Corp., Seattle, WA).

RESULTS

Subject Disposition: Training and Validation Set

Of the 856 subjects with diabetes who were analyzed, 43 (5.0%) were excluded because of missing data for the calculation of the $\Delta$THPS, missing outcome data due to a missed month 1 visit, or loss to follow-up. Of the remaining 813 subjects, 13 (1.5%) were excluded because of treatment failure at or before the month 1 visit—namely, vitrectomy or other surgical procedures (e.g., cryoretinopexy or scleral buckle). Two of these subjects (0.2%) experienced serious adverse events, specifically retinal detachment. For the laser-treatment outcome, 100 (11.7%) subjects were excluded due to PRP initiation before the month 1 visit, which left 700 subjects. The subjects were then divided into a training set and a validation set of 350 subjects each. The training set was used for the evaluation of predictive models and the selection of the threshold.

As described in the Methods section, two experienced clinicians were asked to select the threshold, based on a table of the number of true-positive, false-positive, true-negative, and false-negative outcomes derived from the training set. A threshold of 5.0 was chosen by the clinicians and was then used to classify the patients in the validation set into predicted responders and nonresponders. The performance of those predictions is reported in the next section.

$\Delta$THPS and Successful Laser Treatment

The ROC curve in Figure 2 shows the ability of $\Delta$THPS to predict successful laser treatment for various threshold levels of $\Delta$THPS. The y-axis shows sensitivity, which is the fraction of subjects in whom $\Delta$THPS was above the threshold among those who successfully completed laser treatment. The x-axis shows specificity, which is the fraction of subjects in whom $\Delta$THPS was below the threshold among those who failed to complete laser treatment without vitrectomy. The AUC is 0.845, refuting the null hypothesis of no predictive ability at $P < 0.0001$.

The selected $\Delta$THPS threshold of 5.0 resulted in a sensitivity of 84%, a specificity of 72%, a predictive value of a positive ($\Delta$THPS above threshold) of 57%, and a predictive value of a negative ($\Delta$THPS below threshold) of 91%. A tree diagram of subject outcomes, using the threshold $\Delta$THPS > 5.0, is shown in Figure 3.

$\Delta$THPS by Treatment Group

Figure 4 shows nonparametric density estimates for $\Delta$THPS in the three treatment groups and indicates a skewed distribution. Median $\Delta$THPS for the saline, 55-IU, and 75-IU treatment groups are 2.0, 8.0, and 6.0 respectively. A one-sided Wilcoxon rank sum test of the hypothesis that the ovine hyaluronidase 55-IU response is greater than the saline control response yields a z-score of 4.3664 ($P < 0.0001$). A similar test for the ovine hyaluronidase 75-IU response versus the saline control yields a z-score of 3.4577 ($P = 0.0003$). The difference between the 55- and 75-IU groups is not statistically significant ($P = 0.847$). A Kruskal-Wallis test for the equivalence of $\Delta$THPS in the three treatment groups yields a $\chi^2$ of 20.9626 (2 df; $P < 0.0001$).

DISCUSSION

Enzymatic vitreolysis with highly purified, preservative-free ovine hyaluronidase is emerging as a potential treatment for vitreous hemorrhage. The failure to meet the primary efficacy end point in the phase 3 clinical trials despite meeting all the secondary end points, variable responses to treatment, and a delay of up to 3 months between treatment and resolution have created challenges for patient management under the current treatment algorithm. For the patient who does not respond rapidly (i.e., within 1 month) to an intravitreous hyaluronidase injection, there has been no objective guidance to observe the patient or proceed to vitrectomy.
Results from this analysis demonstrate that based on a non-invasive retinal examination at baseline and at 1 month after injection, the treating physician has a predictive scoring method to determine the likelihood of vitreous hemorrhage clearance after treatment with ovine hyaluronidase. Many patients who will respond to this treatment can be identified earlier, thus avoiding an unnecessary vitrectomy. In addition, the ΔTHPS measurement can identify patients who may not be likely to respond to hyaluronidase treatment. An earlier vitrectomy may improve their quality of life and prevent worsening of their underlying retinal disease.

