Research Article

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Journal of **Comparative Effectiveness Research**

Cost–effectiveness analysis of ocriplasmin versus watchful waiting for treatment of symptomatic vitreomacular adhesion in the USA

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Aim: Evaluate the cost–effectiveness of ocriplasmin in symptomatic vitreomacular adhesion (VMA) with or without full-thickness macular hole ≤400 μm versus standard of care. **Methods:** A state-transition model simulated a cohort through disease health states; assignment of utilities to health states reflected the distribution of visual acuity. Efficacy of ocriplasmin was derived from logistic regression models using Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole trial data. Model inputs were extracted from Phase III trials and published literature. The analysis was conducted from a US Medicare perspective. **Results:** Lifetime incremental cost–effectiveness ratio was US$4887 per quality-adjusted life year gained in the total population, US$4255 and US$10,167 in VMA subgroups without and with full-thickness macular hole, respectively. **Conclusion:** Ocriplasmin was cost effective compared with standard of care in symptomatic VMA.

First draft submitted: 16 August 2019; Accepted for publication: 3 January 2020; Published online: 21 January 2020

Keywords: cost • ocriplasmin • symptomatic vitreomacular adhesion • vitreomacular traction

As the eye ages, the vitreous liquefies and separates from the retina. Symptomatic vitreomacular adhesion (VMA), also referred to as vitreomacular traction (VMT), is a condition in which the vitreous remains attached to the macula despite separation elsewhere, exerting traction and resulting in visual distortion and/or decreased visual acuity (VA) [1]. Symptomatic VMA is a potentially vision-threatening condition that can negatively affect patient quality of life [1–3]. Although symptomatic VMA can resolve spontaneously, this occurs in only approximately 11–32% of eyes [4–6]. If traction persists, a macular defect can develop, which can then progress to full-thickness macular hole (FTMH) [1].

In the past, the standard of care (SOC) for symptomatic VMA was watchful waiting (as the adhesion can separate spontaneously in some cases), and pars plana vitrectomy, if the visual dysfunction persists [7,8]. Although vitrectomy is generally successful in terms of anatomical outcomes [9], patients who undergo vitrectomy may achieve only modest gains in VA (<2 Snellen lines on average [10]), and are at risk of experiencing vitrectomy-associated complications, including cataract development in phakic eyes (studies report >80% within 3 years compared with <25% in fellow eyes) [11,12] and postoperative retinal detachment (2.4% of patients) [12]. Pneumatic vitreolysis has

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also emerged as a potential treatment option for symptomatic VMA, although prospective trial data to support efficacy and safety of this option are currently lacking [13]. Ocriplasmin, approved by the US FDA in 2012, is a nonsurgical treatment option for symptomatic VMA [14] that enzymatically cleaves collagen, fibronectin and laminin, thereby dissolving the proteins at the site of adhesion [14]. The approval for ocriplasmin was, in part, based on the results of the Microplasmin for Intravitreous Injection-Traction Release Without Surgical Treatment (MIVI-TRUST) Phase III trials (NCT00781859 and NCT00798317) [3].

In a first-generation health economic model based on the MIVI-TRUST trials, ocriplasmin was shown to be cost effective in the UK for the treatment of VMT [15]. The findings were used to inform health technology recommendations from several countries, including the UK National Institute for Health and Care Excellence (NICE) recommendations based on the Health Technology Appraisal of ocriplasmin [16] and the Canadian Agency for Drugs and Technologies in Health Common Drug Review [17]. Health technology authorities have acknowledged the value of ocriplasmin as a single nonsurgical intervention, which allows retina specialists to treat patients earlier (after a period of observation and when surgery is not yet indicated), hence reducing the risk of vision loss and of future surgical interventions related to the development of post-vitrectomy cataract. With the recent availability of longer term efficacy and safety data and a revised drug acquisition cost, a second-generation health economic model aimed to investigate the 'value for money' of ocriplasmin within the context of the US healthcare setting. To benefit US-based formulary decision makers and other stakeholders, a cost–effectiveness analysis based on local resource utilization and US Medicare cost estimates was warranted [18]. The objective of this analysis was to evaluate the cost–effectiveness of a single intravitreal injection of ocriplasmin for the treatment of symptomatic VMA with or without (±) FTMH ≤400 µm compared with SOC from a US government payer perspective. These analyses were primarily informed by the Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole (OASIS) study (NCT01429441) [2], a Phase IIIb, randomized, 24-month clinical trial conducted in the USA.

Materials & methods

This economic research was conducted in accordance with the principles of good practice for health economic evaluation published by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), the recommendations for the conduct of cost–effectiveness analysis developed by the US-based Panel on Cost–Effectiveness in Health and Medicine, as well as the UK-based NICE *Guide to the Methods of Technology Appraisal 2013* [19–22].

Decision problem

Population & subgroups

The cost–effectiveness analysis was applied to a population of patients with symptomatic VMA ± FTMH ≤400 µm without epiretinal membrane. This overall population was consistent with that in the OASIS trial [2]. Subgroup analyses were performed based on the presence of FTMH at baseline, namely symptomatic VMA without FTMH (abbreviated as VMA – FTMH) or symptomatic VMA with FTMH ≤400 µm (abbreviated as VMA + FTMH). These subgroups were chosen because the treatment goal in patients with a concurrent FTMH is closure of FTMH, while in patients without FTMH, the goal is to resolve the VMA.

Intervention & comparator

The intervention was a single intravitreal injection of ocriplasmin 0.125 mg. The comparator was SOC, defined as observation or watchful waiting followed by vitrectomy, if needed. Vitrectomy could also be performed after ocriplasmin injection, if needed. In the current model, SOC corresponded to the sham treatment group in the OASIS trial.

Outcome measures

The primary model outcome was the incremental cost–effectiveness ratio (ICER) for the overall population and for each subgroup, expressed as dollars per quality-adjusted life year (QALY), which may be compared with a threshold value (willingness-to-pay for a unit of health outcome). Additional outcome measures included the number of vitrectomies and time spent with blindness. The model accounted for short term costs and impact on health-related quality of life and downstream consequences. The model estimated the average patient life span, adjusted for the patients' quality of life and estimated costs associated with the treatment of interest versus comparator.

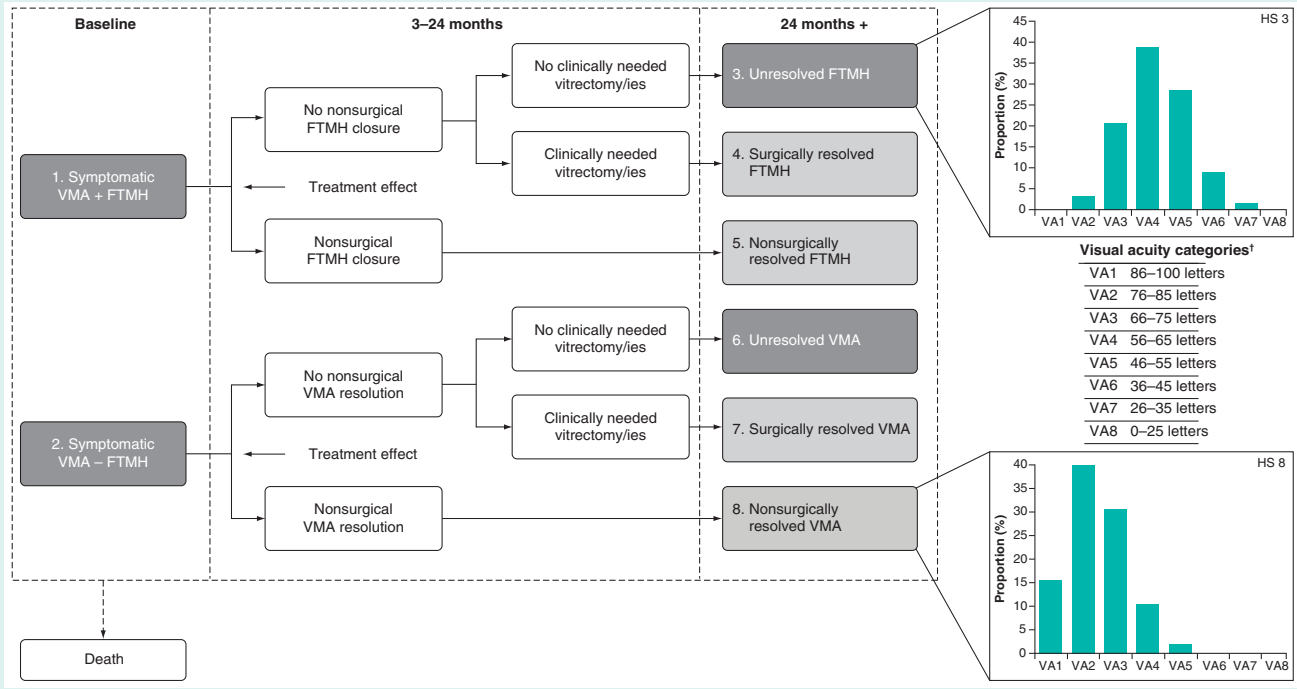

Figure 1. Structure of the partitioned vision distribution model. Eight mutually exclusive disease health states are defined by VMA resolution, FTMH status and vitrectomy history. Patients within each disease health state are distributed across eight VA categories based on BCVA ETDRS letter score. Patients transition between disease health states based on clinical events, such as VMA resolution, FTMH closure and the need for vitrectomy. Dark shaded boxes refer to diseased (unresolved) health states; light shaded boxes refer to cured (resolved) health states at 24 months and beyond.
†Visual acuity categories are based on the 0- to 100-letter ETDRS vision scale.
BCVA: Best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; FTMH: Full-thickness macular hole; VA: Visual acuity; VMA: Vitreomacular adhesion.

