SAFETY PROFILE OF OCRIPLASMIN FOR THE PHARMACOLOGIC TREATMENT OF SYMPTOMATIC VITREOMACULAR ADHESION/TRACTION

PETER K. KAISER, MD,* ANSELM KAMPIK, MD,† BARUCH D. KUPPERMANN, MD, PhD,‡ ANIZ GIRACH, MD,§ STANISLAO RIZZO, MD,¶ ROBERT C. SERGOTT, MD**††

Purpose: To report the safety of intravitreal ocriplasmin injection based on 2 Phase 3 clinical trials in patients with symptomatic vitreomacular adhesion/vitreomacular traction, including when associated with full-thickness macular holes.

Methods: Safety analyses were based on 2 completed Phase 3 studies assessing intravitreal ocriplasmin injection. Adverse events (AEs), serious AEs, and suspected adverse drug reactions are reported. The authors also report AEs of special interest from 8 other completed Phase 2 studies and 2 ongoing studies.

Results: A total of 465 eyes were injected with ocriplasmin (125 µg), and 187 eyes were treated with placebo injection in Phase 3 studies. Overall AE rate was 69.0% in the placebo group and 76.6% for ocriplasmin-treated patients. Most AEs were in the study eye, mild or moderate in severity, and transient. All suspected adverse drug reactions were ocular; the majority was nonserious, of mild intensity, and transient.

Conclusion: Intravitreal ocriplasmin injection provides a generally well-tolerated pharmacologic treatment option for patients with symptomatic vitreomacular adhesion/vitreomacular traction, including when associated with full-thickness macular holes ≤400 µm in diameter.

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Posterior vitreous detachment (PVD) is a normal physiologic process of aging and results from the simultaneous weakening of the adhesion between the posterior vitreous cortex and the interior limiting lamina of the retina, combined with liquefaction of the vitreous.1–4 Posterior vitreous detachment normally progresses to spontaneous separation of the vitreous from the retinal surface without complication. However, sometimes abnormal adhesions remain between the vitreous and retina, and when the macula is involved, this is referred to as vitreomacular adhesion (VMA).5–7 Vitreomacular adhesion can resolve spontaneously but may develop into a progressive pathologic condition known as vitreomacular traction (VMT), which can play a role in the pathogenesis of full-thickness macular hole (FTMH) and is associated with metamorphopsia and reduced visual acuity.3,5,8–10 It has also been reported that the presence of VMA/VMT may be associated with diabetic macular edema, exudative age-related macular degeneration, and myopic traction maculopathy.4,6,11

Until recently, the only intervention for symptomatic VMA/VMT was pars plana vitrectomy, during which the adhesion between the retina and vitreous is surgically removed from the macular surface and the remaining vitreous removed from the eye. Although vitrectomy is almost universally effective at releasing VMT and anatomically closing FTMHs, visual gain does not always occur.11–15 Moderate visual acuity improvement, defined as a gain of ≥2 Snellen lines, is seen in approximately one-third of patients undergoing vitrectomy.16 Moreover, this invasive procedure is associated with risks such as retinal breaks, retinal detachment, endophthalmitis, macular edema, vitreous hemorrhage, retinal pigment epithelium alterations, glaucoma, increased ocular pressure, and cataract formation.17–28 The postsurgery burden of vitrectomy can sometimes be substantial for patients, especially the
required face-down positioning after macular hole (MH) surgery.\textsuperscript{11,29} Given the risks for vitrectomy, the standard of care has generally been to wait until visual symptoms from VMT have deteriorated enough to justify the procedure.\textsuperscript{11,15}

Recently, a nonsurgical intervention for symptomatic VMA/VMT, including when associated with FTMH \( \leq 400 \, \mu m \) in diameter, became available in the form of ocriplasmin (Jetrea; ThromboGenics NV, Leuven, Belgium).\textsuperscript{30,31} Ocriplasmin is a serine protease enzyme that can lyse the molecular substrates responsible for VMA such as fibronectin and laminin.\textsuperscript{32,33} The results of 2 prospective, randomized, placebo-controlled, multicenter Phase 3 studies conducted in 2010 in patients with symptomatic VMA/VMT showed that a single intravitreal ocriplasmin injection resolved VMA/VMT and increased the likelihood of producing a total PVD at Day 28 after injection in significantly more patients when compared with placebo vehicle injection (hereafter referred to as placebo).\textsuperscript{15} Consistent with these observations, a greater proportion of patients treated with ocriplasmin compared with placebo achieved nonsurgical FTMH closure and an improvement in best-corrected visual acuity of \( \geq 3 \) lines on the Early Treatment Diabetic Retinopathy Study chart. Additionally, fewer ocriplasmin-treated patients underwent vitrectomy during the study period, and there was a favorable impact on the 25-item National Eye Institute Visual Functioning Questionnaire (VFQ-25) when compared with placebo patients.\textsuperscript{15} Safety data from the 2 Phase 3 studies demonstrated a higher incidence of ocular adverse events (AEs) in patients who were treated with an intravitreal injection of ocriplasmin compared with patients who received placebo, although the AEs were generally transient.\textsuperscript{15} Here, we undertake a detailed review of the safety of ocriplasmin, with a focus mainly on the results of the completed Phase 3 clinical trials that evaluated intravitreal ocriplasmin injection in patients with symptomatic VMA/VMT.

**Methods**

**Studies Included in the Analysis**

This analysis is based on the data set from the clinical trial program assessing ocriplasmin. These data are provided to complement postmarketing safety data, which will be presented in a timely manner as information becomes available and is assessed. The pooled safety results from 2 completed Phase 3 clinical trials (Studies NCT00781859 [TG-MV-006] and NCT00798317 [TG-MV-007], hereafter referred to as study 006 and study 007) are presented in this safety analysis. The designs of the two studies have been previously published.\textsuperscript{15} Briefly, these were multicenter, randomized, placebo-controlled, double-masked studies in patients with symptomatic VMA/VMT who were either given ocriplasmin 125 \( \mu g \) or placebo by intravitreal injection (both groups received an intravitreal injection volume of 100 \( \mu L \)). Eligible patients were randomized 2:1 (ocriplasmin:placebo) in study 006 (United States only) and 3:1 in study 007 (United States and European Union). The two studies were otherwise identical in design. The primary endpoint was nonsurgical resolution of VMA at Day 28 based on time-domain optical coherence tomography (Stratus OCT; Carl Zeiss Meditec, Dublin, CA) graded at a central reading center. Secondary endpoints were total PVD occurrence and nonsurgical closure of FTMH at Day 28, avoidance of vitrectomy, and mean changes in best-corrected visual acuity and patient-reported VFQ-25 score. In both studies, patients were permitted to undergo vitrectomy after Day 28 if deemed necessary by the investigator.\textsuperscript{15} In both Phase 3 studies, the total number of patients randomized to ocriplasmin and placebo was 464 and 188, respectively; however, 1 patient randomized to placebo received ocriplasmin and was included in the safety population.

