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Ocriplasmin for Treatment of Vitreomacular Traction and Macular Hole

A Systematic Literature Review and Individual Participant Data Meta-Analysis of Randomized, Controlled, Double-Masked Trials

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Abstract

Ocriplasmin is used to treat vitreomacular traction (VMT), with or without full-thickness macular hole (MH). We systematically reviewed the evidence on ocriplasmin's effect on vitreomacular adhesion resolution (VMAR), MH closure, vitrectomy, and best-corrected visual acuity (BCVA) and investigated the effect of baseline covariates on outcome. We applied individual participant data meta-analyses to the entire population and to subgroups defined by MH or epiretinal membrane (ERM) presence. Safety data were pooled and tabulated. Five randomized controlled trials (1067 participants) were included. Six months after treatment, ocriplasmin achieved higher rates of VMAR and MH closure versus control, lowered vitrectomy odds and increased the likelihood of a ≥10-letter BCVA increase. VMAR rates were lower when ERM, broad VMA (>1500 µm), diabetic retinopathy, or pseudophakia were present and higher in younger participants, women, and eyes with MHs. Ocriplasmin-treated participants experienced more short-term visual impairment that was not predictive of final BCVA, as well as vitreous floaters, photopsia, photophobia, eye pain, blurred vision, and dyschromatopsia. The most common serious adverse events for ocriplasmin and control, respectively, were MH progression (22.5%, 17.3%), new MH (1.5%, 3.4%) and retinal detachment (0.8%, 1.2%). Ocriplasmin promotes VMAR and MH closure. Transient visual phenomena are not uncommon.

1. Introduction

The aging vitreous undergoes passive gel liquefaction (syneresis) and vitreoretinal dehiscence with collapse (posterior vitreous detachment) away from the retina.[23] When this natural process does not complete fully, and the vitreous remains attached at the macula, then this may cause vitreomacular traction (VMT), also known as symptomatic vitreomacular adhesion (VMA). Advanced VMT can cause blurred vision and metamorphopsia and can progress to a full-thickness macular hole (MH) with associated reduction in visual acuity.[13] The conventional therapeutic approach for clinically significant VMT is pars plana vitrectomy (PPV) with release of the VMT. The traditional treatment for MH is PPV, internal limiting membrane peel, and intravitreal gas injection.[6]

Ocriplasmin is an enzyme capable of resolving VMT when injected intravitreally, thereby obviating the need for vitrectomy. Approval was based on the Microplasmin for Intravitreous Injection–Traction Release without Surgical Treatment (MIVI-TRUST) studies (referred to hereafter as MIVI 006 and MIVI 007), double-blind randomized controlled trials (RCTs) with a primary endpoint of VMA resolution (VMAR) 28 days after injection without the creation of an anatomical defect (including MH) or the need for vitrectomy. The MIVI trials showed that ocriplasmin-treated participants had a higher chance of achieving VMAR than placebo-treated participants, as evidenced by an odds ratio (OR) of 2.56 (95% confidence interval [CI]: 1.32 to 5.24) in MIVI-006 and 5.13 (95% CI: 1.97 to 17.00) in MIVI 007.[25] The randomized, sham-controlled Ocriplasmin for Treatment of Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) study, showed similar results at 24 months of follow-up.[4]

Subsequent analyses showed that the treatment effect could vary considerably depending on the presence of several baseline characteristics, including MH,

epiretinal membrane (ERM), “broad” (>1500 µm) VMA adhesion size, pseudophakic status, sex, and age.[8; 10; 25]

Two common characteristics, ERM and MH, are particularly important because of their impact on treatment outcomes. Among the MIVI and OASIS populations, ERM and MH were observed in 34.7% and 26.3% of participants, respectively. Among those with ERM treated with ocriplasmin, VMAR at Day 28 was reduced 4-fold as compared to those without ERM.[4; 25] VMT participants with MH are more likely to undergo vitrectomy than those without MH, whether they have been treated with ocriplasmin[16] or not.[26] As ERM and MH affect short- and long-term VMAR and vitrectomy rates, it is important to control for their presence when reporting outcomes.

We conducted a systematic literature review and used individual participant data (IPD) for the meta-analysis of RCT data, since using IPD allows for the identification of participant subgroups that are more or less likely to benefit from treatment. Our aim was to evaluate key clinical outcomes of a single-dose intravitreal injection of ocriplasmin versus control (placebo or sham) for the treatment of adults with VMT with or without MH, considering baseline covariates likely to affect these outcomes.

2. Methods

This study was conducted according to the Preferred Reporting of Items for Systematic Reviews and Meta-Analyses (PRISMA).[19] The systematic review protocol is registered with PROSPERO (CRD42019121138; available at https://www.crd.york.ac.uk/PROSPERO/).

2.1 Literature search

EMBASE (Elsevier), PubMed (National Institute of Health) and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs. No language restrictions were applied. EMBASE and PubMed search terms are listed in the Method of Literature Search section. CENTRAL was searched for the term "ocriplasmin" without applying filters. Two reviewers (KHB, BL) independently conducted title/abstract screening and full text review. Discrepancies were resolved by discussion after an additional review of the studies. The search was completed by June 5, 2019. The PICOS (population, intervention, comparator, outcomes, setting) criteria are listed in the Method of Literature Search section.

Eligible studies were prospective double-masked RCTs with a follow-up of ≥6 months that used a single 125 µg dose of intravitreal ocriplasmin or control (sham or placebo injection) to treat participants with symptomatic VMA/VMT, as diagnosed by optical coherence tomography (OCT). Nonrandomized studies, reviews, editorials, comments, conference abstracts, and other nonpeer-reviewed publications were excluded.

Studies were assessed for quality using the revised Cochrane Risk of Bias tool (RoB version 2).[9] KHB and TLJ carried out independent assessments of bias, which were integrated into the final version.

2.2 Study populations

Baseline demographics were tabulated for each study and treatment group. Because it was anticipated that the presence of ERM and MH might lead to different

outcomes, we explored the distribution of these covariates within the baseline population.

