

Pooled Efficacy Results From Two Multinational Randomized Controlled Clinical Trials of a Single Intravitreal Injection of Highly Purified Ovine Hyaluronidase (Vitrase[®]) for the Management of Vitreous Hemorrhage

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- **PURPOSE:** To evaluate the efficacy of intravitreal ovine hyaluronidase for the management of vitreous hemorrhage.
- **DESIGN:** Two prospective, randomized, placebo-controlled, double-masked studies. Safety data are presented in a companion article in *THE JOURNAL*.
- **METHODS:** Eligible patients with vitreous hemorrhage ≥ 1 month duration; severe at entry with best corrected visual acuity (BCVA) worse than 20/200 were randomized to 55 IU or 75 IU ovine hyaluronidase or saline. Primary efficacy (clearance of hemorrhage sufficient to see the underlying pathology and completion of treatment when indicated) was measured at months 1, 2, and 3. Key secondary endpoints were: ≥ 3 -line improvement in BCVA; hemorrhage density reduction; and therapeutic utility assessment.
- **RESULTS:** The intent-to-treat population for common dose groups (55 IU, 75 IU, saline) consisted of 1125 patients. At baseline, 76.3% had diabetes, 90.4% were not able to read any letters on the eye chart, and mean hemorrhage duration was 120 days. Statistical significance was reached in the 55 IU dose group by months 1 and 2 for the primary efficacy endpoint based on an adjusted *P*-value. By months 1, 2, and 3, 13.2%, 25.5%, and 32.9% of patients (55 IU) reached primary efficacy

compared with 5.5%, 16.2%, and 25.6% of saline-treated patients ($P < .001$; $P = .002$; $P = .025$, respectively). Key secondary endpoints confirmed the treatment effect at both doses and all timepoints ($P \leq .01$).

- **CONCLUSIONS:** Fifty-five IU ovine hyaluronidase showed statistically significant efficacy as early as months 1 and 2. These results were supported by outcomes for three key secondary endpoints. These results suggest a therapeutic utility of ovine hyaluronidase in the management of vitreous hemorrhage. (*Am J Ophthalmol* 2005; 140:573–584. © 2005 by Elsevier Inc. All rights reserved.)

VITREOUS HEMORRHAGE IS A MAJOR VISION-threatening problem. It is estimated that approximately seven cases of dense spontaneous vitreous hemorrhage occur per 100,000 people each year in Europe.¹ If the incidence is equivalent in the United States, approximately 20,000 new cases of vitreous hemorrhage occur annually. In most of the cases, the cause of the vitreous hemorrhage is related to complications from proliferative diabetic retinopathy (PDR). Other common causes include branch or central retinal vein occlusion, posterior vitreous detachment with or without a retinal tear or detachment, and ocular trauma. The presumed pathologic mechanism of vitreous hemorrhage in retinal vascular disease is the development of retinal ischemia which in turn induces neovascularization of the retina. The new abnormal blood vessels that develop grow into the vitreous cavity, using the vitreous as a scaffold, and vitreous traction on these new vessels results in vitreous hemorrhage.

People with type 1 diabetes mellitus have a higher risk of development of PDR compared with those with type II diabetes and, therefore, have more frequent and more

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*A complete list of investigators and institutions where these studies were performed can be found at the end of the article in the Appendix.

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severe ocular complications, such as hemorrhage, retinal tears, and traction detachments.^{2,3} Regardless of the cause, vitreous hemorrhage can result in or may be derived from the development of membranes and traction on the retina. Exacerbation of traction can lead to further damage. Consequently, early visualization of the retina to identify and treat the underlying causative disorder is critical to maximizing the return of visual function.

The initial management of vitreous hemorrhage is often conservative, yet there is evidence that early clearance of vitreous hemorrhage is associated with improved long-term preservation of useful vision and an improved quality of life.^{4,5} Currently, vitreous hemorrhage is managed by waiting for spontaneous resolution (that is, “watchful waiting”) within a predefined time, followed by vitreoretinal surgery when indicated. This watchful waiting period of observation commonly varies between 1 to 3 months, leading to a potential delay in treatment, and an increased likelihood of complications.⁵ When vision is severely diminished, the period of observation may be troublesome for patients. A moderate drop in binocular visual acuity to 20/40 or less is associated with impaired ability to cope with tasks of daily living such as reading and driving,^{6,7} or may be associated in the elderly with increased risk of falls.⁸ For patients who are not surgical candidates, the period of observation may be indefinite as only surgical treatment for nonclearing vitreous hemorrhage is currently available. For these individuals, a nonsurgical option may restore vision at an earlier time point and positively impact their quality of life.