Analysis perspective

The base-case analysis was conducted from the viewpoint of a US government payer, more specifically the Medicare perspective, and considered current and future costs related to the condition [21]. Direct medical care costs included healthcare resources consumed in the provision of the interventions or in dealing with the side effects linked to it. Cost categories included pretreatment costs (optical coherence tomography [OCT], physician consultations for the diagnosis of the condition), treatment costs (cost of intravitreal injection, drug cost, vitrectomy procedure) including two postprocedure follow-up visits, disease-related monitoring costs in case of persistent disease, costs associated with the management of adverse events (AEs) and costs associated with blindness [21].

Model structure

A state-transition model was used to simulate a cohort of patients through eight disease health states throughout the model time horizon (Figure 1). Cost–effectiveness analyses were performed using a short-term (24 months) and lifetime horizon. Vision gradually deteriorates over time, and a lifetime horizon was necessary to assess full impact on costs and outcomes. Utility-adjusted time spent in each health state was summed over the model time horizon to provide estimates of expected QALYs when treated with ocriplasmin or SOC.

In the short-term phase (months 0–24), the starting cohort was simulated using 3-month cycles reflecting transitions between disease health states observed in the OASIS study. The long-term phase started after month 24 and was used to extrapolate long-term clinical (vision) and cost outcomes using annual cycles. Natural history and real-life studies in symptomatic VMA indicate that the majority of clinical events (resolution of VMA, closure of FTMH) or interventions such as vitrectomy occur within 24 months after diagnosis or treatment, respectively [4,23]. Hence, in the extrapolation phase, no further transitions between disease health states were taken into account.

Table 1. Descriptions of the eight mutually exclusive health states.

Health state	Health state description
HS1: VMA + FTMH	Patients with symptomatic VMA with FTMH at baseline.
HS2: VMA – FTMH	Patients with symptomatic VMA without FTMH at baseline.
HS3: Unresolved VMA + FTMH	Patients with baseline FTMH and with unresolved FTMH who did not undergo vitrectomy. Patients may move into this health state if they received ocriplasmin or SOC treatment at baseline but no vitrectomy thereafter. Symptomatic VMA was assumed to persist with unresolved FTMH.
HS4: Surgically resolved FTMH	Patients with baseline FTMH who achieved FTMH closure after vitrectomy. Patients may move into this health state if they received ocriplasmin or SOC treatment at baseline and underwent vitrectomy thereafter. Symptomatic VMA was assumed to be resolved with FTMH closure.
HS5: Nonsurgically resolved FTMH	Patients with baseline FTMH who achieved FTMH closure after ocriplasmin or SOC treatment. Symptomatic VMA was assumed to be resolved with FTMH closure.
HS6: Unresolved VMA – FTMH	Patients without baseline FTMH and with unresolved (persistent) symptomatic VMA who did not undergo vitrectomy. Patients may move into this health state if they received ocriplasmin or SOC treatment at baseline but no vitrectomy thereafter.
HS7: Surgically resolved VMA – FTMH	Patients without baseline FTMH who achieved symptomatic VMA resolution after vitrectomy. Patients may move into this health state if they received ocriplasmin or SOC treatment at baseline and underwent vitrectomy thereafter.
HS8: Nonsurgically resolved VMA – FTMH	Patients without baseline FTMH who achieved symptomatic VMA resolution after ocriplasmin or SOC treatment.

FTMH: Full-thickness macular hole; HS: Health state; SOC: Standard of care; VMA: Vitreomacular adhesion.

However, to reflect the expected natural decline in vision over time, an annual vision decrement was applied, as observed in several population-based studies [24–27].

Disease health states

The model's mutually exclusive disease health states and possible transitions between these states are shown in Figure 1, with detailed descriptions of each disease health state provided in Table 1. Patients were initially allocated to one of two health states, in other words, VMA – FTMH or VMA + FTMH, depending on whether FTMH was present at baseline. Transitions between disease health states were determined by the probability of VMA resolution, FTMH closure and the occurrence of vitrectomy, and were estimated based on patient-level data from the OASIS clinical trial (see clinical inputs section, clinical event probabilities) [2]. Unless otherwise stated, all analyses used the OASIS full analysis set. Rates of nonsurgical symptomatic VMA resolution/FTMH closure were assessed at Month 3, the time at which the incidence of VMA resolution/FTMH closure reached a steady state in OASIS. The number of vitrectomies occurring over each 3-month cycle was determined by interpolating the total number of vitrectomies observed at Month 24 and assuming an exponential distribution. Depending on occurrence of nonsurgical VMA resolution/FTMH closure, and whether a vitrectomy was needed, the patient ended up in one of the six health states at Month 24 (Figure 1). Beyond Month 24, there were no further disease health state transitions (i.e., the cohort entered its long-term extrapolation phase) except for death.

Partitioned vision distribution (visual acuity distribution within health states)

To match disease health states with quality of life outcomes (utilities), a set of mutually exclusive best-corrected visual acuity (BCVA) categories were modeled. VA categories were defined as bands of Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Six sequential VA categories (VA2–VA7) were defined to be ten ETDRS letters apart (Figure 1) to ensure that the category ranges were clinically distinct, yet able to capture smaller improvements in VA. In addition, a change of ten letters or more is considered clinically meaningful [28] and is consistent with the secondary end point in the ocriplasmin clinical trial program [2,3]. Blindness was represented by a letter count of $\leq$35 letters in the better-seeing eye (BSE; VA7 and VA8, Figure 1), consistent with other economic models in ophthalmology [29] and studies that have estimated costs associated with severe vision loss [30,31].

This state-transition model was structured as a partitioned vision distribution model such that each disease health state was associated with a unique distribution of VA categories 1–8 (Figure 2), represented by a beta distribution with parameters estimated from the OASIS trial BCVA data.

Long-term change in vision distributions

In the extrapolation phase, patients were modeled to experience a long-term decline in vision, assumed independent of treatment. This decrement was modeled as an annual (mean) decline in letters and was assumed to be linear