2.3 Outcomes

The main outcomes of interest were binary (success or failure); nonsurgical VMA release, defined as VMAR without the creation of a new anatomic defect or the need for vitrectomy, evaluated at Day 28 and Month 6; nonsurgical MH closure at Month 6 without the need for vitrectomy; and ≥10 Early Treatment Diabetic Retinopathy Study (ETDRS) letter score increase or decrease in best-corrected visual acuity (BCVA) from baseline to Month 6.

The VMAR and MH closure endpoints were considered treatment failures if vitrectomy occurred prior to the assessment time point. Under this algorithm a case of successful VMAR at Day 28 becomes a treatment failure at month 6 if a vitrectomy takes place between these 2 time points. For BCVA increase from baseline to month 6, we considered vitrectomy as a treatment failure in one analysis, and a second analysis reported BCVA increase irrespective of vitrectomy. A BCVA decrease from baseline of ≥10 ETDRS letters was evaluated irrespective of vitrectomy. The last binary outcome was the need for vitrectomy.

For the continuous outcome of BCVA change, we used 2 predefined approaches to calculate mean BCVA change from baseline to month 6. The first approach used the difference between BCVA at month 6 and baseline, irrespective of vitrectomy; in the second approach, participants who underwent vitrectomy had the last previtrectomy BCVA value carried forward.

Our original systematic review and meta-analysis protocol did not specify any analysis of adverse outcomes other than the ≥10 ETDRS letter loss in BCVA. In response to reviewers' comments, we performed a safety analysis of treatment-emergent study eye adverse events (AEs). Adverse events, regardless of causality, were coded to Preferred Terms according to the Medical Dictionary for Regulatory

Activities (MedDRA), which were then pooled for analysis. Adverse events were deemed serious if they were fatal or life-threatening, required or prolonged inpatient hospitalization, resulted in persistent or significant disability or incapacity, were a congenital anomaly or birth defect, if they were deemed an important medical event, or required a medical intervention to avoid any of the above outcomes. In order to harmonize for different lengths of study follow-up, AEs that emerged more than 200 days after dosing were not considered. We used a list of multiple Preferred Terms to increase the detection yield for AEs of special interest, such as visual impairment, dyschromatopsia, intraocular pressure increase, intraocular hemorrhage or inflammation, lens subluxation, and immunogenicity (**Supplementary Table S1**). For the sake of clarity, the Preferred Term “macular hole” was broken down to the non-MedDRA terms “macular hole progression” and “new macular hole”, depending on whether the AE occurred in participants with or without a MH at baseline.

We tabulated all AEs, AEs occurring within 7 days of injection, SAEs, and AEs of special interest.

2.4 Statistical methods

Missing data were imputed by carrying forward the last observed measurement. Participants with missing baseline values for BCVA were considered missing in the analysis for that endpoint unless they underwent vitrectomy at any time prior to the assessment, in which case they were considered nonresponders for binary endpoints.

We used a single-stage mixed-effects model for the IPD analysis with treatment and covariate(s) as fixed effects and study and the interaction between study and treatment as random effects, allowing variation in treatment effect amongst studies around the overall mean treatment effect. The covariates were age (years), sex (male or female), baseline BCVA (ETDRS letters), lens status (phakic, pseudophakic), region (US, Europe, Japan), race (white, nonwhite), broad VMA

(≤1500 μm, >1500 μm), and diabetic retinopathy (absent, present). Binary response variables were modeled using mixed-effects logistic regression with the OR as the summary statistic, whereas mean BCVA change was modeled using a mixed-effects linear model based on the normal distribution, with mean difference as the summary statistic.

The model was first run with treatment as the sole fixed effects variable to produce "unadjusted" ORs. Models were then fitted by adding baseline covariates to the "unadjusted" model in a univariable way. Baseline covariates that were significant at the 5% level were then included together with the treatment in a multivariable model; covariates that remained significant were reported, together with the adjusted treatment effect. Random effects I^2 values were calculated based on unadjusted ORs.

We calculated 95% CIs for the ORs of individual studies using Woolf's (logit) method with the Haldane–Anscombe continuity correction in studies where no events occurred in either arm.[22] We used the *t* distribution to compute CIs for the mean difference of individual studies. Proportions of outcomes within treatment groups were calculated using a mixed-effects model with study as random effect. All analyses were first applied to the entire population and then to the subgroups of VMT without ERM ("VMT"), VMT with ERM ("VMT+ERM"), VMT with MH but without ERM ("MH"), and VMT with MH and ERM ("MH+ERM"). Stata 16 was used for all analyses. Statistical tests were two-sided, and statistical significance was set at an alpha level of .05. No adjustments for multiplicity were made to account for the testing of multiple endpoints.

3. Results

3.1. Literature search procedures

We identified 337 potentially eligible articles from the electronic database search as of 5 June 2019. After removing 106 duplicates, we screened 231 unique records and

excluded 195 based on title or abstract. Thirty-six records underwent full-text review, and 21 were excluded (**Figure 1**). In total, 15 records were included,[1; 2; 3; 4; 7; 8; 10; 11; 12; 14; 15; 24; 25; 28; 30] representing 5 unique RCTs, all sponsored by Oxurion, the manufacturer of ocriplasmin. These included the dose-ranging MIVI-IIT trial (ClinicalTrials.gov identifier: NCT00435539),[24] the pivotal MIVI 006 (NCT00781859) and MIVI 007 (NCT00798317) trials,[25] and the longer-term OASIS trial (NCT01429441).[4] A fifth, unpublished trial (NCT01889251),[2] named J-12-075, was identified through the CENTRAL repository as an entry in the clinicaltrials.gov database. This study was conducted in Japan between July, 2013, and September, 2014. Oxurion made IPD, protocols, and study reports available for all 5 trials.