The conservative choice of threshold, ΔTHPS > 5.0, is based on the paramount need to avoid “false negatives,” which may result in recommendations of vitrectomy for patients who would otherwise respond to hyaluronidase treatment. If vitrectomy decisions were based solely on ΔTHPS, we would anticipate that 4.2% of patients would fall into this “false-negative” category. The false-negative value must be placed in context and compared to the potentially much larger number of potential responders who might undergo vitrectomy in the absence of any predictive guidance.

The potentially subjective nature of the scoring methodology used raises the question of interobserver variability. Regarding this, we note that the scoring system was previously published and validated as part of the clinical trial. The methodology is further validated, since the training set was reproduced in the validation set. Finally, we note that interobserver variability is automatically accounted for in an ROC analysis: the scoring methodology must be reproducible in order for the score to have significant predictive value. A nonreproducible scoring system would result in a nearly straight ROC curve, an AUC near 0.5, and a predictive value near 50%.

Quantitative predictive models and ROC curves are common in many areas of medicine. For example, the CD4
count has been used as a surrogate marker for measuring the RNA human immunodeficiency virus (HIV), and the AUC was 0.76. Another example is the prostate-specific antigen (PSA) test as the surrogate marker for prostate cancer, where the AUC is 0.74 to 0.76. The use of ROC curve analysis in ophthalmology is increasing. We have presented a simple binary decision model to clearly articulate the process and the results of our analysis for vitreous hemorrhage after ovine hyaluronidase intravitreal injection, where the AUC was 0.845. In clinical practice, we anticipate that the ΔTHPS will assist in clinical decision-making for patients with diabetes and severe vitreous hemorrhage (Landers MB, et al. IOVS 2006;47: ARVO E-Abstract 998, Bhavsar AR, et al. IOVS 2006;47:ARVO E-Abstract 975). Patients with “borderline” ΔTHPS could be observed, for example, for an additional month, and re-evaluated. General patient health, candidacy for vitrectomy, and occupational requirements should be considered in addition to the ΔTHPS when deciding to perform surgery.

The ROC curve analysis is dependent on the demographics and the clinical characteristics of the population studied. It should be noted that this population included a control group of subjects who received a saline injection. Since saline injection is not used as a treatment for vitreous hemorrhage, this group would not exist in clinical practice. Of importance, the response rate of subjects in the saline group was lower than in those in the hyaluronidase group. Therefore, the results presented herein are conservative, and the overall treatment benefit is underestimated. In clinical practice, the predictive model may be more useful when the alternative treatment is observation alone. The saline control group was retained to demonstrate that the ΔTHPS-based predictions are valid over a wide range of hyaluronidase dosages, including 0. It is unknown whether the validated predictive model for vitreous hemorrhage and Vitrase, a highly purified form of ovine hyaluronidase, would be applicable to other forms of hyaluronidase including compounded, bovine or other animal, and human recombinant. Separate validation studies would be necessary for each alternative hyaluronidase source, with a design similar to that used in our study.

Note also that all the subjects in this study had what would be characterized as “dense” vitreous hemorrhage, due to the nature of the entry criteria. The median baseline THPS was 46.5 of a possible score of 48.0 (indicating total opacity). Thus, we cannot address the questions of treatment effectiveness or applicability of the model in patients with less severe degrees of vitreous hemorrhage.

The model illustrates that the long-term outcome of hyaluronidase treatment is largely determined by physiological events in the first few weeks, even if they produce only small changes in the ΔTHPS. The mechanisms underlying vitreous hemorrhage clearance are not completely understood and may include vitreous convection currents affecting the diffusion, absorption, and metabolism of the red blood cells. Treatment failure may be due to recurrent vitreous hemorrhage or the formation of epiretinal or vitreoretinal fibrovascular membranes which could interfere with the physical transport of hemoglobin, red blood cells, and cellular and biochemical factors that affect phagocytosis. The results presented may lead to future clinical investigations of the vitreous hemorrhage treatment algorithm. Additional studies may include the development and validation of more sophisticated predictive models, incorporating earlier and more frequent measurements of changes in THPS, as well as additional variables such as the patient’s age or duration of the hemorrhage. Finally, there is the possibility, not considered in these trials, of using ΔTHPS to identify candidates for a second injection of hyaluronidase.

