Ocriplasmin Treatment Leads to Symptomatic Vitreomacular Adhesion/Vitreomacular Traction Resolution in the Real-World Setting: The Phase IV ORBIT Study

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Purpose: To evaluate clinical outcomes and safety up to 12 months after ocriplasmin injection for the treatment of patients with symptomatic vitreomacular adhesion (VMA)/vitreomacular traction (VMT) in a real-world setting.

Design: The Phase IV Ocriplasmin Research to Better Inform Treatment (ORBIT) trial (NCT02079883) was a Phase IV multicenter, prospective, observational study.

Participants: Patients aged ≥18 years with symptomatic VMA/VMT treated with ocriplasmin.

Methods: Patients received a single 0.125 mg intravitreal injection of ocriplasmin. All assessments and treatment decisions were at the discretion of the treating physician. Spectral-domain OCT (SD-OCT) images were analyzed by an independent central reading center (CRC). All enrolled patients were included in demographic, baseline characteristics, and safety analyses. Patients with symptomatic VMA/VMT at baseline determined by CRC were included in baseline ocular characteristics and efficacy analyses.

Main Outcome Measures: Clinical outcomes were measured up to 12 months and included resolution of symptomatic VMA, closure of full-thickness macular hole (FTMH), mean change from baseline in best-corrected visual acuity (BCVA), incidence of vitrectomy, and time to first vitrectomy. Safety outcomes included the incidence and timing of onset of adverse drug reactions (ADRs).

Results: Of the 539 patients enrolled, 480 were determined to have symptomatic VMA/VMT at baseline post-CRC assessment. After treatment with ocriplasmin, the rate of VMA/VMT resolution was 45.8% (95% confidence interval [CI], 41.3–50.4) at month 1 and 59% (95% CI, 54.4–63.4) at months 10 to 12. The rate of FTMH closure was 30.5% (95% CI, 22.4–39.7) at month 1 and 32.2% (95% CI, 23.9–41.4) at months 10 to 12. Mean (standard deviation) change from baseline in BCVA was 1.5 (11.19) letters at month 1 and 5.2 (13.60) letters at months 10 to 12. Vitrectomy was performed in 28.5% of patients, with a median time to vitrectomy of 63 days. Adverse drug reactions were reported by 30.6% of patients; 5.2% experienced a serious ADR.

Conclusions: Results from the ORBIT study demonstrate that treatment with ocriplasmin is effective and well tolerated in patients with symptomatic VMA/VMT in a real-world setting. The percentage of patients with VMA/VMT resolution at month 1 was higher than previously reported in well-controlled clinical trials. No new safety signals were identified. Ophthalmology Retina 2019;3:32-41 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Supplemental material available at www.opthalmologyretina.org.

Symptomatic vitreomacular adhesion (VMA), also known as vitreomacular traction (VMT), is a vision-threatening condition that can cause macular distortion, edema, and formation of macular holes.1-6 Vitreomacular traction is associated with visual disturbances, including photopsia, metamorphopsia, and diminished visual acuity, that can significantly affect patient quality of life.2,3,6-8 Spontaneous resolution of VMT occurs in approximately 10% to 35% of cases.5,9,10 Without resolution, VMT can progress and is associated with vision loss.2,11 The standard treatment for symptomatic VMA/VMT is watchful waiting for disease progression or surgical intervention with pars plana vitrectomy.5,4 Pneumatic vitreolysis has been used by selected retinal specialists for the treatment of symptomatic VMA/VMT; however, it remains an emerging technique for treating this condition and lacks level 1 study support.12

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Ocriplasmin is a recombinant protease with activity against components of the extracellular matrix that forms part of the vitreoretinal interface. The activity of degrading these components is thought to underlie the ability of ocriplasmin to resolve cases of VMA/VMT or close full-thickness macular holes (FTMHs) that are associated with VMA/VMT.\(^4,5,13,14\)

The safety and efficacy of ocriplasmin for the treatment of patients with symptomatic VMA were demonstrated in 2 pivotal Phase III trials (Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment [MIVI-TRUST]), which led to its approval by the US Food and Drug Administration (FDA) in October 2012.\(^5,15\)