3.2. Study characteristics

Trial designs

The 5 trials were conducted according to prespecified protocols and analysis plans. Studies were carried out in accordance with the Declaration of Helsinki, and participants provided written informed consent. Inclusion and exclusion criteria were largely similar across trials. All trials were double-masked. The MIVI-TRUST trials were placebo-controlled, whereas the control group of the other trials received sham injection by an investigator who was not involved in subsequent study assessments. All trials used a treatment-masked central reading center for OCT assessments, and all BCVA measurements used the ETDRS testing protocol.[5] Postinjection follow-up was 6 months for all trials except for OASIS, which had a follow-up of 24 months. Although visit schedules differed between trials, all collected measurements at baseline, day 28, month 3, and month 6. Further details of trial designs are included in **Table 1**.

All trials had low risk of bias when assessed using the Cochrane Risk of Bias tool (**Figure 2** and **Supplementary Table S2**).[9]

Demographics

The 5 trials randomized a total of 1067 participants, 737 (69.1%) of whom were randomized to ocriplasmin and 330 (30.9%) to control. Among those assigned to control, 188 (57.0%) were assigned to placebo. Baseline demographics are summarized in **Table 2**. Approximately a quarter of participants had MH at baseline, and 29.7% were pseudophakic. **Table 3** shows the distribution of baseline ERM, MH, and VMA adhesion width for the 949 participants (88.9%) for whom all 3 assessments were evaluable. Across the entire population (N=1031) with evaluable ERM assessments, only 37 participants (3.6%) had MH as well as ERM at baseline. We do not present separate results for this subgroup because only 9 of all MH+ERM participants were assigned to placebo. The subgroup is, however, included in the "Overall" analyses presented below.

3.3. Results of the meta-analyses

Vitreomacular adhesion resolution

Overall, there was a greater likelihood of VMAR in the ocriplasmin group. The difference between treatment groups was greater at day 28 (**Figure 3A**) than at month 6 (**Figure 3B**). For the overall population, the pooled unadjusted OR for VMAR at day 28 was 7.80 (95% CI: 3.74 to 16.25) for ocriplasmin versus control (**Figure 3A**). Heterogeneity was low overall; significant heterogeneity in the MH subgroup appears mainly due to the results of the Japanese study.

Despite similar unadjusted ORs in the 3 subgroups, VMAR incidence rates within treatment groups differed greatly by subgroup. Ocriplasmin-treated participants in VMT, VMT+ERM, and MH subgroups had VMAR rates of 37.7% (95% CI: 28.6% to 47.8%), 10.7% (95% CI: 6.1% to 17.9%), and 60.6% (95% CI: 49.9% to 70.4%), respectively, at Day 28. Adjusted analyses highlighted several significant covariates. Among these covariates, age, sex, and the presence of broad VMA were most often found to be significant.

Changes in ORs for VMAR between Day 28 (**Figure 3A**) and Month 6 (**Figure 3B**) were driven by the rates of vitrectomy and VMAR post-Day 28, which markedly differed by subgroup. In VMT participants, VMAR increased in the control group from 5.8% (8/133) at day 28 to 15.0% (20/133) at month 6 and in the ocriplasmin group from 37.7% (109/299) at day 28 to 44.6% (129/299) at month 6. In the VMT+ERM subgroup, VMAR in ocriplasmin-treated participants increased from 10.7% (23/222) to 15.9% (34/222) at month 6, while it remained rare in the control group (**Figure 3**). In the MH subgroup however, vitrectomy between day 28 and month 6 resulted in a decrease of VMAR from 60.6% (98/163) to 32.5% (53/163) in ocriplasmin-treated participants, while VMAR remained unchanged in the control group (15/86, 15%). Heterogeneity for the VMAR at Month 6 was low. Adjusted analyses showed that increasing age and presence of broad VMA were significantly associated with decreased OR of VMAR, except in the MH group, where no significant covariates were found.

Macular hole closure

Unadjusted ORs for MH closure at month 6 were 3.98 (95% CI: 2.03 to 7.81) for the overall MH population and 5.70 (95% CI: 2.57 to 12.65) in the MH group without ERM, favoring ocriplasmin treatment. Adjusted ORs were similar to unadjusted values (**Figure 4**); there was no indication of heterogeneity.

Vitrectomy

Odds ratios for vitrectomy at Month 6 significantly favored ocriplasmin in the overall population (pooled unadjusted OR 0.64, 95% CI: 0.48 to 0.86) and in the VMT and MH subgroups (**Supplemental Figure 1**). Heterogeneity estimates were low in all subgroups except VMT+ERM. Among ocriplasmin-treated participants, the incidence of vitrectomy was 9.4% (95% CI: 6.5% to 13.2%) in the VMT subgroup and 53.4% (95% CI: 43.9% to 62.7%) in the MH subgroup. The overall rate of vitrectomy (regardless of treatment) was higher in the Japanese J-12-075 trial than in the other

trials (45.4% vs 22.8%), an observation also reflected in the significant region covariate representing Japan.

No vitrectomies were performed in participants who achieved lasting MH closure. Of the 88 participants who achieved MH closure, only 3 (1 ocriplasmin, 2 control) underwent vitrectomy because of reopening of the MH.

Visual acuity

Ocriplasmin treatment significantly increased the odds of a ≥10-ETDRS-letter BCVA gain in the absence of vitrectomy from baseline to month 6; the unadjusted OR for the overall population was 2.60 (95% CI: 1.77 to 3.82; **Figure 5A**). Adjusted ORs were somewhat higher than unadjusted ORs in the VMT and VMT+ERM subgroups.

Ocriplasmin demonstrated significantly higher odds of a ≥10-ETDRS-letter BCVA gain when this response was considered irrespective of vitrectomy, except in the MH subgroup (**Figure 5B**). Unadjusted ORs were lower than the ORs in the analysis that considered vitrectomy as treatment failure, except in the VMT+ERM subgroup where ocriplasmin performed notably better than control, despite similar rates of vitrectomy (**Figure 5**).