In conclusion, when a patient with diabetes presents with severe vitreous hemorrhage, the clinician may choose to treat off-label, with a single 55-IU intravitreal injection of highly purified, preservative-free, ovine hyaluronidase. The application of the predictive model using the ΔTHPS under this circumstance provides a tool to help guide decision-making and the further management of these patients. Ultimately, the use of such a model will lead to more effective care of patients with diabetes who receive off-label treatment with ovine hyaluronidase for severe vitreous hemorrhage.

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References


**APPENDIX**

**Vitrase for Vitreous Hemorrhage Study Groups**

Australia: M. G. Branley, Royal North Shore Hospital, St. Leonards, NSW, Australia; A. Chang, University of Sydney, Sydney Eye Hospital, Sydney, NSW, Australia; W. Heriot, W. G. Campbell, Royal Victorian Eye and Ear Hospital, East Melbourne, VIC, Australia; L. R. Lee, Royal Brisbane Hospital, Herston, QLD, Australia; P. Mitchell, University of Sydney, Westmead Hospital, Westmead, NSW, Australia; and H. S. Newland, Royal Adelaide Hospital, Adelaide, SA, Australia.

Brazil: S. Abujamra, Clinica de Olhos, Sao Paulo, Brazil; M. P. Avila, Centro Brasilierno de Crugia de Olhos, Goiania, Brazil; M. E. Farah, Universidade Federal de Sao Paulo, Escola Paulista de Medicina, Sao Paulo, Brazil; J. Lavinsky, Hospital de Clinicas de Porto Alegre, Porto Alegre, RS, Brazil; C. A. Moreira, Universidade Federal do Parana, Curitiba, Brazil; and M. G. Ne-hemy, Instituto da Visao, Belo Horizonte, MG, Brazil.

Canada: J. Deschenes, Royal Victoria Hospital, McGill University Health Centre, Montreal, QU, Canada; R. G. Devenyi, The Toronto Western Hospital, Toronto, ON, Canada; J. J. Deschartres, Dalhousie University, Halifax, NS, Canada; M. Erasmus, Saskatoon City Hospital, Saskatoon, Saska., Canada; R. Garcia-Salinas, The Medical Centre, Pasqua Hospital, Regina, Saska., Canada; J. R. Gonder, Ivey Institute of Ophthalmology, London, ON, Canada; P. J. Kertes, University of Ottawa Eye Institute, Ottawa, Ont., Canada; P. E. Ma, University of British Columbia, Vancouver, BC, Canada; and Y. M. Tardif, Centre Hospitalier de l’Univesitse Laval (CHUL), Sainte Foy, QU, Cana-da.

Hungary: A. Berta, Medical University of Debrecen, Debrecen, Hungary; G. Deak, Central Army Hospital of the Hungarian Army, Budapest; L. Kolozsvári, University of Szeged, Albert Szent-Gyorgyi Medical University, Szeged, Hungary; B. Kovacs, Medical University of Pecs, Pecs, Hungary; T. Műhiák, Uzsoki Street Hospital of the Municipality of Capital, Budapest; and G. Slacz, Semmelweis University, Budapest, Hungary.

Italy: E. Balestrazzi, Universita degli Studi dell’Aquila, Coppito, Italy; U. Menchini, Universita degli Studi di Firenze, Firenze, Italy; and M. Stirpe, Fondazione G. B. Bietti per lo Studio e la Ricerca in Oftalmologia, Rome, Italy.

Mexico: A. W. Levine, Fundacion Hospital, Nuestra Senora de la Luz IAP, Cuauhtemoc, Mexico; V. Morales, Asociacion Para Evitar la Ceguera en Mexico, Coyacan, Mexico; and M. A. Qurioz, Instituto de Oftalmologia, Fundacion Conde de Valencia, Col. Obrera, Mexico.

The Netherlands: M. D. de Smet, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; R. W. A. M. Kuijpers, University Hospital Rotterdam, Rotterdam, Netherlands; and J. M. Hooymans, Academic Hospital Groningen, Groningen, The Netherlands.