Frequent office visits and the use of ancillary tests may allow a conservative approach that may be preferred by some patients and surgeons as it avoids the potential complications of surgical intervention. The surgical complications include progressive cataract, recurrent vitreous hemorrhage, intraoperative retinal breaks/detachment, and endophthalmitis.^{9–17} However, frequent visits and testing are costly to patients, especially those from lower socio-economic groups, or in patients with lesser access to social support.^{6,18}

Investigators have considered various pharmacological approaches to lyse or dissipate vitreous hemorrhage or modify the structural characteristics of vitreous to allow bulk diffusion of the blood out of the visual axis. However, no pharmacological intervention for vitreous hemorrhage is currently available. Enzymatic vitreolysis offers several theoretical and practical advantages over conventional practice, including the ability to treat the hemorrhage earlier, in an office setting, and with lower costs. A number of vitreolytic substances have been investigated, including hyaluronidase, plasmin dispase, tissue plasminogen activator, and chondroitinase, with varying effects.¹⁹

These two companion articles describe the use of a single intravitreal injection of preservative-free highly purified ovine hyaluronidase (Vitrace[®], ISTA Pharmaceuticals, Inc). Hyaluronidase cleaves glycosidic bonds of

hyaluronic acid and, to a variable degree, other acid mucopolysaccharides of the connective tissue.²⁰ Dissolution of the hyaluronic acid and collagen complex results in the decreased viscosity of the extracellular cement. This in turn increases the diffusion rate of erythrocytes and exudates along with phagocytes through the vitreous and facilitates red blood cell lysis and phagocytosis.^{13,14}

This article presents the pooled efficacy results from two concurrent parallel phase III, multi-national, randomized controlled clinical trials that evaluated a single intravitreal injection of highly purified ovine hyaluronidase for the management of vitreous hemorrhage. One trial was conducted at centers in North America (Vit-02 study) and the other trial included centers outside of North America (Vit-03 study). The integrated safety data from both of these trials are presented in a companion article in this issue of THE JOURNAL.

METHODS

BEFORE POOLING THE EFFICACY DATA FROM THE TWO phase III clinical trials, the Breslow-Day statistic was used to test whether the odds ratio between ovine hyaluronidase-treated groups and saline treated groups was the same in different studies. The results of the Breslow-Day tests were not statistically significant, indicating that the treatment effect (ovine hyaluronidase vs saline control) was similar in the two phase III studies. Thus, the data from two randomized, parallel-group, double-masked, placebo-controlled clinical trials (Vit-02 and Vit-03) were pooled to evaluate the safety and efficacy of a single intravitreal injection (50 µl) of ovine hyaluronidase compared with sodium chloride 0.9% (saline control).

In the North American (Vit-02) study, three dosages of ovine hyaluronidase were evaluated: 7.5 IU, 55 IU, and 75 IU; the ex-North American (Vit-03) study evaluated the 55 IU and 75 IU dosages of ovine hyaluronidase. Because the 7.5 IU dose was evaluated in only one of the two phase III trials (North America, Vit-02, n = 181), inclusion of the 7.5 IU data in the statistical analysis of the pooled dataset presented in this article might be misleading as a result of the smaller population size of the 7.5 IU group and its impact on the statistical analyses and methodology. Hence, efficacy is compiled from the common dosage groups in both studies, that is, 55 IU, 75 IU, and the saline control (n = 1125). When initiated, the Vit-02 study included an observational control group. After consultation with the United States Food and Drug Administration (FDA), the North American Vit-02 study was amended and the study was reinitiated with a saline intravitreal injection control group. At the time that trial was amended, 71 patients had already been randomized and entered into the study. Of these 71 patients, 18 patients had been randomized to the uninjected observational control group and 18, 18, and 17 patients were

randomized to 7.5 IU, 55 IU, and 75 IU ovine hyaluronidase groups, respectively. The 71 subjects in the initial version of the study that included an observation group were followed for safety outcomes and are included in the data discussed in the companion safety article, but not included in the efficacy analyses presented here.