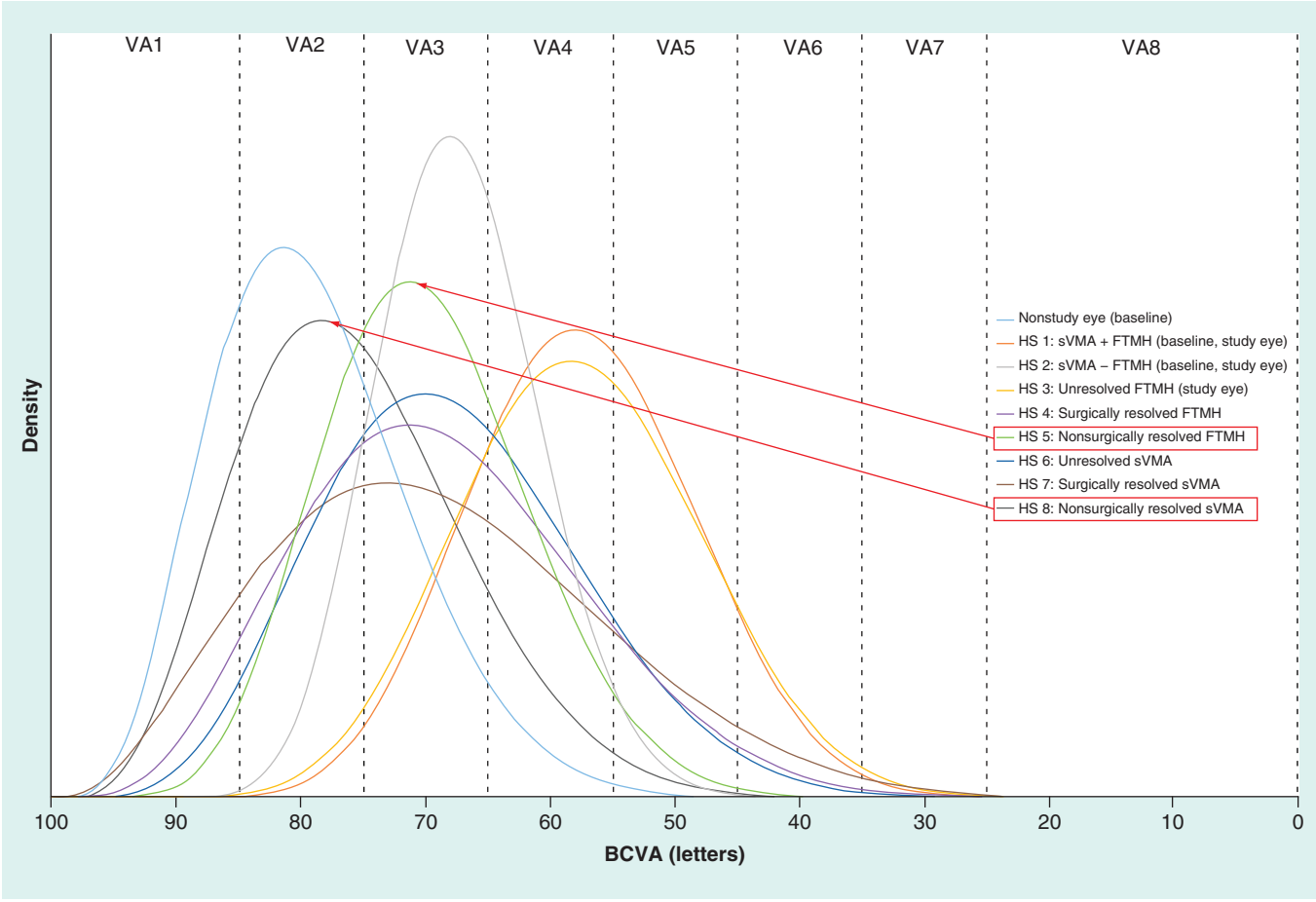

Figure 2. Partitioned vision distribution. A parametric approach was used to model the BCVA distributions associated with each disease health state. Probability density functions determined the proportion of patients across the VA categories. Red boxes highlight the 'better' (i.e., nonsurgically resolved) health states, which have a higher proportion of patients with normal or near-normal VA.
BCVA: Best-corrected visual acuity; FTMH: Full-thickness macular hole; sVMA: Symptomatic vitreomacular adhesion; VA: Visual acuity.

in time; a nonlinear decline of vision was not considered in the absence of evidence. This decrement resulted in the distribution of VA categories changing over time (Supplementary Figure 1). This rate of long-term vision decline depended on the disease health state of each patient at Month 24. Hence, long-term vision was a function of whether a patient had a FTMH at baseline, whether the condition was resolved, and whether that resolution was achieved through a nonsurgical or surgical intervention. Because of differences in disease progression, VA in unresolved eyes declined at a faster rate than VA in resolved eyes. Further, based on expert opinion, the annual VA decrement in eyes with FTMH occurred at a faster pace than in eyes without FTMH. The vision decrement in resolved eyes was set to be equal to VA decline in the age-matched general population (see clinical inputs section, BCVA).

Global vision & utilities

Global vision is a function of both eyes; hence, study-eye (SE) and non-study-eye (NSE) VA were tracked throughout the model time horizon. Both SE and NSE VA distributions were then combined into a joint vision distribution to represent global vision. These were combined multiplicatively, assuming that SE and NSE VA were independent. Utilities were therefore also specified as a function of both eyes. This joint distribution allowed us to distinguish between BSE and worse-seeing eye (WSE), such that published utility values could be applied to this BSE/WSE distribution to estimate patient quality of life outcomes (also see clinical inputs section, utilities). Supplementary Figure 2 illustrates the joint SE/NSE vision distribution used to assign utility values as a function of global vision.

For the SE, VA distributions specific for each disease health state were modeled, however, for the NSE no disease health states were modeled because the NSE was assumed to be latent (no symptomatic VMA). The baseline NSE VA category distribution was estimated from OASIS baseline data and the NSE was further exposed to a natural VA decline. (also see clinical inputs section, BCVA).

Model parameters & data inputs

Clinical inputs

Clinical event probabilities & response to treatment

The effect of treatment with ocriplasmin was modeled through a single parameter for each patient subgroup, in other words, the probability of achieving nonsurgical VMA resolution in the VMA – FTMH subgroup or nonsurgical FTMH closure in the VMA + FTMH subgroup. Logistic regression analysis including treatment was performed on OASIS trial data to estimate the probabilities of these outcomes separately in the two subgroups.

When estimating the probability of VMA resolution, the analysis was based on VMA – FTMH patients at baseline (n = 144) using the model specification:

$$\text{logit}(\pi_i) = \beta_0 + \beta \ \ TRT_i$$

with logit (.) the logit function, π_i the probability of nonsurgical VMA resolution for a patient in treatment group i, β_0 is the intercept, β is the treatment effect and TRT_i is a binary variable denoting whether patient i belongs to the ocriplasmin or sham group. The observed number of patients with resolution in treatment group Y_i, from the total number of patients n_i is assumed to be binomially distributed, so that $Y_i \sim B\ (n_i, \pi_i)$, *where B is binomial distribution*. The probability of nonsurgical VMA resolution for patients receiving ocriplasmin was 56%, versus 21% for sham.

When estimating the probability of FTMH closure, the analysis was based on the patients with FTMH at baseline (n = 76) using the same model specification, but with a different end point in other words, NS FTMH closure. The probability of nonsurgical FTMH closure for patients receiving ocriplasmin was 28%, versus 8% for sham. The output of the logistic regression analyses for nonsurgical VMA resolution and FTMH closure is summarized in Supplementary Table 1.

The probability of vitrectomy was dependent on having unresolved symptomatic VMA or unresolved FTMH, hence a need for surgical intervention, and was assumed to be independent of treatment. OASIS trial data were used to estimate the probability of vitrectomy in the model (Supplementary Table 2). In the OASIS study [2], it was observed that the probability of vitrectomy was dependent on having FTMH at baseline and was therefore estimated separately in the two subgroups. In patients with FTMH without nonsurgical closure, 86.7% underwent a vitrectomy (of the 60 patients with FTMH at baseline who did not experience FTMH closure, a total of 52 underwent a vitrectomy during the 24-month observation). Based on this sample of VMA + FTMH patients, the average number of vitrectomies to achieve FTMH closure was 1.23; therefore, all FTMH vitrectomy-related costs and effects were scaled by this factor. In patients without FTMH and without nonsurgical VMA resolution, 27.5% underwent a vitrectomy (of the 80 patients without FTMH at baseline who did not experience VMA resolution, a total of 22 underwent a vitrectomy during the 24-month observation). Based on this sample of VMA – FTMH patients, the average number of vitrectomies to achieve VMA resolution was 1.04; therefore, all VMA vitrectomy-related costs and effects were scaled by this factor. In terms of timing, the number of vitrectomies that occurred over each 3-month model cycle was determined by interpolating the total number of vitrectomies observed in the 24 months assuming an exponential distribution.

Mortality

During any transition cycle, country-specific general mortality probabilities were used to determine the transition to the absorbing health state death. The 2012 US national life tables [32] were used to capture background mortality. Mortality incidences used in the model were weighted by gender (Supplementary Table 3 [32]).

BCVA in the short-term phase

BCVA distributions for the SE were modeled for each disease health state, including those at baseline (HS1 and HS2) and those at 24 months (HS3–HS8; Table 2). These vision distributions were assumed to be disease health state-specific and independent of treatment.

Table 2. Summary of best-corrected visual acuity distributions included in the model.

Time horizon	Health state	Mean BCVA	Source	Standard deviation	Source
Baseline distribution	Nonstudy eye	79.13	OASIS observed data fitted to minimized squared error	7.90	OASIS observed data fitted to minimized squared error
	HS1: VMA + FTMH	57.82	OASIS observed data	9.81	OASIS observed data
	HS2: VMA – FTMH	66.00	OASIS observed data	8.29	OASIS observed data
24-month distribution (study eye)	HS3: Unresolved VMA + FTMH	57.53	Linear regression model	9.60	OASIS observed data
	HS4: Surgically resolved FTMH	68.37	Linear regression model	11.26	OASIS observed data
	HS5: Nonsurgically resolved FTMH	70.12	Linear regression model	8.23	OASIS observed data
	HS6: Unresolved VMA – FTMH	67.89	Linear regression model	10.39	OASIS observed data
	HS7: Surgically resolved VMA – FTMH	69.88	Linear regression model	13.24	OASIS observed data
	HS8: Nonsurgically resolved VMA – FTMH	75.55	Linear regression model	9.00	OASIS observed data

BCVA: Best-corrected visual acuity; FTMH: Full-thickness macular hole; HS: Health state; OASIS: Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole; VMA: Vitreomacular adhesion.