For the analyses of AEs of special interest, we also report data from 8 additional studies evaluating ocriplasmin administered intravitreally that were completed and 2 studies that were ongoing at the data...
cutoff date of July 24, 2013. Details of the study designs and results of these Phase 2 studies have been published previously, and study overviews are presented here (see Table, Supplemental Digital Content 1, http://links.lww.com/IAE/A321). From the entire safety database of completed trials, the total number of ocriplasmin-treated eyes was 1,008 and total number of control eyes (placebo or sham injection) was 351.

Ethical Considerations

The studies and relevant protocol details were registered at www.ClinicalTrials.gov, and trial identifiers were published previously (see Table, Supplemental Digital Content 1, http://links.lww.com/IAE/A321), which also details the 10 completed studies as of the data cutoff date of July 24, 2013. All studies were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Studies 006 and 007 used a masked central reading center to ensure a consistent interpretation of OCT readings and a Data Monitoring Committee to oversee safety aspects of the clinical program. The study sites determined patient eligibility, and the initial and follow-up OCTs were interpreted by the central reading center.

Patient Populations

The full inclusion criteria of the Phase 3 studies have been reported previously; briefly, patients were eligible if they were aged 18 years or older, had a diagnosis of symptomatic VMA/VMT, and a best-corrected visual acuity of 20/25 or less in the study eye and 20/800 or more in the nonstudy eye. Key exclusion criteria for the studies included proliferative diabetic retinopathy, neovascular age-related macular degeneration, aphakia, high myopia (>–8 diopters), uncontrolled glaucoma, an FTMH >400 μm in diameter, vitreous opacification, lenticular or zonular instability, or history of retinal detachment; and previous vitrectomy, intravitreal injection, or retinal laser photocoagulation in the study eye.

Safety Assessments

Safety assessments included AEs, serious AEs (SAEs), suspected adverse drug reactions (sADRs), and ocular examination findings. Although ocriplasmin is inactivated within several days of intravitreal injection, ocular and nonocular AEs and other safety data were collected for 6 months after injection. Investigators assessed the relationship of AEs or SAEs as being unlikely, remotely, possibly, or probably related to the study drug. Serious AEs were those that met the definition of serious as summarized in the International Conference on Harmonisation guideline.

Safety Analyses

The safety analyses were conducted on all patients allocated to treatment groups based on the treatment received (safety population). Adverse events or SAEs were defined as events that occurred from the time of injection to the last study visit. Adverse events or SAEs were considered “drug related” if the investigator considered the event to be possibly or probably related to study drug and “unrelated” if the investigator considered the relationship to study treatment to be unlikely or remote.

Adverse events were considered to be sADRs if there was a reasonable possibility that these events were treatment related and were based on at least a 2-fold greater incidence in the ocriplasmin group compared with placebo and/or clinical judgment. Based on the single dose and inactivation time of ocriplasmin, sADRs that occurred within 7 days of injection were considered the most appropriate estimate of risk; therefore, sADR data were analyzed from 0 days to 7 days after injection and from Day 8 to the end of the studies.

Adverse event classifications were based on the Medical Dictionary for Regulatory Activities, and preferred terms are reported. Similar Medical Dictionary for Regulatory Activities preferred terms were grouped into categories for AEs of special interest so as not to underestimate the incidence of an event. Adverse events of special interest were based on their potential or actual clinical relevance and included anatomical retinal findings (retinal edema [preferred term for subretinal fluid] and macular edema), events known to be associated with the intravitreal injection procedure, retinal tears and retinal detachments, cataracts, vision function changes (vision alteration, color vision alteration, and electroretinogram [ERG] changes), and subluxation of the lens. The vision alteration category included the following Medical Dictionary for Regulatory Activities preferred terms: metamorphopsia, scotoma, vision blurred, reduced visual acuity, transiently reduced visual acuity, visual field defect, visual impairment, blindness, halo vision, loss of visual contrast sensitivity, and visual brightness.

Anatomical retinal findings were based on AEs and the results of OCT scans with the use of the time-domain Stratus device. In addition, spectral domain OCT images were obtained at some sites, where available.
Results

Patient Disposition and Demographics

From the Phase 3 clinical trials, 465 eyes treated with an intravitreal injection of ocriplasmin 125 μg along with 187 eyes treated with placebo were available for analysis (see Table, Supplemental Digital Content 1, http://links.lww.com/IAE/A321). More than 90% of the patients completed the studies (Table 1). The most common reasons for discontinuation from the studies were withdrawal of consent or loss to follow-up (Table 1). Approximately 1% of patients withdrew from a study because of an AE, with no meaningful differences in the rates of discontinuation reported between the ocriplasmin and placebo groups (Table 1). Five patients from the ocriplasmin group died during the study period with reported causes of death being cerebral hemorrhage, malignant lung neoplasm (two cases), congestive cardiac failure, and metastatic brain cancer. None was reported by the investigator to be related to treatment with study drug. No patients from the control group died during the study period.

Baseline demographics and disease characteristics are presented in Table 2. Overall, the two treatment groups were balanced across all baseline characteristics, with the exception of pseudophakia, which occurred more frequently in the ocriplasmin group.

Overview of Adverse Events

Ocriplasmin was generally well tolerated when administered as an intravitreal injection. Most AEs were ocular and mild or moderate in severity, and the majority occurred in the study eye (Table 3). Adverse events were reported in 76.6% of patients treated with ocriplasmin 125 μg and in 69.0% of patients treated with placebo. Vitreous floaters, conjunctival hemorrhage, eye pain, and photopsias were the most frequently reported ocular AEs in the ocriplasmin group. The percentage of AEs reported more frequently in the placebo group compared with the ocriplasmin group, which included the incidence of new or worsening FTMH, intraocular pressure increase, and cataract. The incidence of nonocular AEs was higher in the ocriplasmin-treated group than in the placebo group (Table 3).

