IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ocriplasmin – Benefit assessment according to § 35a Social Code Book V[1]

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ETDRS	Early Treatment Diabetic Retinopathy Study
G-BA	*Gemeinsamer Bundesausschuss* (Federal Joint Committee)
IQWiG	*Institut für Qualität and Wirtschaftlichkeit im Gesundheitswesen* (Institute for Quality and Efficiency in Health Care)
NEI VFQ-25	National Eye Institute 25-item Visual Function Questionnaire
RCT	randomized controlled trial
SAE	serious adverse event
SGB	*Sozialgesetzbuch* (Social Code Book)
VMA	vitreomacular adhesion
VMT	vitreomacular traction

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ocriplasmin. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter "the company"). The dossier was sent to IQWiG on 30 April 2013.

Research question

The aim of this report is to assess the added benefit of ocriplasmin compared with the appropriate comparator therapy (ACT) according to the approval for the following therapeutic indication: treatment of vitreomacular traction (VMT) in adults, including when associated with a macular hole of diameter ≤ 400 microns.

The G-BA specified the following ACT:

- Subpopulation with asymptomatic VMT: watchful waiting
- VMT population with mild symptoms (e.g. slight worsening of visual acuity, minor visual impairment, no progression of symptoms): watchful waiting
- VMT population with severe symptoms (e.g. progressive deterioration of visual acuity, progressive retinal changes): pars plana vitrectomy.

The company did not seek approval for the subpopulation with asymptomatic VMT. It did not name any ACT and excluded this subpopulation from its research question. Although, in accordance with the G-BA's requirement, the company included the VMT population with severe symptoms in the research question, it did not present any data. The company claimed no added benefit for the two subpopulations.

For the VMT populations with mild symptoms, the company followed the specification of the G-BA.

The assessment was conducted based on patient-relevant outcomes. Only direct comparative randomized controlled trials (RCT) were included in the assessment.

Results

Three relevant studies (Studies TG-MV-004, TG-MV-006, TG-MV-007) were available for the direct comparison of ocriplasmin with watchful waiting in the only relevant subpopulation for which data existed (VMT population with mild symptoms). These were RCTs, in each case approval studies for ocriplasmin. In both groups in each study, a pars plana vitrectomy could be carried out at the investigator's discretion if the disease worsened. This was

considered an acceptable approach, since the possibility of a vitrectomy in the event of disease progression is a treatment option within the watchful waiting procedure. The vast majority of study participants had a mild or moderate visual impairment according to ICD-10, defined by the visual acuity.

Whereas in Study TG-MV-004, the participants of the comparator group received a sham injection, the control groups of studies TG-MV-006 and TG-MV-007 were given a placebo injection. The G-BA specified that the ACT for the VMT population with mild symptoms was to be watchful waiting. Due to the injection of a placebo solution into the vitreous body of participants in the control groups, the risk of bias for these studies is rated as high.

The risk of bias of the TG-MV-004 study was also rated as high, because this benefit assessment only considered a subpopulation from the TG-MV-004 study for which the original randomization of patients no longer applied and the structural equality between the evaluated treatment groups was unclear.

Mortality

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant for the outcome "mortality". Therefore, in the VMT population with mild symptoms, there is no proof of an added benefit or greater harm of ocriplasmin in comparison with watchful waiting for this outcome.

Morbidity (outcome: "improvement in visual acuity ≥ 2 lines")

A responder analysis with a threshold of ≥ 2 lines (corresponding to 10 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) was used for the outcome "improvement in visual acuity". The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant in favour of ocriplasmin. Hence, there is an indication of an added benefit of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms in terms of an improvement in visual acuity.

Vitrectomy

The proportion of patients who, at the investigator's discretion, underwent a pars plana vitrectomy during the course of the study was recorded for this outcome. The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant in favour of ocriplasmin. However, the subsequent assessment of subgroup characteristics produced an indication of an effect modification through the characteristic "baseline visual acuity". Overall, in the VMT population with mild symptoms, there is an indication of an added benefit in patients with mild visual impairment and a hint of an added benefit in patients with moderate visual impairment, in each case with regard to the proportion of patients with vitrectomy.

Health-related quality of life (outcome: National Eye Institute 25-item Visual Function Questionnaire [NEI VFQ-25])

Health-related quality of life of the patients was recorded using an instrument (NEI VFQ-25) considered suitable for VMT patients. The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant. An added benefit of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for this outcome.

Adverse events

Analyses of adverse events

The overall rate of adverse events was only shown as supplementary data. The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant for the outcomes "serious adverse events" and "discontinuation due to adverse events". A greater harm of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for these outcomes.

For the outcome "ocular adverse events", the results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant to the disadvantage of ocriplasmin. However, the subsequent assessment of subgroup characteristics produced an indication of an effect modification through the characteristic "sex". Bearing in mind the subgroup data, a greater harm of ocriplasmin in comparison with the watchful waiting procedure is not proven, due to a marginal effect size for ocular adverse events.

Deterioration in visual acuity ≥ 2 and ≥ 6 lines

For the outcome "deterioration in visual acuity ≥ 2 lines", the meta-analysis on the comparison of ocriplasmin with watchful waiting showed a considerable and inexplicable heterogeneity. For the outcome "deterioration in visual acuity of 6 lines" (corresponding to 30 ETDRS letters), the results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant. An added benefit of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for these outcomes.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug ocriplasmin compared with the ACT are assessed separately for the 3 relevant subpopulations as follows:

Subpopulation with asymptomatic VMT

There were no data for a comparison of ocriplasmin with watchful waiting for the subpopulation with asymptomatic VMT. Hence, the added benefit of ocriplasmin in the subpopulation with asymptomatic VMT in comparison with watchful waiting is not proven.

VMT population with mild symptoms

The data of the VMT population with mild symptoms showed an indication of an added benefit of ocriplasmin compared with the ACT in terms of an improvement in visual acuity (≥ 2 ETDRS lines), an indication of an added benefit for patients with mild visual impairment, as well as a hint of an added benefit for patients with moderate visual impairment, in each case with regard to the proportion of patients with vitrectomy. Based on the effect size, in the VMT population with mild symptoms, the assessment is as follows:

- For patients with mild visual impairment (> 60 ETDRS letters), there is an indication of a major added benefit of ocriplasmin in comparison with watchful waiting.
- For patients with moderate visual impairment (35 to 60 ETDRS letters), there is an indication of a considerable added benefit of ocriplasmin in comparison with watchful waiting.

VMT population with severe symptoms

Since no data were available for a comparison of ocriplasmin with pars plana vitrectomy in the VMT population with severe symptoms, the added benefit of ocriplasmin in this particular population in comparison with pars plana vitrectomy is not proven.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1-3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

2.2 Research question

The aim of this report was to assess the added benefit of ocriplasmin in comparison with the ACT in accordance with its approval for the following therapeutic indication: treatment of VMT in adults, including when associated with a macular hole of diameter ≤ 400 microns [3]. Within this therapeutic indication, a distinction was drawn between patients with asymptomatic VMT, (hereinafter: "subpopulation with asymptomatic VMT") and patients with mild (hereinafter: "VMT population with mild symptoms") or severe symptoms (hereinafter: "VMT population with severe symptoms"). The G-BA specified the ACT separately for these populations as follows:

- Subpopulation with asymptomatic VMT: watchful waiting
- VMT population with mild symptoms (e.g. slight worsening of visual acuity, minor visual impairment, no progression of symptoms): watchful waiting
- VMT population with severe symptoms (e.g. progressive deterioration of visual acuity, progressive retinal changes): pars plana vitrectomy.

The company only included the latter two patient groups in the research question. The company did not seek approval for the subpopulation with asymptomatic VMT. It did not name any ACT and excluded this subpopulation from its research question (see Section 2.7.1 of the full dossier assessment). No added benefit for this subpopulation was claimed in the dossier.

The company followed the G-BA specification concerning the ACT for the VMT populations with mild and severe symptoms.

The assessment of the added benefit of ocriplasmin was carried out versus the ACT specified by the G-BA and in accordance with the allocation of the populations to the research questions within the therapeutic indication. It should be noted that the VMT population with mild symptoms included patients with mild as well as those with moderate symptoms in terms of visual impairment (see Section 2.7.1 of the full dossier assessment). This corresponds to the approach in the dossier. However, this population will hereinafter continue to be called the "VMT population with mild symptoms".