Due to the relatively small number of patients in some of the disease health states, BCVA was estimated via modeling that enabled leveraging more data to inform the BCVA estimate of each disease health state, rather than using only the OASIS study data.

Linear regression models were used to estimate these SE BCVA distributions. Because of differences in treatment goals (i.e., VMA resolution, FTMH closure) and differences in mean baseline BCVA (66 letters, 57 letters), a separate regression model was fitted for disease health states associated with VMA – FTMH (HS6, HS7 and HS8, n = 143) versus VMA + FTMH (HS3, HS4 and HS5, n = 76).

In patients without FTMH, the following model was used to estimate BCVA for patient *i* at visit *j*:

$$BCVA_{i,j} = \beta_0 + \beta_b \ Baseline \ BCVA_i + \beta_{s1} \ VMA \ status1_{i,j} + \beta_{s1} \ VMA \ status2_{i,j} + e_{i.j}$$

with *VMA status 1*$_{i,j}$ equal to 1 when nonsurgical symptomatic VMA resolution for patient *i* by visit *j*, otherwise zero and *VMA status 2*$_{i,j}$ equal to 1 when surgical symptomatic VMA resolution for patient *i* by visit *j*, otherwise zero, and $e_{i,j}$ is the normally distributed random error term. Model regression coefficients indicated that nonsurgical VMA resolution was associated with a approximately eight-letter improvement over unresolved VMA.

In patients with FTMH, BCVA was estimated using the same model specification, substituting FTMH status for VMA status. Model regression coefficients indicated that nonsurgical FTMH closure was associated with a approximately 12–13-letter improvement over non-FTMH closure. The output of the BCVA regression model coefficients in VMA – FTMH and VMA + FTMH patients is summarized in Supplementary Table 4.

Long-term BCVA decline

The values for vision decrements over time were informed by several sources. Our estimate of vision decrement in resolved eyes was based on the Blue Mountains Eye Study, which investigated the long-term change in VA in an older Australian population over a 15-year period [24]. Results indicated a weighted average mean VA decline of 6.85 letters over 15 years, or approximately 0.46 letters per year. For the NSE (no symptomatic VMA), we assumed that VA decline over time was equal to that of the age-matched general population (hence, the same decrement as for the resolved SE).

To estimate the vision decrement in eyes with unresolved VMA + FTMH, the initial VA versus final VA data from the study by Hikichi *et al.* were used [5]. The mean decline in VA over the 60-month follow-up time was estimated at 17.87 letters. Assuming a linear decline in vision over this 60-month period, a mean VA decline of 3.57 letters per year was estimated.

For eyes with unresolved VMA – FTMH, data from a study by Jackson *et al.* were used to inform annual mean VA decline. This decline was estimated over a period of 2.8 months and was upscaled accordingly to a period of 1 year (assuming a linear decline), resulting in an estimated mean annual VA decline of 2.5 letters [7]. We found no

Table 3. Utility values for each visual acuity category.

VA category	ETDRS midpoint	Equivalent logMAR	BSE/Utility
VA1 (86–100 ETDRS letters)	90.5†	-0.11	0.89
VA2 (76–85 ETDRS letters)	80.5	0.09	0.79
VA3 (66–75 ETDRS letters)	70.5	0.29	0.72
VA4 (56–65 ETDRS letters)	60.5	0.49	0.65
VA5 (46–55 ETDRS letters)	50.5	0.69	0.57
VA6 (36–45 ETDRS letters)	40.5	0.89	0.50
VA7 (26–35 ETDRS letters)	30.5	1.09	0.43
VA8 (0–25 ETDRS letters)	20.5†	1.29	0.29

†These midpoints were retained to maintain a ten-letter difference throughout the scale when applying utilities. A midpoint is used to capture the central tendency of patients in the VA health state. If we look at every patient within the VA category 0–25 EDTRS, more patients will have VA closer to 25 letters, than to 0 letters (skewed distribution). This is likely a conservative assumption, as if we lowered the VA category representing blindness to 12.5, a much lower utility value for blindness would be obtained, which would benefit the more effective treatment, ocriplasmin.
BSE: Better-seeing eye; ETDRS: Early Treatment Diabetic Retinopathy Study; logMAR: Logarithm of the Minimum Angle of Resolution; VA: Visual acuity.

Table 4. Utility values as a function of visual acuity in better-seeing eye and worse-seeing eye.

		BSE							
	Visual acuity	VA1	VA2	VA3	VA4	VA5	VA6	VA7	VA8
WSE	VA1	**0.89**	–	–	–	–	–	–	–
	VA2	0.79	**0.79**	–	–	–	–	–	–
	VA3	0.72	0.72	**0.72**	–	–	–	–	–
	VA4	0.65	0.65	0.65	**0.65**	–	–	–	–
	VA5	0.57	0.57	0.57	0.57	**0.57**	–	–	–
	VA6	0.50	0.50	0.50	0.50	0.50	**0.50**	–	–
	VA7	0.43	0.43	0.43	0.43	0.43	0.43	**0.43**	–
	VA8	0.29	0.29	0.29	0.29	0.29	0.29	0.29	**0.29**

Utility values on the lead diagonal (in bold) are the BSE/utility values from the regression analysis assumed to correspond to global vision (i.e., applied to VA categories where vision is the same in both eyes.
BSE: Better-seeing eye; VA: Visual acuity; WSE: Worse-seeing eye.

evidence to inform how long the vision decrement would continue in unresolved eyes. Following expert opinion, it was assumed to limit this annual decline to the first 5 years of the extrapolation phase.

Utilities

Utilities were applied depending on the VA of both the BSE and the WSE. More specifically, utility values associated with VA were derived from a study that used contact lenses to simulate, in the general population, age-related macular degeneration (ARMD) health states (reading limit, legal blindness and untreated ARMD) for which time-trade off (TTO) utility values were elicited [33]. Czoski-Murray *et al.* used regression analyses to estimate the relationship between VA (logMAR) in the BSE and time-trade off values [33]. The age-adjusted regression equation was used to estimate the utility values associated with our model VA categories, assuming an age of 69.1 years and the BCVA midpoints for each VA category (Table 3).

$$\text{TTO utility} = 0.86 - 0.368(\text{logMAR}) - 0.001(\text{age})$$

Given that participants in the Czoski-Murray study wore lenses of the same kind in both eyes, the BSE/utility values estimated from the regression analysis were assumed to correspond to global vision (i.e., the same VA in both eyes). Hence, the BSE utilities reported in Table 3 were applied to the VA categories in which vision was the same in both eyes (diagonal). To attach utility values to the joint distribution of both eyes, a relationship between the WSE and utility was assumed. We assumed that an equivalent change in VA either in the BSE or WSE would generate an equivalent change in utility (i.e., a change from VA1 to VA2 in the WSE will be valued [in terms of utility] at 100% of the same change in the BSE). These assumptions allowed for the utility estimates for all combinations of BSE/WSE (Table 4).

Table 5. Summary of costs associated with treatment†.

Treatment	Pretreatment costs	Treatment costs‡	Post-treatment costs	Total cost
Ocriplasmin	US$131.76	US$2627.70	US$263.52	US$3022.98
SOC	US$131.76	US$0.00	US$263.52	US$395.28
Vitrectomy§ – VMA – FTMH	US$131.76	US$3819.29	US$263.52	US$4214.57
Vitrectomy§ – VMA + FTMH	US$131.76	US$3909.80	US$263.52	US$4305.08

† All costs are sourced from a published analysis by Yu *et al.*, which was based on data from the Centers for Medicare & Medicaid Services and reported in 2018 US dollars [38,39].
‡ Treatment costs include physician, facility, drug and procedure costs. The drug cost of ocriplasmin was based on average sales price per unit reported by CMS (2018 Medicare fee schedule of allowable charges) [39].
§ Costs per vitrectomy surgery.
CMS: Centers for Medicare and Medicaid Services; FTMH: Full-thickness macular hole; SOC: Standard of care; VMA: Vitreomacular adhesion.

Table 6. Adverse event unit costs†.