Serious Adverse Events

Of the SAEs reported in patients treated with ocriplasmin, 41 ocular events occurred in 37 patients, with the majority occurring in the study eye (39 SAEs in 36 patients). In the placebo group, 24 ocular SAEs occurred in the study eye of 20 patients (Table 4). The most common study eye SAEs reported in the ocriplasmin and placebo groups, respectively, were new or worsening FTMH (5.2% and 8.6%), persistent VMT or adhesions (1.1% and 0.5%), reduced visual acuity (0.6% and 0.5%), and rhegmatogenous retinal detachment (0.4% and 1.6%). The incidence of drug-related SAEs was the same (3.2%) for both the ocriplasmin and placebo groups.
Suspected Adverse Drug Reactions

All sADRs reported were ocular in nature, with the majority (414/514 ocriplasmin-treated patients [80.5%] and 59/71 placebo patients [83.1%]) being nonserious, graded as mild in intensity, and transient. Of these, 373 of the 514 (72.6%) of the sADRs in ocriplasmin-treated patients and 47 of the 71 (66.2%) of sADRs in placebo patients had resolved at Month 6. The most common sADRs observed in the study eye of patients who received ocriplasmin were vitreous floaters, eye pain, and photopsias. These were mostly consistent with the intended action of the drug, that is, pharmacologic vitreolysis, or resulted from the injection procedure. The majority of sADRs occurred within 0 days to 7 days after injection (Table 5, Figures 1 and 2).

Retinal Tears/Detachments

The incidence of both retinal tears and retinal detachments occurring in the study eye was generally lower in the ocriplasmin group than in the placebo group. Before vitrectomy, retinal tears without retinal detachment occurred in 1 placebo patient (0.5%) and 1 ocriplasmin patient (0.2%). After vitrectomy, retinal tears occurred in 4 placebo patients (8.0%) and 5 ocriplasmin-treated patients (6.1%). Retinal detachments occurred in no patients in the placebo group before vitrectomy and in 2 patients (0.4%) in the ocriplasmin group. After vitrectomy, retinal detachments occurred in 3 placebo patients (6.0%) and 2 ocriplasmin-treated patients (2.4%).

Adverse Events Related to Intravitreal Injection Procedures

The incidence of AEs known to be associated with the intravitreal injection procedure is presented in Table 6. No clinically meaningful differences were observed between treatment groups for AEs of intraocular hemorrhage or increased intraocular pressure. These events were of mild or moderate intensity. Adverse events of increased intraocular anterior chamber inflammation were reported in a higher proportion of patients in the ocriplasmin versus placebo group (Table 6). Two cases of vitreous chamber inflammation (deemed by the investigator as unrelated to study drug) required intravitreal steroid injections for vitritis. All other cases of anterior chamber or vitreous chamber inflammation resolved spontaneously. Two SAEs of self-limiting intraocular hemorrhage, which were peripheral in nature and not associated with any sequelae, were reported in the ocriplasmin group. Both cases spontaneously resolved within weeks. No intraocular hemorrhage cases were reported in the placebo group. No cases of intraocular infections, including endophthalmitis, were reported in any patient treated with ocriplasmin.

### Table 3. Adverse Events Reported for ≥2% of Patients Treated With Ocriplasmin 125 μg in the Phase 3 Placebo-Controlled Studies (Safety Population)

| System Organ Class | Placebo (n = 187)§ | Ocriplasmin 125 μg (n = 465)§ |
|--------------------|---------------------|--------------------------------|
| Number of patients (%) |                     |                                |
| Any AE              | 129 (69.0)          | 356 (76.6)                     |
| Any nonocular event | 53 (28.3)           | 140 (30.1)                     |
| Any ocular event    | 106 (56.7)          | 324 (69.7)                     |
| Study eye event     | 100 (53.5)          | 318 (68.4)                     |
| Nonstudy eye event  | 22 (11.8)           | 61 (13.1)                      |
| Eye disorders       |                     |                                |
| Any event           | 101 (54.0)          | 321 (69.0)                     |
| Study eye event     | 95 (50.8)           | 314 (67.5)                     |
| Nonstudy eye event  | 20 (10.7)           | 57 (12.3)                      |
| Ocular AEs†         |                     |                                |
| Vitreous floaters   | 16 (8.6)            | 82 (17.6)                      |
| Conjunctival hernage| 24 (12.8)           | 68 (14.6)                      |
| Eye pain            | 11 (5.9)            | 62 (13.3)                      |
| Photopsia           | 5 (2.7)             | 56 (12.0)                      |
| Blurred vision      | 8 (4.3)             | 41 (8.8)                       |
| MH                  | 19 (10.2)           | 36 (7.7)                       |
| Reduced visual acuity| 9 (4.8)           | 30 (6.5)                      |
| Visual impairment†  | 3 (1.6)             | 26 (5.6)                       |
| Retinal edema       | 2 (1.1)             | 25 (5.4)                       |
| Macular edema       | 3 (1.6)             | 19 (4.1)                       |
| Increased intraocular pressure |      | 10 (5.3) | 18 (3.9) |
| Anterior chamber cell| 5 (2.7)            | 17 (3.7)                      |
| Photophobia‡        | 0                   | 17 (3.7)                       |
| Vitreous detachment | 3 (1.6)             | 13 (2.8)                      |
| Ocular discomfort   | 2 (1.1)             | 13 (2.8)                      |
| Iritis              | 1 (0.5)             | 13 (2.8)                      |
| Cataract            | 8 (4.3)             | 12 (2.6)                      |
| Dry eye             | 2 (1.1)             | 11 (2.4)                      |
| Metamorphopsia      | 1 (0.5)             | 11 (2.4)                      |
| Conjunctival hyperemia| 4 (2.1)          | 10 (2.2)                      |
| Vitreous adhesions  | 2 (1.1)             | 10 (2.2)                      |
| Retinal degeneration| 1 (0.5)            | 10 (2.2)                      |
| Nonocular AEs       |                     |                                |
| Bronchitis          | 3 (1.6)             | 13 (2.8)                      |
| Headache            | 4 (2.1)             | 12 (2.6)                      |
| Nausea              | 1 (0.5)             | 12 (2.6)                      |

*As defined by MedDRA.
†Includes study eye and nonstudy eye AEs.
‡Two reports of photosensitivity (Study 006) that occurred in the study eye were coded to the preferred term, photosensitivity reaction. These events may represent two additional reports of photophobia.
§One patient who was randomly assigned to placebo inadvertently received ocriplasmin; therefore, the safety population included patients who actually received ocriplasmin or placebo.

Suspected Adverse Drug Reactions

All sADRs reported were ocular in nature, with the majority (414/514 ocriplasmin-treated patients [80.5%] and 59/71 placebo patients [83.1%]) being nonserious, graded as mild in intensity, and transient. Of these, 373 of the 514 (72.6%) of the sADRs in ocriplasmin-treated patients and 47 of the 71 (66.2%) of sADRs in placebo patients had resolved at Month 6. The most common sADRs observed in the study eye of patients who received ocriplasmin were vitreous floaters, eye pain, and photopsias. These were mostly consistent with the intended action of the drug, that is, pharmacologic vitreolysis, or resulted from the injection procedure. The majority of sADRs occurred within 0 days to 7 days after injection (Table 5, Figures 1 and 2).