The assessment was conducted based on patient-relevant outcomes. Only direct comparative RCTs were included in the assessment. This corresponds with the approach of the company.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Company sources in the dossier:

- List of studies on ocriplasmin (studies completed up to 18 February 2013)
- Bibliographical literature search for studies on ocriplasmin (last search 18 February 2013)
- Search in trial registries for studies on ocriplasmin (last search 18 February 2013)

The Institute's own searches to check the company's search results:

- Search in trial registries for studies on ocriplasmin (last search on 16 May 2013)

The results of this check produced no deviations from the study pool described in the dossier. Only studies on the research question ocriplasmin in comparison with watchful waiting in the VMT population with mild symptoms were available. No data were available for the other populations.

Further information on the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[b] (yes/no)	Third-party study (yes/no)
TG-MV-004[a]	yes	yes	no
TG-MV-006[a]	yes	yes	no
TG-MV-007[a]	yes	yes	no

a: A sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas placebo solution was injected into the vitreous body in TG-MV-006 and TG-MV-007.
b: Study for which the company was sponsor, or in which the company was otherwise financially involved.
RCT: randomized controlled trial

The study pool corresponds to the study pool of the company.

Patients within the study population given approval-compliant treatment

The study population also included patients with a macular hole > 400 µm, who were thus not treated in accordance with the current approval for ocriplasmin. Where available, results for the approval-compliant target population were analysed for the assessment of the research question. In addition, results were not available for all outcomes of relevance for the VMT population with mild symptoms. Since the proportion of patients with a macular hole > 400 µm and the patients with severe symptoms totalled less than 6% (see Table 16 in

Section 2.7.2.3.2 of the full dossier assessment) and this order of magnitude was rated as low, results of the total target or study population were also used if only these were available. Hereinafter, the particular population analysed is always specified.

Section 2.6 contains a list of data sources cited by the company for the studies included by the Institute.

Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4, Sections 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Study characteristics

Table 3 and Table 4 describe the 3 studies included in the benefit assessment.

Characteristics of the studies and the interventions

The 3 studies TG-MV-004, TG-MV-006 and TF-MV-007 were blinded, multicentre RCTs each lasting 6 months. Participants were adults with symptomatic vitreomacular adhesion (VMA). In the European approval based on these studies, the therapeutic indication refers to the treatment of "vitreomacular traction". An examination of the content of the approval documents [4] showed that the population of the submitted studies was suitable for investigating the research question of the benefit assessment (see Section 2.7.2.4.1 of the full dossier assessment). This corresponds to the company's statement.

Table 3: Characteristics of the studies included – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TG-MV-004	RCT, Phase II, double blind[b], parallel, controlled, multicentre (3 centres)	Adults over 18 years with symptomatic vitreomacular adhesion (VMA)	Sequential inclusion of 61 patients in 4 cohorts, randomized to ocriplasmin or control watchful waiting with single sham injection[c]: Cohort 1: ocriplasmin 75 µg (N = 12), control (N = 3) Cohort 2: ocriplasmin 125 µg (N = 12), control (N = 3) Cohort 3: ocriplasmin 175 µg (N = 13), control (N = 3) Cohort 4: ocriplasmin 125 µg/ several injections (N = 12), control/several sham injections (N = 3) Patients considered in the benefit assessment: ocriplasmin 125 µg (n = 13[d]), control (n = 9[e])	6 months (180 days)	Belgium 3/2007 – 1/2009	Primary outcome: Proportion of patients with non-surgical resolution of a focal VMA on Day 14 after injection Secondary outcomes: Improvement in best corrected visual acuity (BCVA[f]), vitrectomy, health-related quality of life, adverse events
TG-MV-006	RCT, Phase III, double blind, parallel, controlled, multicentre (42 centres)	Adults over 18 years with symptomatic VMA	Ocriplasmin 125 µg (N = 219) watchful waiting with single placebo[c] (N = 107)	6 months (180 days)	USA 12/2008 – 3/2010	Primary outcome: Proportion of patients with non-surgical resolution of a focal VMA on Day 28 after injection Secondary outcomes: Improvement in best corrected visual acuity (BCVA[f]), vitrectomy, health-related quality of life, adverse events

(continued)

Table 3: Characteristics of the studies included – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection) (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TG-MV-007	RCT, Phase III, double blind, parallel, controlled, multicentre (48 centres)	Adults over 18 years with symptomatic VMA	Ocriplasmin 125 µg (N = 245) watchful waiting with single placebo[c] (N = 81)	6 months (180 days)	Europe and USA 12/2008 – 6/2010	Primary outcome: Proportion of patients with non-surgical resolution of a focal VMA on Day 28 after injection Secondary outcomes: Improvement in best corrected visual acuity (BCVA[f]), vitrectomy, health-related quality of life, adverse events

a: Primary outcomes contain information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Patients and outcome assessors were blinded. Those carrying out the ocriplasmin and sham injection were not blinded.
c: Sham injection was used in the control arm of Study TG-MV-004 (i.e. without puncture of the vitreous body), whereas placebo solution was injected into the vitreous body in TG-MV-006 and TG-MV-007.
d: One patient of Cohort 3 received 129 µg ocriplasmin injection after randomization and was analysed together with patients of Cohort 2 (ocriplasmin 125 µg).
e: 9 patients included 3 patients with sham injection from Cohort 2 and another 6 patients with single sham injection from Cohorts 1 and 3 (included in the FAS analysis documents of the dossier).
f: Number of correctly read single letters was reported in the dossier documents as best corrected visual acuity – in this benefit assessment called "ETDRS letters".
BCVA: best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; N: number of randomized patients; RCT: randomized controlled trial; VMA: vitreomacular adhesion

Table 4: Characteristics of the interventions – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study	Intervention	Control	Concomitant therapy
TG-MV-004	Single ocriplasmin injection 125 µg intravitreal into study eye[a, b]	Watchful waiting with single sham injection[c]	Observation up to Day 28, vitrectomy possible (optional) during the study after Day 28 (e.g. if no improvement). Vitrectomy permitted at any time if visual acuity deteriorates ≥ 2 ETDRS lines or underlying disease worsens
TG-MV-006	Single ocriplasmin-injection125 µg intravitreal into study eye[a]	Watchful waiting with single placebo injection[c]	Observation up to Day 28, vitrectomy possible (optional) during the study after Day 28 (e.g. if no improvement). Vitrectomy permitted at any time if visual acuity deteriorates ≥ 2 ETDRS lines or underlying disease worsens
TG-MV-007	Single ocriplasmin injection 125 µg intravitreal into study eye[a]	Watchful waiting with single placebo injection[c]	Observation up to Day 28, vitrectomy possible (optional) during the study after Day 28 (e.g. if no improvement). Vitrectomy permitted at any time if visual acuity deteriorates ≥ 2 ETDRS lines or underlying disease worsens

a: The eye meant is the one with the worse visual acuity.
b: One patient of Cohort 3 received 129 µg ocriplasmin injection after randomization and was analysed together with patients of Cohort 2 (ocriplasmin 125 µg).
c: Sham injection was used in the control arm of Study TG-MV-004 (i.e. without puncture of the vitreous body), whereas placebo solution was injected into the vitreous body in TG-MV-006 and TG-MV-007.
ETDRS: Early Treatment Diabetic Retinopathy Study; RCT: randomized controlled trial

Only some of the patients from the TG-MV-004 study were relevant for the benefit assessment: in this study, 61 patients were successively treated in 4 cohorts with different doses of ocriplasmin. The randomization of patients to treatment with ocriplasmin or a sham injection took place within the individual cohorts. In Cohort 2 with the approved dose of 125 µg ocriplasmin, 15 participants were randomized, of which 12 received ocriplasmin and 3 the sham injection. In the dossier, however, those patients from Cohorts 1 and 3 who received a single sham injection (instead of repeated injection) were also considered relevant and were included in the analysis. Therefore, in the subsequent presentation, this number amounted to 9 patients in the control group. This procedure means that the original randomization of the study was no longer ensured for all analysed patients. The risk of bias at study level is therefore rated as high (see “Assessment of the risk of bias at study level” at the end of this section).

