Supplementary materials

Table S1 – Search strategy for patient reported outcomes & patient experience (Pubmed Medline)

Search	*Search terms*
1.	"quality of life" OR "qol" OR "hrqol" OR "hrql"
2.	"quality adjusted life year" OR "qaly"
3.	"health state" OR "health status"
4.	"quality-adjusted life years" OR ("quality-adjusted" AND "life" AND "years")
5.	("healthy" AND "years" AND "equivalents") OR "healthy years equivalents" OR "hye" OR "life quality"
6.	"utilities" OR "utility"
7.	"wellbeing" OR "well being"
8.	"short form 36" OR "sf 36" OR "sf36"
9.	"short form 12" OR "sf 12" OR "sf12"
10.	"euroqol" OR "eq 5d"
11.	"quality of wellbeing scale" OR "qwb"
12.	"health utilities index" OR "hui" OR "hui-3"
13.	"medical outcomes survey" OR "medical outcomes study" OR "mos"
14.	"rosser"
15.	"time trade off" OR "tto"
16.	"standard gamble"
17.	"magnitude estimation"
18.	"willingness to pay" OR "wtp"
19.	"patient preferences" OR "patient perspectives"
20.	"visual functioning questionnaire" OR "visual functioning" OR "vfq" OR "nei vfq"
21.	"CatQuest"
22.	"MacDQoL"
23.	"utility index" OR "vfq ui"
24.	"vision bolt on item"
25.	"patient reported outcome" OR "patient reported outcome measure"
26.	"functional outcomes"
27.	"patient outcomes"
28.	"visual function"
29.	"visual function 14" OR "visual function 14 index" OR "visual function 14 questionnaire" OR "visual function 14 score"
30.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

Table S2 –Excluded studies

Author(s)	*Year*	*Reason for exclusion*
1. Timothy L. Jackson et al.	2013	Literature review on VMT, symptomatic VMA
2. D H W Steel & A J Lotery	2013	Clinical Review. Reference to MIVI-TRUST studies
3. Pravin U Dugel et al.	2015	Analysis relationship VMA resolution and MH closure
4. Lescrauwaet B et al.	2016	Abstract of original research published in 2017
5. Joondeph B C et al.	2016	Clinical outcome measures and safety parameters
6. Francesco Morescalchi et al.	2016	Clinical and safety review
7. T.L. Jackson et al.	2016	Abstract of original research published in 2017
8. Flynn H W and Relhan N	2017	Review of management options
9. Kleanthis Manousaridis et al.	2017	Real world data on clinical and/or safety outcomes
10. Andrea Cacciamani et al	2017	Microperimetry
11. James E Neffendorf et al.	2017	Reports MIVI TRUST VFQ paper by Varma & Stalmans
12. Srinivas R Sadda et al.	2017	Microperimetry as a relevant biomarker for visual function.
13. Praveen Dugel	2016	Abstract of original research published in 2016
14. Gordon GM, Avery RL	2017	Cost analysis only, abstract only
15. Dimopoulos S. et al.	2015	Natural history spontaneous resolution
16. Tadayoni R. et al.	2015	Description of study design, Abstract only
17. Lei S., Wei W.B.	2014	Review article
18. Gairy K., et al.	2014	Cost modeling
19. Lanzetta P	2014	Abstract only
20. Jackson T. et al.	2014	Abstract only
21. Moro L. et al	2014	Cost modeling
22. Bennison C et al.	2016	Cost modeling
23. Wu et al.	2016	Natural history
24. Li L, Du H, Li M, Hui Y.	2015	Full text article in Chinese
25. Lescrauwaet B. et al.	2013	Abstract only, data subsequently reported in other papers
26. Huang J., Wen D., Wang Q.	2012	Letter, data subsequently reported in peer reviewed paper
27. de Smet M.D. et al.	2009	Clinical outcomes only
28. Silva	2016	Efficacy and safety outcomes only, Abstract only
29. Duker et al	2016	Efficacy and safety outcomes only, Abstract only
30. Khanani A. et al.	2018	Clinical and safety outcomes only
31. Calvin Mein	2017	Conference presentation, Non-peer reviewed

Table S3: Comparison VFQ-25 data

Data from the Metamorphopsia (MeMo) study as well as the National Eye Institute Visual Function Questionnaire (NEI VFQ) Psychometric Field Test study are reported here to contextualize anatomical, visual function and patient-reported outcomes in patients with VMT. The MeMo study was a prospective multicenter observational non-drug study on patient-reported prevalence and severity of metamorphopsia and its impact on quality of life in patients recently diagnosed with VMT. The study by Mangione et al. was a prospective observational cohort study of persons with chronic eye diseases, low vision and a healthy reference sample with the aim to develop and test the psychometric properties of the a 25-item version of the NEI Visual Function Questionnaire (VFQ-25).

