

Safety Results of Two Phase III Trials of an Intravitreal Injection of Highly Purified Ovine Hyaluronidase (Vitrase[®]) for the Management of Vitreous Hemorrhage

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• **PURPOSE:** To evaluate the safety of intravitreal ovine hyaluronidase for the management of vitreous hemorrhage.

• **DESIGN:** Two prospective, randomized, placebo-controlled, double-masked studies. Pooled efficacy data are presented in a companion article in this issue of THE JOURNAL.

• **METHODS:** Subjects with vitreous hemorrhage ≥ 1 month, severe at entry and best corrected visual acuity (BCVA) worse than 20/200 in the study eye were randomized to 7.5 IU, 55 IU, 75 IU ovine hyaluronidase, saline, or no injection. Assessments occurred on day 1, week 1, months 1, 2, 3, 6, and then every 6 months for as long as 32 months. Assessments included history, ocular symptoms, adverse events, BCVA, intraocular pressure, external eye examination, slit-lamp biomicroscopy, fundus examination, B-scan ultrasonography, and fundus photography.

• **RESULTS:** Of 1362 subjects in the safety population, 1344 received hyaluronidase or saline and 18 no treatment. Iritis was the most common ocular adverse event, occurring in 33.3%, 62.1%, 58.9%, and 62.1% of saline, 7.5 IU, 55 IU, and 75 IU-treated subjects. In eyes with more than mild iritis, a dose response was

observed: 8.9%, 20.2%, 33.7%, and 39.7% of saline, 7.5 IU, 55 IU, and 75 IU-treated subjects, respectively, were noted to have moderate or severe iritis. Retinal detachments (RDs) were reported in 9.5% of study eyes: 26 (6.9%), 22 (11.1%), 35 (9.3%), and 45 (11.5%) in the saline, 7.5 IU, 55 IU, and 75 IU-treated subjects. Overall, 1.8% of study eyes had rhegmatogenous RD: 1.1%, 2.5%, 1.6%, and 2.3% of saline, 7.5, 55, and 75 IU treated subjects. Cataracts occurred similarly across treatment groups. No injection-related infectious endophthalmitis was reported.

• **CONCLUSIONS:** No serious safety issues were reported after a single intravitreal injection of ovine hyaluronidase. RD incidence was not statistically different between groups. Iritis manifesting as an acute self limited inflammation was the most common adverse event, occurred in a dose response fashion, but was not noted to result in a serious adverse event in any hyaluronidase treated eye. (Am J Ophthalmol 2005;140:585–597. © 2006 by Elsevier Inc. All rights reserved.)

VITREOUS HEMORRHAGE IS AN IMPORTANT CAUSE of painless sudden loss of vision. The most common causes of vitreous hemorrhage are proliferative diabetic retinopathy, branch or central retinal vein occlusion, posterior vitreous detachment with or without a retinal tear or detachment, and trauma. The clinical impact of vitreous hemorrhage is apparent in three areas: decreased visual acuity, obscuration of important and potentially treatable ocular pathology, and complications related to the vitreous hemorrhage and its resolution.^{1,2} Currently, vitreous hemorrhage is managed by waiting for spontaneous resolution within a predefined time (that is, “watchful waiting”), followed by vitreoretinal surgery when indicated. The period of observation commonly varies between 1 to 3 months depending on hemorrhage

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etiology, and can represent a time of significantly reduced quality of life for the patient. For patients who are not surgical candidates, the observation period may be prolonged because there are no nonsurgical treatments for vitreous hemorrhage currently available. Regardless of whether the hemorrhage clears spontaneously or requires vitrectomy for clearance, it may be important to identify underlying pathology and treat it as soon as possible.

Vitreous hemorrhage can be surgically managed in a number of etiologies; however, the risks of surgical complications exist.³⁻¹⁰ Although modern vitrectomy procedures carry relatively limited risks, there can be untoward outcomes, including progressive cataract, recurrent vitreous hemorrhage, intraoperative retinal breaks and detachment, rubeosis iridis, neovascular glaucoma, and endophthalmitis. Investigators have considered various pharmacological approaches to lyse or dissipate vitreous hemorrhage or modify the structural characteristics of the vitreous gel to allow the relocation of the blood out of the visual axis. This article describes the use of a single intravitreal injection of highly purified ovine hyaluronidase, which represents the first concerted effort to introduce a safe and efficacious pharmacological, enzymatic treatment as an addition to the armamentarium for the management of vitreous hemorrhage. The goal of treatment with an intravitreal injection of ovine hyaluronidase is to provide a safe treatment alternative to reduce and/or clear vitreous hemorrhage density sufficiently to provide earlier visualization of the retina. This would facilitate the physician's ability to diagnosis the underlying retinal pathology and assess the need for additional treatment, as well as restore the subject's visual acuity when there is adequate retinal function. This may reduce the risk of further complication and improve the subject's quality of life.

Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and, to a variable degree, some other acid mucopolysaccharides of the connective tissue.¹¹ Dissolution of the hyaluronic acid and collagen complex results in the liquefaction of the vitreous. This, in turn, increases the diffusion rate of erythrocytes and phagocytes through the vitreous and facilitates red blood cell lysis and phagocytosis.^{12,13} Hyaluronidase in another form (less purified bovine testicular protein enzyme with thimerosal as a preservative; Wydase) has been widely used in ophthalmology for approximately 40 years as a spreading or diffusing agent, most commonly to enhance the effect of injectable local anesthetics. However, this bovine hyaluronidase/thimerosal formulation was designed as a spreading agent and not for intravitreal injection and is no longer on the market in the United States. On 5 May 2004, the United States Food and Drug Administration (FDA) approved the preservative-free, highly purified ovine hyaluronidase formulation (Vitrace[®]), the pharmaceutical agent discussed in this article, for use as an adjuvant to increase the absorption and dispersion of other injected drugs.

This article presents the integrated safety results from two phase III, randomized, controlled clinical trials that studied a single intravitreal injection of highly purified ovine hyaluronidase for the management of vitreous hemorrhage. The trials were conducted in North America (Vit-02 Study) and outside of North America (Vit-03 Study). The pooled efficacy data from both of these trials are presented in a companion article in this issue of THE JOURNAL.

METHODS

THE DATA FROM TWO RANDOMIZED, PARALLEL-GROUP, double-masked clinical trials were integrated to evaluate the safety of a single intravitreal injection (50 μ l) of ovine hyaluronidase compared with 0.9% sodium chloride USP (saline). One clinical trial (Vit-02) was conducted in North America (Canada, United States, and Mexico) with 821 subjects from 73 sites and the other clinical trial (Vit-03) was conducted in Europe, South Africa, South America, and Australia with 541 subjects from 58 sites. Before the initiation of the ex-North American trial (Vit-03), the trial in North America originally incorporated a watchful waiting control group. However, to meet the regulatory requirement for "adequate and well-controlled studies" in accordance with International Committee for Harmonization (ICH) Guideline E10, the North American trial was amended after consultation with the FDA to replace the uninjected watchful waiting control group with a saline intravitreal injection control group. At the time the North American trial was amended, 71 subjects had already been randomized and entered into the study. Of these 71 subjects, 18 subjects had been randomized to the uninjected watchful waiting control group and 18, 18, and 17 subjects were randomized to 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups. After the protocol was amended, these 71 subjects were followed as part of the safety population, but were excluded from statistical analyses for efficacy. Thus, both the North American and ex-North American trials were ultimately conducted with a saline intravitreal injection control and were identical in design with the exception of the doses studied. The North American trial had a small subset of subjects who received no test agent (that is, the watchful waiting control group) and evaluated three doses of ovine hyaluronidase (7.5 IU, 55 IU, and 75 IU). In contrast, the ex-North American trial had no watchful waiting control group and evaluated two doses of ovine hyaluronidase (55 IU and 75 IU), because of restrictions on the study design imposed by international regulatory agencies.