Further studies have highlighted the critical role that patient selection has in maximizing outcomes after treatment with ocriplasmin. Subgroup analyses have demonstrated higher VMA/VMT resolution rates in groups of patients defined by the presence of select baseline ocular characteristics compared with groups not having those features. These include phakic lens in the treated eye, focal adhesion \(\leq 1500\ \mu m\), absence of an epiretinal membrane (ERM), or presence of an FTMH \(\leq 400\ \mu m\).\(^5,16,17\)

Findings from the 24-month Phase IIIb Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) study, which included some of these baseline predictors as inclusion/exclusion criteria, supported the safety and efficacy of ocriplasmin, but also the need for strategic patient selection when evaluating treatment options for patients with symptomatic VMA.\(^14\)

The pivotal MIVI-TRUST and Phase IIIb OASIS studies applied predefined enrollment criteria that excluded patients with complex cases, which are nevertheless encountered in everyday clinical practice. To investigate the effects of ocriplasmin in a real-world setting, the Phase IV Ocriplasmin Research to Better Inform Treatment (ORBIT) trial (NCT02079883) was designed to evaluate clinical outcomes and safety up to 12 months after ocriplasmin injection for the treatment of patients with symptomatic VMA/VMT.

### Materials and Methods

**ORBIT Study: Design, Patients, and Treatment**

ORBIT study was a multicenter, prospective, observational Phase IV study in patients with symptomatic VMA/VMT consecutively enrolled from 91 retina sites in the United States. The study was conducted according to the International Conference for Harmonization Guideline for Good Clinical Practice. The study protocol was approved by the institutional review board or ethics committee at each trial site, and informed consent was obtained from each patient before enrollment. Patient confidentiality protocols were followed in compliance with the Health Insurance Portability and Accountability Act.

Eligible patients were \(\geq 18\) years of age, had a diagnosis of symptomatic VMA/VMT, and received treatment with a single intravitreal injection of ocriplasmin 0.125 mg (administered according to the physician’s standard of care that was consistent with the product label). Patients who received ocriplasmin for any reason other than the FDA-approved indication (the treatment of symptomatic VMA)\(^18\) were excluded from the study. Patients who were concurrently enrolled in studies that involved other ocular medications, procedures, or imaging analyses were also excluded.

Eligible patients were prospectively enrolled on the day of injection.\(^19\) The eye that received an injection of ocriplasmin was the study eye. In some cases, the fellow eye received an injection of ocriplasmin at a later date, at which time the fellow eye became known as the “treated fellow eye.”

Because the study was observational in nature, the frequency and timing of patient follow-up visits were at the discretion of the treating physician. The schedule of follow-up examinations, procedures, and laboratory tests was also according to each physician’s standard of care. There were no restrictions on prior or concomitant medications.

To allow for physician discretion in the follow-up schedule, postinjection data were collated into a defined series of timepoints that were predetermined in the statistical analysis plan. To achieve this, the entire follow-up period was divided into 6 consecutive segments, and each segment was assigned a timepoint as follows: week 1 (1−\(\leq 11\) days), month 1 (>11≤\(\leq 42\) days), months 2 to 3 (>42≤\(\leq 105\) days), months 4 to 6 (>105≤\(\leq 195\) days), months 7 to 9 (>195≤\(\leq 285\) days), and months 10 to 12 (>285 days).

### Study End Points

Preplanned study end points included the resolution of VMA/VMT without subsequent vitrectomy (postresolution vitreotomy was not considered as a failure), nonsurgical closure of FTMH, mean change from baseline in best-corrected visual acuity (BCVA), incidence of vitrectomy, and mean and median time to first vitrectomy for patients who required the procedure.

Spectral domain OCT (SD-OCT) was used to assess vitreoretinal interface anatomy, resolution of VMA/VMT, and status of FTMH according to the standard of care of the treating physician. The type of SD-OCT equipment used was at the discretion of the treating physician (CIRRUS HD-OCT 500, Carl Zeiss Meditec, Inc, Dublin, CA; Optos, Marlborough, MA; Optovue, Inc, Fremont, CA; Spectralis OCT, Heidelberg Engineering Inc, Franklin, MA; Topcon OCT-1000, Topcon Medical Systems, Inc, Oakland, NJ; Topcon OCT-2000, Topcon Medical Systems, Inc). All SD-OCT images were submitted to a central reading center (CRC) (Digital Angiography Reading Center, New York, NY) for independent review and measurement of defined parameters. This analysis was performed postinjection, and the information was not used for treatment decisions.