Retinal Tears/Detachments

The incidence of both retinal tears and retinal detachments occurring in the study eye was generally lower in the ocriplasmin group than in the placebo group. Before vitrectomy, retinal tears without retinal detachment occurred in 1 placebo patient (0.5%) and 1 ocriplasmin patient (0.2%). After vitrectomy, retinal tears occurred in 4 placebo patients (8.0%) and 5 ocriplasmin-treated patients (6.1%). Retinal detachments occurred in no patients in the placebo group before vitrectomy and in 2 patients (0.4%) in the ocriplasmin group. After vitrectomy, retinal detachments occurred in 3 placebo patients (6.0%) and 2 ocriplasmin-treated patients (2.4%).

Adverse Events Related to Intravitreal Injection Procedures

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Cataracts

The incidence of cataract formation or progression in the study eye of patients in the Phase 3 studies was lower in the ocriplasmin group compared with the placebo group (Table 7). There were no acute cataracts before vitrectomy, with most cataract progression occurring after vitrectomy. In the ocriplasmin-treated group, 4.8% phakic patients (14/293) had cataract AEs before vitrectomy and 18.2% phakic patients (10/55) had cataract AEs after vitrectomy. A similar pattern was seen in the phakic patients in the placebo group (5.2% [7/134] vs. 22.0% [9/41], before vs. after vitrectomy). As the follow-up period was only 6 months, it is expected that more cataract-related AEs would be reported in the postvitrectomy patients with a longer follow-up.

Acute Reductions in Visual Acuity

The number of patients who had acute vision loss defined as ≥2-line decrease in vision within the first 7 days was higher in the ocriplasmin group compared with the placebo group (Table 7). There were no acute cataracts before vitrectomy, with most cataract progression occurring after vitrectomy. In the ocriplasmin-treated group, 4.8% phakic patients (14/293) had cataract AEs before vitrectomy and 18.2% phakic patients (10/55) had cataract AEs after vitrectomy. A similar pattern was seen in the phakic patients in the placebo group (5.2% [7/134] vs. 22.0% [9/41], before vs. after vitrectomy). As the follow-up period was only 6 months, it is expected that more cataract-related AEs would be reported in the postvitrectomy patients with a longer follow-up.

Vitreomacular adhesion resolution was strongly associated with a higher incidence of vision alteration. In many cases, the vision alteration was associated with presumed traction or development of subretinal fluid. In the subset of patients who did not have baseline subretinal fluid (ocriplasmin-treated patients, n = 255; placebo patients, n = 106), the number that developed subretinal fluid by Day 7 was higher in the ocriplasmin group (73/255, 28.6%) than in the placebo group (12/106, 11.3%); however, by the end of the study, the incidence in both groups was comparable (10.9% and 12.6% for ocriplasmin and placebo, respectively). Full-thickness macular hole progression or formation was recorded in 7 ocriplasmin-treated patients (19.4%) and 1 placebo patient (33.3%) (FTMH progression is shown in Figure 4); and progression of VMT was seen in 12 ocriplasmin-treated patients (33.3%) and no patients receiving placebo. Thus, the majority of acute vision loss seen in the clinical trials was due to either MH progression/formation or VMT progression in 19 ocriplasmin-treated patients (52.7%).

Of the patients with reduction in visual acuity between Day 0 and Day 7, 6 ocriplasmin-treated patients and 2 patients from the placebo group still had ≥2-line vision decrease from baseline at Month 6. The reasons for persistent vision decrease in these patients are presented in Table 8. Briefly, in the ocriplasmin-treated group, 3 patients had complications from vitrectomy. 1 patient withdrew consent so no additional follow-up is expected, and 1 patient was still awaiting vitrectomy for VMT progression. The persistent vision decrease in the final patient was not explained; this patient showed VMA resolution by
Month 6 (Figure 5). Of the two placebo group patients with persistent vision decrease, one had withdrawn consent and the other developed a nonarteritic ischemic optic neuropathy.

The number of patients who had acute vision loss, defined as ≥2-line vision decrease at the end of the study, was higher in the ocriplasmin group (36/465 [7.7%] vs. 11/187 [5.9%]). Of the 11 placebo patients,

| Preferred Term* | Placebo (n = 187) | Ocriplasmin 125 μg (n = 465) | Placebo (n = 187) | Ocriplasmin 125 μg (n = 465) |
|-----------------|------------------|-----------------------------|------------------|-----------------------------|
| Number of patients (%) |                 |                             |                  |                             |
| Vitreous floaters  | 5 (2.7)          | 60 (12.9)                   | 14 (7.5)         | 78 (16.8)                   |
| Eye pain          | 6 (3.2)          | 49 (10.5)                   | 11 (5.9)         | 61 (13.1)                   |
| Photopsia         | 2 (1.1)          | 47 (10.1)                   | 5 (2.7)          | 55 (11.8)                   |
| Blurred vision    | 1 (0.5)          | 30 (6.5)                    | 5 (2.7)          | 39 (8.4)                    |
| Reduced visual acuity | 0               | 19 (4.1)                    | 8 (4.3)          | 29 (6.2)                    |
| Retinal edema     | 0                | 17 (3.7)                    | 2 (1.1)          | 25 (5.4)                    |
| Photophobia       | 0                | 15 (3.2)                    | 0                | 17 (3.7)                    |
| Visual impairment | 0                | 15 (3.2)                    | 2 (1.1)          | 25 (5.4)                    |
| Anterior chamber cell | 1 (0.5)       | 12 (2.6)                    | 5 (2.7)          | 17 (3.7)                    |
| Iris              | 0                | 9 (1.9)                     | 0                | 12 (2.6)                    |
| Ocular discomfort | 2 (1.1)          | 8 (1.7)                     | 2 (1.1)          | 13 (2.8)                    |
| Metamorphopsia    | 0                | 7 (1.5)                     | 1 (0.5)          | 10 (2.2)                    |
| Vitreous detachment | 0               | 7 (1.5)                     | 2 (1.1)          | 12 (2.6)                    |
| Miosis            | 0                | 5 (1.1)                     | 0                | 5 (1.1)                     |
| Corneal abrasion  | 0                | 4 (0.9)                     | 0                | 5 (1.1)                     |
| Dry eye           | 1 (0.5)          | 4 (0.9)                     | 2 (1.1)          | 11 (2.4)                    |
| Conjunctival irritation | 0              | 3 (0.6)                     | 0                | 4 (0.9)                     |
| Eyelid edema      | 0                | 3 (0.6)                     | 1 (0.5)          | 7 (1.5)                     |
| Macular edema     | 0                | 3 (0.6)                     | 3 (1.6)          | 19 (4.1)                    |
| Ocular hyperemia  | 1 (0.5)          | 3 (0.6)                     | 1 (0.5)          | 4 (0.9)                     |
| Pupils unequal    | 0                | 2 (0.4)                     | 0                | 3 (0.6)                     |
| Scotoma           | 0                | 2 (0.4)                     | 0                | 5 (1.1)                     |
| Visual field defect | 0                | 2 (0.4)                     | 1 (0.5)          | 3 (0.6)                     |
| Diplopia          | 0                | 0                           | 0                | 4 (0.9)                     |
| Macular degeneration | 0            | 0                           | 1 (0.5)          | 6 (1.3)                     |
| Retinal degeneration | 0             | 0                           | 1 (0.5)          | 8 (1.7)                     |
| Retinal pigment epitheliopathy | 0       | 0                           | 0                | 7 (1.5)                     |