In these two multicenter trials, the safety population was defined as all subjects who were sequentially assigned according to a computer-generated randomization list to a treatment group and who had at least one posttreatment assessment. Of the 1362 subjects included in the safety

population, 966 were injected with ovine hyaluronidase, 378 were injected with saline, and 18 were not injected (that is, the original watchful waiting control group). The studies were designed such that the primary efficacy end-point (clearance of vitreous hemorrhage sufficient to see the underlying pathology and completion of treatment, when indicated, by the month 3 visit) was evaluated up to 3 months posttreatment. This article summarizes safety data collected for this population through at least the 3-month time point, with some subjects followed for as long as 32 months. All data were collected under protocols conducted in accordance with the principles stated in the Declaration of Helsinki. The protocols were approved by the institutional review board or ethics committee used by each site, and all subjects provided written informed consent.

Male and female subjects were eligible for enrollment if they were 18 years or older and had a vitreous hemorrhage of any etiology excluding trauma in the study eye that had been present for at least 1 month, and that was dense enough at entry to obscure visualization of the fundus on indirect ophthalmoscopy such that no retinal detail was visible posterior to the equator. Eligible subjects had best corrected visual acuity (BCVA) worse than 20/200 in the study eye.

Subjects were excluded if they had corneal abnormalities that would have precluded fundus observation or accurate intraocular pressure (IOP) readings with an applanation tonometer or a Tono-Pen[®]; ocular infection or inflammation or a history of herpetic corneal lesion; current or prior retinal detachments, retinal tears or breaks, or intraocular tumor; more than one severe vitreous hemorrhage within the 6 months before the onset of the present hemorrhage; vitreous hemorrhage associated with ocular trauma; previous vitrectomy; hemorrhage that was old and organized; no light perception (NLP) in either eye before or at screening; or a history of sickle cell disease.

Eligible patients were sequentially assigned according to a computer generated randomization list to one of four (North American Vit-02 Study) or three (ex-North American Vit-03 Study) treatment groups in a 1:1:1:1 ratio and a 1:1:1 ratio, respectively. If a subject presented for randomization with a qualifying vitreous hemorrhage in both eyes, only one eye (the right eye, designated the study eye) was entered into the study. Treatment consisted of a single intravitreal injection (50 μ l) of 7.5 IU, 55 IU, or 75 IU ovine hyaluronidase (equivalent to 9.3, 68, or 93 USP units, respectively) or saline (0.9% sodium chloride solution) through the pars plana using a 30-gauge needle and local anesthesia. The physician's standard preoperative regimen to ensure antisepsis of the injection site was followed. The use of the following were allowed, but not required by the protocol: povidone solution or swab, topical antibiotics, eyelid speculum, and digital massage. The recommended injection location was in the superior temporal quadrant or in the inferior temporal quadrant,

through the pars plana, approximately 3.5 to 4 mm from the limbus. To ensure the integrity of the study masking procedures, an unmasked person not involved in the treatment or evaluation of the subject was chosen in advance at each site to select the appropriate test agent vial as determined by the randomization sequence, prepare the test agent, and deliver the test agent to the masked injecting investigator. Masking of the investigator and subject was maintained throughout the duration of the study.

Subjects were assessed posttreatment on day 1, week 1, and months 1, 2, 3, 6, 12, and then every 6 months. Assessments performed during the study consisted of medical/ophthalmic history, ocular symptoms, adverse events, concomitant medications, BCVA, IOP, external eye examination, slit-lamp biomicroscopy, dilated fundus examination, B-scan ultrasonography, and fundus photography. BCVA was recorded using Bailey-Lovie visual acuity charts at 4 m or 10 feet distance. If the subject was unable to see any letters at a distance of 1 m or 2.5 feet (for example, subject's vision is count fingers or worse), then the visual acuity level and distance was recorded. The protocol prohibited the use of any drugs prescribed specifically for the treatment of vitreous hemorrhage, whether by indication or outside of the labeled indication. Topical and systemic concurrent medications were allowed at the discretion of the investigator as long as the investigator felt that the medications would not interfere with the evaluation of safety or efficacy in the study and were not being prescribed specifically for the treatment of vitreous hemorrhage. A vitrectomy could have been performed at any time during the course of the study as deemed clinically necessary by the investigator.

Baseline characteristics were analyzed using either a one-way analysis of variance (ANOVA) for numeric response variable, or an appropriate categorical analysis (for example, χ^2 and/or Fisher's exact test) for categorical response frequencies. Adverse event summaries were provided using descriptive statistics. Statistical significance was on the basis of a generalized Fisher's exact test that compared incidence among and between the saline and ovine hyaluronidase treatment groups. History and duration of vitreous hemorrhage in the study eye was summarized for the pooled intent-to-treat population (ITT) from the saline-control study ($n = 1306$) and is shown comparatively with the 18 subjects assigned to the watchful waiting control group in the original protocol.

All ocular signs and symptoms were graded on the case report forms (CRF) and assessments for anterior segment intraocular signs are summarized in Table 1. Baseline data were collected from CRFs at the screening visit. Adverse event data (all adverse events reported regardless of causality) were collected from the adverse event reports recorded by the individual investigators on the CRFs. The verbatim terms were entered into the Medical Dictionary for Regulatory Activities (MedDRA) term system (Version

TABLE 1. Ovine Hyaluronidase for Vitreous Hemorrhage: Assessment Grading Scales for Anterior Segment Intraocular Signs

Anterior chamber-cells	
0 =	None-No cells seen
1 =	Mild-1–15 cells
2 =	Moderate-16–25 cells
3 =	Severe-26–50 cells
4 =	Hypopyon->50 cells, hypopyon formation (indicate size of hypopyon)
Anterior chamber-flare	
0 =	None-No Tyndall effect
1 =	Mild-Tyndall beam in the anterior chamber has a mild intensity, iris and lens are clear
2 =	Moderate-Tyndall beam in the anterior chamber is of strong intensity, iris and lens are hazy
3 =	Severe-Tyndall beam is very intense. The aqueous has a white, milky appearance
Iris status (Present or Absent)	
Normal dilation-	If absent, include # mm dilation
Rubeosis-	If present, specify clock hour(s) where present
Posterior synechiae-	If present, specify clock hour(s) where present
Lens status/pathology-nuclear sclerosis	
0 =	None-None present
1 =	Mild-Subtle yellowing of the nucleus
2 =	Moderate-Moderate yellowing of the nucleus
3 =	Severe-Dense brunescence of the nucleus
Lens status/pathology-cortical cataract	
0 =	None-None present
1 =	Mild-Minimal peripheral cortical spokes with clear visual axis
2 =	Moderate-Significant peripheral cortical spokes with clear visual axis
3 =	Severe-Significant peripheral cortical spokes partially obscuring visual axis
Lens status/pathology-posterior subcapsular opacity:	
Location and size documented, no grading scale used.	