In these two studies, 131 centers in the United States, Canada, Mexico, Hungary, Italy, the Netherlands, Poland, Spain, United Kingdom, Australia, Brazil, and South Africa enrolled 1306 patients who were screened and randomized after the study was amended to a saline control as described above. This article presents the final 3-month pooled efficacy results for the intent-to-treat (ITT) population for those patients in the three common dose groups, a total of 1125 patients.

All data were collected under protocols conducted in accordance with the principles stated in the Declaration of Helsinki. The protocol was approved by each institutional review board or ethics committee administering each site. All patients provided written informed consent.

Male and female subjects were eligible for enrollment if they were 18 years or older and had a vitreous hemorrhage in the study eye that had been present for at least 1 month, and which 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.

Candidates 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 Tonopen; 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 (for example, yellow ochre in color, "chicken fat" in appearance); 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 patient presented with a qualifying vitreous hemorrhage in both eyes, only one eye (the right eye, designated the study eye) was entered into the study. Treatment in Vit-02 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 (sodium chloride 0.9% solution); the Vit-03 study evaluated 55 IU and 75 IU ovine hyaluronidase vs saline.

Injections were made through the pars plana using a 30-gauge needle and local anesthesia. The physician's usual and customary preoperative regimen to ensure antisepsis of the injection site was followed. These options were offered, but not required by the protocol: povidone solution or swab, topical antibiotics, eyelid speculum, and digital massage. The recommended injection site was the pars plana, 3.5 mm to 4 mm posterior to the limbus in the superior temporal or inferior temporal quadrant. To ensure the integrity of the study masking, an assistant not involved in the treatment or evaluation of the patient was chosen in advance at each study center 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. Because the study drug is a lyophilized powder requiring reconstitution in vehicle, an assistant not involved in the treatment or evaluation prepared the syringes containing study drug or the saline control. Reconstitution of the lyophilized powder yielded a clear solution indistinguishable from the saline control and ensured appropriate masking was maintained. Masking of the investigator and patient was maintained throughout the duration of the study.

Clinical ocular assessments were performed at day 1, week 1, and months 1, 2, and 3 following injection for efficacy and safety outcomes, and at month 6, and every 6 months thereafter for safety outcomes. Assessments performed at each visit during the study consisted of comprehensive medical and ophthalmic history, ocular symptoms, adverse events, concomitant medications, BCVA, IOP, external eye examination, slit-lamp biomicroscopy, and dilated fundus examination. B-scan ultrasound tests were required at the initial screening visit and at visit 4 (week 1) to document the absence or presence of retinal detachment. In addition, at months 1, 2, 3, 6, and 12, B-scan ultrasound tests were performed when the media were not clear enough to allow visualization of the fundus to rule out retinal tear or detachment. BCVA was recorded by means of Bailey-Lovie visual acuity charts at 4 m (or 10 feet), or 2 m (or 5 feet), or 1 m (or 2.5 feet) distance, depending on the subject's level of vision. If the subject was unable to see any letters at a distance of 1 m or 2.5 feet, then the visual acuity level and distance was recorded (for example, subject's vision is counting fingers or worse). Topical and systemic concurrent medications were allowed at the discretion of the investigator as long as the medications would not interfere with the study and were not being prescribed specifically for the treatment of vitreous hemorrhage.