*As defined by MedDRA.

Fig. 1. Postinjection AEs in the study eye considered sADRs in the Phase 3, randomized, placebo-controlled studies—Day 0 to Day 7 (safety population). Ant., anterior; VA, visual acuity. Data on file, ThromboGenics.
7 (3.7%) had complications from vitrectomy, 1 (0.5%) had MH progression and had not undergone vitrectomy, 1 (0.5%) had active wet age-related macular degeneration, 1 (0.5%) had ischemic optic neuropathy, and 1 was not evaluable. Of the 36 ocriplasmin-treated patients, 11 (2.4%) had complications from vitrectomy, 17 (3.7%) were awaiting pars plana vitrectomy because of VMT or MH progression, 1 (0.2%) had vision loss because of unknown etiology, and 2 (0.4%) were not evaluable.

Formation or Progression of Full-Thickness Macular Hole Adverse Events

Formation or progression of FTMH reported as an AE was observed in the study eye in 9.6% of placebo group patients and 6.7% of ocriplasmin group patients. Overall in the studies, there was a significantly higher (40.6%) nonsurgical FTMH closure rate in ocriplasmin-treated patients compared with those who received placebo (10.6%, \( P < 0.001 \)). In patients in whom nonsurgical FTMH closure was not observed by Day 28, the MH diameter increased from baseline, with larger increases in the ocriplasmin versus the placebo groups. The ranges of mean change from baseline in FTMH width at Day 7, Day 28, and Month 6 visits were \(-275.0 \mu m\) to \(493.0 \mu m\), \(-324.0 \mu m\) to \(499.0 \mu m\), and \(-324.0 \mu m\) to \(749.0 \mu m\), respectively, for ocriplasmin-treated patients, and \(-112.0 \mu m\) to \(373.0 \mu m\), \(-162.0 \mu m\) to \(361.0 \mu m\), and \(-138.0 \mu m\) to \(623.0 \mu m\), respectively, for placebo patients. Nonsurgical FTMH closure occurred in 30 of 420 (7.1%), 41 of 417 (9.8%), and 79 of 435 (18.2%) of ocriplasmin-treated patients at Day 7, Day 28, and Month 6, respectively, and 0 of 171 (0.0%), 5 of 173 (2.9%), and 32 of 178 (18.0%) of placebo patients at Day 7, Day 28, and Month 6, respectively. Patients in whom nonsurgical FTMH closure was not achieved were permitted to undergo vitrectomy after Day 28, which subsequently resulted in FTMH closure in approximately 90% of these patients. There was no difference in surgical FTMH closure with vitrectomy between ocriplasmin and placebo.

**Table 6. Summary of AEs Known to Be Associated With the Intravitreal Injection Procedure; AEs in the Study Eye During the 2 Phase 3 Placebo-Controlled Studies (Safety Population)**

| System Organ Class                  | Placebo (n = 187), n (%) | Ocriplasmin 125 µg (n = 465), n (%) |
|-------------------------------------|--------------------------|-------------------------------------|
| Number of patients (%)              |                          |                                     |
| Intraocular hemorrhage              | 7 (3.7)                  | 11 (2.4)                            |
| Retinal hemorrhage                  | 4 (2.1)                  | 8 (1.7)                             |
| Vitreous hemorrhage                 | 2 (1.1)                  | 3 (0.6)                             |
| Hyphemiac                           | 0                        | 1 (0.2)                             |
| Optic nerve sheath hemorrhage       | 1 (0.5)                  | 0                                   |
| Optic disk hemorrhage               | 0                        | 0                                   |
| Intraocular inflammation            | 7 (3.7)                  | 33 (7.1)                            |
| Anterior chamber cell               | 5 (2.7)                  | 17 (3.7)                            |
| Anterior chamber flare              | 2 (1.1)                  | 6 (1.3)                             |
| Iritis                              | 0                        | 12 (2.6)                            |
| Vitreitis                           | 0                        | 2 (0.4)                             |
| Iridocyclitis                       | 0                        | 1 (0.2)                             |
| Vireal cells                        | 0                        | 1 (0.2)                             |
| Anterior chamber inflammation       | 0                        | 1 (0.2)                             |
| Iris adhesions                      | 1 (0.5)                  | 0                                   |
| Increase in intraocular pressure    | 10 (5.3)                 | 19 (4.1)                            |
| Increased intraocular pressure      | 10 (5.3)                 | 18 (3.9)                            |
| Ocular hypertension                | 0                        | 1 (0.2)                             |
Adverse Events of Special Interest

Data on vision-related AEs, dyschromatopsia, ERG changes, and serious acute vision decrease (≥6 lines) are presented from the 2 Phase 3 trials. In addition, given the infrequency of AEs of special interest in the Phase 3 trials, we also present data from the additional clinical trials that were completed by the data cutoff date of July 24, 2013, to provide a larger patient pool for the AEs of special interest (see Table, Supplemental Digital Content 1, http://links.lww.com/IAE/A321). Therefore, for this analysis of AEs of special interest, the total number of ocriplasmin-treated eyes was 1,008 and total number of controls (placebo or sham injection) was 351 eyes.

Serious and/or Severe Transient Acute Vision Decreases

Vision drops reported as serious and/or severe AEs by the treating physician were observed in 9 of the 1,008 ocriplasmin-treated patients. Rapid VMA resolution was observed in all nine cases and the acute visual impairment resolved in all cases. The median time to recovery of visual acuity was approximately 2 weeks, with the exception of 1 patient with exudative age-related macular degeneration and macula-off rhegmatogenous retinal detachment who took 1 year to recover vision to baseline (Table 9). The lack of resolution of the vision loss was considered by the investigator to be due to the patient’s concomitant disease.