Parameter	Unit cost (per occurrence)
Cataract	US$2154.06
Retinal detachment	US$3791.02
Vitreous hemorrhage	US$1745.85
Cystoid macular edema	US$809.00
Retinal break	US$1555.55
Macular hole	US$3413.11
Retinal tear	US$1555.55

† All costs are sourced from a published analysis by Yu *et al.* which was based on data from the Centers for Medicare & Medicaid Services and reported in 2018 US dollars [38; Appendix 2]. The following adverse events were not associated with any costs and therefore were not listed: night blindness, transient blindness, iridocyclitis, retinal toxicity, vitreous floaters, photopsia, visual impairment, chromatopsia, blurred vision, photophobia and metamorphopsia.

In addition, a disutility was associated with specific events such as the occurrence of the AEs retinal detachment, vitreous hemorrhage and cataract [34–36]; presence of metamorphopsia due to unresolved disease [37]; and disutility associated with vitrectomy (based on expert opinion). Supplementary Table 2 documents the decrement value and the (limited) duration of the applied disutility.

AEs

AEs were modeled for each treatment (i.e., ocriplasmin and sham), and for vitrectomy. Adverse event (AE) incidences observed with treatment were applied in the first model cycle. This was justified on the basis that treatment with ocriplasmin consists of a single intravitreal injection administered at model entry. The model allowed for vitrectomy to occur in the first 24 months of the simulation; therefore, AE incidences for vitrectomy were applied throughout the first 8 model cycles, at the time the surgery was modeled to occur.

Treatment-specific AE rates were sourced from the OASIS clinical trial. AEs with an incidence of 5% or greater and all serious AEs were included. Most AE incidences associated with vitrectomy were sourced from a published analysis by Yu *et al.* that used Centers for Medicare and Medicaid Services (CMS) data (2008–2012 Outpatient and Carrier [Part B] 5% standard analytical files) [38], except for the AE rate of cataract surgery, which is a longer-term risk associated with vitrectomy. The rate of postvitrectomy cataract surgery was sourced from studies by Jackson *et al.* that reported complication rates over a 3-year period [7,12]. The AE rates for ocriplasmin, sham and vitrectomy and data sources are shown in Supplementary Table 2.

Economic inputs

Cost inputs included pretreatment, treatment and post-treatment costs (Table 5 [38,39]) and AE costs (Table 6 [38]). Pretreatment costs consisted of the cost of one physician visit and OCT scan. Treatment costs comprised physician, facility, drug acquisition and injection administration for ocriplasmin and physician and facility fee for a vitrectomy procedure as reported by Yu *et al.* (Supplementary Table 2 [38]). Post-treatment cost included two postprocedure follow-up visits [38]. Disease-related monitoring included costs for patients with an unresolved condition, in other words, unresolved VMA or unresolved FTMH. AE unit cost represented the cost per event for up to 2 years [38].

Table 7. Model assumptions.

Dimension	Model assumptions
Disease health states	FTMH closure was the primary end point of interest for patients with FTMH at baseline, and upon closure of the FTMH, the symptomatic elements of VMA/VMT were resolved.
	Symptomatic VMA resolution/closure of FTMH occurred within 3 months of baseline, if applicable.
	Patients who opted for surgery had successful surgical resolution of their underlying symptomatic VMA/FTMH (although not necessarily on their first vitrectomy).
	The patient cohort was simulated in the short-term model (with a cycle length of 3 months) for a period of 2 years. Post 2 years, no further disease health state transitions took place and the model entered its long-term extrapolation phase (with an annual cycle length).
	No transitions between disease health states were possible during the long-term period (beyond 24 months).
Vision health states	A parametric approach (beta distribution) to model the vision health state distributions was a suitable approach.
	The application of visual outcomes to disease health states was treatment independent (i.e., there was no vision difference/benefit to being in a disease health state depending on which treatment had been administered previously).
	The nonstudy eye was latent (i.e., it had no disease activity or involvement with symptomatic VMA); and therefore, no disease health states were modeled for the nonstudy eye.
	Patients with unresolved symptomatic VMA experienced a faster rate of long-term BCVA decline compared with resolved eyes to reflect the progressive nature of the disease.
	Beyond 60 months, BCVA of patients with unresolved symptomatic VMA/FTMH declined at the same rate as in the general population/resolved eyes.
	Study eyes that were resolved of symptomatic VMA and were free of a FTMH (i.e., HS4, 5, 7 and 8) experienced mean BCVA decline in line with that of the age-matched general population.
	Long-term BCVA decline was not affected by whether a patient had achieved surgical or nonsurgical VMA resolution/FTMH closure.
	For the nonstudy eye, mean BCVA decline over time was equal to that of the age-matched general population.
	Long-term BCVA decline was linear in time.
Vitrectomy	Vitrectomy occurred only in Months 3, 6, 9, 12, 15, 18, 21 and 24 (i.e., no vitrectomies occurred beyond this point).
	The number of vitrectomies occurring over each 3-month cycle was interpolated using an exponential distribution.
	The likelihood of vitrectomy, conditional on the absence of nonsurgical VMA resolution/FTMH closure, was the same for all treatments.
Utilities	Changes in BCVA in the worse-seeing eye carried the same impact (100%) on utilities as an equivalent change in BCVA in the best-seeing eye.
Costs	The cost for diagnosis was the same for all treatments.
	Treatment with ocriplasmin and SOC incurred the same short-term post-treatment follow-up costs.

BCVA: Best-corrected visual acuity; FTMH: Full-thickness macular hole; HS: Health state; SOC: Standard of care; VMA: Vitreomacular adhesion; VMT: Vitreomacular traction.

Total costs associated with AEs were estimated by applying the AE rates to the distribution of patients across the health states to obtain the number of AEs per cycle; the number of AEs was then multiplied by the AE unit cost.

The cost of blindness was estimated at US$21,813 including direct medical costs only [40], and was applied to eyes in VA7 and VA8. Total cost of blindness for each treatment was calculated by multiplying the total number of years with blindness by the cost per year of experiencing blindness.

Costs of physician office eye visits, vitrectomy procedures and ocriplasmin injection administration were based on the published analysis by Yu *et al.*, which incorporated CMS payment schedules for 2018 [38]. The drug cost of ocriplasmin was based on average sales price per unit reported by CMS (2018 Medicare fee schedule of allowable charges) [39]. All costs were reported in 2018 US dollars [38]. Costs and outcomes were discounted at an annual rate of 3% [41].

Base-case analysis & key model assumptions

Our base-case analysis presented the results obtained from the economic evaluation with the most likely or preferred set of assumptions and input values described above. Our sensitivity analyses then explored how the model results deviate from those of the base-case analysis when input values and/or modeling assumptions are altered. Key assumptions of the base-case model are shown in Table 7. In the base-case analysis, the mean age was set at 69.1 years, and 67% of the population was taken to be female, per the OASIS trial population [2].

Sensitivity analyses

The level of confidence and uncertainty were tested by examining the sensitivity of the model results to changes in its inputs (parameters) at the lifetime and 2-year time horizon. We performed sensitivity analyses to examine

Table 8. Base-case analysis discounted results per patient at the lifetime and 2-year horizon[†].

Analysis	Outcome	VMA ± FTMH		VMA – FTMH		VMA + FTMH	
		Ocriplasmin	SOC	Ocriplasmin	SOC	Ocriplasmin	SOC
Lifetime horizon							
Values accrued	– QALYs (total)	8.34	7.98	8.42	7.95	8.18	8.06
	– Costs (US$, total)	US$5864	US$4133	US$4279	US$2276	US$8868	US$7653
ICER	Cost (US$) per QALY	–	US$4887	–	US$4255	–	US$10,167
Probability of being cost effective at[‡]:	– US$50,000 per QALY[§]	96.3%		96.2%		81.1%	
	– US$100,000 per QALY[§]	97.1%		97.2%		86.2%	
2-year horizon							
Values accrued	– QALYs (total)	1.29	1.24	1.34	1.28	1.20	1.16
	– Cost (US$, total)	US$5864	US$4133	US$4279	US$2275	US$8868	US$7653
ICER	Cost (US$) per QALY	–	US$34,657	–	US$37,527	–	US$37,535
Probability of being cost effective at[‡]:	– US$50,000 per QALY[§]	68.8%		64.2%		46.6%	
	– US$100,000 per QALY[§]	91.6%		88.4%		71.0%	

[†]Discounting at 3% per year for costs and outcomes.
[‡]Based on probabilistic sensitivity analysis (cost–effectiveness acceptability curve).
[§]Based on commonly accepted ICER willingness-to-pay thresholds defined by Institute for Clinical and Economic Review.
Model outcomes for time spent in blindness are not reported because the simulation generated a negligible number of accumulated blind years. Patients were rarely classified as being blind defined as <36 letters in the BSE.
BSE: Best-seeing eye; FTMH: Full-thickness macular hole; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year; SOC: Standard of care (watchful waiting followed by vitrectomy, if needed); VMA: Vitreomacular adhesion.

the influence of uncertainties in the base-case model inputs and to judge the robustness of the findings. Sensitivity analyses included one-way (where each parameter is varied individually to isolate the consequences of the parameter on the results of the study) and probabilistic sensitivity analyses (drawing values for each parameter from its uncertainty distribution at the same time), in which input parameters were varied based on their 95% CIs. A specific distribution was defined for each parameter where the mean of the distribution was typically equal to the point estimate, and the standard error set according to available distributional information provided in the original source. If distributional information was not available, the standard error was assumed to be 20% of the mean estimate.