Poland: J. Kaluzny, Klinika Chorob Oczu, Bydgoszcz, Po-land; M. Kmer-Muszynska, Medical Academy, Warsaw, Poland; J. Nawrocki, Medical Academy, Lodz, Poland; H. Nizankowska, Wroclaw University of Medicine, Wroclaw, Poland; K. Pecold, K. Marcinkowski University of Medical Sciences, Poznan, Poland; P. Phillips, Main Regional Hospital, Poznan, Poland; S. Pojda, Silesian School of Medicine, Bytom, Poland; K. Raczynska, Ophthalmology Clinic, Gdansk, Poland; and Z. Zagorski, Ophthalmology Chair and Clinic, Lublin, Poland.

South Africa: J. Acton, Private Practice, Bellville, South Af-rica; C. M. Johnston, Groote Schuur Hospital, Observatory, Cape Town, South Africa; J. J. Krouse, Private Practice, Alber-ton, Aberante, Alberton, South Africa; L. P. Kruger, Private Practice, Northcliff, Johannesburg, South Africa; A. Peters, Add-ington Hospital, Durban, South Africa; K. N. Rivett, Private Practice, Southernwood, East London, South Africa; J. S. Roelofse, Pretoria Eye Institute, Arcadia, South Africa; A. A. Stulting, Nasionale Hospital, Bloemfontein, South Africa; K. Woods, Newlands Surgical Clinic, Claremont, Cape Town, South Africa.

Spain: F. Clement-Fernandez, Hospital de la Princesa, Ma-drid, Spain; M. S. de Figueroa-Diez, Hospital Ramon y Cajal, Madrid, Spain; M. D. Navea-Tejerina, Hospital Universitario La Fe, Valencia, Spain; and J. M. Ruiz Moreno, Instituto Oftalmologico de Alicante, Alicante, Spain.

United Kingdom: H. Atta, Aberdeen Royal Infirmary, Aber-deen, Scotland, UK; A. G. Casswell, Sussex Eye Hospital, BRIGHT- ton, East Sussex, UK; A. Chopard, East Surrey Hospital, Redhill, Surrey, UK; R. H. B. Gray, Bristol Eye Hospital, Bristol, UK; C. Groenevald, Royal Liverpool University Hospital, Liverpool, UK; J. D. A. McHugh, Kings College Hospital, London; C. S. Ng, H. M. Stanley Hospital, St. Asaph, Denbighshire, UK; P. H. Rosen, Oxford Eye Hospital, Oxford, UK; K. P. Stannard, Royal Victoria Infirmary, Newcastle On Tyne, UK; K. K. Swa, Princess Alexandra Eye Pavilion, Royal Infirmary of Edinburgh, Edin-burgh, Scotland, UK; T. H. Williamson, St. Thomas’ Hospital, London, UK; and D. Verma and C. Edrich, Hull Royal Infirmary, Hull, UK.

United States: A. N. Antonszyn, Charlotte Eye, Ear, Nose, and Throat Association, Charlotte, NC; R. L. Avery, Private Practice, Santa Barbara, CA; G. A. Bertolucci, Eye Medical Center of Fresno, Fresno, CA; A. R. Bhavsar, Retina Center PA, Minneapolis, MN; R. H. Bradford, Jr, Dean A. McGee Eye Institute, Oklahoma City, OK; R. L. Brownlow, Jr, Vistar Retinal Consultants, Roanoke, VA; A. J. Brucker, Scheie Eye Institute, Philadelphia, PA; M. M. Carim, Carim Eye and Retina Center, Wyomissing, PA; M. E. Castilloles, Private Practice, Chula Vista, CA; C. K. Chan, Southern California Desert Retina Consultants, Palm Springs, CA; N. A. Chaudhry, New England Retina Associates, New London, CT; T. B. Connor, Jr., Medical College of Wisconsin, Milwaukee, WI; F. H. Davidorf, Ohio State University, Columbus, OH; A. R. Dayan, Retina Consultants of Southern Colorado, Colorado Springs, CO; D. S. Dyer, Retina Associates of Kansas City, Kansas City, MO; A. M. Eaton
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