The primary efficacy endpoint was defined by clearance of vitreous hemorrhage sufficient to see the underlying pathology and to complete treatment, when indicated, by the month 3 visit. A patient was classified as a treatment success if the patient's vitreous hemor-

rhage in the study eye had cleared sufficiently for diagnosis of the underlying pathology and one of the following criteria were met within the month 3 visit window: (1) laser treatment of the underlying condition was completed; (2) visualization of the retina revealed that surgery was required and was performed to correct the underlying pathology (for example, vitrectomy for macular traction detachment); or (3) visualization of the macula and a minimum of 180 degrees of the vitreous base was performed, and the underlying cause of the hemorrhage was documented, through a fundus photograph, to have been resolved without the need for further therapy. Laser treatment was considered completed for PDR or central retinal vein occlusion if panretinal photocoagulation (PRP) was completed in 6 or more clock hours extending from the anterior border of the posterior pole to the equator and/or beyond, with the size and spacing of laser burns performed as specified by the Diabetic Retinopathy Study/Early Treatment of Diabetic Retinopathy Study (DRS/ETDRS) protocol for standard PRP (that is, 500 μ m spots separated by one-half burn width space). For branch retinal vein occlusion, laser treatment was considered completed when a modified sector PRP in the affected quadrants such that 3 or more clock hours were treated with laser extending from the anterior border of the posterior pole to the equator and/or beyond, with the size and spacing of laser burns as specified by the DRS/ETDRS protocol for standard PRP (that is, 500 μ m spots separated by one-half burn width space).

The key secondary endpoints evaluated were the proportion of patients with: at least a 3-line improvement in BCVA in the study eye; reduction in vitreous hemorrhage density; and clinical assessment of therapeutic utility by the investigator (clearance of the hemorrhage sufficient to diagnose the underlying pathology). Improvement in BCVA was defined as an improvement of at least 3 lines of vision (0.3 logMAR units) by month 1, 2, or 3. In cases where vitrectomy or recurrent vitreous hemorrhage occurred, determination of BCVA was made before that event. For patients who were unable to see any letters on the Bailey-Lovie chart, vision was recorded as light perception (LP), hand motion (HM), or counting fingers (CF). Because LP is a crudely defined measurement, in these trials LP was assigned a logMAR of 2.0. For logistical and analytic purposes, we classified poor patient vision into one of two additional categories, counting fingers at 2 feet (2/200 or logMAR 1.8) and hand motions at 2 feet (logMAR of 1.9). By means of this conservative methodology, a change from LP to CF was considered mathematically equivalent to a 2-line improvement.²¹

For the evaluation of reduction of vitreous hemorrhage, hemorrhage density grades were assessed by means of indirect ophthalmoscopy with the lens of choice of the investigator, wide angle contact lens examination, or other technique as deemed appropriate by the investigator in

each of 12 clock hours and defined as follows: Grade 0—anatomical details of the retina are visible and pathology is easily treatable; Grade 1—retinal detail is visible, some hemorrhage present but laser photocoagulation would still be possible; Grade 2—large retinal vessels are visible, but central retinal detail is not visible enough to adequately place panretinal photocoagulation posterior to the equator; Grade 3—red reflex is visible but no central retinal detail (retinal blood vessels) is seen posterior to the equator; and Grade 4—no red reflex. Patients were considered to have attained the reduction in hemorrhage density secondary endpoint if the density reduced from grades 3 or 4 at baseline in all 12 clock hours to a grade 0 or 1 in at least 6 clock hours in the study eye, except for patients with branch retinal vein occlusion (BRVO). For patients with BRVO, a reduction to a grade 0 or 1 in at least 3 clock hours in the study eye was required.

Finally, a clinical assessment of therapeutic utility was evaluated. This was defined as clearance of hemorrhage sufficient to diagnose the underlying pathology, and plan (though not necessarily initiate) treatment, if necessary. This endpoint was essentially the same as the primary endpoint with the exception that it did not require treatment of the underlying pathology and/or documentation of the treatment (for example, completed laser therapy or fundus photograph) in order for the patient to be considered a treatment success, and was similar to the endpoint used in the phase IIb trials.

• **STATISTICAL METHODOLOGY:** A sample size of 170 subjects per treatment arm in each study was calculated to provide at least 80% power and an overall significance level of 0.05 (2-tailed test) for detecting differences in success rates between groups.²² The sample size calculation was assessed by the Data Safety Monitoring Board (DSMB) at each interim analysis to determine if any of the design assumptions appeared to be invalid. No adjustment of sample size was recommended by the DSMB.