Overall, mean BCVA change from baseline, irrespective of vitrectomy, was significantly better in the ocriplasmin group, although the absolute change was modest (unadjusted mean change difference: 1.69 [95% CI: 0.32 to 3.06]) (**Supplemental Figure 2A**). Results for the analysis that carried forward the last previtrectomy BCVA values to Month 6 were similar (**Supplemental Figure 2B).**

Overall, the risk of a ≥10-letter decrease from baseline to month 6 in BCVA irrespective of vitrectomy was not significantly different between ocriplasmin and control (unadjusted OR: 0.95 [95% CI: 0.50 to 1.79]; **Figure 6**). Among subgroups, risk estimates tended to favor control in the VMT+ERM subgroup (unadjusted OR: 3.58 [95% CI: 0.71 to 18.04]) and ocriplasmin in the MH subgroup (unadjusted OR:

297 0.42 [95% CI: 0.15 to 1.16]). Heterogeneity was moderate in all except the MH
298 subgroup.

299 **Safety**

300 Treatment-emergent AEs are tabulated in **Supplemental Table 3**. Common AEs that
301 occurred at higher frequency in the ocriplasmin group (n = 737) than in control (n =
302 330) included vitreous floaters (19.7% vs 6.4%), photopsia (13.6% vs 2.7%),
303 photophobia (5.0% vs 0%), eye pain (12.9% vs 5.5%), blurred vision (8.7% vs 2.4%),
304 and visual impairment (7.3% vs 1.8%). The incidence of conjunctival hemorrhage
305 was similar in placebo and ocriplasmin-treated participants (13.3% and 14.4%,
306 respectively) and lower in the sham group (5.6%) (data not shown).

307 In participants with baseline MH, macular hole progression occurred in 50 of 200
308 (25.0%) ocriplasmin-treated participants versus 18 of 98 (18.4%) control-treated
309 participants. In participants with VMT, new MH occurred in 16 of 537 (3.0%)
310 ocriplasmin-treated participants vs 10 of 232 (4.3%) participants in the control group.

311 Retinal detachment occurred in 4 (1.2%) participants in the control group, vs 14
312 (1.9%) participants in the ocriplasmin group, 9 of which occurred among the 115
313 ocriplasmin-treated participants of the J-12-075 trial (7.8%), with the event being
314 diagnosed within 11 days after injection in 8 of these 9 Japanese participants. Six out
315 of the 9 cases of retinal detachment were judged nonserious, and 4 of these
316 recovered without vitrectomy. Retinal tears were not more common in the
317 ocriplasmin-treated group (1.6%) than in the control group (3.0%). Fourteen cases of
318 subretinal fluid were observed in the ocriplasmin-treated group (1.9%) vs 1 (0.3%) in
319 the control group.

320 **Table 4** lists the frequency of several AEs of special interest, as defined by the
321 Preferred Terms listed in **Supplemental Table 1**. Visual impairment-related AEs
322 were most common (185 [25.1%] in ocriplasmin, 41 [12.4%] in control), while
323 cataract-related AEs occurred in 48 ocriplasmin-treated participants (6.5%) vs 25

control-treated participants (7.6%). Intraocular inflammation AEs were reported in 74 ocriplasmin-treated participants (10.0%) vs 12 control participants (3.6%). Dyschromatopsia-related event terms occurred in 33 (4.5%) ocriplasmin-treated participants vs 2 (0.6%) in the control group. Out of these 33 cases, 31 (94%) were reported in the OASIS and J-12-075 trials.

In ocriplasmin-treated participants, most visual impairment-related AEs occurred during the first week post-dose (124 of 185 cases, 67.0%). The vast majority of these early-onset visual impairment cases (107 of 124, 86.3%) recovered during follow-up. We explored the evolution of BCVA in these ocriplasmin-treated participants with early-onset visual impairment. Out of the 17 ocriplasmin-treated participants who had early-onset visual impairment that did not resolve, 2 (12%) lost ≥10 ETDRS letters, while 4 (24%) gained ≥10 ETDRS letters. Among the 107 participants whose early-onset visual impairment resolved, 7 (6.5%) lost ≥10 ETDRS letters while 41 (38.3%) gained ≥10 ETDRS letters. Overall, among the 124 ocriplasmin-treated participants with early-onset visual impairment, 9 (7.3%) had a ≥10 ETDRS letter loss, while 45 (36.3%) gained ≥10 ETDRS letters. Early-onset visual impairment after ocriplasmin treatment was therefore not associated with worse BCVA outcomes. Likewise, among the 34 ocriplasmin-treated participants who reported dyschromatopsia-related events, none experienced a ≥10 ETDRS letter loss while 15 (44%) experienced a ≥10 ETDRS letter gain.

One case of lens dislocation was observed 50 days post-dose in a 76-year-old woman participant in the J-12-075 trial who was treated with ocriplasmin. The participant was phakic and had no evidence of ERM, MH, or diabetic retinopathy. The event was classified as nonserious, of moderate severity, probably related to treatment, and no vitrectomy was done. Visual acuity was 72 ETDRS letters at baseline and 74 letters at the end of follow-up (Month 6).

One case of photoreceptor toxicity was reported in a 62-year-old phakic woman with MH and without ERM who was treated with ocriplasmin in the OASIS trial. The AE started 6 days after the dosing date, at which time the participant also complained of dim vision, vitreous floaters and decreased night vision. The investigator reported iritis and abnormal color vision tests. The MH was enlarged 14 days post-dose, and vitrectomy was performed 18 days post-dose. Eight days post-vitrectomy, retinal degeneration, retinal artery stenosis, and retinal hemorrhage were reported. Moderate anisometropia was reported 117 days after dosing, and the patient reported flashing lights as well as lavender and green blotches in the visual field approximately 8 months after treatment. Virtually all of the above AEs were ongoing at the end of the 24-months follow-up. Visual acuity decreased from a baseline of 57 to 54 prior to vitrectomy and was 50 letters at month 6. At months 9 and 24, BCVA was 71 and 70 letters, respectively, a 13-letter increase from baseline.

Supplemental Table 4 summarizes SAEs for all treatment groups according to relatedness and outcome. Serious adverse events were not more common in ocriplasmin group than in the control group, and the majority of SAEs recovered during follow-up.