Results

Base-case analysis

The model estimated that ocriplasmin is cost effective compared with SOC at the lifetime horizon (Table 8). In patients with VMA ± FTMH ≤400 μm (overall population), ocriplasmin treatment was associated with an incremental gain of 0.35 QALY and cost of US$1731, corresponding to an ICER of US$4887 per QALY gained. In patients with VMA – FTMH, ocriplasmin treatment was associated with an incremental gain of 0.47 and cost of US$2003, corresponding to an ICER of US$4255 per QALY gained. In patients with VMA + FTMH, ocriplasmin treatment was associated with an incremental gain of 0.12 and cost of US$1215, corresponding to an ICER of US$10,167 per QALY gained.

In the overall population, the average number of vitrectomies was 0.34 with ocriplasmin versus 0.48 with SOC. The average number of vitrectomies with ocriplasmin versus SOC was 0.12 and 0.22, respectively, in patients with VMA – FTMH, and 0.75 versus 0.97 in patients with VMA + FTMH. The estimated number of vitrectomies did not change from the 2-year horizon to the lifetime horizon.

Ocriplasmin was also cost effective at an alternative time horizon of 2 years (consistent with the OASIS study), though costs per QALY gained were higher than that of the lifetime horizon (Table 8), with an ICER of US$34,657 per QALY gained for patients with VMA ± FTMH ≤400 μm, US$37,527 for patients with VMA – FTMH and US$37,535 for patients with VMA + FTMH.

Probability of being cost effective

The probability of being cost effective at the US willingness-to-pay thresholds of US$50,000 and US$100,000 was examined at the lifetime horizon and 2-year horizon for the overall population and the subgroups (Table 8). At

the lifetime horizon, in patients with VMA ± FTMH and in the subgroup of patients with VMA – FTMH, the probability of ocriplasmin being cost effective at US willingness-to-pay thresholds of US$50,000 and US$100,000 per QALY was >96%. The probability of ocriplasmin being cost effective in the subgroup of patients with VMA + FTMH was 81.1% at the US$50,000 and 86.2% at the US$100,000 willingness-to-pay thresholds. At the 2-year horizon, the probability of being cost effective was lower than at the lifetime horizon for the overall population and both subgroups. Similar to what was observed with the lifetime horizon, the probability of being cost effective at the 2-year horizon was lowest in the subgroup of patients with VMA + FTMH.

Uncertainty analysis

We performed uncertainty analyses at the lifetime and 2-year time horizons for all patient populations. At the lifetime horizon, the one-way sensitivity analysis demonstrated that in the overall population, the top three influential inputs were the probability of nonsurgical VMA resolution rate with watchful waiting, the unit cost of ocriplasmin treatment, and nonsurgical FTMH closure with watchful waiting (Supplementary Figure 3). The cost–effectiveness scatter planes analysis at the lifetime horizon demonstrated that ocriplasmin resulted in additional QALYs gained at additional cost when compared with SOC (Supplementary Figure 4).

At the 2-year time horizon, the one-way sensitivity analysis demonstrated that in the overall population, the top three influential inputs were nonsurgical FTMH closure rate with watchful waiting, nonsurgical VMA resolution rate with watchful waiting, and the unit cost of ocriplasmin (Supplementary Figure 5). The cost–effectiveness scatter planes analysis at the 2-year time horizon demonstrated that ocriplasmin resulted in additional QALYs gained at additional cost when compared with SOC (Supplementary Figure 6). The benefits of ocriplasmin treatment were linked to sustained long-term improvement in BCVA when compared with SOC. Thus, the shorter the time horizon, the higher the cost per QALY gained with ocriplasmin.

Model validation

To assess model accuracy, we compared the changes in BCVA from the OASIS clinical trial with the BCVA values generated from the partitioned vision model. The model estimates were mostly consistent with observed BCVA values across disease health states, though a couple of health states (HS3, HS5) had differences in BCVA distribution compared with observed values (Figure 3). The results of this validation analysis demonstrated that each of these distributions compared well with the observed values and that the model was able to predict BCVA distribution across most disease health states. This finding was likely a result of the smaller sample size in OASIS for VMA + FTMH (compared with VMA – FTMH), while the modeled distribution was based on a regression model that leveraged data outside of the observed samples (potentially more accurately reflecting the overall analysis population).

Discussion

This is the first cost–effectiveness study of ocriplasmin based on evidence from a randomized, Phase III, clinical trial conducted in the USA and from a US Medicare perspective. This study demonstrated that treatment with ocriplasmin compared with SOC met commonly accepted cost–effectiveness thresholds, both at short- and long-term time horizons. Uncertainty analyses showed the results were robust and supported the cost–effectiveness profile for ocriplasmin.

Our cost–effectiveness analysis was applied to a population with VMA ± FTMH ≤400 μm. We also performed subgroup analyses because clinical trial and observational study data indicated that patients without or with FTMH differed in their treatment goals (i.e., VMA resolution or FTMH closure), their baseline BCVA outcomes and the likelihood of requiring vitrectomy [2,3,7,12]. The results from our analysis demonstrated that these differences influence cost–effectiveness. Ocriplasmin was cost effective versus SOC in both the subgroup analyses, but more cost-effective for patients with VMA – FTMH than for those with VMA + FTMH. The difference in cost–effectiveness between these two subgroups was driven in large part by the proportion of patients with unresolved FTMH requiring vitrectomies before Month 24.

The modeled population was based on that of the US-based OASIS trial, which is expected to reflect how patients are treated in the USA. Consistent with current clinical practice, the OASIS trial used sham injection over placebo (saline) as the control and evaluated anatomical end points with spectral domain OCT [2]. OASIS results compared favorably with those of the MIVI-TRUST registration studies, showing higher VMA resolution for ocriplasmin (41.7 and 26.5%, respectively) which was maintained over 24 months of follow-up [2,3]. Furthermore, based on