Sample size calculations were made based on the proportion of patients with treatment success from two previous prospective, randomized, parallel-group phase IIb studies. Treatment success in these phase IIb studies was defined as adequate clearing of the hemorrhage to permit appropriate diagnosis or the start of treatment at day 56. Doses of ovine hyaluronidase studied in these earlier studies were 7.5 IU, 37.5 IU, and 75 IU. There was no control group used in the phase IIb studies.

In these phase III studies, analyses were based on the intent-to-treat (ITT) population defined as all randomized patients who had a screening visit. Baseline characteristics were analyzed using either a one-way analysis of variance (ANOVA) for numeric response variables or an appropriate categorical analysis (for example, χ^2 and/or Fisher exact test) for categorical response frequencies.

Efficacy endpoints were analyzed based on success rates using the continuity corrected two-sample Z-test to com-

TABLE 1. 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 Study) and Outside of North America (Vit-03 Study)

	Vit-02 (N = 750)*	Vit-03 (N = 556)	Integrated (N = 1125)
Gender			
Male	52.4%	50.2%	51.6%
Age (mean, years) [†]	61.9 (n = 748)	61.9 (n = 553)	62.0
Ethnicity			
White	50.8%	84.0%	67.6%
Black	5.5%	9.7%	7.7%
Asian	3.5%	3.6%	3.5%
Other	40.1%	2.7%	21.2%
Diabetic status			
Non-diabetic	17.3%	28.6%	23.7%
Diabetic	82.7%	71.4%	76.3%
Type I	52.9%	69.3%	59.4%
Type II	47.1%	30.7%	40.6%
BCVA			
Unable to read any letters on the eye chart [‡]	86.9%	95.0%	90.4%*
Hemorrhage duration (Days)			
Mean (SD)	116.9 (104.6)	125.3 (113.0)	120.4 (110.0)

*Includes the 7.5 IU ovine hyaluronidase dose group.

[†]Age and gender data were missing for one patient who was randomized to 55 IU ovine hyaluronidase in Vit-02. One patient randomized to the saline group in Vit 02 had a calculated age that resolved to zero because of a missing birth year. These patients were not included in the calculations for age and gender. In Vit-03, three patients had a birth date that resulted in a calculated age of zero because of missing birth years (two saline control group patients, one 55 IU ovine hyaluronidase patient). These patients were not included in the calculation for age. One 75 IU ovine hyaluronidase patient (Vit-03) was missing a gender value. This patient was not included in the calculations for gender.

[‡]Unable to read any letters on the eye chart includes baseline BCVA that was light perception, hand motion, or count fingers.

pare the pooled 55 IU and 75 IU hyaluronidase doses to the pooled saline group (equivalent to the χ^2 test). Success rates were computed for each treatment group as $P_{\text{suc}} = 100(S/N)\%$ where P_{suc} was success rate, S was the number of patients in the group whose outcome was classified as a success, and N was the number of patients in the treatment group for the analysis population. A last observation carried forward (LOCF) method was used.

Four separate interim analyses were performed for each study to allow the DSMB to evaluate safety and efficacy. For the primary efficacy endpoint to reach statistical significance, the computed *P*-value must have been less than the Lan-DeMets alpha level with an O'Brien-Fleming boundary adjusted for each interim look to be declared significant at the overall 0.05 level.^{23,24} Thus, after the fourth interim analysis, the *P*-value would have to be .0459 in the Vit-02 study and .0464 in the Vit-03 study. For the analysis of the pooled primary efficacy dataset, a further adjustment of the *P*-value is warranted. Utilizing the DSMB interim analysis final adjusted *P*-value as the basis ($P = .046$), a further adjustment was made for the two common doses (55 IU and 75 IU) and three timepoints (months 1, 2, and 3). Thus, the *P*-value for the primary efficacy endpoint would have to be .008 (.046/6) to reach significance.

The comprehensive, integrated safety results of the two phase III studies are described in detail in the companion safety article in THE JOURNAL.