A sham or placebo injection was used in the control arms in the studies TG-MV-004, TG-MV-006 and TG-MV-007 in order to guarantee blinding. The patients of the TG-MV-006 and TG-MV-007 studies received an intravitreal placebo injection, i.e. a solution was injected into the eye. Despite this intervention, the studies were considered suitable for the assessment of the added benefit of ocriplasmin in comparison with watchful waiting. However, the giving of an injection is considered as a factor that can distort the corresponding results (see Section 2.7.2.4.2 of the full dossier assessment and Table 6). On the other hand, in Study TG-MV-004, a sham injection was used. This was performed using a blunt needle which did not penetrate the eye. This meant that the surgeon was not blinded. However, as the outcome assessor was not the same person as the surgeon, this did not result in an increase in the risk of bias of the study (see Table 6).

In all 3 studies, patients were followed up after the injection of ocriplasmin or after the sham or placebo injection and, at the investigator's discretion, could undergo a pars plana vitrectomy from Day 28 after the injection (or earlier in exceptional cases). This condition was rated as of no concern, because the possibility of a vitrectomy on progression of the disease is a treatment option in the context of watchful waiting. Therefore the treatment in the studies is applicable to the present research question.

Characteristics of the study populations

Table 5 shows the characteristics of patients in the studies included.

The average age of the patients was 72 years and the proportion of women was about twice that of men. The average level of visual acuity was in the range of a minor visual impairment according to ICD-10 (65 ETDRS letters). A macular hole was present in around one-fifth of patients at the start of the study, and an epiretinal membrane in about two-fifths. Based on the patient characteristics, no differences could be found between the studies that were of relevance to the assessment.

Table 5: Characteristics of the study populations – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study Group	N	Age[a] [Years] Mean (SD)	Sex[a] [f/m] %	Visual acuity [ETDRS letters][a] Mean (SD)	Patients with macular hole[b] at start of study[c] n (%)	Patients with ERM at start of study[c] n (%)	Geographic region [USA/Europe] %	Treatment discontinuations[c] n (%)
TG-MV-004								
Ocriplasmin	13[d]	74.2 (5.7)	61.5/38.5	59.4 (9.90)	1 (7.7)	n. k.	0/100[e]	0 (0)
Watchful waiting (with sham injection[f])	9	67.7 (8.7)	33.3/66.7	56.2 (15.85)	3 (33.3)	n. k.	0/100[e]	0 (0)
TG-MV-006								
Ocriplasmin	211	71.6 (10.16)	66.8/33.2	65.1 (10.50)	49 (23.2)	86 (39.3)	100/0[g]	19 (8.7)
Watchful waiting (with placebo injection[f])	105	71.1 (10.12)	55.2/44.8	65.7 (9.50)	30 (28.6)	35 (32.7)	100/0[g]	9 (8.4)
TG-MV-007								
Ocriplasmin	234	72.7 (7.60)	66.2/33.8	64.5 (12.79)	38 (16.2)	98 (40.0)	45/55[c]	10 (4.1)
Watchful waiting (with placebo injection[f])	80	70.2 (10.91)	68.8/31.3	65.2 (11.33)	14 (17.5)	33 (40.7)	44/56[c]	7 (8.6)

a: Information for the target population.
b: Total of patients with AAO-Stages 2 and 3.
c: Information for the study population.
d: One patient, who was randomized into Cohort 3 (ocriplasmin 175 µg), received an injection with 129 µg and was analysed in Cohort 2 (ocriplasmin 125 µg). This led to a discrepancy in the number of randomized patients of Cohort 2 (Table 3), that will no longer be noted subsequently.
e: The study was only carried out in Europe (Belgium).
f: Sham injection was used in the control arm of Study TG-MV-004 (i.e. without penetration into the vitreous body), whereas placebo solution was injected into the vitreous body in TG-MV-006 and TG-MV-007.
g: The study was only carried out in the USA.
AAO: American Academy of Ophthalmology Retina Panel; ERM: epiretinal membrane; ETDRS: Early Treatment Diabetic Retinopathy Study; f: female; m: male; N: number of randomized patients with macula hole ≤ 400µm; n. k.: not known; RCT: randomized controlled trial; SD: standard deviation

The patients in the studies had only a minor or moderate (i.e. non-severe) impairment of visual acuity. As in the rationale described in Section 2.7.1 of the full dossier assessment, the patients were rated for the assessment as patients with mild symptoms. Therefore, the studies were included for the assessment of the added benefit of ocriplasmin in the VMT population with mild symptoms (see Section 2.7.1 of the full dossier assessment). The approach corresponded to that of the company.

The studies were carried out in the USA and Europe. The influence of the region was investigated in corresponding subgroup analyses (see Section 2.7.2.4.3 of the full dossier assessment).

Risk of bias at study level

Table 6 shows the risk of bias at study level.

Only a subpopulation from Study TG-MV-004, for whom the original randomization of patients was no longer present and the structural equality between the analysed treatment groups was unclear, was used in this benefit assessment. The risk of bias of the study is rated as high. This assessment does not correspond with that of the company, who did not address the problem of broken randomization and who rated the study's risk of bias as low.

The risk of bias for studies TG-MV-006 and TG-MV-007 is also rated as high. This deviates from the company's view, which rated the risk of bias of all studies as low. The reason lies in the assessment of the influence of the administered placebo injection in the control groups of the TG-MV-006 and TG-MV-007 studies. In contrast to the company's assessment, this additional invasive intervention in the group that was supposed to represent watchful waiting as the ACT, is considered as a potential distorting factor (see Section 2.7.2.4.2 of the full dossier assessment).

Table 6: Risk of bias at study level – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Non-selective reporting	No other aspects	Risk of bias at study level
			Patient	Treating staff			
TG-MV-004[a]	yes	yes	yes	no	yes	no[b]	high
TG-MV-006[a]	yes	yes	yes	yes	yes	no[c]	high
TG-MV-007[a]	yes	yes	yes	yes	yes	no[c]	high

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
b: Questionable structural equality of the treatment groups in the subpopulation analysed.
c: Potentially distorting effects through placebo injection cannot be excluded.
RCT: randomized controlled trial

Further information about study design, study populations and the risk of bias at study level can be found in Module 4, Sections 4.3.1.2.1, 4.3.1.2.2 and as well as in Appendix 4-G of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results on added benefit

The following patient-relevant outcomes were considered in the present assessment on the VMT population with mild symptoms:

- All-cause mortality
- Improvement in visual acuity (≥ 2 ETDRS lines)
- Vitrectomy
- Health-related quality of life (based on NEI VFQ-25)
- Overall rate of adverse events (only shown as supplementary data)
- Serious adverse events
- Discontinuation due to adverse events
- Deterioration in visual acuity (≥2 and ≥ 6 ETDRS lines)
- Ocular adverse events

The choice of patient-relevant outcomes differed partly from that of the company, who used further outcomes in Module 4 of the dossier. In addition, the outcome “ocular adverse events” was rated as patient-relevant and included in the benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

Table 7 shows for which outcomes data were available in the studies included. Data were available from all studies on the outcomes included in the benefit assessment.

Table 7: Matrix of outcomes – RCT, direct comparison: ocriplasmin vs. watchful waiting (with sham or placebo injection)

Study	Outcomes									
	All-cause mortality	Improvement in visual acuity ≥ 2 ETDRS lines	Vitrectomy	Health-related quality of life (NEI VFQ-25, Responders)	Adverse events	Serious adverse events	Discontinuation due to adverse events	Deterioration in visual acuity ≥ 2 ETDRS lines	Deterioration in visual acuity ≥ 6 ETDRS lines	Ocular adverse events
TG-MV-004[a]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
TG-MV-006[a]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
TG-MV-007[a]	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
ETDRS: Early Treatment Diabetic Retinopathy Study; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; RCT: randomized controlled trial

Table 8 describes the risk of bias for these outcomes. The risk of bias of all included outcomes of Study TG-MV-004 was rated as high, as was that of the outcomes of studies TG-MV-006 and TG-MV-007, with the exception of mortality. This deviates from the company's assessment, which rated the risk of bias of the outcomes in Table 8 as low for all studies, if these were shown in Module 4. (Due to the lack of surgeon blinding, only in Study TG-MV-004 did the company rate the risk of bias of the outcome "vitrectomy" as high.) This differing assessment is because the Institute, unlike the company, assessed the risk of bias of all studies at study level as high (see Section 2.3.2).