The BCVA was measured using the Snellen Equivalent or Pinhole test (or other methods according to the treating physician’s standard of care). The BCVA was then converted into Early Treatment Diabetic Retinopathy Study (ETDRS) letters for analysis. When BCVA was recorded using both the Snellen Equivalent and Pinhole test, the higher of the 2 values was used for analysis (after conversion to ETDRS letters).

Safety parameters included the type, incidence, and time of onset of adverse drug reactions (ADRs), number of patients with loss of \(\geq 3\) ETDRS lines from baseline in BCVA at months 10 to 12, and mean change from baseline in intraocular pressure (IOP) measured during the injection visit. Serious ADRs are defined per the FDA guidelines for industry.\(^19\) The anterior and posterior segments of the treated eyes were also assessed for safety using slit-lamp and dilated retinal examinations, respectively.

### Statistical Analysis

Patient demographics, baseline characteristics, and safety analyses included all patients who received an injection of ocriplasmin in the study eye. Ocular characteristics and efficacy analyses were limited to patients who received an injection of ocriplasmin in the study eye, had VMA/VMT at baseline (as determined by
independent assessment of SD-OCT by the CRC), and had data from at least 1 follow-up visit. Planned analyses were performed to evaluate potential differences in outcomes between subgroups that were defined by the following baseline demographics, procedural characteristics, and ocular characteristics: age (< 65 years, ≥ 65 years), position of patient during injection (upright, supine), BCVA (< 65, 65–75, > 75 ETDRS letters), lens status (phakic, pseudophakic), diameter of VMA/VMT (≤ 500, > 500–< 1500, > 1500 μm), presence of FTMH (present, absent), width of FTMH (categorized as ≤ 250, > 250–< 400, > 400 μm), presence of ERM (present, absent), and presence of subretinal fluid (SRF) (present, absent). The rates of VMA/VMT resolution and nonsurgical FTMH closure were analyzed with the last observation carried forward methodology. Changes in BCVA were analyzed with an observed cases approach. Time to vitrectomy or ADR was calculated as the date that the event occurred minus the date of ocriplasmin injection plus 1 day.

Descriptive statistics for continuous variables and change from baseline variables were calculated and reported as means with standard deviations (SDs), medians, and 95% confidence intervals (CI), where appropriate. Categorical data were summarized and reported as percentages with 95% CI for the percentage (Clopper—Pearson method), where appropriate.

**Results**

**Study Population**

A total of 539 patients were enrolled in the study on the basis of the diagnosis of symptomatic VMA/VMT by the treating physician and treatment with ocriplasmin. These patients were included in the “all treated patients” group for the analysis of safety outcomes. An independent analysis of baseline SD-OCT scans by the CRC found that only 480 patients had confirmed VMA/VMT. These patients were included in the “patients with VMA/VMT at baseline” group for the analysis of effectiveness outcomes. Nineteen patients were included in the independent analysis of baseline SD-OCT scans by the CRC. Five were excluded because symptomatic VMA/VMT was not confirmed by the CRC. Forty-seven patients (8.7%) did not complete the study; 25 were lost to follow-up (4.6%), 6 died (1.1%), 8 withdrew consent (1.5%, reasons not related to ADRs), 1 was withdrawn by the treating physician (0.2%, reason not related to ADRs), 1 was withdrawn for protocol violation (0.2%), and 6 discontinued for reasons categorized as “other” (1.1%, 1 [0.2%] related to treatment). Ocular interventions before the study treatment were recorded for 237 patients (44%). The most common interventions were cataract surgery (32.5%), laser surgery (8.3%), vascular endothelial growth factor inhibitors (7.5%), other intravitreal injections (1.9%), and corticosteroids (1.3%). Baseline demographics and ocular characteristics based on SD-OCT analysis by the CRC are presented in Tables 1 and 2.

**Effectiveness Outcomes**

**Nonsurgical Vitreomacular Adhesion/Vitreomacular Traction Resolution.** Nonsurgical resolution of VMA/VMT without subsequent vitrectomy was observed in 27.7% (133/480 patients; 95% CI, 23.7–31.9) of patients at week 1; 45.8% (220/480 patients; 95% CI, 41.3–50.4) of patients had resolution of VMA/VMT at month 1; and 59.0% (283/480 patients; 95% CI, 54.4–63.4) of patients had resolution at month 12 (Fig 1). The overall median time to resolution without subsequent vitrectomy was 13 days.