Dyschromatopsia and Electroretinogram Changes

Although not formally tested in the Phase 3 clinical study protocols, dyschromatopsia (determined by Roth 28-hue test) and/or ERG changes were reported in 18 of the 1,008 ocriplasmin-treated patients (1.8%). Two of these patients also had serious acute vision loss and are included in the analysis above. Dyschromatopsia alone was reported in 16 of the 1,008 of the

Table 7. Summary of Cataract AEs in the Study Eye in the Completed Phase 3 Placebo-Controlled Studies (Safety Population)

| Preferred Term                        | Placebo (n = 187) | Ocriplasmin (n = 465), n (%) | Placebo (n = 134) | Ocriplasmin (n = 293), n (%) |
|---------------------------------------|-------------------|-------------------------------|-------------------|-----------------------------|
|                                      | n (%), n (%)      |                               | n (%), n (%)      |                             |
| Any lens opacity-related event        | 17 (9.1), 26 (5.6)| 16 (11.9), 24 (8.2)           |                   |                             |
| Cataract                              | 8 (4.3), 11 (2.4)| 8 (6.0), 11 (3.8)             |                   |                             |
| Cataract nuclear                      | 3 (1.6), 5 (1.1) | 3 (2.2), 5 (1.7)              |                   |                             |
| Cataract subcapsular                  | 1 (0.5), 4 (0.9) | 1 (0.7), 4 (1.4)              |                   |                             |
| Posterior capsule opacification       | 3 (1.6), 4 (0.9) | 2 (1.5), 2 (0.7)              |                   |                             |
| Cataract cortical                     | 3 (1.6), 3 (0.6) | 3 (2.2), 3 (1.0)              |                   |                             |

Fig. 3. Acute vision loss decrease with VMA resolution: sample improvement seen in Phase 3 studies up to Month 6.
ocriplasmin-treated patients (1.6%) (Table 10) and was generally described as “yellowish vision.” The majority of cases (11/16) were reported from 2 uncontrolled open-label clinical studies conducted in the same center where the same investigator administered most of the intravitreal injections. Median time to onset was 1 day, and median time to resolution was 3 months. All symptoms were mild and all but two cases resolved. Of the cases that did not resolve, 1 patient died after study completion and 1 patient was lost to follow-up; therefore, dyschromatopsia status is not known for either patient.

Full-field ERG abnormalities were observed in 10 ocriplasmin-treated patients from all completed and ongoing trials (Table 10). All of these full-field ERG changes were mild decreases in a-wave and b-wave amplitude, and there were no cases of isoelectric findings. Of the 10 patients with ERG changes, 8 also reported dyschromatopsia and are included in the 18 patients mentioned above. The median time to onset of abnormal ERGs was 1 week and ranged from 1 week to 1 month. The ERG changes resolved in 6 patients by the data cutoff date, with a median time to resolution of 6 months. Vitreomacular adhesion resolution was observed in 14 of the 18 patients with dyschromatopsia and/or ERG changes and was confirmed in 10 patients. Of the four patients who did not show VMA resolution, three were not available for follow-up, and the remaining patient had confounding vitelliform dystrophy.

**Lens Subluxation**

One case of lens subluxation and 1 case of phacodonesis were noted during the 10 completed and 2 ongoing clinical trials at the data cutoff date of July 24, 2013. The patient with lens subluxation was a 4-month-old premature male infant who had...

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Table 8. Patients With Persistent Vision Decrease at End of Study in the Completed Phase 3 Placebo-Controlled Studies

| Patient No. | Visual Acuity (ETDRS) | Patient Reason for Initial | Pars Plana | Reason for Persistent Loss |
|-------------|-----------------------|---------------------------|------------|---------------------------|
|             | Baseline Day 7 Day 28 Month 6 | MH Progression | PPV complication cataract |
| Ocriplasmin | 1 76 61 62 66 Yes | MMH Progression | PPV complication foveal atrophy |
|             | 2 70 58 42 42 Yes* | VMT to MH | PPV complication failed MH closure |
|             | 3 75 46 55 39 Yes* | Not known | VMA resolution, loss persisted |
|             | 4 53 33 46 42 No | MH Progression | PPV required |
|             | 5 77 66 73 66 No | VNAION/ optic disk edema | Unknown, consent withdrawn |
|             | 6 60 50 29 29 No | MH Progression | Unknown, consent withdrawn |

Placebo

| Patient No. | Visual Acuity (ETDRS) | Pars Plana Vitrectomy | Reason for Initial | Reason for Persistent Loss |
|-------------|-----------------------|-----------------------|-------------------|---------------------------|
| 1 69 55 56 Not known | VMT progression | PPV complication cataract |
| 2 53 28 29 42 No | NAION/ optic disk edema | Unknown, consent withdrawn |

*Patient received two PPVs.

ETDRS, Early Treatment Diabetic Retinopathy Study; NAION, nonarteritic ischemic optic neuropathy; PPV, pars plana vitrectomy.
significant ongoing medical conditions and very low birth weight and was undergoing vitrectomy for a retinal detachment because of retinopathy of prematurity. The patient was treated with ocriplasmin 175 μg (0.1 mL), a higher dose than the recommended 125 μg dose, but approximately half of the injection volume refluxed out because of the small volume of the eye. During vitrectomy, the lens appeared to be slightly displaced nasally, and loss of zonules was suspected. No disrupted zonules were seen. The infant received the same ocriplasmin dose/volume in the fellow eye 1 week later, which was preceded by an anterior chamber tap, with no reflux of ocriplasmin and no lens subluxation seen. One patient was noted to have phacodonesis when they underwent vitrectomy 323 days after injection of ocriplasmin 125 μg.

**Discussion**

This combined safety analysis of 2 Phase 3 studies demonstrates that ocriplasmin is generally well tolerated when administered as an intravitreal injection. In addition, AEs of special interest were examined from the Phase 2 studies in addition to the 2 Phase 3 studies to get a complete picture of the safety of ocriplasmin. In the Phase 3 studies, no meaningful differences between the ocriplasmin and placebo groups were
observed with respect to the incidence of nonocular AEs. Overall, the nonocular events reported during clinical studies were consistent with an elderly population with underlying medical conditions followed for a 6-month period. 

Most of the AEs reported in the Phase 3 studies were ocular in nature, which is consistent with the route of administration and the rapid autolytic inactivation of ocriplasmin in the eye. Additionally, any ocriplasmin absorbed systemically is rapidly (within seconds) inactivated by α2-antiplasmin in the circulation, and the clearance from the circulation of the inactive ocriplasmin/α2-antiplasmin complex has a half-life of several hours. 