Table 8: Risk of bias at study and outcome level – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Study	Study level	Outcomes								
		All-cause mortality	Improvement in visual acuity ≥2 ETDRS lines	Vitrectomy	Health-related quality of life (NEI VFQ-25, Responders)	Serious adverse events	Discontinuation due to adverse events	Deterioration in visual acuity ≥ 2 ETDRS lines	Deterioration in visual acuity ≥ 6 ETDRS lines	Ocular adverse events
TG-MV-004[a]	high	high	high	high	high	high	high	high	high	high
TG-MV-006[a]	high	low	high	high	high	high	high	high	high	high
TG-MV-007[a]	high	low	high	high	high	high	high	high	high	high

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
ETDRS: Early Treatment Diabetic Retinopathy Study; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; RCT: randomized controlled trial

Further information about the choice of outcomes and risk of bias at outcome level can be found in Module 4, Sections 4.3.1.2.2, 4.3.1.3 and 4.3.2.1.3 of the dossier and in Sections 2.7.2.4.2 and 2.7.2.4.3 of the full dossier assessment.

Table 9 summarizes the results from the comparison of ocriplasmin and watchful waiting in the VMT population with mild symptoms. Where necessary, the data from the company's dossier were supplemented by the Institute's own calculations.

No data were available on the comparison with the G-BA's specified ACT (watchful waiting or pars plana vitrectomy) for the subpopulation with asymptomatic VMT and the VMT population with severe symptoms.

Table 9: Results – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection; VMT population with mild symptoms)

Outcome category Outcome Study	Ocriplasmin		Watchful waiting (with sham or placebo injection[a])		Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality[b]					
TG-MV-004	13	0 (0)	9	0 (0)	n. c.
TG-MV-006	219	3 (1.4)	107	0 (0)	4.47[c] [0.40; 50.15]
TG-MV-007	245	1 (0.4)	81	0 (0)	3.78[c] [0.04; 352.93]
Total	477	4 (0.8)	197	0 (0)	4.31[c] [0.51; 36.38][d]; p = 0.18[d]
Morbidity					
Improvement in visual acuity ≥ 2 lines (10 ETDRS letters)					
TG-MV-004	13	6 (46.2)	7	2 (28.6)	1.62 [0.44; 5.99]
TG-MV-006	210	63 (30.0)	105	16 (15.2)	1.97 [1.20; 3.23]
TG-MV-007	226	58 (25.7)	77	12 (15.6)	1.65 [0.94; 2.90]
Total	449	127 (28.3)	189	30 (15.9)	1.81 [1.26; 2.58][d] p = 0.001[d]
Vitrectomy					
TG-MV-004	13	1 (7.7)	7	2 (28.6)	0.27 [0.03; 2.47]
TG-MV-006	210	39 (18.6)	105	30 (28.6)	0.65 [0.43; 0.98]
TG-MV-007	226	32 (14.2)	77	17 (22.1)	0.64 [0.38; 1.09]
Total	449	72 (16.0)	189	30 (15.9)	0.63 [0.46; 0.88][d, e] p = 0.006[d, e]
Health-related quality of life					
NEI VFQ-25 (Responders)					
TG-MV-004	13	4 (30.8)	7	0 (0.0)	5.14 [0.32; 83.70][e]
TG-MV-006	192	82 (42.7)	97	37 (38.1)	1.12 [0.83; 1.51][e]
TG-MV-007	214	93 (43.5)	71	20 (28.2)	1.54 [1.03; 2.31][e]
Total	419	179 (42.7)	175	57 (32.6)	1.30 [0.95; 1.77][d, e] p = 0.097[d, e]
Adverse events					
Overall rate of adverse events					
TG-MV-004	13	10 (76.9)	9	6 (66.7)	
TG-MV-006	212	174 (82.1)	104	75 (72.1)	
TG-MV-007	226	160 (70.8)	80	50 (64.9)	

(continued)

Table 9: Results – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection; VMT population with mild symptoms) (continued)

Outcome category Outcome Study	Ocriplasmin		Watchful waiting (with sham or placebo injection[a])		Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value
Serious adverse events [f]					
TG-MV-004	13	2 (15.4)	7	0 (0.0)	2.86 [0.16; 52.42]
TG-MV-006	211	26 (12.3)	104	13 (12.5)	0.99 [0.53; 1.84]
TG-MV-007	226	29 (12.8)	77	10 (13.0)	0.99 [0.51; 1.93]
Total	450	57 (12.7)	188	23 (12.2)	1.01 [0.64; 1.59][d]; p = 0.96[d]
Discontinuation due to adverse events[b]					
TG-MV-004	13	0 (0)	9	0 (0)	n. c.
TG-MV-006	219	2 (0.9)	107	2 (1.9)	0.46[c] [0.06, 3.71]
TG-MV-007	245	2 (0.8)	81	0 (0)	3.80[c] [0.15, 94.34]
Total	477	4 (0.8)	197	2 (1.0)	0.86[c] [0.15; 4.97][d]; p = 0.86[d]
Deterioration in visual acuity ≥ 2 lines (10 ETDRS letters)					
TG-MV-004	13	0 (0.0)	7	0 (0.0)	n. c.
TG-MV-006	210	22 (10.5)	105	5 (4.8)	2.20 [0.86; 5.65]
TG-MV-007	226	13 (5.8)	77	6 (7.8)	0.74 [0.29; 1.87]
Total	Heterogeneity: Q = 2.65, p = 0.103, I^2 = 62.3%				
Deterioration in visual acuity ≥ 6 lines (30 ETDRS letters)					
TG-MV-004	13	0 (0)	7	0 (0)	n. c.
TG-MV-006	210	3 (1.4)	105	1 (0.9)	1.46 [0.18; 11.79]
TG-MV-007	226	3 (1.3)	77	1 (1.3)	1.02 [0.11; 9.82]
Total	449	6 (1.3)	189	2 (1.1)	1.24 [0.27; 5.75][d]; p = 0.78[d]
Ocular adverse events[b, f, g]					
TG-MV-004	13	8 (61.5)	9	5 (55.6)	1.11 [0.54; 2.29][e]
TG-MV-006	220	163 (74.1)	106	65 (61.3)	1.21 [1.02; 1.43][e]
TG-MV-007	245	162 (66.1)	81	42 (51.9)	1.28 [1.02; 1.60][e]
Total	478	333 (69.7)	196	112 (57.1)	1.23 [1.07; 1.40][d, e] p = 0.003[d, e, h]

(continued)

Table 9: Results – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection; VMT population with mild symptoms) (continued)

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
b: Numbers for target population (TG-MV-004) or study population (TG-MV-006, TG-MV-007). Results for VMT population with mild symptoms were not available, which did not lead to a reduction in the certainty of results (see comments on the description of the populations in Section 2.7.2.3.2 of the full dossier assessment).
c: Peto odds ratio.
d: Value from meta-analysis.
e: Institute's calculation.
f: For discussion of the potential bias of the results on SAE (and other ocular AE) see Section 2.7.2.4.3 of the full dossier assessment.
g: Operationalization: all adverse events located in the eye.
h: No conclusions based on the overall effect because of an indication of a relevant effect modification through the characteristic "sex" (see end of this section).
CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; N: number of patients analysed; n: number of patients with event; n. c.: not calculable; n. k.: not known; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; RCT: randomized controlled trial; RR: relative risk; VMT: vitreomacular traction

For the VMT population with mild symptoms, only results from the target population (Study TG-MV-004) or the study population (Studies TG-MV-006 and TG-MV-007) were available for the outcomes "mortality", "discontinuation due to adverse events" and "ocular adverse events". This means that patients with severe symptoms (visual acuity < 0.1 or 35 ETDRS letters) were also included in the results of all studies, and that patients with a macular hole > 400 µm who were not treated in accordance with the approval were considered in the analyses of studies TG-MV-006 and TG-MV-007. However, due to low proportions of patients in these categories, this did not lead to any reduction in the informative value (see comments on the populations in Section 2.7.2.3.2 of the full dossier assessment). Results on the relevant subpopulation were available for all other outcomes.

Mortality

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting for the outcome "mortality" were not statistically significant. An added benefit or greater harm of ocriplasmin in comparison with watchful waiting in the VMT population with mild symptoms is therefore not proven for this outcome. This corresponds to the company's assessment.