RESULTS

A TOTAL OF 1125 PATIENTS WITH PERSISTENT VITREOUS hemorrhage were randomized to 55 IU (n = 365), 75 IU (n = 377), and saline (n = 383) in the two studies. Patients were enrolled at 131 investigative centers in: the United States (n = 383, 34.0%); Canada (n = 99, 8.8%); Mexico (n = 87, 7.7%); Europe (Poland [n = 182, 16.2%]; Hungary [n = 87, 7.7%]; United Kingdom [n = 64, 5.7%]; Spain [n = 20, 1.8%]; Italy [n = 14, 1.3%]; the Netherlands [n = 8, 0.7%]); Brazil (n = 117, 10.4%); South Africa (n = 48, 4.3%); and Australia (n = 16, 1.4%).

A total of 330 (90.4%), 355 (94.2%), and 361 (94.3%) patients in the 55 IU, 75 IU, and saline groups, respectively, completed the month 3 visit. Baseline characteristics were similar between the two studies. At baseline, 858 (76.3%) patients had diabetes and 1180 (90.4%) were unable to read any letters on the eye chart. The mean duration of vitreous hemorrhage was 120.4 days (Table 1).

TABLE 2. Cumulative Percentages of Subjects Achieving Clearance of Vitreous Hemorrhage Sufficient to See Underlying Pathology and Complete Treatment by Month 3 Visit

	Saline Control (N = 383)	55 IU (N = 365)	75 IU (N = 377)
Month 1	5.5%	13.2%	10.6%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .010
Month 2	16.2%	25.5%	21.2%
Pairwise <i>P</i> -value*		<i>P</i> = .002	<i>P</i> = .083
Month 3	25.6%	32.9%	30.5%
Pairwise <i>P</i> -value*		<i>P</i> = .025	<i>P</i> = .144

Data represent the percentage of patients attaining primary efficacy on or before the indicated visit (month 1, 2 or 3). Patients were considered a success if the hemorrhage cleared sufficiently to facilitate the diagnosis of the underlying retinal pathology and to provide treatment, if necessary, of the underlying pathology. Patients were recorded as a success dependent on completion of treatment, if necessary, or documentation that no further treatment was necessary to treat the underlying pathology.

*Pairwise comparisons of the 55 IU and 75 IU doses of ovine hyaluronidase to saline were based on the 2-tailed Z-test with no multiplicity adjustments.

TABLE 3. Cumulative Percentages of Subjects Attaining ≥ 3-Line Improvement in BCVA by Month 3 Visit

	Saline Control (N = 383)	55 IU (N = 365)	75 IU (N = 377)
Month 1	20.1%	30.7%	27.9%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .013
Month 2	27.4%	41.1%	38.2%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .002
Month 3	34.5%	44.9%	43.5%
Pairwise <i>P</i> -value*		<i>P</i> = .004	<i>P</i> = .011

*Pairwise comparisons of the 55 IU and 75 IU doses of ovine hyaluronidase to saline were based on the 2-tailed Z-test with no multiplicity adjustments.

A statistically significant proportion of patients reached primary efficacy by months 1 and 2 for the 55 IU dose group based on the adjusted *P*-value (*P* < .001 and *P* = .002). The percentage of patients reaching primary efficacy by month 1 in the 55 IU, 75 IU, and saline groups was 13.2%, 10.6%, and 5.5% (*P* < .001 and *P* = .010, respectively, Table 2). By month 2, 25.5%, 21.2%, and 16.2% of patients treated with 55 IU, 75 IU, and saline reached primary efficacy (*P* = .002, *P* = .083, respectively). By month 3, 32.9%, 30.5%, and 25.6% of patients treated with 55 IU, 75 IU, and saline reached the primary efficacy endpoint (*P* = .025, *P* = .144, respectively).

TABLE 4. Cumulative Percentages of Subjects Reaching the Reduction in Vitreous Hemorrhage Density Endpoint by Month 3 Visit

	Saline Control (N = 383)	55 IU (N = 365)	75 IU (N = 377)
Month 1	11.0%	20.3%	19.1%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .002
Month 2	21.4%	32.9%	30.2%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .006
Month 3	28.5%	38.6%	38.2%
Pairwise <i>P</i> -value*		<i>P</i> = .003	<i>P</i> = .005

*Pairwise comparisons of the 55 IU and 75 IU doses of ovine hyaluronidase to saline were based on the 2-tailed Z-test with no multiplicity adjustments.