**Predetermined Subgroup Analysis of Nonsurgical Vitreomacular Adhesion/Vitreomacular Traction Resolution.** Analyses were performed to compare rates of nonsurgical VMA/VMT resolution over the course of the study between subgroups that were defined by baseline demographics and ocular or procedural characteristics (Fig 2). The rate of nonsurgical VMA/VMT resolution at month 12 was higher among patients aged < 65 years (80.9% [95% CI, 71.2–88.5]) compared with patients aged ≥ 65 years at baseline (54.0% [95% CI, 48.9–59.0]). The position of the patient, upright or supine, during the injection had no impact on patients achieving VMA/VMT resolution (56.9% [95% CI, 46.7–66.6] vs. 59.6% [95% CI, 54.4–64.6]).

The magnitude of ocriplasmin effect on VMA/VMT resolution varied according to the lens status. Resolution rates of VMA/VMT at month 12 were higher for patients in whom the treated eye was phakic (65.9% [95% CI, 60.4–71.1]) vs. pseudophakic (45.1% [95% CI, 37.2–53.1]); patients with a baseline VMA/VMT diameter ≤ 500 μm (65.0% [95% CI, 59.6–70.1]) vs. those with a baseline diameter > 500–< 1500 μm (41.2% [95% CI, 32.1–50.8]); patients with FTMH at baseline (72.0% [95% CI, 63.0–79.9]) vs. those in whom FTMH was absent at baseline (54.7% [95% CI, 49.4–59.9]); and patients without ERM at baseline (61.6% [95% CI, 51.9–70.6]) or absence (58.2% [95% CI, 52.9–63.2]) of SRF at baseline.

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**Table 1. Demographic Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study Eye</th>
<th>Patients with VMA/VMT at Baseline (N=480)*</th>
</tr>
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<tr>
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<td>All Treated (N=539)</td>
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<tr>
<td></td>
<td>Patients</td>
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</tr>
<tr>
<td>Age</td>
<td>Mean yrs (SD)</td>
<td>71.1 (8.25)</td>
</tr>
<tr>
<td></td>
<td>&lt; 65 yrs, n (%)</td>
<td>105 (19.5)</td>
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<td>≥ 65 yrs, n (%)</td>
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<td>Gender, n (%)</td>
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<td></td>
<td>Female</td>
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<tr>
<td></td>
<td>Non-Hispanic</td>
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</tr>
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</table>

SD = standard deviation; SD-OCT = spectral-domain OCT; VMA = vitreomacular adhesion; VMT = vitreomacular traction (symptomatic VMA).

*Based on SD-OCT analysis by the central reading center.
Nonsurgical Full-Thickness Macular Hole Closure

Nonsurgical closure of FTMH was observed in 17.8% (95% CI, 11.4–25.9) of patients at week 1, 30.5% (95% CI, 22.4–39.7) of patients at month 1, and 32.2% (95% CI, 23.9–41.4) of patients at month 3. Rates of nonsurgical FTMH closure at month 3 were highest among patients with FTMH width ≤250 μm compared with those with FTMH width ≥250 to 400 μm and >400 μm at baseline: 42.4% (95% CI, 30.3–55.2), 24.2% (95% CI, 11.1–42.3), and 10.5% (95% CI, 1.3–33.1), respectively (Fig 3).

Visual Acuity

Of the 3944 visual acuity measurements performed during the study, 2589 (65.6%) were derived from the maximum of the Snellen Equivalent and Pinhole tests. There were 1187 (30.1%) measurements reported using only the Snellen Equivalent test, 12 (0.3%) using only the Pinhole test, and 156 (4.0%) using unspecified other methods.

The percentage of patients with VMA/VMT at baseline with a gain of ≥2 and ≥3 lines from baseline by ETDRS prior to vitrectomy is shown in Figure 4. “Prior to vitrectomy” corresponds to evaluations in patients without vitrectomy during the study or previtrectomy evaluations in patients with vitrectomy during the study. A gain of ≥2 lines from baseline was experienced by 18.7% (95% CI, 14.9–23.0) of patients at month 1 and 32.5% (95% CI, 24.0–41.9) at months 10 to 12. A gain of ≥3 lines from baseline was experienced by 12.3% (95% CI, 9.1–16.0) of patients at month 1 and 24.6% (95% CI, 17.0–33.5) at months 10 to 12.