Morbidity

Improvement in visual acuity ≥2 lines (10 ETDRS letters)

A responder analysis with a threshold of ≥ 2 ETDRS lines was used for the outcome "improvement in visual acuity" (see Section 2.7.2.4.3 of the full dossier assessment). The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant in favour of ocriplasmin. Bearing in mind the high risk of bias of the studies, there is therefore an indication of an added benefit of ocriplasmin in comparison with

the ACT with regard to an improvement in visual acuity in the VMT population with mild symptoms. This deviates from the company's assessment, which assumed a proof of added benefit for this outcome, because it rated the risk of bias of all 3 studies as low.

Vitrectomy

The proportion of patients who underwent, at the investigator's discretion, a pars plana vitrectomy during the study was recorded for the outcome described in the dossier as "need for vitrectomy". The results of the corresponding meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant in favour of ocriplasmin. However, during the subsequent assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "baseline visual acuity". This meant that any conclusions about the added benefit relating to this outcome had to be drawn on the basis of the subgroups. The subgroup analyses and the related interpretation of the results and documentation of the evidence can be found at the end of this section. Under consideration of the subgroup data and the high risk of bias of the studies, there is an indication of an added benefit in patients with mild visual impairment and a hint of an added benefit in patients with moderate visual impairment, in each case with regard to the patients with vitrectomy.

Health-related quality of life (based on the NEI VFQ-25)

The health-related quality of life of patients was recorded with NEI VFQ-25, which has been validated for persons with chronic eye disorders and is considered suitable for VMT patients. The benefit assessment used the responder analysis reported in the dossier (see Section 2.7.2.4.3 of the full dossier assessment). The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant. An added benefit of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for this outcome. This deviates from the company's assessment, which assumed proof of added benefit for the health-related quality of life. This judgement was based on a responder analysis, in which patients who had undergone a vitrectomy were classed as non-responders. However, for the present research question, this assessment is not considered adequate (see Section 2.7.2.4.3 of the full dossier assessment).

Adverse events

Overall rate of adverse events

The outcome "overall rate of adverse events (AE)" is shown in Table 9 only as supplementary data. The results of this outcome were not included in the assessment, because they were generally considered not interpretable. Therefore, no comments are made on the company's assessment of this outcome.

Serious adverse events

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant for the outcome "serious adverse events (SAE)". A greater harm of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is

therefore not proven for this outcome (see Section 2.7.2.4.3 of the full dossier assessment for a discussion on the risk of bias in the recording of SAEs and other ocular AEs). This corresponds to the company's assessment.

Discontinuation due to adverse events

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting for the outcome "discontinuation due to adverse events" were not statistically significant. A greater harm of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for this outcome. This corresponds with the company's assessment.

Deterioration in visual acuity≥ 2 and ≥ 6 lines (10 and 30 ETDRS letters)

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting showed a considerable heterogeneity ($p < 0.2$, see Figure 89 on p. 277 of Module 4 of the dossier, Population with baseline visual acuity ≥ 35 ETDRS letters) for the outcome "deterioration in visual acuity ≥ 2 ETDRS lines". No factor could be identified that might explain this heterogeneity. Due to the heterogeneity, it was not meaningful to show an overall estimator. Consideration of the results of the individual studies did not enable any clear direction of effect to be identified and none of the individual studies showed a statistically significant result.

The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were not statistically significant different for the outcome "deterioration in visual acuity of 6 lines".

A greater harm of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms is therefore not proven for these outcomes. This corresponds with the company's assessment.

Ocular adverse events

All AE that were coded with the location "eye" were recorded for the outcome "ocular adverse events". The results of the meta-analysis on the comparison of ocriplasmin with watchful waiting were statistically significant to the disadvantage of ocriplasmin for this outcome. However, in the subsequent assessment of subgroup characteristics, there was an indication of an effect modification by the characteristic "sex". This means that possible conclusions on added benefit regarding this outcome are drawn on the basis of subgroups. The subgroup analyses and the related interpretation of the results and documentation of the evidence can be found in the next subsection. Consideration of the subgroup data showed that a greater harm of ocriplasmin in comparison with watchful waiting is not proven for ocular adverse events.

Subgroup analyses

In order to identify a possible effect modification, selected subgroups were investigated to see whether heterogeneous treatment effects were present. Only some of the subgroup

characteristics, and their analysis and thresholds, were pre-defined in the studies (see Section 2.7.2.2 of the full dossier assessment). Corresponding analyses carried out by the company for the outcomes it considered relevant were submitted, but not on the relevant subpopulation with mild symptoms. Based on the small proportions of patients with severe symptoms, this approach did not lead to a reduction in the informative value of the evidence (see Section 2.7.2.3.2 of the full dossier assessment).

Subgroup analyses on the following characteristics were considered for this benefit assessment of the research question on the VMT population with mild symptoms:

- Age (< 65/≥ 65)
- Sex
- Baseline visual acuity (35 to 60/> 60 ETDRS letters)
- Region (USA/Europe)
- Existence/non-existence of an epiretinal membrane at the start of the study

Table 10 lists p-values of the interaction tests from the subgroup analyses of the comparison of ocriplasmin with watchful waiting on the included outcomes.

Table 10: Summary of interaction tests of the relevant subgroup analyses – RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Outcome	**Subgroups**[a]				
	Sex	**Age**	**Baseline visual acuity in ETDRS letters**	**Region**	**ERM at start of study**
	(Men/ Women)	**(< 65 years/ ≥ 65 years)**	**(35-60/> 60)**	**(USA/ Europe)**	**(present/not present)**
All-cause mortality	n. k.[b]	n. k.[b]	n. k.[b]	n. k.[b]	n. k.[b]
Improvement in visual acuity ≥2 lines (10 ETDRS letters)	0.68	0.51	0.551	0.965[c]	0.57
Vitrectomy	0.96	0.93	**0.064**[c]	0.544[c]	0.99
Health-related quality of life (NEI VFQ-25 Responders)	n. k.[d]	n. k.[d]	0.616[c]	0.287[c]	n. k.
SAEs	**0.14**	0.78	**0.037**[c]	0.483[c]	0.94
Discontinuation due to AE	n. k.[b]	n. k.[b]	n. k.[b]	n. k.[b]	n. k.[b]
Deterioration in visual acuity ≥ 2 lines (10 ETDRS letters)	0.70	0.87	0.601[c]	0.746[c]	0.26
Deterioration in visual acuity ≥ 6 lines (30 ETDRS letters)	0.85	0.46	0.913[c]	0.442[c]	0.93
Ocular AEs	**0.103**[c]	0.962[c]	0.517[c]	0.819[c]	n. k.

Bold: Indication or proof of an interaction
a: Interaction tests based on Studies TG-MV-004, TG-MV-006 and TG-MV-007. Interaction tests on ERM at start of study based on Studies TG-MV-006 and TG-MV-007.
b: Due to low number of events, the company did not carry out any subgroup analyses.
c: Institute's calculation.
d: No valid subgroup analyses available.
AE: adverse event; ETDRS: Early Treatment Diabetic Retinopathy Study; ERM: epiretinal membrane; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; n. k.: not known; SAE: serious adverse event

Only the results on subgroups and outcomes for which at least indications of an interaction between treatment effect and subgroup characteristic were found are presented below. The condition imposed for proof of different subgroup effects was a statistically significant interaction ($p < 0.05$). A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

There was an indication ($p < 0.2$) of an effect modification by the characteristic "sex" for both the outcomes "SAE" and "ocular AE". In addition, there was proof of an effect modification ($p < 0.05$) by baseline visual acuity for the outcome "SAE" and an indication of an effect

modification regarding the outcome "vitrectomy". The subgroup results in the individual studies on these 4 constellations are shown in Table 11 below.

