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Results of the 2-Year Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) Randomized Trial

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Purpose: The Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) trial was designed to evaluate the long-term efficacy and safety profile of ocriplasmin for the treatment of symptomatic vitreomacular adhesion (VMA)/vitreomacular traction, including full-thickness macular hole (FTMH).

Design: Phase 3b, randomized, sham-controlled, double-masked, multicenter clinical trial.

Participants: Sample size was 220 subjects (146 ocriplasmin, 74 sham) randomized in a 2:1 ratio to receive intravitreal ocriplasmin 0.125 mg or sham injection.

Methods: The trial involved 12 visits over 24-months. Inclusion criteria included presence of VMA and best-corrected visual acuity (BCVA) of 20/32 or worse in the study eye. Exclusion criteria included FTMH >400 μm, presence of epiretinal membrane (ERM), and aphakia in the study eye.

Main Outcome Measures: The primary efficacy end point was the proportion of subjects with pharmacologic VMA resolution at day 28. Secondary efficacy end points were assessed at month 24 and included proportion of subjects with BCVA gain from baseline, nonsurgical FTMH closure, vitrectomy, and Visual Function Questionnaire 25 (VFQ-25) outcomes.

Results: The OASIS trial met its primary end point with pharmacologic VMA resolution at day 28 being significantly higher in the ocriplasmin group (41.7%) compared with the sham group (6.2%). The treatment effect was maintained until study end. In the ocriplasmin group, pharmacologic VMA resolution at day 28 was higher in subgroups with the following baseline characteristics compared with the complementary subgroups without them: presence of focal VMA, presence of FTMH, absence of ERM, and phakic lens status. In the ocriplasmin group, 50.5% of subjects had a ≥2-line improvement in BCVA from baseline compared with 39.1% of subjects in the sham group. The nonsurgical FTMH closure rate was 30.0% for the ocriplasmin group compared with 15.4% for the sham group. All other secondary end points also favored ocriplasmin over sham. Regarding safety, most adverse events were mild to moderate, had a short onset time, and were transient, with no new safety signals identified.

Conclusions: The OASIS trial demonstrates the long-term efficacy and safety of ocriplasmin, providing improved resolution of symptomatic VMA compared with previous phase 3 trials with no additional safety signals identified. *Ophthalmology 2016;■:1–16 © 2016 by the American Academy of Ophthalmology.*

Ocriplasmin is a smaller fragment of the plasmin enzyme and was approved as the first nonsurgical treatment for vitreomacular traction (VMT), also referred to as symptomatic "vitreomacular adhesion" (VMA).[1] Ocriplasmin was approved by the Food and Drug Administration in 2012 after 2 MIVI-TRUST phase 3 clinical trials established its efficacy and safety (TG-MV-006 [NCT00781859] and TG-MV-007 [NCT00798317]).[2] These trials enrolled overall 652 subjects with symptomatic VMA (464 received intravitreal ocriplasmin injection, and 188 received intravitreal placebo injection). A total of 26.5% of subjects receiving ocriplasmin achieved the primary end point of pharmacologic VMA resolution at day 28 compared with 10.1% of subjects receiving placebo ($P < 0.001$).[2]

The Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) study is a phase 3b clinical trial with a follow-up period of up to 24 months to provide long-term results on the efficacy and safety of ocriplasmin. On the basis of data from the 6-month phase 3 trials, the OASIS trial protocol was designed to include subjects with ocular characteristics previously shown to be associated with higher VMA resolution, namely, subjects without epiretinal membrane (ERM) and macular hole of ≤400 μm. The trial also was designed to assess additional outcome measurements,

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including visual function measurements (Amsler grid, Pelli-Robson contrast sensitivity score, Roth 28-hue color vision test) and anatomic measurements (ellipsoid zone status in the central 1-mm cube, external limiting membrane status in the central 1-mm cube, subretinal fluid) to better understand and further characterize how the anatomic and functional changes correlate. Further analyses of these subgroups will be published in a separate article.

A few recent case studies have reported abnormal electroretinogram (ERG) readings in some patients after ocriplasmin treatment.[3–5] To address the limitations of case studies and those of the MIVI-TRUST phase 3 trials and to better understand the incidents occurring in postmarketing reports, an ERG substudy (62 subjects) was initiated as part of OASIS. In addition, a microperimetry substudy (27 subjects) was added to OASIS to further analyze more refined structural and functional aspects of the retina with respect to VMA resolution and best-corrected visual acuity (BCVA). Full results of both substudies will be published separately.