The percentage of patients who gained ≥2 ETDRS lines from baseline at months 10 to 12 was higher among those whose BCVA was <65 ETDRS letters at baseline (48.2%, 95% CI, 34.7–62.0) compared with those with 65 to 75 ETDRS letters (32.3%, 95% CI, 16.7–51.4) or >75 ETDRS letters (0.0%) at baseline. Position of the patient during injection had no effect on the rate of ≥2- or ≥3-line BCVA gains from baseline (months 10–12: 45% [95% CI, 23.1–68.5] with ≥2-line gain and 35% [95% CI, 15.4–59.2] with ≥3-line gain for those injected in the upright position; 30.1%...
[95% CI, 21.0–40.5] with ≥2-line gain; and 22.6% [95% CI, 14.6–32.4] with ≥3-line gain for those in the supine position).

Mean (SD) change from baseline in BCVA was +1.5 (11.19) ETDRS letters at month 1 and +5.2 (13.60) ETDRS letters at months 10 to 12 (Fig 5). A subgroup analysis based on the position of the patient at injection showed no obvious effect on change from baseline in BCVA (months 10–12: +4.7 [14.90] ETDRS letter change from baseline for upright position; +5.5 [13.41] ETDRS letter change from baseline for supine position). At months 10 to 12 postinjection, the mean (SD) change from baseline in patients with postocriplasmin injection vitrectomy during the study (+5.1 [20.06] ETDRS letters) was not different from that observed in patients without postocriplasmin injection vitrectomy during the study (+5.2 [13.60] ETDRS letters) (Table 3).
During the study, 28.5% (137/480) of patients underwent vitrectomy. The reasons for vitrectomy were management of an ocriplasmin-related adverse event (5 [1.0%]), no response to treatment but the disease was stable (71 [14.8%]), no response to treatment but the disease progressed (34 [7.1%]), and unable to determine (27 [5.6%]). Of these 137 patients, 25% had vitrectomy on or before day 41, and 75% had vitrectomy on or before day 91. The median time to first vitrectomy was 63.0 days. The number of vitrectomies and the mean and median times to first vitrectomy, based on subgroups defined by the presence of various ocular characteristics at baseline, are presented in Table S4 (available at www.ophthalmologyretina.org). The longest median time to vitrectomy was in the group without FTMH at baseline (68.0 days to first vitrectomy). The shortest median time to vitrectomy was among patients with FTMH/C21 400 mm at baseline (45.0 days to first vitrectomy), compared with 56.0 days for the group with FTMH/C21 250 to 400 mm and 50.0 days for those with FTMH/C20 250 mm. The presence of FTMH at baseline was associated with more vitrectomies during the study, and patients with FTMH larger than 400 mm had more vitrectomies than those with smaller FTMH. Fewer vitrectomies were performed in patients with SRF than in those without SRF at baseline. However, baseline lens status, presence of ERM, and VMA/VMT diameter did not appear to be baseline predictors of vitrectomy during the study.

### Safety Outcomes

A total of 405 ADRs were reported in 165 patients (30.6%). All events were ocular (Table S5, available at www.ophthalmologyretina.org). For all patients who experienced an ADR, at least 1 event occurred in the treated eye (388 events). The most frequently reported ADRs were photopsia (13.5%), vitreous floaters (9.6%), and reduced visual acuity (6.7%). Most ADRs (67.2%) had an onset between day 0 and day 7 postinjection (Table S6, available at www.ophthalmologyretina.org). Five (1.1%) ADRs (vitreous floaters [2 patients], foreign body sensation in eyes [1 patient], metamorphopsia [1 patient], and SRF [1 patient]) had an onset between month 6 and month 12. Forty-five serious ADRs were reported in 28 patients (5.2%) (Table S5). The most commonly reported serious ADRs were photopsia (1.1%), miosis (1.1%), and reduced visual acuity (1.1%). All other serious ADRs occurred with a frequency of less than 1% (≤5 patients). Most serious ADRs (60.0%) occurred between day 0 and day 7 postinjection (Table S6). No serious ADRs had an onset between month 6 and month 12, and no patients discontinued the study because of a serious ADR. The events that were ongoing at the end of the study were...
visual acuity reduced (2 severe events), macular hole (1 moderate and 1 severe event), pupillary reflex impaired (1 mild and 1 moderate event), retinal detachment (1 severe event), and photophobia (1 moderate event). A BCVA loss of 2 lines or more was observed in 9 patients by months 10 to 12. Seven deaths were reported during the study; none were considered related to the study or study drug. Endophthalmitis, uveitis, deaths were reported during the study; none were considered related to the study or study drug. Endophthalmitis, uveitis, zonular dehiscence, photoreceptor dehiscence, disruption of ellipsoid zone, and lens dislocation were not reported during the study.