Table 11: Subgroups with at least indications of interaction: RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection)

Outcome Characteristics Study Subgroup	Ocriplasmin		Watchful waiting (with sham or placebo injection[a])		Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
Vitrectomy						
Baseline visual acuity in letters ETDRS[b]						
TG-MV-004						
35-60	6	1 (16.7)	3	2 (66.7)	0.25 [0.04; 1.77]	
> 60	7	0 (0.0)	4	0 (0.0)	n. e.	
TG-MV-006						
35-60	65	25 (38.5)	33	12 (36.4)	1.06 [0.61; 1.83]	
> 60	145	14 (9.7)	72	18 (25.0)	0.39 [0.20; 0.73]	
TG-MV-007						
35-60	67	17 (25.4)	20	7 (35.0)	0.72 [0.35; 1.50]	
> 60	159	15 (9.4)	57	10 (17.5)	0.54 [0.26; 1.13]	
Total					Interaction:	0.064[c]
35-60	138	43 (31.2)	56	21 (37.5)	0.85 [052; 1.37][c]	0.500[c]
> 60	311	29 (9.3)	133	28 (21.1)	0.44 [0.27; 0.72][c]	0.001[c]
SAEs						
Sex[d]						
TG-MV-004						
Men	5	0 (0)	6	0 (0)	n. e.	
Women	8	2 (25.0)	3	0 (0)	2.22 [0.14; 36.49]	
TG-MV-006						
Men	70	4 (5.7)	47	6 (12.8)	0.45 [0.13; 1.50]	
Women	142	22 (15.5)	57	7 (12.3)	1.26 [0.57; 2.79]	
TG-MV-007						
Men	79	6 (7.6)	25	3 (12.0)	0.63 [0.17; 2.35]	
Women	155	23 (14.8)	55	8 (14.5)	1.02 [0.49; 2.15]	
Total					Interaction:	0.14[c]
Men	154	10 (6.5)	78	9 (11.5)	0.52 [0.22; 1.28][c]	0.16[c]
Women	305	47 (15.4)	115	15 (13.0	1.15 [0.68; 1.97][c]	0.60[c]

(continued)

Table 11: Subgroups with at least indications of interaction: RCT, direct comparison: ocriplasmin versus watchful waiting (with sham or placebo injection) (continued)

Outcome Characteristic Study Subgroup	Ocriplasmin		Watchful waiting (with sham or placebo injection[a])		Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]	p-value
Baseline visual acuity in ETDRS letters[b]						
TG-MV-004						
35-60	6	1 (16.7)	3	0 (0.0)	1.71 [0.09; 32.93]	
> 60	7	1 (14.3)	4	0 (0.0)	1.88 [0.09; 37.63]	
TG-MV-006						
35-60	65	16 (24.6)	33	3 (9.1)	2.71 [0.85; 8.64]	
> 60	146	10 (6.8)	71	10 (14.1)	0.49 [0.21; 1.11]	
TG-MV-007						
35-60	67	13 (19.4)	20	3 (15.0)	1.29 [0.41; 4.09]	
> 60	159	16 (10.1)	57	7 (12.3)	0.66 [0.37; 1.17]	
Total					Interaction:	0.037[c, e]
35-60	138	30 (21.7)	56	6 (10.7)	1.86 [0.84; 4.08][c]	0.12[c]
> 60	312	27 (8.7)	132	17 (12.9)	0.66 [0.37; 1.17][c]	0.15[c]
Ocular AEs						
Sex[d]						
TG-MV-004						
Men	5	2 (40.0)	6	4 (66.7)	0.60 [0.18; 2.02][e]	
Women	8	6 (75.0)	3	1 (33.3)	2.25 [0.43; 11.71][e]	
TG-MV-006						
Men	70	43 (61.4)	47	29 (61.7)	1.00 [0.74; 1.33][e]	
Women	142	113 (79.6)	57	35 (61.4)	1.30 [1.04; 1.62][e]	
TG-MV-007						
Men	79	51 (64.6)	25	14 (56.0)	1.15 [0.79; 1.69][e]	
Women	155	103 (66.5)	55	28 (50.9)	1.31 [0.98; 1.73][e]	
Total					Interaction:	0.103[c, e]
Men	154	96 (62.3)	78	47 (60.3)	1.03 [0.82; 1.29][c, e]	0.800[c, e]
Women	305	222 (72.8)	115	64 (55.7)	1.31 [1.10; 1.56][c, e]	0.002[c, e]

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
b: Information for the VMT population with mild symptoms.
c: Value from meta-analysis.
d: Information for the target population (patients with macular hole ≤ 400 µm).
e: Institute's calculation.

AE: adverse event; CI: confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; N: number of patients analysed; n: number of patients with event; n. e.: not evaluable; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VMT: vitreomacular traction

The results for the outcome "serious adverse events" were not statistically significant (see Table 9), but there was an indication of interaction regarding the characteristics "sex" and "baseline visual acuity". Results of the subgroup analyses showed no statistically significant effect either in the individual studies, or in the corresponding meta-analysis on one of the subgroups. Therefore there is no proof of a greater harm of ocriplasmin in comparison with the ACT in the VMT population with mild symptoms for the outcome "SAE".

The result was statistically significant for the outcome "vitrectomy" and there was an indication of interaction concerning the characteristic "baseline visual acuity". Meta-analysis of the results of the subgroup analysis showed a statistically significant effect solely in patients with a baseline visual acuity > 60 ETDRS letters, but not in those with a value of 35 to 60. A representation of the meta-analysis on this subgroup analysis is shown below (Figure 1).

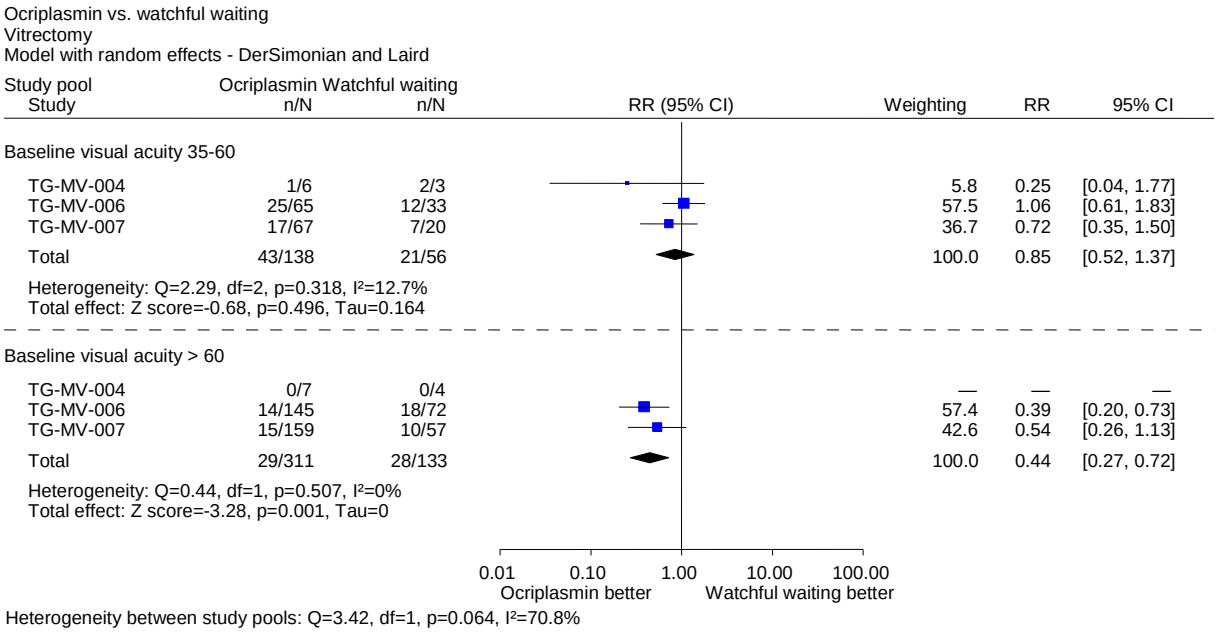

Figure 1: Subgroup analysis – baseline visual acuity (35 to 60/> 60 ETDRS letters), outcome "vitrectomy", ocriplasmin versus watchful waiting in VMT population with mild symptoms

The visual assessment of the subgroup analysis for the outcome "vitrectomy" according to baseline visual acuity shows that, in contrast to the other subgroup, although in the comparison of patients with moderate visual impairment (> 60 ETDRS letters) the effect estimator was in the direction in favour of ocriplasmin, the difference was not statistically significant.

Overall, there is an indication of an added benefit in patients with mild visual impairment in terms of the proportion of patients with vitrectomy. For patients with moderate visual impairment – despite a non-significant effect – there is a hint of an added benefit in terms of

the proportion of patients with vitrectomy, because only an indication of interaction is present and the results of the total population are statistically significant. This deviates from the company's assessment, which assumed proof of added benefit for this outcome, which was "particularly marked" in those patients with a visual acuity more than 60 letters ETDRS. This difference is because the company rated the risk of bias of all 3 studies as low and interpreted the results of the subgroup analysis without downgrading the certainty of results.