In preclinical studies, at doses far exceeding the dose for intravitreal use and large enough to deplete the circulating α2-antiplasmin, the remaining ocriplasmin is cleared with a half-life of approximately 1 hour. 

In an in vitro pharmacokinetic study, the inactivation profile of ocriplasmin in human vitreous fluid, obtained from random vitrectomy patients, was investigated over time. The study concluded that after 72 hours of incubation at +37°C in human pooled vitreous fluid, <0.6% of initial active ocriplasmin was detected. 

The pharmacokinetic profile of ocriplasmin was also determined after a single intravitreal injection of ocriplasmin 125 μg at different time points before vitrectomy. Within 2 hours to 4 hours, by 24 hours, and at 7 days after a single 125 μg dose injection, the mean active ocriplasmin concentration in vitreous was reduced to <25%, <5%, and below the lower level of quantification, respectively, when compared with the mean active ocriplasmin concentration seen directly after injection. These pharmacokinetic studies have revealed that when ocriplasmin is injected into the eye, the drug immediately begins a process of autolysis and thereafter follows second-order kinetics until all the drug is removed from the eye (within 7 days). This is further substantiated by pharmacodynamic data, which reveal that the majority of the efficacy (VMA resolution) occurs within 7 days of injection, and virtually all anatomic effects are evident by Day 28. As expected, the visual functional improvement tends to occur over the next few weeks and months after anatomic resolution.

Also consistent with the rapid inactivation of ocriplasmin is that most sADRs occurred within the first 7 days after injection. The sADRs were generally nonserious, mild in intensity, and resolved. The most frequently reported AEs and sADRs were consistent with pharmacologic vitreolysis or were associated with the injection procedure itself. Adverse events such as vitreous floaters (with a median time to resolution of 18 and 35 days for ocriplasmin and placebo, respectively) or photopsia (median time to resolution of 4 and 3 days for ocriplasmin and placebo, respectively) are often reported after spontaneous PVD. In the current safety analysis, a higher proportion of ocriplasmin-treated patients was shown to have AEs or sADRs, such as vitreous floaters and photopsia, compared with the control groups, and the presence of vitreous floaters or photopsia was associated with VMA resolution. Although the phenomenon of photopsia is consistent with the pharmacologic action of ocriplasmin, it is unlikely that the photopsias would still occur in the absence of total PVD, and as such, may be indicative of a drug reaction in some patients.

Acute vision loss (best-corrected visual acuity decrease from baseline ≥10 letters within 7 days) was more likely to occur in the ocriplasmin-treated
groups, with evidence of subsequent recovery to within 5 letters of their baseline visual acuity and a median time to recovery of 14 days. Interestingly, VMA resolution occurred in more than half of these patients treated with ocriplasmin, which is approximately twice the rate reported in the overall study population of the Phase 3 studies. Rapid VMA resolution was also observed in all nine cases of patients who experienced serious and/or severe acute visual impairment after ocriplasmin injection. Recovery of vision in all of these patients occurred within a median time of 2 weeks after the injection. All patients were observed to have VMA release.

In addition, VMA resolution was achieved in at least 55% of patients with dyschromatopsia and/or ERG changes after ocriplasmin treatment. The use of ERG in the clinical setting allows the detection of abnormal retinal function and may help in differentiating visual loss from retinopathy versus optic neuropathy. Of note, full-field ERG is known to be highly sensitive but of limited specificity and can be influenced by the patient’s age, medication, previous

| Study      | Dyschromatopsia | ERG Time to Resolution | Visual Acuity (ETDRS) | VMA Resolution Day 28 |
|-----------|----------------|------------------------|-----------------------|-----------------------|
| TG-MV-006 | Yes            | No follow-up expected*| 55                    | No                    |
| TG-MV-006 | Yes            | No follow-up expected*| 74                    | Yes                   |
| TG-MV-006 | Yes            | 19 months              | 63                    | Yes                   |
| TG-MV-007 | Yes            | 12 months              | 80                    | Yes                   |
| TG-MV-007 | Yes            | 3 months               | 60                    | Yes                   |
| TG-MV-008 | Yes            | 2 months               | 67                    | Yes                   |
| TG-MV-008 | Yes            | 28 weeks‡             | 49                    | Yes                   |
| TG-MV-008 | Yes            | 3 months               | 63                    | Yes                   |
| TG-MV-008 | Yes            | 7 months               | 62                    | Yes                   |
| TG-MV-008 | Yes            | 3 months               | 60                    | Yes                   |
| TG-MV-010 | Yes            | 1 month                | 75                    | Yes                   |
| TG-MV-010 | Yes            | 3 months               | 61                    | No                    |
| TG-MV-010 | Yes            | 11 months              | 84                    | No                    |
| TG-MV-010 | Yes            | 3 months               | 95                    | NA                    |
| TG-MV-010 | Yes            | 7.5 months             | 90                    | NA                    |
| TG-MV-010 | Yes            | 3 months               | 85                    | NA                    |
| TG-MV-005 | No             | NA                     | 72                    | No                    |
| TG-MV-008 | No             | NA                     | 60                    | No                    |

*Patient died 18 months after the injection date (cause of death unknown).
†Patient also had concurrent ERG changes.
‡Patient did not have a baseline ERG.
§Patient had underlying vitelliform macular degeneration.
¶Resolution was reported during a follow-up visit 28 weeks after injection but may have occurred earlier.

ETDRS, Early Treatment Diabetic Retinopathy Study; ERG, electroretinogram; NA, not available.
ophthalmic surgery, specifically vitrectomy, and underlying retinal disease. In all cases where an ERG change was detected and follow-up was documented, the changes normalized by the end of follow-up with the exception of one patient with vitelliform dystrophy. In patients with no follow-up ERGs, visual acuity was significantly improved.

The visual function side effects seen after ocriplasmin injection are primarily believed to be driven by a direct or indirect effect on the photoreceptors (rods and cones) with evidence of relatively rapid recovery and transient damage. More research may be needed to fully understand the reversibility and long-term outcome of acute induced ocriplasmin-included anatomical and functional abnormalities. In patients with ERG changes, this leads to a-wave and b-wave decreases. In patients with dyschromatopsia, the changes may appear to be related to transient changes in the s-cones, the cause of which is yet unknown. Additional evidence of this transient effect comes from Freund et al48 and Singh et al49 who reported transient changes seen in the outer retinal layers on spectral domain OCT, with all cases recovered or recovering. As time-domain OCT was used in the majority of patients in the Phase 3 studies, these effects were not previously seen. Degradation of intraretinal proteins such as laminin after ocriplasmin injection has been suggested in case reports as a cause of panretinal dysfunction,50 with one case demonstrating a diffuse enzymatic effect of ocriplasmin on photoreceptors distant from the areas of VMA,51 but both these case reports have limited follow-up data, and further work is required to clarify these enzymatic effects. All the patients who had dyschromatopsia and/or ERG findings did not experience lasting visual function deficit, as there was recovery to within 1 line of baseline visual acuity in all cases (Table 10). Similarly, the OCT changes also returned to normal within 1 month.