Ocular Symptoms

The percentage of patients (all treated patients group) with a loss of ≥2 and ≥3 lines from baseline by ETDRS is presented in Figure 6. Of the patients who lost ≥2 lines, atrophy was observed in 10% or more of the ellipsoid zone in 2 of 7 patients at month 1 and 2 of 5 patients at the end of study. Also within the group of patients who lost ≥2 lines, 10% or more of the ellipsoid zone-retinal pigment epithelium layer had a thickness of less than 20 μm in 3 of 7 patients at month 1 and 2 of 5 patients at end of study. Thirty-seven of 420 patients (8.8%) at month 1 and 13 of 165 patients (7.9%) at months 10 to 12 shifted from continuous ellipsoid zone at baseline to discontinuous ellipsoid zone. Seven of the 125 patients with a BCVA assessment at months 10 to 12 experienced a loss of ≥3 lines on the ETDRS chart from baseline in BCVA at the considered timepoint. Of these 7 patients, 4 had wet age-related macular degeneration (2 of those without VMA/VMT resolution), 1 had proliferative diabetic retinopathy and glaucoma, 1 had dry age-related macular degeneration (no VMA resolution), and 1 had ERM, ocular hypertension, vitreous adhesion, dry eye, and posterior capsular opacification (no VMA resolution). All other patients had VMA resolution.

Among patients with available IOP measurements (N=98), the mean (SD) difference from baseline in IOP was 5.1 (7.16) mmHg when measured on the day of injection as per the standard practice and −0.4 (3.73) mmHg at week 1. There were no safety signals based on slit-lamp, dilated retinal examinations, or SD-OCT measurements.

Discussion

The ORBIT study was conducted in clinical practices around the United States and demonstrated that treatment with ocriplasmin in a real-world setting is effective and well tolerated up to 12 months in patients with symptomatic VMA/VMT. Because this was an observational study, all treatment decisions remained with the clinicians according to their own standard of care.

Resolution of VMA/VMT at month 1 in the ORBIT study (45.8%) was comparable to that reported in the OASIS study (41.7%) and higher than in MIVI-TRUST pivotal clinical trials (26.5%). The difference in rates between this study and the MIVI-TRUST trials is likely due in part to some treating physicians who may have considered anatomic baseline predictors of ocriplasmin success when selecting patients for treatment. For example, the absence of an ERM is a demonstrated predictor of nonsurgical resolution of symptomatic VMA with ocriplasmin treatment. However, baseline ERM status had no impact on subsequent vitrectomy. In the ORBIT study, a higher percentage of patients did not have an ERM at baseline (75.4%) compared with the MIVI-TRUST trials (60.3%). The results of the subgroup analyses, showing VMA/VMT resolution rates by the absence or presence of select baseline predictors, including ERM, phakic lens, and diameter of VMA/VMT, further support the predictive nature of these anatomic features.
One strength of the ORBIT study was the use of an independent CRC to read and measure SD-OCT scans. After the treating physicians diagnosed patients with symptomatic VMA/VMT and enrolled them in the ORBIT study, independent evaluation of SD-OCT scans found that only 89.1% of these patients had confirmed VMA/VMT. This 10.9% error rate in deciphering SD-OCT imagery is striking, especially considering that a physician can use OCT to identify anatomic characteristics, such as the presence of an ERM or a very small VMA diameter, that are clues to the chances of ocriplasmin success. The SD-OCT technology used in this study is highly sensitive, provides improved axial resolution compared with the time-domain technology used in the MIVI-TRUST trials, and can detect transient changes to the outer retinal layers after ocriplasmin treatment.20–23 Even with the use of an advanced SD-OCT technology, the high error rate in misidentifying VMA/VMT suggests a need for greater education on OCT-based interpretation of the vitreoretinal interface when determining the type of intervention for treatment of VMA/VMT. However, it is also possible that the SD-OCT scans submitted to CRC may not have captured the area of adhesion (or the lack of adhesion).