4. Discussion

So far, systematic reviews and meta-analyses on the use of ocriplasmin in VMT or MH have been based on aggregate data extracted from publications.[20] These aggregate data represent a summary of the IPD for each study and do not offer the flexibility of comprehensive subgroup analyses. Using an IPD rather than aggregate data approach to a meta-analysis of RCTs facilitates the investigation of whether an intervention is more or less beneficial for different types of participants and can be more effective in reducing heterogeneity than meta-analyses that are limited to published data.[27; 29] This IPD-based meta-analysis reports the entire body of randomized evidence on ocriplasmin and is, to our knowledge, the largest published

to date. The availability of individual participant data for all trials allowed us to identify clinically relevant participant subgroups and to conduct a detailed analysis of key treatment outcomes while adjusting for significant baseline covariates.

The main strength of this meta-analysis lies in our approach to the inherent heterogeneity of the studied population. Prior analyses of the primary endpoint of the MIVI-TRUST trials[25] (VMAR at Day 28) used univariate subgroup analysis[8] or multivariate analysis[10] to identify baseline covariates relevant to treatment efficacy. Unfortunately, such analyses have limited clinical utility when multiple baseline covariates overlap, as was the case in our study population. We therefore chose not to limit our analysis to the overall population, but to explore outcomes and covariates in three large and clinically distinct subgroups defined by baseline ERM and MH status.

Our multivariate meta-analysis showed that, among the selected endpoints, Day 28 VMAR was most affected by baseline covariates, particularly in the VMT subgroup, where ORs of treatment success increased from 10.20 (unadjusted; 95% CI: 4.09 to 25.40) to 20.02 (95% CI: 7.80 to 51.40) when adjusted. Importantly, all efficacy outcomes favored ocriplasmin regardless of covariate adjustment, except for the rate of vitrectomy at month 6 in the VMT+ERM subgroup.

We also describe outcomes that were previously unreported (eg, VMAR at month 6, and the evolution of VMAR outcomes between day 28 and month 6), or were reported differently across trials (e.g., categorical change in BCVA reported irrespective of vitrectomy versus nonsurgical BCVA change).

In our meta-analysis of VMAR and MH closure, participants who underwent vitrectomy prior to an evaluation time point were considered treatment failures, even if they had been treatment successes at a prior time point. This stringent definition was particularly pertinent for VMAR outcomes in ocriplasmin-treated participants with MH, where a 60.6% VMAR rate at Day 28 (**Figure 3A**) decreased to 32.5% at month

6 (**Figure 3B**), due to surgical interventions post–day 28. In the VMT subgroup, however, VMAR incidence continued to increase in both the control and ocriplasmin groups. In 15.5% (20/129) of ocriplasmin-treated VMT participants, VMAR occurred between day 28 and month 6. These observations show that VMAR, when measured at day 28, tends to overestimate the eventual treatment benefit in the MH subgroup, and underestimate the effectiveness of the intervention in the VMT subgroup.

The effect of treatment on BCVA outcomes is notoriously difficult to evaluate since intercurrent vitrectomy is very common in the VMT/MH population; pooled vitrectomy incidence rates in control-assigned participants were 18.8% (95% CI: 13.0% to 26.3%) in the VMT subgroup and 72.0% (95% CI: 50.7% to 86.5%) in the MH subgroup. Visual acuity outcomes irrespective of vitrectomy are more relevant from a public health perspective since they reflect a “real-world” situation after one or more interventions; however, this perspective tends to disregard the additional inconvenience to patients that is associated with vitrectomy, which was more common in the control arm. An analysis that considers vitrectomy as treatment failure provides a better reflection of ocriplasmin treatment efficacy. We chose to report both analysis types because we believe that either approach has merit, and they are complementary in the overall assessment of BCVA outcomes.

Lastly, our analyses across subgroups highlight the fact that similar ORs may represent entirely different clinical realities in terms of absolute risk differences, especially for the outcome of VMAR and vitrectomy at Month 6.

This meta-analysis has several shortcomings. First, the size of the database (5 trials, 1067 participants) is relatively small given the binary nature of most endpoints. Nevertheless, this is the largest database of RCTs in this condition. A second limitation is that most participants were recruited in the United States, except for the J-12-075 trial, which was conducted in Japan. The latter was characterized by higher

rates of vitrectomy than other trials, regardless of assigned treatment. On the other hand, the 204 European participants enrolled in MIVI 007 had significantly lower odds of vitrectomy at month 6. In the absence of other explanatory variables, these discrepancies highlight the fact that vitrectomy is not a “hard” outcome, but rather the outcome of a discussion between participant and physician, where other intangible factors might play a role. Lastly, while the focus of this meta-analysis is mostly on efficacy, the endpoint of a ≥10 ETDRS letter decrease in BCVA at month 6 was included as an overall, objective safety measure.

This paper is the first to exhaustively report all study eye AEs and SAEs observed during the first 200 post-treatment days at the MedDRA Preferred Term level. This approach provides a higher degree of granularity than higher-level AE terms. In addition, we clustered several Preferred Terms reflecting the same clinical entities, to identify medically important AEs.

The reporting of some AEs in our meta-analysis may be confounded due to the technical progress in OCT imaging that occurred while the ocriplasmin clinical program was ongoing. Since OASIS and J-12-075 were the only trials to exclusively use SD-OCT, it is likely that some finer anatomical defects, such as subretinal fluid, went undetected in the older trials.

We confirmed a higher incidence of vitreous floaters, photopsia, photophobia, eye pain, blurred vision and visual impairment in ocriplasmin-treated participants. These AEs were especially prevalent during the first week after dosing, which suggests their association with the process of an accelerated vitreomacular release. While these symptoms may be very distressing to those who experience them, they were generally transient and self limited. Furthermore, our analysis shows that the odds of increasing BCVA by ≥10 ETDRS letters were greater for ocriplasmin-treated patients, while the risk of losing ≥10 ETDRS letters did not differ between treatments.