TABLE 5. Cumulative Percentages of Subjects Attaining Clearance of Hemorrhage Sufficiently for Investigator to Diagnose and Treat by Month 3 Visit. (Clinical Assessment of Therapeutic Utility Endpoint)

	Saline Control (N = 383)	55 IU (N = 365)	75 IU (N = 377)
Month 1	11.2%	23.3%	22.5%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> < .001
Month 2	21.4%	35.3%	32.1%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .001
Month 3	28.5%	40.8%	39.3%
Pairwise <i>P</i> -value*		<i>P</i> < .001	<i>P</i> = .002

*Pairwise comparisons of the 55 IU and 75 IU doses of ovine hyaluronidase to saline were based on the 2-tailed Z-test with no multiplicity adjustments.

A statistically significant improvement in BCVA was seen (proportion of patients with at least a 3-line improvement or 0.3 logMAR units in the study eye, Table 3). By month 1, 30.7% and 27.9% of patients in the 55 IU and 75 IU ovine hyaluronidase groups, respectively, had at least a 3-line improvement in BCVA compared with 20.1% of patients in the saline group (*P* < .001 and *P* = .013 for the 55 IU and 75 IU groups, respectively, vs saline). By month 2, 41.1% and 38.2% of patients in the 55 IU and 75 IU treatment groups had at least 3-line improvement in BCVA compared with 27.4% of patients in the saline group (*P* < .001 and *P* = .002, respectively). By month 3, 44.9% and 43.5% of patients in the 55 IU and 75 IU treatment groups had at least a 3-line improvement in BCVA compared with 34.5% of patients in the saline group (*P* = .004 and *P* = .011, respectively).

The analysis of the investigator graded reduction in vitreous hemorrhage density also showed statistical significance in the 55 IU and 75 IU dose groups compared with saline by months 1, 2, and 3 (Table 4). By month 1, for

patients in the 55 IU and 75 IU treated groups, there was a clinically relevant reduction in hemorrhage density from grade 3 or 4 (dense hemorrhage in all 12 clock hours) to grade 0 or 1 (minimal residual hemorrhage in 6 clock hours or more for patients with PDR and 3 clock hours for patients with BRVO) compared with the patients in the saline group: 20.3% and 19.1% vs 11.0%, respectively ($P < .001$ and $P = .002$ for the 55 IU and 75 IU groups vs saline). This effect persisted through months 2 and 3. By month 2, 32.9%, and 30.2% of patients in the 55 IU and 75 IU groups compared with 21.4% of patients in the saline group attained a reduction in vitreous hemorrhage ($P < .001$ and $P = .006$ for the 55 IU and 75 IU groups, respectively, vs saline). By month 3, 38.6%, and 38.2% of patients in the 55 IU and 75 IU groups compared with 28.5% of patients in the saline group attained a reduction in vitreous hemorrhage vs saline ($P = .003$ and $P = .005$ for the 55 IU and 75 IU groups, respectively).

In the analysis of the clinical assessment of therapeutic utility (clearance of the hemorrhage sufficient to diagnose the underlying pathology), there was a statistically significant difference for patients in the 55 IU and 75 IU treatment groups compared with saline-treated patients by months 1, 2, and 3 (Table 5). By month 1, 23.3%, and 22.5% of patients in the 55 IU ($P < .001$), and 75 IU ($P < .001$) groups, respectively, reached this endpoint compared with 11.2% of patients in the saline group. By month 2, 35.3% and 32.1% of patients in the 55 IU ($P < .001$) and 75 IU ($P = .001$) groups, respectively, reached this endpoint compared with 21.4% of patients in the saline group. By month 3, 40.8%, and 39.3% of patients in the 55 IU ($P < .001$), and 75 IU ($P = .002$) groups, respectively, reached this endpoint compared with 28.5% of patients in the saline group.

A comprehensive analysis of the safety of an intravitreal injection of ovine hyaluronidase from two phase III studies is provided in the companion safety article in THE JOURNAL.