In this study, the percentage of patients with nonsurgical FTMH closure increased until month 3 (32.2%) and then remained unchanged until the end of the study. This FTMH closure rate is similar to those reported in the OASIS trial, in which 30.0% of patients in the ocriplasmin group had nonsurgical FTMH closure at month 3.14 Also similar to the OASIS trial, the rates of FTMH closure were highest for patients who had small FTMH at baseline (<250 μm).

Photopsia (13.5%), vitreous floaters (9.6%), and visual acuity reduced (6.7%) were the most frequent ADRs observed in this real-world study. The incidence rates of these ADRs were lower than those reported in the OASIS study (29.5%, 37.7%, and 12.3%, respectively), but marginally higher than in the MIVI-TRUST study for photopsia (11.8%) and vitreous floaters (16.8%).5,14 Differences in ADR rates likely reflect the variations in study designs, the observational nature of the ORBIT study, and the absence of a visit schedule or frequent follow-ups. Notably, no patient discontinued the ORBIT study because of serious ADRs, which were infrequent. Indeed, photopsia, miosis, and visual acuity reduced (1.1% each) were the most common serious ADRs reported. Furthermore, the ADRs observed with ocriplasmin treatment were transient because the majority of the serious ADRs (37/45 events) resolved by the end of the study. Although visual acuity reduced was the most common ADR, only 2 patients had visual acuity reduced as an ongoing serious ADR at the end of the study. Overall, there were no new safety signals observed with ocriplasmin treatment in a real-world setting, and the safety profile is consistent with previous ocriplasmin studies conducted in patients with symptomatic VMA/VMT.5,14

Study Limitations
Like any other observational study, ORBIT has limitations inherent to its design. The schedules of follow-up visits and assessments were at the discretion of the treating physicians, and patients needed only 1 follow-up visit to be included in the study. The lack of a consistent follow-up program across sites introduced the potential for missing data from patients lost to follow-up (8.7% of patients did not complete the study, and only 125/480 patients had a 12-month BCVA assessment). Moreover, studies have shown the development of posterior vitreous detachment with intravitreal injections.24 Thus, the inclusion of patients with prior or concomitant medications, including ocular injections, in the ORBIT study may have a confounding effect on the study outcomes. The use of SD-OCT machines by different manufacturers also could confound interpretation of the results. However, the independent assessment of SD-OCT images by a single reading center and the qualitative instead of quantitative assessment of SD-OCT images have mitigated this risk. One other limitation is that the visual acuity measurements were not standardized across the centers, which can hinder direct comparisons. However, most measurements were performed using the Snellen Equivalent or Pinhole tests and were converted to ETDRS letters.

Although observational studies have limitations, they have the advantage of investigating the greater heterogeneity of patient population and medical intervention as per local standard of care, which is meant to support findings that are more generalizable to real-world, everyday clinical practice when compared with well-controlled randomized clinical trials.

Conclusions
The ORBIT study demonstrated that treatment with ocriplasmin in a real-world setting is effective and well tolerated in patients with symptomatic VMA/VMT. Anatomic and visual outcomes from this study confirm data from previous clinical studies, including the OASIS study and pivotal MIVI-TRUST clinical trials. The high rates of VMA resolution and FTMH closure observed in this study may be due to the use of strategic patient selection by the treating physicians and the additional advantages of effective use of SD-OCT technology.

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References


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Abbreviations and Acronyms:  
ADR = adverse drug reaction; BCVA = best-corrected visual acuity; CI = confidence interval; CRC = central reading center; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Study; FDA = Food and Drug Administration; FTMH = full-thickness macular hole; IOP = intraocular pressure; MIVI-TRUST = Microplasmin for Intravitreous Injection-Traction Release without Surgical Treatment; OASIS = Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; ORBIT = Ocriplasmin Research to Better Inform Treatment; SD = standard deviation; SD-OCT = spectral-domain OCT; SRF = subretinal fluid; VMA = vitreomacular adhesion; VMT = vitreomacular traction.  

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