The results were statistically significant for the outcome "ocular adverse events" and an indication of an interaction was demonstrated concerning the characteristic "sex". Meta-analysis of the results of the subgroup analysis showed a statistically significant effect exclusively for women, but not for men. The representation of the meta-analysis on this subgroup analysis is shown below (Figure 2).

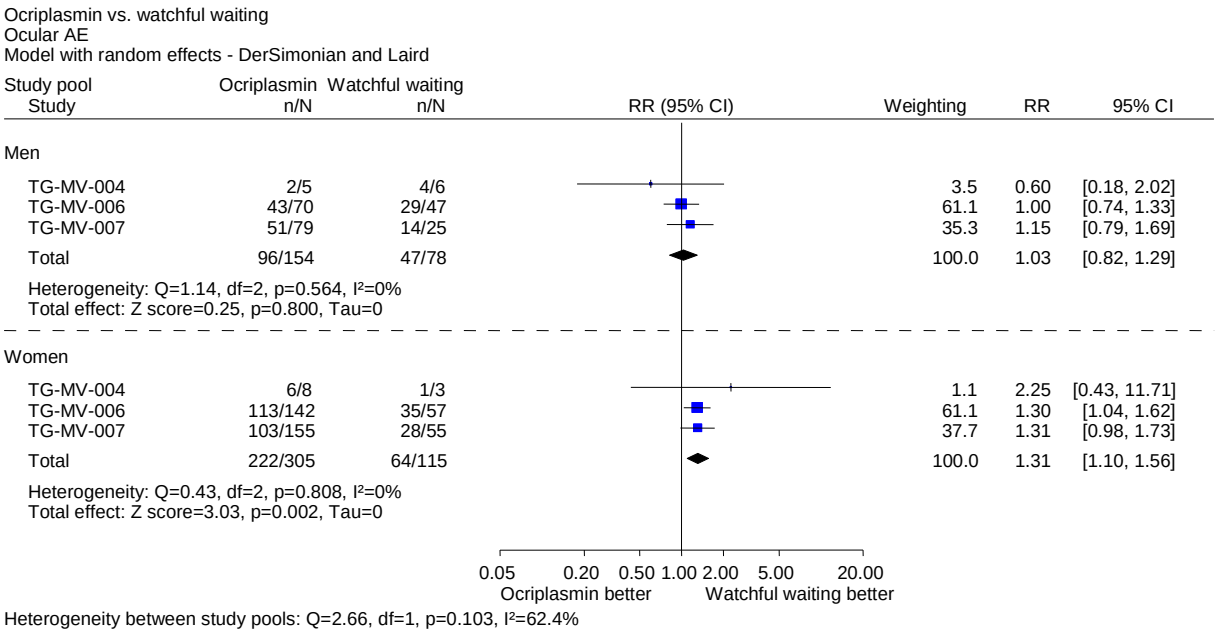

Figure 2: Subgroup analysis – sex, ocular AE, ocriplasmin versus watchful waiting in VMT population with mild symptoms

However, because the effect size was only marginal (the upper confidence interval was above the threshold of 0.9), even on separate consideration of the subgroup of women, a greater harm of ocriplasmin is not proven. Overall, in the comparison of ocriplasmin with the ACT, a greater harm for the outcome "ocular adverse events" in the VMT population with mild symptoms is not proven (see Table 12 in Section 2.5.1).

Further information about choice of outcomes and risk of bias at outcome level and outcome results can be found in Module 4, Sections 4.2.5.2, 4.3.1.2.2 and 4.3.1.3 of the dossier and in Sections 2.7.2.4.2, and 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of the added benefit

The derivation of extent and probability of added benefit at outcome level is presented below for the 3 subpopulations, taking into account the various outcome categories and effect sizes. The methods used for this purpose are explained in Appendix A of Benefit Assessment A11-02 [2].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The decision on added benefit is made by the G-BA.

2.5.1 Assessment of added benefit at outcome level

VMT population with mild symptoms

The data presented in Section 2.4 produced the following evaluations for ocriplasmin in comparison with the ACT (watchful waiting) in the VMT population with mild symptoms:

- an indication of an added benefit in terms of an improvement in visual acuity (≥ 2 ETDRS lines),
- an indication of an added benefit in patients with mild visual impairment in terms of the proportion of patients with vitrectomy,
- a hint of an added benefit in patients with moderate visual impairment in terms of the proportion of patients with vitrectomy.

The results on visual acuity were assigned to the outcome category “non-serious/non-severe symptoms/late complications”, since the study participants had, on average, only a mild visual impairment according to ICD-10 (65 ETDRS letters, see Table 5). This was also reflected in the assignment of the majority of study participants to the VMT population with mild symptoms.

The results on vitrectomy were assigned to the outcome category “serious/severe symptoms/ late complications”, because it is highly probable that the operated patients develop a cataract.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Extent of added benefit at outcome level: ocriplasmin versus watchful waiting (with sham or placebo injection; VMT population with mild symptoms)

Outcome category **Outcome**		**Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])/** **Proportion of events/** **Effect estimator [95% CI][b]** **p-value[b]/** **probability[c]**	**Derivation of extent[d]**
Mortality			
All-cause mortality		0.8% vs. 0% Peto OR: 4.31 [0.51; 36.38] p = 0.18	Added benefit not proven
Morbidity			
Improvement in visual acuity ≥ 2 lines (10 ETDRS letters)		28.3% vs. 15.9% RR: 1.81 [1.26; 2.58] RR: 0.55 [0.39; 0.79][e] p = 0.001 Probability: "indication"	Outcome category: "non-severe/non-serious symptoms/late complications" $CI_o < 0.80$ Added benefit, extent: "considerable"
Vitrectomy	Mild visual impairment (> 60 ETDRS letters)	9.3% vs. 21.1% RR: 0.44 [0.27; 0.72] p = 0.001 Probability: "indication"	Outcome category: "serious/severe symptoms/late complications" $CI_o < 0.75$ Added benefit, extent: "major"
	Moderate visual impairment (35-60 ETDRS letters)	31.2% vs. 37.5% RR: 0.85 [0.52; 1.37] p = 0.500 Probability: "hint"	Outcome category: "serious/severe symptoms/late complications" Added benefit, extent: "not quantifiable", at most "considerable"[f]
Health-related quality of life			
NEI VFQ-25 (Responders)		42.7% vs. 32.6% RR: 1.30 [0.95; 1.77] p = 0.097	Added benefit not proven
Adverse events			
SAEs		12.7% vs. 12.2% RR: 1.01 [0.64; 1.59] p = 0.96	Greater/lesser harm not proven.
Discontinuation due to AEs		0.8% vs. 1.0% Peto OR: 0.86 [0.15; 4.97] p = 0.86	Greater/lesser harm not proven.
Deterioration in visual acuity ≥ 2 lines (10 ETDRS letters)		Heterogeneity of results; no statistically significant results in the individual studies	Greater/lesser harm not proven.

(continued)

Table 12: Extent of added benefit at outcome level: ocriplasmin versus watchful waiting (with sham or placebo injection; VMT population with mild symptoms) (continued)

Outcome category **Outcome**		**Ocriplasmin vs. watchful waiting (with sham or placebo injection[a])/** **Proportion of events/** **Effect estimator [95% CI][b]/** **p-value[b]/** **probability[c]**	**Derivation of extent[d]**
Deterioration in visual acuity ≥ 6 lines (30 ETDRS letters)		1.3% vs. 1.1% RR: 1.24 [0.27; 5.75] p = 0.78	Greater/lesser harm not proven.
Ocular AEs	Men	62.3% vs. 60.3% RR: 1.03 [0.82; 1.29] p = 0.800	Greater/lesser harm not proven.
	Women	72.8% vs. 55.7% RR: 1.31 [1.10; 1.56] RR: 0.76 [0.64; 0.91][e] p = 0.002	Outcome category: “non-serious/severe adverse events” $CI_u > 0.90$ Greater/lesser harm not proven[g]

a: Sham injection (i.e. without puncture of the vitreous body) was used in the control arm of Study TG-MV-004, whereas in TG-MV-006 and TG-MV-007, placebo solution was injected into the vitreous body.
b Value from meta-analysis.
c: Probability provided, if statistically significant differences were present.
d: Estimations on effect size made with different limits depending on the outcome category, based on the upper limit of the confidence interval (CI_o).
e: Institute's calculation, direction of effect reversed in order to enable immediate use of limits to derive the added benefit.
f: In view of the results of the total population (upper limit of the 95% confidence threshold at 0.88), the extent of added benefit can, at most, be “considerable”.
g: Since upper limit of the confidence interval was above the specified threshold of 0.90.
AE: adverse event ; CI: confidence interval; CI_u: upper limit of confidence interval; ETDRS: Early Treatment Diabetic Retinopathy Study; NEI VFQ-25: National Eye Institute 25-item Visual Function Questionnaire; OR: odds ratio; RR: relative risk; SAE: serious adverse event; VMT: vitreomacular traction; vs.: versus

Subpopulation with asymptomatic VMT

No data were available in the dossier for the comparison of ocriplasmin with the ACT therapy (watchful waiting) in the subpopulation with asymptomatic VMT.