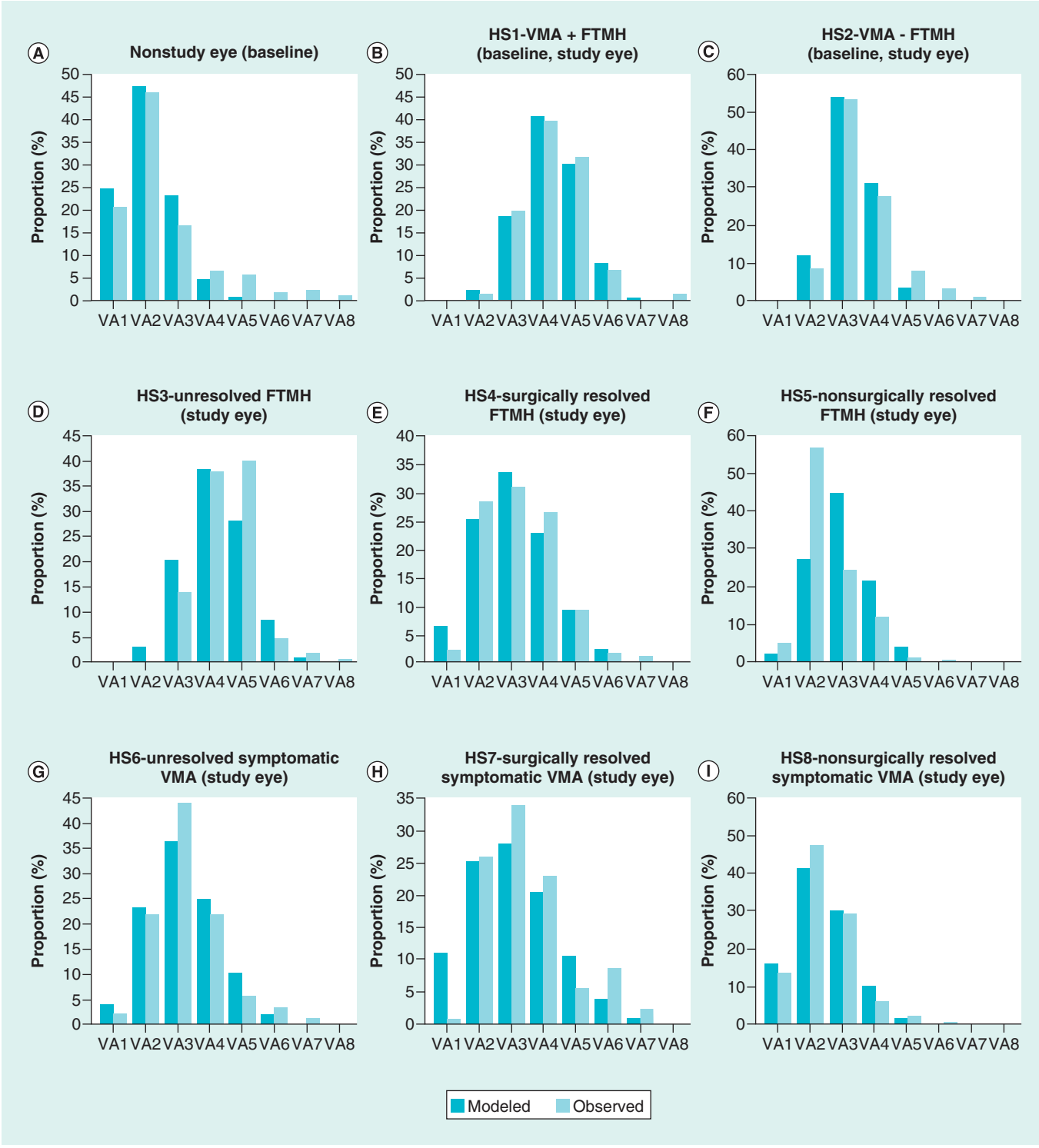

Figure 3. Model validation for best-corrected visual acuity distributions according to disease health state.
BCVA: Best-corrected visual acuity; FTMH: Full-thickness macular hole; HS: Health state; VA: Visual acuity; VMA: Vitreomacular adhesion.

predictive baseline characteristics identified from the MIVI-TRUST trials [42,43], subgroup analysis of OASIS data showed that ocriplasmin-treated patients who had focal VMA, FTMH, absence of epiretinal membrane or phakic lens status at baseline had higher VMA resolution rates than patients without those characteristics [2]. Since the FDA approval in 2012, retina specialists have gained significant clinical experience with ocriplasmin and have adopted a patient selection approach to increase the chances of treatment success. This refined patient selection process has been confirmed in a recent meta-analysis on the use of ocriplasmin in real-world settings which reported a nonsurgical VMA release rate of 45.1% (95% CI: 40.3–50.1) consistent with that seen in OASIS [2,44]. Because the probability of VMA resolution is one of the influential parameters for the cost–effectiveness of ocriplasmin, it is likely that this current patient selection may further improve cost–effectiveness in the clinic. Future recommendations for research include an update of the cost–effectiveness with evidence from real-world studies.

No other cost–effectiveness analyses of ocriplasmin using randomized evidence have been performed using patients from a USA setting, although previous cost–effectiveness analyses from the UK [15] and Italy [45] based on the MIVI-TRUST registration trials showed that ocriplasmin was cost effective versus watchful waiting. Few costing studies have been reported in the treatment of symptomatic VMA. A budget-impact analysis in the USA and Spain concluded that ocriplasmin versus SOC offset some drug costs by reducing the number of vitrectomies [38] or resulted in cost savings over a 5-year period [46].

A 2014 cost evaluation in the USA setting showed a lower cost with pars plana vitrectomy compared with ocriplasmin [47], while a more recent cost evaluation found ocriplasmin to be more cost effective than vitrectomy [47,48]. However, interpretation of the results is limited by the failure of both studies to report an incremental analysis of cost–effectiveness for each alternative intervention versus the comparator (SOC) [47,48]. The current cost–effectiveness analysis overcomes some of the aforementioned limitations through the use of an incremental approach and reflects up-to-date clinical and cost data for the different treatment options. In addition, our use of estimates sourced from randomized clinical trials ensured that patient populations were comparable between intervention and control arms. A societal perspective including, for example, costs of lost productivity or caregiver time was not included due to challenges in data collection and a lack of consensus on the appropriate methodology [21,49].

Since ocriplasmin is indicated in patients with symptomatic VMA without underlying ocular conditions such as proliferative retinopathy, exudative ARMD, retinal vein occlusion and other ocular conditions, appropriate patient selection would exclude those with a broad array of ocular comorbidities [2,14]; this implies that our analysis population may reflect those seen in real-world settings. In addition, postapproval studies of ocriplasmin confirm the widespread practice of patient selection based on positive predictive factors [44], which is expected to improve effectiveness and cost–effectiveness. Finally, treatment with ocriplasmin consists of a single intravitreal injection followed by vitrectomy if the condition does not resolve. Because this one-off treatment followed by a potential rescue treatment (vitrectomy) was accounted for in the OASIS clinical trial, it was also implicitly applied within the model.

Several steps were taken to ensure the face validity and scientific accuracy of the model. First, we adhered to established cost–effectiveness modeling guidelines including those from the International Society for Pharmacoeconomics and Outcomes Research throughout the modeling process [19,21,50,51]. Next, a panel of clinical and health economic experts validated the model concept and key assumptions and was involved in the appraisal and interpretation of the model outcomes. Finally, the reporting of our economic evaluation adhered to Good Reporting Practices standards for economic evaluations of health interventions (CHEERS checklist) [52]. Validating model outcomes observed in the control group with natural history data comes with its limitations. A meta-analysis of natural history studies in VMA – FTMH patients reported an incidence of spontaneous release of 26.3% (95% CI: 21.9–30.7) [53], while the incidence of VMA resolution in VMA – FTMH sham-treated patients was 18.8% at Month 6 (11.0% in the overall population). This observation could be attributed to differences in the studied populations in that patients seeking treatment and entering the healthcare system are likely those patients who will not experience spontaneous VMA release (concept of 'depletion of susceptibles'), so the model outcomes are not directly comparable with the natural history of the disease. Nevertheless, the proportion of sham-treated patients in the nonsurgically resolved disease health state at Month 24 was 20% in the VMA – FTMH group and 7% in the VMA + FTMH group (most patients had vitrectomy). In addition, the proportion of sham-treated patients undergoing a vitrectomy at Month 24 was 21.7% in the VMA – FTMH group and 80% in the VMA + FTMH group, which compared well with the trial data (Supplementary Table 5) [2]. Furthermore, our BCVA linear regression indicated an approximately eight-letter improvement with nonsurgical VMA resolution,

which is consistent with a recent systematic review and meta-analysis that showed approximately ten-letter increase with VMA resolution based on natural history studies [53].

Our analysis was subject to several limitations. Our modeling approach did not include the development of FTMH following persistent VMA. The number of these patients is expected to be small and including them in the analysis would have increased model complexity without providing significant additional information. As a consequence, potentially fewer patients developed FTMH in both treatment arms of the model than might be found in the clinical setting; but this can be considered conservative because nonsurgical VMA resolution rates were lower with sham.

Certain limitations stemmed from key model assumptions. No clinical events were modeled beyond the 24-month OASIS observation period given the lack of data available and to control model complexity. Similarly, our model contained the assumption that patients who underwent vitrectomy would experience successful surgical resolution of their underlying symptomatic VMA/FTMH, although not necessarily on their first vitrectomy. Given the lower resolution and closure rates with sham, both simplifying assumptions would likely have introduced some bias against ocriplasmin. Several assumptions regarding long-term decline in BCVA were necessary to accommodate the lack of data in this area. However, inputs for long-term vision decrement parameters were examined in best- and worst-case scenarios and demonstrated that changes in long-term BCVA assumptions had negligible impact on cost–effectiveness results. Furthermore, our literature-based approach to the estimation of long-term visual decline only accounted for a linear decline. This may not accurately reflect real-world settings; however, the same approach was applied to both treatment arms, and the impact of this simplifying assumption on the ICER was negligible (Supplementary Table 6).

Another limiting assumption to consider is the application of a linear relationship between VA in the BSE and utility estimates. A threshold for meaningful change may vary depending on the patient's baseline VA; however, assuming data availability in symptomatic VMA, such an approach for utilities would better fit a microsimulation rather than a cohort model. Instead, we explored the assignment of utilities to binary VA categories determined by the threshold of >70 ETDRS letters, generally indicating driving vision, which may reflect a meaningful difference to patient quality of life. This simplifying assumption resulted in higher cost per QALYs while still generating ICERs within acceptable thresholds for cost–effectiveness (Supplementary Table 6).