Observational non-drug studies like MeMo, and the controlled ocriplasmin trials reveal the impact of VMT on the patient's day-to-day functioning. The MIVI-TRUST and OASIS trials collected VFQ-25 data prior to treatment with ocriplasmin or control. Baseline VFQ-25 subscale scores from observational and controlled trials in VMT are summarized in Table S3, jointly with the scores for a healthy reference group examined in the NEI VFQ Field Test by Mangione et al. 2001.

All pairwise combinations between VMT patients from investigational (MIVI, OASIS) and VMT patients in observational studies (MeMo) vs. the reference groups were statistically significant at $P < 0.05$, except for the subscales ocular pain, color vision and driving in the comparison MeMo vs. reference group.

Table S3. VFQ-25 subscale scores in RCT and observational VMT studies vs. health reference group

VFQ-25 subscale scores	**Reference group** (N = 122)	**VMT - MIVI, OASIS** (N = 870)	**VMT - MeMo** (N = 185)
General health	69 ± 24	61 ± 24	62 ± 25
General vision	83 ± 15	63 ± 16	70 ± 17
Near vision	92 ± 13	69 ± 21	80 ± 20
Distance vision	93 ± 11	75 ± 20	84 ± 18
Driving	87 ± 18	76 ± 24	84 ± 26
Peripheral vision	97 ± 10	83 ± 22	89 ± 19
Color vision	98 ± 8	94 ± 14	97 ± 13
Ocular pain	90 ± 15	84 ± 19	86 ± 18
Role difficulties	93 ± 13	72 ± 26	81 ± 24
Dependency	99 ± 6	88 ± 20	92 ± 22
Social functioning	99 ± 3	91 ± 16	95 ± 15
Mental health	92 ± 12	71 ± 23	79 ± 24
VFQ-25 composite score	93 ± 7	79 ± 15	84 ± 16

Table S4. Responder analysis for VFQ-25 composite score across studies (month 6 data) – vitrectomy considered a failure

Response criteria: Composite score[a]	Ocriplasmin % (n/N)	Control % (n/N)	Difference (%) (95% CI)[b]	p-value[c]
Change from baseline ≥ 5 points				
MIVI-TRUST	28.4 (131/462)	18.2 (34/187)	10.2 (3.3, 17.1)	0.007
OASIS[d]	31.0 (45/145)	9.6 (7/73)	21.4 (11.3, 31.6)	<0.001
COMBINED	29.0	14.7	15.2 (4.1, 26.2)	0.007

n:number of subjects with a success for the endpoint; N:number of subjects in the dataset.
[a]The composite score is calculated as the mean of the 11 vision-targeted subscale scores, excluding the general health rating question. [b]Difference and confidence intervals (CI) between treatment groups are based on the percentage of responses. [c]For individual studies, the p-value is from Fisher's exact test, comparing control and ocriplasmin. For combined studies, pooling of risk differences was based on random effects model using the method of DerSimonian & Laird. [d]Estimate based non-stratified treatment effect, not weighted by FTMH strata.

Tables S5-S7: Sensitivity analysis

From the MIVI-TRUST and OASIS PCA output, we observed that the response measures VFQ-CS and BCVA were shared. We used these to derive an alternative VFR criterion and synthesized the visual function response results based on these common endpoints.

Table S5. Responder analysis for VFR across studies (month 6 data)

Response criteria:	Ocriplasmin % (n/N)	Control % (n/N)	Difference (%) (95% CI)[b]	p-value[c]
Visual Function Response[a]				
MIVI-TRUST	45.5 (212/466)	30.1 (53/176)	15.4 (7.2-23.5)	<0.001
OASIS[d]	47.6 (69/145)	23.3 (17/73)	24.3 (11.6-37.0)	0.001
COMBINED	46.0	27.9	18.5 (10.1-26.8)	<0.001

n:number of subjects with a success for the endpoint; N:number of subjects in the dataset.
[a]Response criteria based on the dimensions that are common in the MIVI-TRUST and OASIS VFR namely the VFQ-composite score and BCVA score. [b]Difference and confidence intervals (CI) between treatment groups are based on the percentage of responses. [c]For individual studies, the p-value is from Fisher's exact test, comparing control and ocriplasmin. For combined studies, pooling of risk differences was based on random effects model using the method of DerSimonian & Laird. [d]Estimate based non-stratified treatment effect, not weighted by FTMH strata.