3.3) to derive a system organ class and an appropriate MedDRA term. The cumulative incidence for a particular MedDRA term was used to determine the total number of each event. Summary tabulations of MedDRA-coded adverse events were given as an incidence (that is, first occurrence of a particular adverse event in each subject) and number of events (that is, frequency of occurrence). Because subjects received only one intravitreal injection of the assigned test agent, “incidence” is expressed as a percentage rather than a rate (that is, number of subjects with an adverse event/treatment-year). For analysis purposes, all adverse events were graded by severity (mild, moderate, or severe) and relatedness to the test agent (unknown/unlikely, probably, or possibly), as determined by the investigator.

RESULTS

THIS REPORT SUMMARIZES DATA FOR ALL 1362 (100%) SUBJECTS with at least one postbaseline visit, and for 1202 (88.3%), 985 (72%), and 654 (48%) subjects who were evaluated for 3, 6, and 12 months postinjection, respec-

tively. Of these 1362 subjects, 18 subjects were not treated (that is, the uninjected watchful waiting control group), 378 subjects received an injection of saline, and 198, 377, and 391 subjects received an injection of 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase, respectively. In total, 966 subjects received an injection of ovine hyaluronidase. Where pairwise comparison data are presented, the population excludes those subjects in the Watchful Waiting Control Study (that is, 18, 18, 18, and 17, for no injection, 7.5 IU, 55 IU, and 75 IU dose groups, respectively).

Demographics and baseline characteristics were similar across the saline, 55 IU, and 75 IU ovine hyaluronidase groups (Table 2). The differences at baseline for the 7.5 IU ovine hyaluronidase group can be attributed to this dose group being used only in the North American trial. Thus, the 7.5 IU dose group had a smaller number of subjects than the 55 IU and 75 IU ovine hyaluronidase groups and a higher Hispanic representation. For the watchful waiting control group, the differences in baseline statistics can be attributed to the small number of subjects (n = 18) included in this group. Overall, the demographics and baseline characteristics support a robust safety database for analyses with no apparent inadequacies in representation

TABLE 2. Ovine Hyaluronidase for Vitreous Hemorrhage: Gender, Age, Ethnicity, Diabetic Status, and Best Corrected Visual Acuity Characteristics of Subjects Completing a 3-Month Visit for Centers in North America (Vit-02 trial) and Outside of North America (Vit-03 trial)

Characteristic	Control Groups		Ovine Hyaluronidase Dose Groups		
	Watchful Waiting (n = 18)	Saline (n = 378)	7.5 IU (n = 198)	55 IU (n = 377)	75 IU (n = 391)
Age (median, years)*	67.5 (n = 18)	63 (n = 375)	60 (n = 198)	62 (n = 375)	63 (n = 391)
Gender					
Male	13 (72.2%)	183 (48.4%)	100 (50.5%)	193 (51.2%)	215 (55%)
Ethnicity					
Caucasian	7 (38.9%)	255 (67.5%)	97 (49%)	250 (66.3%)	265 (67.8%)
Hispanic†	5 (27.8%)	65 (17.2%)	74 (37.4%)	73 (19.4%)	70 (17.9%)
Black	3 (16.7%)	31 (8.2%)	11 (5.6%)	26 (6.9%)	32 (8.2%)
Other‡	3 (16.7%)	27 (7.1%)	16 (8.1%)	28 (7.4%)	24 (6.1%)
Diabetic status					
Non-Diabetic	2 (11.1%)	86 (22.8%)	25 (12.6%)	104 (27.6%)	80 (20.5%)
Diabetes	16 (88.9%)	292 (77.2%)	173 (87.4%)	273 (72.4%)	311 (79.5%)
Type I	5 (31.3%)	169 (57.9%)	106 (61.3%)	164 (60.1%)	187 (60.1%)
Type II	11 (68.7%)	123 (42.1%)	67 (38.7%)	109 (39.9%)	124 (39.9%)
Best corrected visual acuity‡					
n (ITT)	18	383	181	365	377
Light perception	1 (5.6%)	97 (25.3%)	21 (11.6%)	84 (23.0%)	86 (22.8%)
Hand motion	11 (61.1%)	172 (44.9%)	88 (48.6%)	176 (48.2%)	180 (47.7%)
Count fingers	5 (27.8%)	75 (19.6%)	53 (29.3%)	73 (20.0%)	76 (20.2%)
Read letters (20/800 or better)	1 (5.6%)	31 (8.1%)	19 (10.5%)	30 (8.2%)	33 (8.8%)
Missing or NA	0 (0.0%)	8 (2.1%)	0 (0.0%)	2 (1.0%)	2 (0.5%)

*Three subjects in the saline group and two subjects in the 55 IU group had missing birth years and thus were not included in the calculation of age. One subject each in the 55 IU group and the 75 IU group had missing gender values.

†The term “Hispanic” was not an option on either the North American or ex-North American case report forms. The Hispanic category was reported in the “Other” category.

‡Best corrected visual acuity (BCVA) summarized for the ITT population (n = 1324).

of gender or race. The age data were reflective of the vast majority of the at-risk populations. A total of 1065 (78.2%) of subjects had diabetes, and 1198 (90.5%) entered the study with off-chart vision (worse than 20/800). Proliferative diabetic retinopathy (PDR) was reported by the investigator as the probable cause of vitreous hemorrhage in the majority of subjects ($\geq 68.5\%$); the PDR rate was similar across treatment groups (Table 3). The mean duration of vitreous hemorrhage was also similar across treatment groups. At baseline, vitreous hemorrhage in the study eye was present for 119.1, 120.9, 117.7, and 124.3 days in the saline, 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively.

In total, 69 deaths were reported. The incidence of deaths was comparable between the saline group (4.2%) and the 7.5 IU (4.0%), 55 IU (4.5%), and 75 IU (5.6%) ovine hyaluronidase groups. The majority of deaths were cardiac in nature. These deaths were consistent with the past medical history of the subject population studied. Sixty-four (92.8%) of the 69 deaths reported occurred at least 1 month postinjection. Of the five deaths that occurred within 1 month postinjection, four were cardiovascular in nature (that is, stroke [9 days postinjection],

cardiac arrest/cardiomyopathy [21 days postinjection], cardiac arrest [26 days postinjection], and coronary infarction [26 days postinjection]); 1 death was caused by hepatitis (9 days posttreatment). There were no drug-related, serious systemic adverse events reported during the clinical trials.