The incidence of retinal detachment (Preferred Term) in ocriplasmin-treated participants was 8-fold higher in the J-12-075 trial (9 of 115, 7.8%) as compared to the other trials (6 of 622, 1.1%) (RR 8.11; 95% CI: 2.94 to 22.36; P = .0001). The reasons for this discrepancy are not clear. Possible explanations include the fact that populations of Asian descent have a higher prevalence of myopia, [17; 31] which has been described as a predisposing factor for retinal detachment.[18; 21]

The most common treatment-emergent AE in ocriplasmin-treated participants was visual impairment. Visual impairment with onset during the first week after injection recovered in 86.3% of cases and was not associated with worse outcomes in terms of BCVA.

5. Conclusion

This systematic review and IPD meta-analysis of RCTs shows that ocriplasmin, as compared to controls, increased the odds of VMAR, MH closure, and a ≥10 ETDRS letter gain in BCVA by month 6, while it decreased the odds of vitrectomy. There was no difference between ocriplasmin and control in the odds of a ≥10 ETDRS letters BCVA decrease at month 6. Our IPD analysis showed that efficacy outcomes generally favored ocriplasmin, despite outcome variations across subgroups defined by the presence of ERM and MH. Increasing age, male gender, and presence of broad VMA were associated with decreased treatment response.

Early-onset visual impairment was common after ocriplasmin treatment, but not associated with worse BCVA outcomes. Patients who are candidates for ocriplasmin treatment should be counseled on the possibility of this adverse reaction and reassured that it is not predictive of long-term visual acuity outcomes.

6. Method of Literature Search

Search strategy

A systematic review protocol was developed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (www.prisma-statement.org). The protocol is registered with PROSPERO (CRD42019121138; available at https://www.crd.york.ac.uk/PROSPERO/). The bibliographic databases EMBASE (Elsevier), PubMed (National Institute of Health), and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for RCTs from inception up to June 5, 2019. We did not use any date or language restrictions in the electronic search for studies. **Tables 5 and 6** list the search terms used for PubMed and EMBASE, respectively. CENTRAL was searched for the term "ocriplasmin" without applying filters. Records were screened and selected as described above.

Study selection criteria

The PICOS criteria of this systematic literature review are listed in **Table 7**.

Eligible studies were prospective double-masked RCTs with a follow-up of at least 6 months that evaluated a single 125-µg dose of intravitreal ocriplasmin versus control (sham or placebo injection) to treat participants with symptomatic VMA/VMT, as diagnosed by optical coherence tomography (OCT). Nonrandomized studies, reviews, editorials, comments, conference abstracts, and other non–peer-reviewed publications were excluded.

Data extraction

The following characteristics of included studies were extracted from protocols, study reports and datasets: (1) description of trial designs and demographics including definition of target condition, inclusion and exclusion criteria, randomization and study treatments, country/region and year of publication; (2) participant characteristics at baseline including age (years), sex (male vs female), race (white, nonwhite), region (US, Europe, Japan); (3) study eye characteristics at baseline including lens status (phakic, pseudophakic), broad VMA (≤1500 µm, >1500 µm), diabetic retinopathy (absent, present), macular hole (absent, present), epiretinal

membrane (absent, present), BCVA study eye and follow eye (ETDRS letters); (4) outcomes of interest including VMAR without the creation of a new anatomic defect (including MH) or the need for vitrectomy, evaluated at Day 28 and Month 6, MH closure at Month 6 without need for vitrectomy, best-corrected visual acuity (BCVA) at Month 6, need for vitrectomy; (5) description of the intervention and of the comparator for the control group.

Quality assessment

Quality of studies was assessed using the revised Cochrane Collaboration Risk of Bias tool (version 2). Two reviewers (co-authors) independently carried out assessments of bias. Discrepancies were resolved by discussion.

CRediT author statements:

TLJ: Conceptualization, Methodology, Writing - Original draft, Review & Editing, Supervision.

JH: Conceptualization, Methodology, Writing - Review & Editing.

KHB: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing - Original draft, Review & Editing, Visualization, Supervision, Project administration, Funding acquisition.

LD: Conceptualization, Methodology, Formal analysis, Data curation, Writing - Original draft, Review & Editing.

BL: Conceptualization, Methodology, Writing - Review & Editing

Conflict of interests:

TLJ reports no personal conflicts of interest (COIs) in relation to this work. His employer receives site payments for participants enrolled onto commercial trials sponsored by Oxurion NV. **JH** reports no relevant COIs. She is a consultant for KalVista, Novartis, Spark Therapeutics, Lowy Medical Research Institute, and Bionic Sight LLC. She participates in data safety monitoring for Aura Bioscience and is the chair of DSMB for Janssen. Additionally, she is the director for Bristol-Myers Squibb. **KHB** provides medical and health economic consulting services to several biopharmaceutical companies including Oxurion NV and Santen Inc. **LD** is a consultant at Oxurion and was paid to contribute to this meta-analysis. **BL** provides health economic and health outcomes consulting services to several pharmaceutical companies, including Oxurion and Santen Inc.

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KHB had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. The study was funded by Oxurion NV (formerly ThromboGenics). The funding source had no involvement in the study design; in the analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. We thank Paul Willems, MD for his insights on the pharmacovigilance-related aspects of the manuscript.

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650 Table 1: Description of trial designs