Table S6. VFR responder analysis by VMA outcome across studies (month 6 data)

Response criteria:	VMA release % (n/N)	Persisting VMA % (n/N)	Difference (%) (95% CI)[b]	p-value[c]
Visual Function Response[a]				
MIVI-TRUST	59.7 (80/134)	37.9 (185/488)	21.8 (12.4-31.1)	<.001
OASIS[d]	55.2 (37/67)	32.5 (49/151)	22.8 (8.7-36.8)	0.003
COMBINED	58.2	36.5	22.1 (14.3-29.9)	<.001

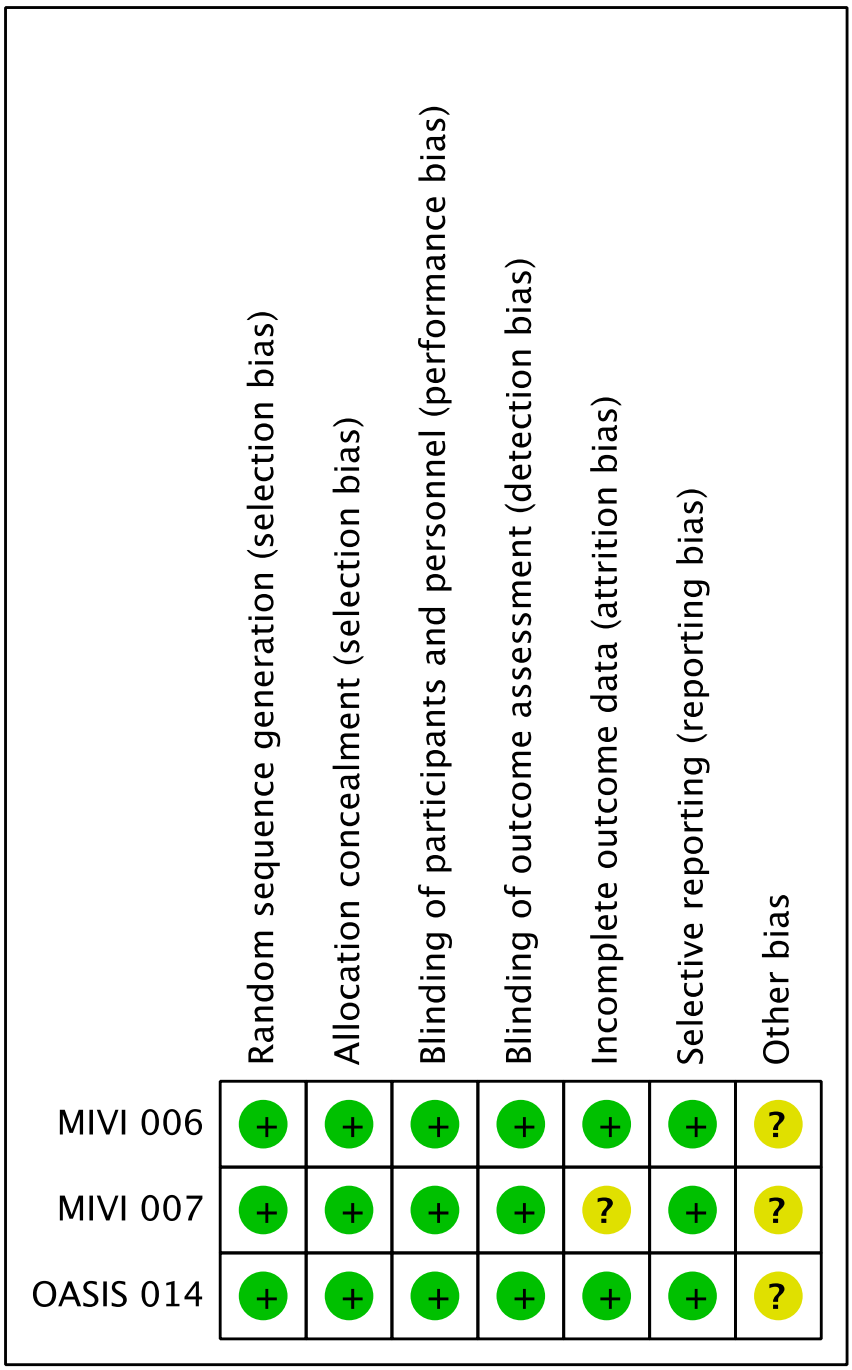
n:number of subjects with a success for the endpoint; N:number of subjects in the dataset.
[a]Response criteria based on the dimensions that are common in the MIVI-TRUST and OASIS VFR namely the VFQ-composite score and BCVA score. [b]Difference and confidence intervals (CI) between treatment groups are based on the percentage of responses. [c]For individual studies, the p-value is from Fisher's exact test, comparing VMA release and persisting VMA. For combined studies, pooling of risk differences was based on random effects model using the method of DerSimonian & Laird. [d]Estimate based non-stratified treatment effect, not weighted by FTMH strata.