The OASIS trial was designed to bring a considerable long-term update to the efficacy and safety profile of ocriplasmin by following subjects over a period of up to 24 months using more advanced technology, as well as a larger variety of visual function assessments and subgroup analyses based on baseline characteristics to determine their potential impact on the end points.

Methods

Overall Trial Design and Enrollment

The OASIS (clinicaltrials.gov identifier: NCT01429441) is a phase 3b, randomized, sham-controlled, double-masked, multicenter clinical trial to investigate the long-term (up to 24 months) efficacy and safety of a single intravitreal injection of ocriplasmin 0.125 mg in subjects with symptomatic VMA/VMT, including full-thickness macular hole (FTMH) of $\leq$400 μm. The trial sample size was 220 subjects (146 ocriplasmin, 74 sham), all enrolled in the United States. The eligibility of subjects was determined by the investigators.

Ethics

Subjects were required to provide written informed consent before enrollment in the trial and the conduct of any trial-related procedures. The final protocol including amendments and informed consent forms was submitted to the institutional review board for approval. The trial adhered to the provisions of the guidelines of the World Medical Association Declaration of Helsinki. This trial was conducted in compliance with the trial protocol and all federal, local, or regional requirements, including with the Health Insurance Portability and Accountability Act.

Inclusion and Exclusion Criteria

Inclusion criteria (study eye) included the presence of VMA (i.e., central vitreal adhesion within 6-mm optical coherence tomography [OCT] field surrounded by elevation of the posterior vitreous cortex) that in the investigator's opinion was related to decreased visual function (e.g., metamorphopsia, decreased visual acuity, other visual symptom), as well as BCVA of 20/32 or worse in the study eye and BCVA of 20/800 or better in the nonstudy eye.

Exclusion criteria (study eye) included history or current evidence of proliferative retinopathy, exudative age-related macular degeneration, or retinal vein occlusion; vitreous hemorrhage or any other vitreous opacification; FTMH of >400 μm diameter; presence of ERM; aphakia; history of vitrectomy; and uncontrolled glaucoma.

Randomization and Masking

Consecutive, eligible subjects who met the inclusion/exclusion criteria were randomized in a 2:1 allocation ratio to receive ocriplasmin 0.125 mg or sham injection. Randomization was stratified on the basis of the presence or absence of FTMH at baseline and was centralized through an interactive voice response system. The trial was conducted in a double-masked manner. To maintain the masking of the investigator, an unmasked injecting physician was assigned to perform the injection and access the interactive voice response system to receive the assigned treatment. The unmasked personnel did not perform or participate in any other trial-related procedures or assessments.

Crossover

The trial allowed for an optional crossover treatment for subjects who met certain eligibility criteria during the month 12 visit or at any time beyond. Subjects eligible for optional crossover treatment had continued VMA (VMT) in the study eye confirmed on spectral domain optical coherence tomography (SD OCT) by the investigator were indicated for additional treatment and met at least 1 of the following criteria as evidence of disease progression at the month 12 visit or any time beyond: visual acuity decrease by $\geq$10 BCVA letters, new or worsening metamorphopsia, or new idiopathic macular hole or worsening of existing macular hole $\leq$400 μm in diameter. Optional crossover treatment also was allowed for subjects who were scheduled for vitrectomy at any time during the trial after the day 28 visit. Crossover subjects received the opposite treatment to the one they were initially randomized to, while the masking in the trial was maintained. Subjects initially randomized to ocriplasmin were allowed to cross over to sham to ensure the double-masked nature of the study for the entire duration of the trial.

Study Treatment and Plan

For subjects randomized to ocriplasmin injection, 0.125 mg ocriplasmin was injected midvitreous. For subjects randomized to sham injection, a syringe identical to that used in subjects randomized to ocriplasmin was used, and the syringe hub was pressed against the conjunctiva to mimic an actual injection procedure. The trial involved 12 study visits: baseline visit, which could be performed up to 2 weeks before injection day visit (day 0), and 24 months of postinjection follow-up at day 7, day 28, and every 3 months thereafter (months 3, 6, 9, 12, 15, 18, 21, and 24). The first subject was enrolled on November 2, 2011, and the last subject was completed on October 22, 2014. The trial was conducted at 25 sites in the United States.

Primary and Secondary End Points

The primary efficacy end point of the OASIS trial was the proportion of subjects with pharmacologic VMA resolution at day 28. Secondary end points were assessed at month 24 and irrespective of vitrectomy (where applicable): proportion of subjects with a $\geq$2-line improvement in BCVA from baseline; proportion of FTMHs that closed without vitrectomy as determined by the