Definition of target condition	• MIVI IIT, the earliest trial, defined the target condition as a partial central posterior vitreous detachment, with the vitreous still attached to the foveal area (documented on OCT and/or ultrasound) causing secondary macular edema ≥250 µm in the central subfield on OCT, or on 1 of the individual radial scans of the macular area. • The remaining trials defined the target condition as OCT-documented central vitreous adhesion within a 6-mm OCT field surrounded by elevation of the posterior vitreous cortex that, in the opinion of the investigator, was related to decreased visual function (such as metamorphopsia, decreased BCVA, or other visual complaint).
Inclusion and exclusion criteria	• All trials included participants aged ≥18 years with OCT-documented VMA/VMT. • The maximum allowed BCVA in the study eye was 70 ETDRS letters in MIVI IIT; 80 letters in MIVI 006, MIVI 007, and J-12-075; and 75 letters in OASIS. • Those with ERM were excluded from OASIS, while the Japanese J-12-075 trial allowed for the inclusion of participants with ERM unless it was located at the site of adhesion. The other trials included participants with ERM. • Individuals were excluded from all trials if they had proliferative diabetic retinopathy, neovascular age-related macular degeneration, retinal vascular occlusion, aphakia, high myopia (more than −8 diopters), uncontrolled glaucoma, MH >400 µm in diameter, vitreous opacification, lenticular or zonular instability, or a history of retinal detachment in either eye.
Randomization and study treatment	• With the exception of the early dose-ranging MIVI-IIT trial, all participants assigned to ocriplasmin received a single 125-µg intravitreal injection. ○ For the MIVI-IIT trial, only those who received a single 125-µg dose of ocriplasmin or sham were included in the current analysis. • The MIVI 006 and MIVI 007 trials used a visually identical placebo (saline) injection as control treatment. For the other trials, participants assigned to control received a sham injection administered by an investigator who was not involved in subsequent clinical assessments. • Randomization was managed by an interactive voice response system. In the MIVI IIT trial, randomization was balanced. The ocriplasmin to control randomization ratio was 2:1 in the MIVI 006, OASIS, and J-12-075 trials and 3:1 in MIVI 007.
Endpoints	• In MIVI-IIT, the primary endpoint was total PVD at Day 14, although VMAR at Day 28 and Month 6 were also reported. • In subsequent trials, the primary endpoint was VMAR at Day 28, without the creation of an anatomical defect or the need for subsequent vitrectomy.

Abbreviations: BCVA, best-corrected visual acuity; ERM, epiretinal membrane; ETDRS, Early Treatment Diabetic Retinopathy Study; MH, macular hole; OCT, optical coherence tomography; PVD, posterior vitreous detachment, VMA, vitreomacular adhesion; VMAR, vitreomacular adhesion resolution; VMT, vitreomacular traction.

651

652 Table 2: Baseline demographics of included trials

Study	**MIVI IIT**		**MIVI 006**		**MIVI 007**		**OASIS**		**J-12-075**	
Country/Region	**Belgium**		**USA**		**USA/Europe**		**USA**		**Japan**	
	Control	Ocriplasmin	Control	Ocriplasmin	Control	Ocriplasmin	Control	Ocriplasmin	Control	Ocriplasmin
N	(N=12)	(N=13)	(N=107)	(N=219)	(N= 81)	(N=245)	(N=73)	(N=145)	(N=57)	(N=115)
Demographics										
Age (years), mean (SD)	69.8 (8.62)	74.2 (5.70)	71.1 (10.04)	71.5 (10.25)	70.2 (10.85)	72.6 (7.56)	68.5 (11.01)	69.4 (10.02)	68.6 (9.18)	68.1 (7.32)
Women, n (%)	6 (50.0)	8 (61.5)	59 (55.1)	148 (67.6)	56 (69.1)	166 (67.8)	45 (61.6)	102 (70.3)	32 (56.1)	59 (51.3)
White, n (%)	12 (100.0)	13 (100.0)	97 (90.7)	195 (89.0)	77 (95.1)	233 (95.1)	64 (87.7)	131 (90.3)	0 (0.0)	0 (0.0)
Study eye characteristics										
Pseudophakic, n (%)	3 (25.0)	6 (46.2)	29 (27.1)	91 (41.6)	24 (29.6)	81 (33.1)	22 (30.1)	39 (26.9)	11 (19.3)	11 (9.6)
DR, n (%)	1 (8.3)	4 (30.8)	7 (6.5)	12 (5.5)	8 (9.9)	18 (7.3)	3 (4.1)	6 (4.1)	3 (5.3)	6 (5.2)
MH, n (%)	4 (33.3)	1 (7.7)	32 (29.9)	57 (26.0)	15 (18.5)	49 (20.0)	26 (35.6)	50 (34.5)	21 (36.8)	43 (37.4)
ERM, n (%)[a]	N/A	N/A	35 (32.7)	86 (39.3)	33 (40.7)	98 (40.0)	17 (23.3)	33 (22.8)	13 (22.8)	35 (30.4)
Broad VMA, n (%)[b]	N/A	N/A	19 (17.8)	47 (21.5)	22 (27.2)	56 (22.9)	8 (11.0)	8 (5.5)	3 (5.3)	11 (9.6)
BCVA (letters), mean (SD)										
Study eye	56.0 (14.86)	59.4 (9.90)	65.3 (9.83)	64.5 (10.86)	64.9 (11.58)	63.4 (13.69)	62.4 (11.05)	63.5 (8.89)	66.5 (9.29)	65.4 (8.77)
Fellow eye	77.2 (9.45)	81.9 (8.08)	72.6 (16.50)	75.6 (15.44)	74.6 (17.95)	74.4 (14.86)	77.3 (13.82)	72.4 (18.43)	79.2 (10.64)	77.7 (12.36)

Abbreviations: BCVA, best-corrected visual acuity; CRC, central reading center; DR, diabetic retinopathy; ERM, epiretinal membrane; MH, macular hole; N/A, not available; SD, standard deviation; VMA, vitreomacular adhesion.
[a]The OASIS protocol excluded participants with ERM; however, 50 of 218 participants (22.9%) nonetheless had ERM at baseline. Thirty-four of these cases (15.6%) were deemed significant by the CRC. ERM status was not evaluable in 36 participants (25 of 25 in MIVI IIT, 5 of 326 in MIVI 006, and 6 of 326 from MIVI 007).
[b]Broad VMA status was not measured in MIVI IIT (25 participants) and could not be determined in 83 participants (71 in the MIVI trials and 12 in OASIS).

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654 Table 3: Distribution of MH and ERM status according to width of VMA adhesion among the 949
655 participants who had evaluable measurements for all 3 parameters

	VMA width ≤1500 µm		VMA width >1500 µm		
	ERM absent	ERM present	ERM absent	ERM present	Total
	N (%)	N (%)	N (%)	N (%)	N (%)
VMT	367 (38.7)	158 (16.6)	48 (5.1)	114 (12.0)	687 (72.4)
MH	221 (23.3)	31 (3.3)	7 (0.7)	3 (0.3)	262 (27.6)
Total	**588 (62.0)**	**189 (19.9)**	**55 (5.8)**	**117 (12.3)**	**949 (100.0)**

Note: Percentages in cells represent the proportion of cases vs the total population of 949 participants who had evaluable measurements for the presence of ERM, MH, and broad VMA.
Abbreviations: ERM, epiretinal membrane; MH, vitreomacular traction with macular hole; VMA, vitreomacular adhesion; VMT, vitreomacular traction (without macular hole or ERM).