Anatomical retinal findings are also consistent with the mechanism of action and efficacy of ocriplasmin, which has previously been shown to be associated with the resolution of the underlying condition and the nonsurgical closure of MHs. In this safety analysis, a higher proportion of patients in the placebo group had AEs or SAEs of formation or progression of their FTMH than patients treated with ocriplasmin. In these studies, overall there was up to a 40.6% nonsurgical FTMH closure in ocriplasmin-treated patients compared with 10.6% patients who received placebo. In the 59 of 100 patients (59%) in whom nonsurgical FTMH closure was not achieved by Day 28, the diameter of the MH was found to increase in size after ocriplasmin injection, often accompanied by an increase in subretinal fluid. Some of these patients also had release of their VMA with lack of MH closure. Many of these patients subsequently underwent vitrectomy, with closure of the MH after vitrectomy achieved in 88.8% of patients in both treatment groups. This outcome compares favorably with hole closure rates in the recent literature of vitrectomy for MH surgery without ocriplasmin.

As vitrectomy was permitted in the Phase 3 studies after Day 28 if the investigator considered it necessary, the safety results included in this analysis may be confounded by the AEs that occurred during and after vitrectomy. As patients in the placebo group were more likely to undergo vitrectomy than patients in the ocriplasmin group, any effects of vitrectomy on the incidence of AEs were likely to be more pronounced for the placebo group than for the ocriplasmin group. No increased risk for adverse outcomes, however, was observed in ocriplasmin-treated patients requiring subsequent vitrectomy.

Cataract is a very common complication of vitrectomy occurring in the majority of phakic patients, thereby leading to the need for an additional surgical procedure. In both treatment groups in the Phase 3 studies, a higher incidence of cataract was observed in phakic patients after vitrectomy than in phakic patients who did not undergo vitrectomy. Therefore, the trend toward decreased incidence of cataract-related AEs in the ocriplasmin group compared with the placebo group was consistent with the lower rate of vitrectomy in the ocriplasmin group. There was no evidence of increased cataract formation in the ocriplasmin-treated group before vitrectomy.

Retinal tears are also frequently reported in the literature during and after vitrectomy, with a reported incidence of approximately 15%. In contrast, retinal tears were reported in a much lower proportion of patients in the Phase 3 trials (0.2% of ocriplasmin-treated patients and 0.5% of placebo patients). Therefore, although there is a risk for retinal tear or retinal detachment after treatment with ocriplasmin, the risk is no worse after intravitreal injection or after naturally occurring PVD induction. The risk for retinal breaks after intravitreal administration of other compounds ranged from 7% to 23%, which is a much higher rate than seen with ocriplasmin.

Ocular AEs such as intraocular hemorrhage, intraocular inflammation, intraocular infection, and increased intraocular pressure are risks known to be associated with the intravitreal injection procedure and were included as AEs of special interest. For example, there are reports of transient volume-related incidents after intravitreal injection of other products in the literature. In comparison with other studies, a systematic review of data from 14,866 intravitreal
injections in 4,382 eyes gave a prevalence of retinal detachment of 0.9% per injection (3.9% per eye) and prevalence of hemorrhage of 1.3% per injection (6.0% per eye). The prevalence of ocular hypertension was 1.2% per injection (5.6% per eye), and prevalence of endophthalmitis was 0.3% per injection (0.9% per eye). In the Phase 3 studies, the same technique and volume were used for both the ocriplasmin and placebo injections. Therefore, the incidence of these events in the placebo group serves as a measure of the procedural risk associated with the intravitreal injection, where a higher incidence of these types of events in the ocriplasmin group compared with placebo would suggest a drug effect separate from a procedure-related event. Of note, the injection volume used in these studies was 0.1 mL rather than the 0.05 mL typically used with other intravitreal injections, such as anti-vascular endothelial growth factor injections. In the Phase 3 studies, no clinically meaningful differences in the incidence of intraocular hemorrhage or increased intraocular pressure in the study eye were observed between treatment groups. In contrast, a higher proportion of ocriplasmin-treated patients had AEs of intraocular inflammation.

Lens subluxation was also included as an AE of special interest in this analysis based on preclinical data. It was observed after administration of intravitreal ocriplasmin in 3 animal models (rabbits, Cynomolgus monkeys, and Götttingen mini-pigs) at ocriplasmin concentrations ≥41 µg/mL vitreous volume, a concentration above the intended clinical concentration of 29 µg/mL (ThromboGenics data on file, 2013). In many of those animal cases, the subluxation was not seen until repeated injections were performed, which is not performed in clinical practice. To date, there has been one case of lens subluxation and one case of phacodonesis observed in clinical trials evaluating intravitreal ocriplasmin. In the case of the lens subluxation patient, the length of time from ocriplasmin injection and the fact that no previous clinical signs or lens problems were reported before vitrectomy potentially confound the causality in this patient.

Based on the proteolytic activity of ocriplasmin and the nonclinical and clinical findings, the risk for lens subluxation in adults is considered to be low.

In conclusion, pharmacologic vitreolysis with an intravitreal ocriplasmin injection provides a pharmacologic treatment option for patients with symptomatic VMA/VMT including VMT associated with MH of diameter ≤400 μm. By resolving the underlying condition, ocriplasmin treatment was associated with a lower incidence of disease progression-related sequelae and a lower incidence of vitrectomy-related complications. The pharmacologic action of ocriplasmin on the vitreous and vitreoretinal interface, however, can cause symptoms associated with changes in tractional forces caused by ocriplasmin, which has a transient pharmacologic effect on the retina in a subset of eyes, particularly in the first week after injection. Across all AEs, the rates of long-term symptoms and vision loss were low. As such, ocriplasmin seems to be a generally safe and well-tolerated therapeutic option for VMA/VMT. Postmarketing studies will continue to explore the AEs of acute vision loss, MH enlargement, ERG changes, and development of subretinal fluid to help clarify such events for physicians and their patients.

Key words: acute vision loss, adverse event, dyschromatopsia, electroretinogram, intravitreal injection, lens subluxation, macular hole, ocriplasmin, symptomatic vitreomacular adhesion, vitreomacular traction.

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