The incidences of ocular adverse events affecting the study eye (whether or not they were considered related to the treatment) are summarized in Table 4. Iritis was the most common ocular adverse events reported that affected the study eye. Transient, self-limited, sterile iritis has been known to be associated with the use of intravitreal purified ovine hyaluronidase. Iritis was seen in all treatment groups, including saline. A dose-dependent increase in inflammation was seen in the ovine hyaluronidase groups in the moderate-to-severe events of iritis (Table 5). Overall, iritis in the study eye was reported in a total of 126 (33.3%), 123 (62.1%), 222 (58.9%), and 243 (62.1%) subjects in the saline, 7.5 IU, 55 IU, and 75 IU groups, respectively. Noninfectious hypopyon were occasionally seen, were observed in ovine hyaluronidase-treated eyes only, and in a dose-dependent manner (0.5%, 1.6%, and 5.4% in the 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively). All hypopyon resolved with topical

TABLE 3. Ovine Hyaluronidase for Vitreous Hemorrhage: Summary of History of Vitreous Hemorrhage in Study Eye Intent-to-Treat Population (N = 1324)

	Control Groups		Ovine Hyaluronidase Dose Groups		
	Watchful Waiting (n = 18)	Saline (n = 383)	7.5 IU (n = 181)	55 IU (n = 365)	75 IU (n = 377)
Probable cause:					
Proliferative diabetic retinopathy	15 (83.3%)	278 (72.6%)	149 (82.3%)	250 (68.5%)	281 (74.5%)
Central retinal vein occlusion	1 (5.6%)	20 (5.2%)	10 (5.5%)	17 (4.4%)	17 (4.5%)
Branch retinal vein occlusion	0 (0.0%)	18 (4.7%)	6 (3.3%)	25 (6.5%)	10 (2.7%)
Exudative macular degeneration with choroidal neovascular membrane	1 (5.6%)	20 (5.2%)	4 (2.2%)	14 (3.6%)	15 (4.0%)
Macroaneurysm	0 (0.0%)	1 (0.3%)	0 (0.0%)	2 (0.5%)	1 (0.3%)
Hemorrhagic posterior vitreous detachment	1 (5.6%)	6 (1.6%)	3 (1.7%)	11 (2.9%)	8 (2.1%)
Other	0 (0.0%)	6 (1.6%)	0 (0.0%)	10 (2.6%)	11 (2.9%)
Missing or NA	0 (0.0%)	34 (8.9%)	9 (5.0%)	36 (9.4%)	34 (9.0%)
Duration (days) at entry:					
Mean (N)	101.1 (18)	119.1 (376)	120.9 (179)	117.7 (361)	124.3 (371)
SD	65.7	115.0	96.7	102.2	112.4
Min-Max	33–263	15–1383	21–610	29–695	6–997
≤28 days	0 (0.0%)	2 (1.0%)	2 (1.1%)	0 (0.0%)	2 (0.5%)
29–90 days	10 (55.6%)	195 (50.9%)	86 (47.5%)	290 (76.9%)	182 (48.3%)
>90 days	8 (44.4%)	179 (46.7%)	91 (50.3%)	256 (67.9%)	187 (49.6%)
Missing or NA	0 (0.0%)	7 (1.8%)	2 (1.1%)	5 (1.3%)	6 (1.6%)

anti-inflammatory therapy. These hypopyon were sterile and resolved within 2 to 7 days, and did not lead to removal of any subjects from the clinical trials. The occurrence of iritis, severe iritis, or hypopyon did not appear to be related to iris color for any subgroup (brown, blue, hazel, or gray iris colors). Most events of iritis were reported by day 1 postinjection with an incidence by day 1 of 23.5%, 42.9%, 52.5%, 59.1% in the saline, 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively, compared with an overall incidence of 33.3%, 62.1%, 58.9%, and 62.1% for those groups. Except for one adverse event of iritis in the saline group, none of these events occurring within 1 day postinjection were considered serious. Iritis was transient and by day 8 postinjection, the incidence of iritis was comparable across treatment groups and had decreased to approximately 5% to 6% in all groups. Iritis responded to topical anti-inflammatory therapy when utilized. In subjects with iritis and reduction in hemorrhage density, 97% had iritis that occurred before the subject achieved a reduction in hemorrhage density.

Blindness (no light perception) was a rare event in this study and there was no statistically significant difference between groups in the controlled studies (overall $P \geq .174$). A total of 31 subjects had an adverse event of no light perception reported in the study eye. Of the 31 reported cases, 20 occurred after a subsequent intraocular procedure, for example, vitrectomy or cataract surgery. Five of the remaining 11 reported cases of blindness were

transient, and one was considered as night blindness. Each of the remaining five cases that were ongoing at the time of subject discontinuation from the study were not considered related to the treatment and primarily attributable to other underlying conditions.

There was no report of infectious endophthalmitis related to the intravitreal injection of ovine hyaluronidase (966 subjects) or saline (378 subjects). There were two reports of endophthalmitis in the study, both of which were noted at the 6-month postinjection visit and both of which occurred after a subsequent ocular surgical procedure 6 to 14 weeks before the development of the endophthalmitis. In one case, endophthalmitis was noted 6 months after saline injection (and 3.5 months after vitrectomy). This case was not treated as the subject was NLP after failed retinal detachment surgery repair. The other case was one of presumed fungal endophthalmitis, which occurred 5.5 months after 55 IU ovine hyaluronidase injection (and 6 weeks after a vitrectomy). This case was treated with intravitreal amphotericin, though it was culture negative, and was noted to have resolved within 2 weeks.

Retinal detachments were reported in a total of 128 (9.5%) of 1344 eyes during the conduct of these trials: 26 (6.9%), 22 (11.1%), 35 (9.3%), and 45 (11.5%) subjects in the saline, 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively (Table 6A). Of these 128 eyes with retinal detachments, three were acute rhegmatogenous

TABLE 4. Ovine Hyaluronidase for Vitreous Hemorrhage: Incidence of Ocular Adverse Events Affecting the Study Eye Safety Population (N = 1362)