VMT population with severe symptoms

No data were available in the dossier for the comparison of ocriplasmin with the ACT therapy (pars plana vitrectomy) in the VMT population with severe symptoms.

2.5.2 Overall conclusion on added benefit

VMT population with mild symptoms

Table 13 and Table 14 summarize the results considered in the overall conclusion on the extent of added benefit, divided according to the relevant subgroups.

Table 13: Patients with mild visual impairment (> 60 ETDRS letters): positive and negative effects from the assessment of ocriplasmin compared with watchful waiting

Positive effects	Negative effects
Indication of an added benefit – Extent: "considerable" (non-serious/non-severe symptoms/late complications: improvement in visual acuity ≥ 2 lines [10 ETDRS letters])	
Indication of an added benefit – Extent: "major" (serious/severe symptoms/late complications: vitrectomy)	
ETDRS: Early Treatment Diabetic Retinopathy Study	

Based on the available results, in the overall assessment at outcome level, there remain only 2 positive effects for the group of patients with mild visual impairment. These consist of an indication of a considerable added benefit in the outcome category "non-serious/non-severe symptoms/late complications" (improvement in visual acuity ≥ 2 lines [10 ETDRS letters]) and an indication of a major added benefit in the outcome category "serious/severe symptoms/late complications" (vitrectomy).

In summary, for patients with mild visual impairment (> 60 ETDRS letters) there is an indication of a major added benefit of ocriplasmin compared with watchful waiting.

Table 14: Patients with moderate visual impairment (35 to 60 ETDRS letters): positive and negative effects from the assessment of ocriplasmin compared with watchful waiting

Positive effects	Negative effects
Indication of an added benefit – Extent: "considerable" (non-serious/non-severe symptoms/late complications: improvement in visual acuity ≥ 2 lines [10 ETDRS letters])	
Hint of an added benefit – Extent: "non-quantifiable", at most "considerable" (serious/severe symptoms/late complications: vitrectomy)	
ETDRS: Early Treatment Diabetic Retinopathy Study	

Based on the available results, in the overall assessment at outcome level, there remain only 2 positive effects for the group of patents with moderate visual impairment. These consist of an indication of a considerable added benefit in the outcome category "non-serious/non-severe symptoms/late complications" (improvement in visual acuity ≥ 2 lines [10 ETDRS

letters]) and a hint of a non-quantifiable added benefit (extent: at most "considerable") in the outcome category "serious/severe symptoms/late complications" (vitrectomy).

In summary, for patients with moderate visual impairment (35 to 60 ETDRS letters) there is an indication of a considerable added benefit of ocriplasmin compared with watchful waiting.

Subpopulation with asymptomatic VMT

No data were available for a comparison of ocriplasmin with watchful waiting in the subpopulation with asymptomatic VMT (see Section 2.7.2.1 of the full dossier assessment). Hence, the added benefit of ocriplasmin in the subpopulation with asymptomatic VMT compared with watchful waiting is not proven.

VMT population with severe symptoms

No data were available for a comparison of ocriplasmin with pars plana vitrectomy in the VMT population with severe symptoms (see Section 2.7.2.1 of the full dossier assessment). Hence, the added benefit of ocriplasmin in the VMT population with severe symptoms compared with pars plana vitrectomy is not proven.

2.5.3 Extent and probability of added benefit – Summary

The extent and probability of added benefit for the benefit assessment of ocriplasmin in comparison with the ACT for the relevant subpopulations can be summarized as follows:

Table 15: Ocriplasmin: extent and probability of added benefit

Subpopulation		**Appropriate comparator therapy**	**Extent and probability of the added benefit**
Subpopulation with asymptomatic VMT		Watchful waiting	Added benefit not proven
VMT population with mild symptoms	Patients with mild visual impairment (> 60 ETDRS letters)	Watchful waiting	Indication of an added benefit (Extent: "major")
	Patients with moderate visual impairment (35-60 ETDRS letters)	Watchful waiting	Indication of an added benefit (Extent: "considerable")
VMT population with severe symptoms		Pars plana vitrectomy	Added benefit not proven
VMT: vitreomacular traction			

The overall assessment deviates from that of the company, who claimed proof of a considerable added benefit for VMT patients with mild symptoms.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

TG-MV-004

Ergänzende Darstellung der Subgruppen nach Alter, Geschlecht (Zulassungspopulation): Studien TG-MV-004, TG-MV-006, TG-MV-007 [Supplementary presentation of subgroups according to age and sex (approval population): studies TG-MV-004, TG-MV-006, TG-MV-007] [unpublished].

Alcon Laboratories. Additional analyses for study: a randomized, sham-injection controlled, double masked, ascending-dose, dose-range-finding trial of microplasmin intravitreal injection for non-surgical PVD induction for treatment of vitreomacular traction: the MIVI-IIT (microplasmin for vitreous injection II-traction) trial; study TG-MV-004 [unpublished]. 2013.

Stalmans P, Delaey C, De Smet MD, Van Dijkman E, Pakola S. Intravitreal injection of microplasmin for treatment of vitreomacular adhesion: results of a prospective, randomized, sham-controlled phase II trial (the MIVI-IIT trial). Retina 2010; 30(7): 1122-1127.

ThromboGenics. A randomized, sham-injection controlled, double masked, ascending-dose, dose-range-finding trial of microplasmin intravitreal injection for non-surgical PVD induction for treatment of vitreomacular traction: the MIVI-IIT (microplasmin for vitreous injection II-traction) trial; study TG-MV-004; clinical study report [unpublished]. 2011.

TG-MV-006

Ergänzende Darstellung der Subgruppen nach Alter, Geschlecht (Zulassungspopulation): Studien TG-MV-004, TG-MV-006, TG-MV-007 [Supplementary presentation of subgroups according to age and sex (approval population): studies TG-MV-004, TG-MV-006, TG-MV-007] [unpublished].

Chiltern, ThromboGenics. Additional analyses for study: Ocriplasmin; a randomized, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non surgical treatment of focal vitreomacular adhesion; study TG-MV-006 [unpublished]. 2013.

Stalmans P, Benz MS, Gandorfer A, Kampik A, Girach A, Pakola S et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med 2012; 367(7): 606-615.

Stalmans P, Girach A, Haller JA. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes: the authors reply. N Engl J Med 2012; 367(21): 2054.

ThromboGenics. Ocriplasmin: a randomized, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non surgical treatment of focal vitreomacular adhesion; study TG-MV-006; clinical study report [unpublished]. 2011.

TG-MV-007

Ergänzende Darstellung der Subgruppen nach Alter, Geschlecht (Zulassungspopulation): Studien TG-MV-004, TG-MV-006, TG-MV-007 [Supplementary presentation of subgroups according to age and sex (approval population): studies TG-MV-004, TG-MV-006, TG-MV-007] [unpublished].

Chiltern, ThromboGeneics. Additional analyses for study: Ocriplasmin; a randomized, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non surgical treatment of focal vitreomacular adhesion; study TG-MV-007 [unpublished]. 2013.

Stalmans P, Benz MS, Gandorfer A, Kampik A, Girach A, Pakola S et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med 2012; 367(7): 606-615.

Stalmans P, Girach A, Haller JA. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes: the authors reply. N Engl J Med 2012; 367(21): 2054.

ThromboGenics. Ocriplasmin: a randomized, placebo controlled, double masked, multicenter trial of microplasmin intravitreal injection for non surgical treatment of focal vitreomacular adhesion: study TG-MV-007; clinical study report [unpublished]. 2011.

References for English extract

Please see full dossier assessment for full reference list.

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