The use of utilities from a study that simulated central vision loss with ARMD health states including reading limit, legal blindness and untreated ARMD may be considered a limitation of our approach. However, patients with symptomatic VMA may have central vision loss (e.g., scotoma with FTMH) or have limited reduction in VA but experience distorted vision. Central vision was captured in OASIS by ETDRS letters. The partitioned vision distribution (Figure 2) modeled the distribution of patients' vision as observed in OASIS and confirms that in more severe stages of the condition (+ FTMH), a higher proportion of patients reside in worse VA categories compared with those who have less severe stages (– FTMH).

Symptomatic VMA is primarily a unilateral condition; therefore, our assessment of utilities might overestimate the impact of the condition because VA may be less impaired when only one eye is affected, or patients may adapt to change and rely on vision in the BSE, so the utility will be driven by vision in the BSE. Overall visual function is dependent on both eyes, so modeling the NSE allowed for combining vision of both eyes into a joint distribution that possibly yielded a more accurate assessment of overall vision and vision-related quality of life. Because VA was tracked in SE and NSE, the model enabled distinguishing between VA in BSE and WSE. Utilities were applied to the BSE, and changes in the WSE were equally valued (in terms of utilities) as changes in the BSE, based on expert opinion. In absence of any data, we explored the alternative assumption that a gain in utility following improved vision in the WSE would be discounted at 30% of that experienced following the same improved vision in the BSE [15,54]. Results indicated that ICERs remained largely within accepted thresholds for cost–effectiveness (Supplementary Table 6).

The timing of vitrectomies was modeled as an exponential distribution, and represented the risk of vitrectomy as a single hazard rate further calibrated to produce the total number of vitrectomies observed in OASIS by Month 24. Although the majority of vitrectomies occurred within the first 6 months (17 of 24 in VMT – FTMH subgroup; 50 of 56 in VMT + FTMH subgroup) rather than being exponentially distributed, this approach was deemed reasonable in absence of alternative parameterizations. The economic model accrued costs and QALYs associated with vitrectomies observed in the first 24 months regardless of exact timing of the event (except for the minor discounting effect in Year 2), so this assumption is not expected to alter the results.

A strength of the current model is that it required fewer data to model VA distribution than our previous UK-perspective model [15]. Using a measure of central tendency (mean) to describe vision over time makes the model more transparent than more traditional ophthalmology cost–effectiveness models, which typically use state transition processes. Typical ophthalmology models describe a patient's vision profile through a set of mutually exclusive vision states defined by ETDRS letters read, and a matrix of transition probabilities that determine movements between these vision states. While the UK model based on the MIVI-TRUST Phase III clinical trials was considered novel and scientifically accurate [15], it was also relatively inflexible regarding the volume of patient-level data that was needed. The data requirements were granular, which made the addition of other trial data challenging. Because the sample size of OASIS was much smaller than the integrated MIVI-TRUST analysis set, a more flexible approach allowing the input of fewer data to power the analysis was needed. Partitioned vision distribution modeling provides the opportunity to better leverage data to inform each disease health state BCVA distribution. Visual acuity was parameterized by a mean and standard deviation and assumed to follow a (scaled) beta distribution. The probability density function was then applied to determine the distribution of patients across eight mutually exclusive VA categories. This approach offers a simpler, more clinically intuitive methodology to simulate patient vision as it requires only three vision parameters (BCVA: mean, standard deviation and change in mean over time).

Sensitivity analyses indicated that results from this cost–effectiveness analysis of ocriplasmin were reasonably robust to changes in some of the model's assumptions, increasing the level of confidence that a reviewer or decision-maker could have in the model outcomes.

In conclusion, compared with commonly reported thresholds per QALY gained [21], the base-case and sensitivity results of this cost–effectiveness analysis showed that a single intravitreal injection of ocriplasmin in the management of symptomatic VMA ± FTMH ≤400 μm was cost effective versus SOC over a 2-year and lifetime horizon. Ocriplasmin offers a nonsurgical, potentially curative treatment option when administrated to a carefully selected patient population, thereby reducing the long-term risk of cataract development and surgery. This single intravitreal injection is less burdensome to the patient and allows earlier treatment of the condition in patients for which vitrectomy is not warranted. This type of cost–effectiveness data may be informative for formulary decision-making in the USA.

Summary points

- Symptomatic vitreomacular adhesion (VMA) is a potentially vision-threatening condition; less than one-third of cases resolve spontaneously.
- In the past, standard of care (SOC) for symptomatic VMA was watchful waiting and pars plana vitrectomy, if necessary.
- Ocriplasmin, a nonsurgical treatment option for symptomatic VMA, was approved by the US FDA in 2012.
- We evaluated the cost–effectiveness/cost utility of a single intravitreal injection of ocriplasmin for the treatment of symptomatic VMA with or without (±) full-thickness macular hole (FTMH) ≤400 μm compared with SOC from a US Medicare perspective.
- A state-transition cost–effectiveness model was developed to simulate patient transitions between eight disease health states over time. Analyses were stratified by FTMH at baseline.
- Clinical efficacy parameters were based on the Ocriplasmin for Treatment for Symptomatic Vitreomacular Adhesion Including Macular Hole study, a randomized Phase IIIb study conducted in the USA.
- In patients with symptomatic VMA ± FTMH ≤400 μm, ocriplasmin treatment generated additional quality-adjusted life years (QALYs; 8.34 vs 7.98) at an increased cost (US$5864 vs US$4133) versus SOC at the lifetime horizon.
- The lifetime incremental cost–effectiveness ratio was US$4887 per QALY gained. The probability of being cost effective was 96.3% at a willingness-to-pay threshold of US$50,000 per QALY and 97.1% at a threshold of US$100,000.
- The cost–effectiveness of ocriplasmin was better for patients with symptomatic VMA without FTMH than for those with symptomatic VMA plus FTMH ≤400 μm. The difference in cost–effectiveness between these two subgroups was driven in large part by the proportion of patients with unresolved FTMH requiring vitrectomy before Month 24.
- In summary, treatment with ocriplasmin compared with SOC met commonly accepted thresholds for cost–effectiveness, both at short- and long-term time horizons.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0117

Acknowledgments

Meeting presentation: Similar analyses using 2016 cost data were presented at ISPOR EU 2018

Financial & competing interests disclosure

The study was funded by Oxurion (formerly ThromboGenics), Iselin, New Jersey. Oxurion participated in the design and conduct of the study; the collection, management, analysis and interpretation of the data; and the preparation, review and approval of the manuscript. AM Khanani is a consultant for Genentech, Oxurion (formerly ThromboGenics), Allergan, Aerpio, Alcon, Alimera Sciences, Allegro, Roche, Opthea, Polyphotonix, Recens Medical, Notal and Novartis Pharma AG. He receives research support from Genentech, Oxurion, Allergan, Aerpio, Alcon, Novartis AG, Ophthotech, Neurotech, DigiSight, Opthea, Recens Medical and Clearside. PU Dugel is a consultant to Bausch + Lomb, Genentech, Alcon, NeoVista, MacuSight, ArcticDx, ORA, Novartis, Allergan, Santen, Inc., Opthotech, Lux Bioscience, DigiSight, Roche, TopCon, Acucela, Pentavision, ORA, Stealth Biotherapeutics, Annidis, Clearside Biomedical, Optovue, Pentavision, Neurotech, Lutronic, Alimera Sciences, DOSE Medical, Aerpio, Omeros, Shire Human Genetics, Opthea, Graybug Vision, Irenix, ByeOnics, PanOptica, Chengdu Kanghong Biotechnology and SciFluor Life Sciences. He is an equity owner of ArcticDx, Opthotech, DigiSight, Annidis, Clearside Biomedical, Alimera Sciences, Aerpio and PanOptica. JA Haller is a consultant for Merck, Janssen, Novartis, Oxurion (formerly ThromboGenics), KalVista, Spark Therapeutics and Lowry Medical Research Institute. She is also a director of Celgene. AL Wagner is a consultant for Oxurion (formerly ThromboGenics). B Lescrauwaet is a health outcomes consultant for several pharmaceutical companies, including Oxurion (formerly ThromboGenics). R Schmidt was a consultant for Oxurion (formerly ThromboGenics) at the time of project development and analysis. C Bennison is a consultant for Oxurion (formerly ThromboGenics).

Medical writing assistance was provided by DP Young, PhD, and K O'Leary, PhD, from Fishawack Communications Inc. and was funded by Oxurion (formerly ThromboGenics).

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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