MedDRA Preferred Term	Control Groups		Ovine Hyaluronidase Dose Groups		
	Watchful Waiting (n = 18)	Saline (n = 378)	7.5 IU (n = 198)	55 IU (n = 377)	75 IU (n = 391)
Incidence: $\geq 20\%$ [†]					
Abnormal sensation in eye	2 (11.1%)	68 (18.0%)	62 (31.3%)	101 (26.8%)	114 (29.2%)
Conjunctival edema*	1 (5.6%)	59 (15.6%)	48 (24.2%)	96 (25.5%)	89 (22.8%)
Eye irritation*	10 (55.6%)	111 (29.4%)	90 (45.5%)	132 (35.0%)	139 (35.5%)
Eye pain*	2 (11.1%)	84 (22.2%)	72 (36.4%)	139 (36.9%)	161 (41.2%)
Intraocular pressure increased**	3 (16.7%)	39 (10.3%)	40 (20.2%)	42 (11.1%)	40 (10.2%)
Iritis*	4 (22.2%)	126 (33.3%)	123 (62.1%)	222 (58.9%)	243 (62.1%)
Lacrimation increased*	4 (22.2%)	87 (23.0%)	65 (32.8%)	124 (32.9%)	139 (35.5%)
Ocular hyperemia*	4 (22.2%)	140 (37.0%)	113 (57.1%)	202 (53.6%)	215 (55.0%)
Photophobia*	6 (33.3%)	60 (15.9%)	59 (29.8%)	86 (22.8%)	102 (26.1%)
Visual acuity reduced*	4 (22.2%)	74 (19.6%)	77 (38.9%)	101 (26.8%)	98 (25.1%)
Vitreous floaters*	6 (33.3%)	67 (17.7%)	63 (31.8%)	88 (23.3%)	100 (25.6%)
Vitreous hemorrhage*	2 (11.1%)	66 (17.5%)	70 (35.4%)	91 (24.1%)	90 (23.0%)
Incidence: 10% to 19% [†]					
Cataract nuclear	5 (27.8%)	34 (9.0%)	27 (13.6%)	37 (9.8%)	29 (7.4%)
Cataract subcapsular*	2 (11.1%)	26 (6.9%)	33 (16.7%)	29 (7.7%)	38 (9.7%)
Photopsia*	0 (0.0%)	22 (5.8%)	22 (11.1%)	45 (11.9%)	38 (9.7%)
Retinal detachment	3 (16.7%)	26 (6.9%)	22 (11.1%)	35 (9.3%)	45 (11.5%)
Incidence: 5% to 9% [†]					
Cataract cortical	5 (27.8%)	27 (7.1%)	14 (7.1%)	30 (8.0%)	31 (7.9%)
Conjunctival hemorrhage	0 (0.0%)	25 (6.6%)	11 (5.6%)	14 (3.7%)	18 (4.6%)
Corneal disorders NOS	0 (0.0%)	8 (2.1%)	6 (3.0%)	17 (4.5%)	25 (6.4%)
Corneal edema	1 (5.6%)	12 (3.2%)	17 (8.6%)	20 (5.3%)	24 (6.1%)
Corneal erosion	1 (5.6%)	24 (6.3%)	10 (5.1%)	25 (6.6%)	17 (4.3%)
Erythema NEC	0 (0.0%)	15 (4.0%)	8 (4.0%)	21 (5.6%)	20 (5.1%)
Eye discharge	0 (0.0%)	18 (4.8%)	10 (5.1%)	23 (6.1%)	20 (5.1%)
Eyelid edema	0 (0.0%)	15 (4.0%)	12 (6.1%)	29 (7.7%)	25 (6.4%)
Hypopyon (non-infectious)* [§]	0 (0.0%)	0 (0.0%)	1 (0.5%)	6 (1.6%)	21 (5.4%)
Iris adhesions	2 (11.1%)	13 (3.4%)	9 (4.5%)	13 (3.4%)	27 (6.9%)
Macular edema	1 (5.6%)	11 (2.9%)	16 (8.1%)	11 (2.9%)	19 (4.9%)
Rubeosis iridis	1 (5.6%)	19 (5.0%)	16 (8.1%)	17 (4.5%)	19 (4.9%)
Vision blurred	0 (0.0%)	5 (1.3%)	10 (5.1%)	5 (1.3%)	4 (1.0%)
Blindness NEC (no light perception)	1 (5.6%)	4 (1.1%)	9 (4.5%)	6 (1.6%)	9 (2.3%)
Incidence $\leq 4\%$ (selected events only)					
Endophthalmitis					
Injection/drug related	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Post-surgical (on/after 6-month visit)	0 (0.0%)	1 (0.26%)	0 (0.0%)	1 (0.27%)	0 (0.0%)

NOS = not otherwise specified; NEC = not elsewhere classified.

*Represents ophthalmologically important adverse events that occurred at an overall statistically significant different ($P \leq 0.05$, Fisher's exact test) incidence among the ovine hyaluronidase and saline group.

[†]Any ocular adverse event that occurred within the specified incidence range in any treatment group is included in this table.

^{**}Represents subjects with intraocular pressure increased that coded to the Investigations MedDRA organ class system.

[§]Represents subjects with hypopyon coded to the Eye Disorders MedDRA organ class system. One subject in the saline control group had an event of hypopyon coded to the Infections and Infestations MedDRA organ class system.

^{||}One case of hypopyon in the saline group was observed at the 6-month post injection visit (which was 3.5 months after vitrectomy).

[¶]One case of presumed fungal endophthalmitis in the 55 IU group was observed at the 6-month post injection visit (which was 6 weeks after a vitrectomy).

TABLE 5. Ovine Hyaluronidase for Vitreous Hemorrhage: Incidence of Iritis at Baseline and by Maximum Severity at Any Time Posttreatment

	Control Groups		Ovine Hyaluronidase Dose Groups		
	Watchful Waiting	Saline	7.5 IU	55 IU	75 IU
Number of subjects	18	378	198	377	391
Number of subjects with iritis at baseline	1 (5.6%)	12 (3.2%)	4 (2.0%)	11 (2.9%)	20 (5.1%)
Number of subjects with iritis any time posttreatment	4 (22.2%)	126 (33.3%)	123 (62.1%)	222 (58.9%)	243 (62.1%)
Maximum severity any time posttreatment					
None	14 (77.8%)	252 (66.7%)	75 (37.9%)	155 (41.1%)	148 (37.9%)
Mild	4 (22.2%)	96 (25.4%)	83 (41.9%)	95 (25.2%)	88 (22.5%)
Moderate	0 (0.0%)	23 (6.1%)	31 (15.7%)	83 (22.0%)	102 (26.1%)
Severe	0 (0.0%)	7 (1.9%)	9 (4.5%)	44 (11.7%)	53 (13.6%)
Hypopyon (non-infectious)*	0 (0.0%)	0 (0.0%)*	1 (0.5%)	6 (1.6%)	21 (5.4%)
Number of subjects with iris adhesions (posterior synechiae) any time posttreatment	2 (11.1%)	13 (3.4%)	9 (4.5%)	13 (3.4%)	27 (6.9%)

*Represents subjects with hypopyon coded to the Eye Disorders MedDRA organ class system. One subject in the saline control group had an event of hypopyon coded to the Infections and Infestations MedDRA organ class system.

TABLE 6A. Ovine Hyaluronidase for Vitreous Hemorrhage: Summary of All Retinal Detachments (Study Eye) by Type

	Saline (n = 378)	Ovine Hyaluronidase Dose Groups			Total (All Groups) (n = 1344)
		7.5 IU (n = 198)	55 IU (n = 377)	75 IU (n = 391)	
Total number of subjects with RD	26 (6.9%)	22 (11.1%)	35 (9.3%)	45 (11.5%)	128 (9.5%)
Type of RD:					
Rhegmatogenous	4 (1.1%)	5 (2.5%)	6 (1.6%)	9 (2.3%)	24 (1.8%)
Traction	16 (4.2%)	13 (6.6%)	26 (6.9%)	22 (5.6%)	77 (5.7%)
Traction/rhegmatogenous	2 (0.5%)	1 (0.5%)	3 (0.8%)	4 (1.0%)	10 (0.7%)
Serous	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Unknown	3 (0.8%)	3 (1.5%)	0 (0.0%)	10 (2.6%)	16 (1.2%)

RD = retinal detachment.