DISCUSSION

THESE TWO PHASE III, PLACEBO CONTROLLED, MULTINATIONAL studies represent the first large-scale attempt to evaluate the efficacy of an enzymatic agent for the management of vitreous hemorrhage. At the present time, the only management options for vitreous hemorrhage are observation or pars plana vitrectomy. Enzymatic vitreolysis potentially offers several advantages over current standard practice, including the ability to diagnose and treat the eye earlier, lower costs, and greater patient availability. In these phase III trials, the primary efficacy endpoint was defined as clearance of vitreous hemorrhage sufficient to see the underlying pathology and completion of treatment, when indicated, by month 3. While the primary efficacy endpoint was to be achieved by month 3, in fact it was

seen as early as month 1, the earliest time-point at which efficacy was assessed, and through month 2 in a statistically significant proportion of patients treated with a single intravitreal injection of 55 IU ovine hyaluronidase. In fact, the relative difference in the primary efficacy of 55 IU ovine hyaluronidase compared with saline was greatest by month 1. Similarly, the relative difference by month 2 was greater than by month 3. Furthermore, the three key secondary endpoints described in this article (improvement in BCVA, reduction in hemorrhage density and clinical assessment of therapeutic utility) are corroborative of this finding: the endpoints were reached with statistical significance by month 1 and persisted through month 3.

The fact that the greatest relative treatment effect was seen by month 1, the earliest time point evaluated, may be consistent with the mechanism of action of this enzyme. Ovine hyaluronidase has a relatively short half-life of 60 to 112 hours in ocular tissues, so the initiation of the complex enzymatic cascade leading to subsequent vitreous hemorrhage clearance occurs within this period. By the month 1 time point, no significant enzymatic activity is present. Therefore, the month 1 results may most closely reflect the greatest effect of ovine hyaluronidase itself on the vitreous hemorrhage, with the subsequent clearance of residual vitreous hemorrhage attributable to slower degradative processes. Given that the presence of vitreous hemorrhage obscures the ability to treat underlying pathology the early clearance seen with ovine hyaluronidase is advantageous. During the observation (watchful waiting) period, the underlying pathology remains untreated, potentially increasing the risk of further complications from the underlying pathology if the hemorrhage does not clear. Additionally, the patient's quality of life can be severely affected during the observation period primarily a result of decreased visual acuity and depth perception if the patient has useful vision in the fellow eye.

This study had several inherent limitations. A study designed to evaluate clearance of vitreous hemorrhage has not been performed to date, and as a result there were no objective and quantifiable efficacy endpoints previously validated. For example, the primary efficacy endpoint for this study required the completion of a procedure and was a surrogate measure of efficacy which has not yet been validated. There were also limitations in the key secondary endpoints, including BCVA. Most patients ($n = 1180$, 90.4%) who entered the study were unable to read any letters on the eye chart in the study eye. It was not possible to obtain pre-vitreous hemorrhage visual acuity, hence, the improvement in visual acuity was limited to the extent of the unknown pre-hemorrhage BCVA. The other key secondary endpoints (reduction of vitreous hemorrhage density and clinical assessment of therapeutic utility) were by necessity subjective, given the difficult nature of trying to quantify clearance of vitreous hemorrhage, and the lack of any quantitative measurement device. Additionally, it is possible to hypothesize that the saline injection control

may have itself reduced the vitreous hemorrhage density, for example, by mechanical induction of a posterior vitreous detachment or by a hydrodynamic mechanism. Therefore a sham injection that would not have the potential to induce these changes may have been a more appropriate control. Regardless, a saline injection as the control group was required by the FDA. Finally, because only a single injection of ovine hyaluronidase was allowed in the study, any residual significant vitreous hemorrhage which remained at 3 months or occurred after 3 months was typically treated with vitrectomy. Therefore, no long term follow-up data comparing efficacy parameters between groups are interpretable.

In summary, this pooled analysis of two phase III clinical trials evaluating the efficacy of ovine hyaluronidase for the management of persistent vitreous hemorrhage demonstrated that a single injection of 55 IU ovine hyaluronidase resulted in a statistically significant effect on the primary efficacy endpoint at months 1 and 2 (even adjusting for multiple doses and multiple timepoints). Analyses of three key secondary efficacy endpoints confirm the primary efficacy outcome. The fact that the greatest relative treatment effect was seen by month 1 may be of clinical utility to retinal specialists, as this may allow earlier treatment of the underlying pathology while minimizing the risk to the patient.

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