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657 Table 4: Adverse events of special interest

Adverse event of interest	Control n of 330 (%)	Control, recovered n, (%)[a]	Ocriplasmin n of 737 (%)	Ocriplasmin, recovered n, (%)[a]
Visual impairment	41 (12.4)	21 (51.2)	185 (25.1)	133 (71.9)
Visual impairment (onset 7d)	4 (1.2)	3 (75.0)	124 (16.8)	107 (86.3)
Intraocular inflammation	12 (3.6)	10 (83.3)	74 (10.0)	67 (90.5)
Retinal/macular edema	9 (2.7)	4 (44.4)	60 (8.1)	38 (63.3)
Cataract	25 (7.6)	12 (48.0)	48 (6.5)	22 (45.8)
Intraocular pressure increased	21 (6.4)	19 (90.5)	39 (5.3)	34 (87.2)
Dyschromatopsia	2 (0.6)	2 (100.0)	33 (4.5)	28 (84.8)
Intraocular hemorrhage	10 (3.0)	8 (80.0)	28 (3.8)	20 (71.4)
Retinal detachment	14 (4.2)	11 (78.6)	23 (3.1)	17 (73.9)
Immunogenicity	0 (0.0)	0 (0.0)	13 (1.8)	13 (100.0)

[a]Recovered cases are the proportion of cases who had the adverse event of interest.

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659 Table 5: PubMed search terms (search June 5, 2019)

Search	Query	Items found
#1	Search ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]))	5,734,770
#2	Search ocriplasmin	318
#3	Search (#1 and #2)	114

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661 Table 6: EMBASE search terms (search June 5, 2019)

Search	Query	Results
#1	random*:ab,ti	1,407,087
#2	'health care quality'/exp	2,988,278
#3	clinical NEXT/1 trial*	1,654,644
#4	#1 OR #2 OR #3	4,954,644
#5	'ocriplasmin'/mj	267
#6	#4 AND #5	163

662 Table 7: PICOS criteria

Parameter	Criteria
Population	Adult participants with vitreomacular traction/symptomatic vitreomacular adhesion diagnosed by OCT.
Intervention	Ocriplasmin 125 µg single intravitreal injection.
Comparator	Placebo or sham injection.
Outcomes	Resolution of vitreomacular adhesion at Day 28 and Month 6. Vitrectomy at Month 6. MH closure at Month 6. BCVA increase/decrease of ≥10 ETDRS letters from baseline. BCVA mean change from baseline to Month 6. VFQ-25 score.
Setting/design	Randomized controlled trials with at least 6 months follow-up.

Abbreviations: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study (testing protocol); MH, macular hole; OCT, optical coherence tomography; VFQ-25, National Eye Institute visual function questionnaire, 25-item survey.

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Figure 1: PRISMA study flow diagram

Figure 2: Risk of bias assessment

This Risk of Bias Tool has 7 parameters: 1) random sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other sources of bias, such as those introduced by baseline imbalances. Each parameter was assessed as low risk, high risk, or unclear risk. Abbreviations: VMAR, vitreomacular adhesion resolution.

Figure 3: Vitreomacular resolution, overall and by subgroups

Panel A: Vitreomacular resolution at Day 28; Panel B: Vitreomacular resolution at Month6
Abbreviations: adj, adjusted; bVMA, "broad" vitreomacular adhesion (i.e., adhesion diameter >1500 µm); CI, confidence interval; DR, diabetic retinopathy; ERM, epiretinal membrane; MH, vitreomacular traction with macular hole (without ERM); OR, odds ratio; Phet, P value of χ^2 test for heterogeneity; unadj, unadjusted; VMT, vitreomacular traction (without macular hole or ERM).

Figure 4: Macular hole closure at Month 6

Abbreviations: adj, adjusted; BCVA, best-corrected visual acuity; CI, confidence interval; MH, vitreomacular traction with macular hole (without macular hole or ERM); OR, odds ratio; Phet, P value of χ^2 test for heterogeneity; unadj, unadjusted.

Figure 5: ≥10-letter BCVA increase at Month 6, overall and by subgroups

Panel A: Vitrectomy considered as failure; Panel B: Irrespective of vitrectomy
Abbreviations: adj, adjusted; BCVA, best-corrected visual acuity; bVMA, "broad" vitreomacular adhesion (i.e., adhesion diameter >1500 µm); CI, confidence interval; ERM, epiretinal membrane; EUR, Europe; JPN, Japan; MH, vitreomacular traction with macular hole (without ERM); OR, odds ratio; Phet, P value of χ^2 test for heterogeneity; unadj, adjusted; VMT, vitreomacular traction (without macular hole or ERM).

Figure 6: BCVA ≥10-letter decrease from baseline to Month 6, irrespective of vitrectomy

Abbreviations: adj, adjusted; BCVA, best-corrected visual acuity; CI, confidence interval; ERM, epiretinal membrane; EUR, European; MH, vitreomacular traction with macular hole (without ERM); OR, odds ratio; Phet, P value of χ^2 test for heterogeneity; unadj, unadjusted; VMT, vitreomacular traction (without macular hole or ERM).

Appendix: Supplementary tables and figures

Table S1: Risk of bias – detailed analysis

Table S3: All study eye adverse events up to 200 days post-dose, with outcomes, and early-onset adverse events, by treatment group

Table S4: All study eye serious adverse events up to 200 days post-dose, with outcomes, by treatment group

Supplemental Figure 1: Incidence of vitrectomy at Month 6, overall and by subgroups
Supplemental Figure 2: Mean BCVA change from baseline to Month 6