TABLE 6B. Ovine Hyaluronidase for Vitreous Hemorrhage: Retinal Detachments by Vitrectomy Status, Type, and Time to Diagnosis Overall

Post-injection Time to RD Diagnosis	0–7 days	8–30 days	31–90 days	>90 days
No pars plana vitrectomy				
Rhegmatogenous	2 (0.15%)*	1 (0.07%)	4 (0.30%)	7 (0.52%)
Traction	0 (0.0%)	9 (0.70%)	23 (1.71%)	42 (3.13%)
Traction/rhegmatogenous	0 (0.0%)	0 (0.0%)	3 (0.22%)	4 (0.30%)
Unknown	0 (0.0%)	0 (0.0%)	3 (0.22%)	12 (0.89%)
After pars plana vitrectomy				
Rhegmatogenous	0 (0.0%)	0 (0.0%)	0 (0.0%)	10 (0.74%)
Traction	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.22%)
Traction/rhegmatogenous	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.22%)
Serous	0 (0.0%)	0 (0.0%)	1 (0.07%)	0 (0.0%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.07%)

RD = retinal detachment.

*Denominator used to calculate rate for all groups was the total number of eyes with RD (n = 1344).

TABLE 7. Summary of Lens Status by Maximum Severity Any Time Posttreatment (Study Eye), Any Time Previtrectomy, and Any Time Postvitrectomy Following Ovine Hyaluronidase for Vitreous Hemorrhage*

	Saline (n = 378)	Ovine Hyaluronidase Dose Groups		
		7.5 IU (n = 198)	55 IU (n = 377)	75 IU (n = 391)
Subjects phakic at baseline	320	142	310	305
No nuclear sclerosis at baseline	119 (37.2%)	27 (19.0%)	120 (38.7%)	109 (35.7%)
No cortical cataracts at baseline	201 (62.8%)	78 (54.9%)	205 (66.2%)	186 (61.0%)
No posterior subcapsular opacity at baseline	66 (20.6%)	21 (14.8%)	53 (17.1%)	57 (18.7%)
Number of subjects with cataract (study eye) posttreatment	99 (26.2%)	69 (34.8%)	91 (24.1%)	95 (24.3%)
Time to cataract onset:				
Day 0–Day 1	1 (0.3%)	1 (0.5%)	4 (1.1%)	6 (1.5%)
Day 2–Day 7	2 (0.5%)	3 (1.5%)	4 (1.1%)	3 (0.8%)
Day 8–Day 30	9 (2.4%)	4 (2.0%)	13 (3.4%)	6 (1.5%)
Day 31–Day 60	7 (1.9%)	11 (5.6%)	6 (1.6%)	10 (2.6%)
Day 61–Day 90	6 (1.6%)	5 (2.5%)	14 (3.7%)	13 (3.3%)
Day 91–Day 180	30 (7.9%)	19 (9.6%)	14 (3.7%)	20 (5.1%)
>Day 180	44 (11.6%)	26 (13.1%)	36 (9.5%)	37 (9.5%)

*Results are stratified by baseline symptom severity.

retinal detachments, occurring within the first month after injection, for an incidence of 0.22% (3 of 1344). These three retinal detachments were reported at three investigative centers in the Vit-03 (ex-North America) study, and all occurred within the 55 IU dose group. Among rhegmatogenous retinal detachments, 87.5% (21 of 24) occurred ≥ 31 days postinjection and 41.7% (10 of 24) occurred after vitrectomy (Table 6B). Overall, rhegmatogenous retinal detachments were reported in 1.1% (4 of 378), 2.5% (5 of 198), 1.6% (6 of 377), and 2.3% (9 of 391) of eyes in the saline, 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively, representing an overall rate of 1.8% (24 of 1344) of all injected eyes. Most retinal detachments (5.7%, 77 of 1344) were identified as traction retinal detachments: 4.2% (16 of 378); 6.6% (13 of 198); 6.9% (26 of 377), and 5.6% (22 of 391) for the saline, 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively. The remaining 27 retinal detachments all occurred ≥ 31 days after injection, and were listed as unidentified (16 of 1344, 1.2%), combination traction/rhegmatogenous (10 of 1344, 0.7%), and serous (1 of 1344, 0.1%).

Table 7 provides a summary of lens status in the study eye any time posttreatment, previtrectomy, and postvitrectomy. There were no differences between ovine hyaluronidase and saline groups in the incidence of cataracts, with the exception of subcapsular cataracts, which were reported in 26 (6.9%), 33 (16.7%), 29 (7.7%), and 38 (9.7%) subjects in the saline, 7.5 IU, 55 IU, and 75 IU groups, respectively. The pairwise comparison for the 7.5 IU group vs saline was statistically significant (Table 4). This statistically significant difference, however, was not seen with the higher ovine hyaluronidase dose groups compared with saline (55 IU, $P = .88$; 75 IU, $P = .41$).

Nuclear cataracts occurred most commonly after a vitrectomy, and were mild-to-moderate in severity. The incidence of mild cortical cataracts both pre- and postvitrectomy was similar. A total of 62 (9.3%) subjects developed a mild cortical cataract before vitrectomy, while 54 (8.1%) subjects experienced this event postvitrectomy. Posterior subcapsular cataracts occurred in 16 (8.1%) subjects before vitrectomy and in four (2.0%) subjects postvitrectomy.

There was no statistical difference in the incidence of IOP between the saline, and 55 IU and 75 IU dose groups. While a statistically significant difference in the incidence of increased IOP was seen between the 7.5 IU and saline groups, no notable differences were observed in the mean minimum and maximum IOP posttreatment changes from baseline across treatment groups (Table 8). The 7.5 IU group did, however, demonstrate the greatest mean minimum and mean maximum change (-4.2 and 4.8) compared with the saline, 55 IU, and 75 IU groups.

DISCUSSION

TWO PHASE III CLINICAL TRIALS COMPRISE THE SOURCE OF the integrated safety data included in this report. The safety population consisted of 1362 subjects, of which 966 eyes were exposed to a single intravitreal injection of ovine hyaluronidase. This study carefully evaluated systemic events (including deaths) and ocular events occurring in the study eye (including iritis, retinal detachment, cataracts, and glaucoma).