Table S7. Treatment effect on VFR at month 6, by VMA subgroup

	Ocriplasmin % (n/N)	Control % (n/N)	Difference (%) (95% CI)[b]	p-value[c]
VMA release				
MIVI-TRUST	61.0 (72/118)	50.0 (8/16)	11.0 (-15.0-37.0)	0.426
OASIS[d]	58.1 (36/62)	20.0 (1/5)	38.1 (9.0-75.2)	0.165
COMBINED	60.0	40.2	21.3 (-4.8-47.4)	0.110
Persisting VMA				
MIVI-TRUST	42.7 (140/328)	28.1 (45/160)	14.6 (5.8-23.3)	0.002
OASIS[d]	39.8 (33/83)	23.5 (16/68)	16.2 (1.7-30.8)	0.038
COMBINED	42.1	26.6	15.0 (7.5-22.5)	<0.001

n:number of subjects with a success for the endpoint; N:number of subjects in the dataset.
[a]Response criteria based on the dimensions that are common in the MIVI-TRUST and OASIS VFR namely the VFQ-composite score and BCVA score. [b]Difference and confidence intervals (CI) between treatment groups are based on the percentage of responses. [c]For individual studies, the p-value is from Fisher's exact test, comparing control and ocriplasmin. For combined studies, pooling of risk differences was based on random effects model using the method of DerSimonian & Laird. [d]Estimate based non-stratified treatment effect, not weighted by FTMH strata.

Figure S1: Risk of bias summary: review authors' judgement about each risk of bias item for each included study (based on published and unpublished sources)



Random sequence generation and allocation

All three trials clearly described randomization and allocation concealment. In MIVI 006 and MIVI 007 a centralized telephone-based system with blocks of treatment assigned to sites was used. In OASIS 2016 a centralized interactive voice response system was used.

Blinding of participants and personnel, blinding of outcome assessment

All three trials adequately masked participants and investigators (MIVI 006; MIVI 007; OASIS 014). In the case of OASIS 014, the study was conducted in a double-masked manner. To maintain the masking of the investigator, an unmasked injecting physician was assigned the perform the injection. The unmasked personnel did not perform or participate in any study-related procedures or assessment.

Incomplete outcome data

We graded the risk of bias as unclear in two studies. In MIVI 007 unclear risk was due to study discontinuations being unequal in different study groups (placebo 8.6%, ocriplasmin 4.1%). In OASIS 014, 220 participants were randomized. However, based on the Central Reading Centre assessment, 50 patients with ERM, 14 patients with a FTMH >400 microns, and 7 patients with no adhesions at baseline were found to be incorrectly enrolled.

Selective reporting

All studies reported on the prespecified secondary PRO outcome (MIVI 006; MIVI 007; OASIS 014).

Other bias

Two studies (MIVI 006; MIVI 007) reported a baseline imbalance between study groups (in the ocriplasmin group pseudophakia was more common than in the placebo group; there were more women in the ocriplasmin group than in the placebo group). In addition, it was unclear how the analysis dealt with the intercurrent event of vitrectomy. Therefore, risk of other bias was graded as unclear for all three studies.

Visual Function Response: Choice of the composite measures and difference between the two RCTs in this endpoint

There is no validated measure to assess the overall impact of VMT on self-reported functional vision. Patients with VMT tend to present with relatively well-preserved visual acuity, which makes visual acuity assessment less suitable as a measure of success. On the other hand, the VFQ-25 does not specifically assess visual symptoms such as metamorphopsia. Therefore, a composite measure was developed to comprehensively evaluate changes in vision-related functioning as experienced by patients. Using the MIVI-TRUST and OASIS datasets, a well-established data reduction technique was applied to simplify the multidimensional datasets of visual outcomes (like the VFQ-25) to a limited set of uncorrelated new variables. First, all available baseline visual outcomes data were grouped together, irrespective of randomized assignment, and included in a principal component analysis (PCA). A PCA works by grouping together closely correlated questions into new variables called principal components (PC). The PCs are ordered by the amount of variation in the data they capture so that the first few PCs are the most relevant. In as second step, clinical correlates ("proxy measures") were sought that correlated highly with the most relevant PCs. In both the MIVI-TRUST and OASIS datasets, the PC1 correlated best with the VFQ-25 composite score (VFQ-CS). In the MIVI trials, the VFQ-25 driving subscale (VFQ-Driving) correlated best with the PC2, while in OASIS, the PC2 and PC3 correlated best with VFQ-25 mental health subscale

(VFQ-MHS). In both datasets, BCVA correlated poorly with either of the PCs and was therefore considered to add independent information.