Of the 1362 subjects included in the safety population, 69 deaths (5.1%) were reported. The incidence of deaths was comparable among the saline control group and the

TABLE 8. Summary of Minimum and Maximum Intraocular Pressure (IOP) Posttreatment Change from Baseline Following Ovine Hyaluronidase for Vitreous Hemorrhage

	Control Groups		Ovine Hyaluronidase Dose Groups		
	Watchful Waiting (n = 18)	Saline (n = 378)	7.5 IU (n = 198)	55 IU (n = 377)	75 IU (n = 391)
Number of subjects	17	378	197	377	391
Baseline IOP mean (SE)	16.2 (1.0)	15.0 (0.2)	15.4 (0.3)	14.9 (0.2)	14.7 (0.2)
Minimum IOP change from baseline mean (SE)	-4.8 (0.8)	-2.9 (0.2)	-4.2 (0.3)	-3.5 (0.2)	-3.5 (0.2)
Maximum IOP change from baseline mean (SE)	0.8 (1.1)	3.4 (0.3)	4.8 (0.6)	2.8 (0.2)	3.3 (0.3)

ovine hyaluronidase treated groups. Collectively, the data suggest that a single intravitreal injection of ovine hyaluronidase was not a factor contributing to the incidence of death. This conclusion is further supported by the comparable death rate at one year in the Diabetic Retinopathy Vitrectomy Study (DRVS). The population in these trials were adults with considerable systemic diseases, particularly diabetes mellitus, hypertension, heart disease, and frequently renal disorders. The deaths seen in this study were probably related to the underlying medical condition, and not the injection or study drug.

The relevant ocular safety issues in injected eyes were of two general patterns: (1) acute iritis, which was associated with ovine hyaluronidase use in a dose-dependent fashion, and (2) complications associated with underlying pathologic processes. Acute iritis and its accompanying symptoms were common in all groups by day 1 postinjection. These findings were seen in one-third of the eyes injected with saline and approximately 60% of the eyes treated with ovine hyaluronidase. Iritis was generally transient, easily managed with or without topical anti-inflammatory therapy, and not reported as serious. The safety data suggest that two factors contribute to the development of early posttreatment iritis: the injection-related inflammation that was noted in both the saline and ovine hyaluronidase groups as well as the drug-induced iritis in those eyes receiving an intravitreal injection of ovine hyaluronidase.

An adverse event related to the severe iritis occasionally seen in this study was acute, sterile, self-limited hypopyon in a small number of ovine hyaluronidase treated eyes. Similar to the less severe forms of iritis more commonly seen, hypopyon was also managed successfully with topical anti-inflammatory therapy and did not lead to removal of subjects from the trials. It is possible that the occurrence of either iritis or hypopyon was a biologic indicator of the dissipation of vitreous hemorrhage, or that the iritis-induced changes lead to more rapid clearance of the hemorrhage, because iritis and vitreous hemorrhage reduction were both more common in the higher dose groups. It is important to note that the inflammatory hypopyon seen

with hyaluronidase looked clinically different than endophthalmitis in that they were not associated with pain, conjunctival hyperemia, or chemosis, and were noted to clear spontaneously.

In any treatment involving intravitreal injections, the possible serious complication of endophthalmitis is a major concern. In these phase III studies, a total of 1344 subjects were given a single intravitreal injection in the study eye (including 966 that received highly purified ovine hyaluronidase). There were no eyes that developed injection or drug-related endophthalmitis.

Ocular adverse events such as retinal detachment and cataracts were as frequent in saline treated eyes as ovine hyaluronidase treated-eyes and more likely related to the underlying pathologic processes than to ovine hyaluronidase. For example, 60.2% of the retinal detachments were tractional, consistent with underlying disease progression rather than as a result of the injection itself or study drug. Additionally, most of the retinal detachments (90.6%) occurred at least 31 days after injection of saline or ovine hyaluronidase. The overall incidence of rhegmatogenous retinal detachment was 1.8% at any time postinjection regardless of treatment group. Only three rhegmatogenous retinal detachments, which were reported within 30 days of injection, were likely to be attributed to the injection procedure. For eyes that underwent intravitreal ovine hyaluronidase injection and subsequent vitrectomy, there was no increased risk of retinal detachment as a surgical complication as compared with saline-injected eyes.

The results of these studies show that the incidence of cataracts was not different across treatment groups, regardless of cataract type or severity, with the exception of subcapsular cataract in the 7.5 IU ovine hyaluronidase group. This difference is likely attributed to the smaller number of subjects included in the 7.5 IU dose group. With respect to intraocular pressure, no clinically significant changes were observed during the course of the studies in any treatment group. While the overall *P* value for IOP increase did not show statistical significance (*P* = .0936), there was an apparent difference in the incidence of increased IOP for the 7.5 IU treatment group compared

with the saline group ($P \leq .035$) only. This difference was not significant for the comparisons of 55 IU ($P = 1.000$) or 75 IU ($P = .724$) with saline. The mean IOP change for any subject group at any visit compared with baseline varied no more than -1.1 to $+1.0$ mm Hg. The likely reason for the statistically significant increase in IOP in the 7.5 IU group is related to its smaller sample size, which resulted in greater fluctuations in mean minimum and maximum IOP. A diagnosis of glaucoma was not observed in association with the test agents or injection procedure in any eye.

In conclusion, the data from these phase III studies demonstrate that an intravitreal injection of ovine hyaluronidase has a favorable safety profile. The primary ocular adverse event associated with the use of ovine hyaluronidase was acute, self-limited anterior inflammation. This ovine hyaluronidase-associated iritis was seen in a dose-dependent fashion, resolved with or without treatment, without sequelae, and was not reported as serious. Other adverse events were more related to the progression of underlying pathology. Additionally, clinical experience has demonstrated that these injections do not prohibit or complicate subsequent vitrectomies when they are required.¹⁴

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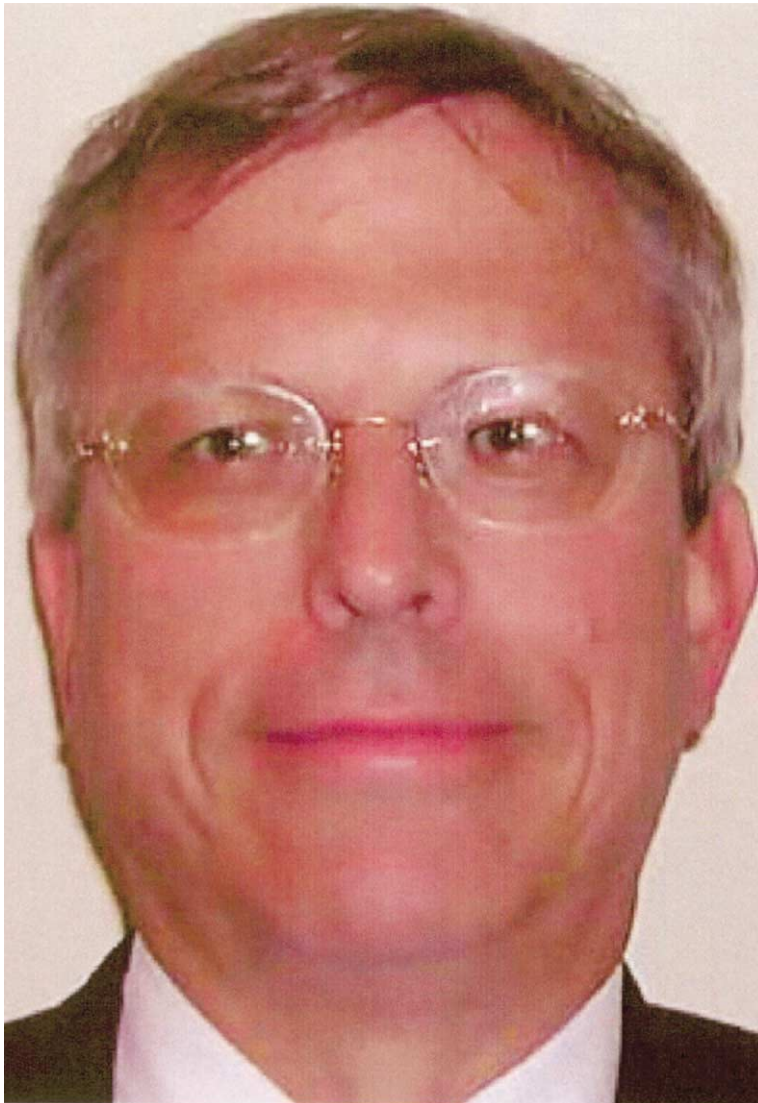
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 Dean A. McGee Eye Institute, Oklahoma City, OK
 Robert L. Brownlow, Jr., MD
 Vistar Retinal Consultants, Roanoke, VA
 Alexander J. Brucker, MD
 Scheie Eye Institute, Philadelphia, PA
 Moiz M. Carim, MD
 Carim Eye & Retina Center, Wyomissing, PA
 Maria E. Castillejos, MD
 Private Practice, Chula Vista, CA
 Clement K. Chan, MD
 Southern California Desert Retina Consultants, Palm Springs, CA
 Nauman A. Chaudhry, MD
 New England Retina Associates, London, CT
 Thomas B. Connor, Jr., MD
 Medical College of Wisconsin, Milwaukee, WI
 Frederick H. Davidorf, MD
 Ohio State University, Columbus, OH
 Alan R. Dayan, MD
 Retina Consultants of Southern Colorado, Colorado Springs, CO
 David S. Dyer, MD
 Retina Associates of Kansas City, Kansas City, MO
 Alexander M. Eaton, MD (*replaced by Rick Glasser, MD*)
 Eye Centers of Florida, Fort Myers, FL
 Robert E. Engstrom, Jr., MD
 Olive View/UCLA Medical Center, Sylmar, CA
 Robert B. Feldman, MD
 Florida Eye Clinic, Altamonte Springs, FL
 Gregory M. Fox, MD
 Hunkeler Eye Centers, Kansas City, MO
 Charles A. Garcia, MD
 Retinal Vascular Center, Houston, TX
 Kurt A. Gitter, MD
 Private Practice, New Orleans, LA
 Louis C. Glazer, MD
 Vitreo-Retinal Associates, Grand Rapids, MI
 Victor H. Gonzalez, MD
 Valley Retina Institute, PA, McAllen, TX
 Paul B. Griggs, MD
 Virginia Mason Medical Center, Seattle, WA
 Joseph M. Gunn, MD
 Southeastern Retina Associates, PC, Knoxville, TN
 G. Robert Hampton, MD
 Retina Vitreous Surgeons of Central New York, Syracuse, NY
 Nancy M. Holekamp, MD
 Barnes Retina Institute, St. Louis, MO
 Eric R. Holz, MD
 Cullen Eye Institute, Baylor College of Medicine, Houston, TX
 Henry L. Hudson, MD
 Retina Centers, PC, Tucson, AZ
 Peter K. Kaiser, MD
 Cleveland Clinic Foundation, Cleveland, OH

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 Natural Vision, Fresno, CA
 Bruce J. Keyser, MD
 Robert Wood Johnson Medical School, Retina Vitreous Center,
 New Brunswick, NJ
 Gregg T. Kokame, MD
 Retina Center at Pali Momi, Aiea, HI
 Baruch D. Kuppermann, MD, PhD
 University of California, Irvine, Irvine, CA
 Kameran Lashkari, MD (*replaced by John W. McMeel, MD*)
 Schepens Retina Associates, Boston, MA
 Howard S. Lazarus, MD
 American Eye Institute, New Albany, IN
 King Y. Lee, MD
 Private Practice, Shawnee Mission, KS
 Ronni M. Lieberman, MD
 Private Practice, New York, NY
 Naresh Mandava, MD
 University of Colorado Health Sciences Center, Denver, CO
 Sam E. Mansour, MD (*replaced by Joseph A. Eliason, MD*)
 Santa Clara Valley Medical Center, San Jose, CA
 H. Richard McDonald, MD
 Private Practice, San Francisco, CA
 Pauline T. Merrill, MD
 Illinois Retina Associates SC, Chicago, IL
 Juan Orellana, MD
 Carolina Eye Associates, PA, Raleigh, NC
 Stephan S. Pappas, Jr., MD
 Retina Consultants, PC, Bethesda, MD
 Arun C. Patel, MD
 Retinal Consultants, Sacramento, CA
 Samir C. Patel, MD
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 Scott E. Pautler, MD
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 Scott D. Pendergast, MD
 Retina Associates of Cleveland, Cleveland, OH
 Carl D. Regillo, MD
 Wills Eye Hospital, Philadelphia, PA
 Steven R. Sanislo, MD
 California Vitreoretinal Center, Menlo Park, CA
 Jerry Sebag, MD
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 Christopher Seery, MD
 Retina Associates of New Jersey, Milburn, NJ
 Eric P. Shakin, MD
 Long Island Vitreo Retinal Consultants, Great Neck, NY
 Peter L. Sonkin, MD
 Retina-Vitreous Associates, Nashville, TN
 Marvin Sperling, MD (*replaced by Matthew Paul, MD*)
 Danbury Eye Physicians and Surgeons, Danbury, CT
 Joseph Tauber, MD (*replaced by Abraham Poulouse, MD*)
 Felix N. Sabates Eye Associates, Prairie Village, KS
 Michael P. Teske, MD
 John Moran Eye Center, Salt Lake City, UT
 Edgar L. Thomas, MD
 Retina Vitreous Associates Medical Group, Beverly Hills, CA
 John T. Thompson, MD
 Retina Specialists, Baltimore, MD
 Keye L. Wong, MD
 Sarasota Retina Institute, Sarasota, FL
 Ingrid Zimmer-Galler, MD
 Wilmer Eye Institute, Johns Hopkins University, School of
 Medicine, Baltimore, MD



Biosketch

Baruch D. Kuppermann, MD, PhD, is Chief of the Retina Service, Director of Clinical Research, and an Associate Professor of Ophthalmology and Biomedical Engineering at University of California at Irvine. Dr Kuppermann has been the lead national investigator for several multicenter trials evaluating new drugs and devices for the treatment of diabetic retinopathy, age-related macular degeneration, and the ocular complications of AIDS. He served as the co-lead international investigator for the Vitrase for Vitreous Hemorrhage trials presented here.



Biosketch

Edgar L. Thomas, MD, is a member of the Retina-Vitreous Associates Medical Group in Los Angeles. Clinical research has been a significant part of his professional career in private practice developing an office based clinical research center participating in more than 15 research trials. He was also the co-lead investigator in the Phase III SnET2 (Photrex) Clinical Trial for Treatment of Neovascular AMD. He was lead investigator in the Phase II Vitrase trial and co-lead international investigator for the Vitrase for Vitreous Hemorrhage trials presented here.