HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

4 December 2013

JETREA 0.5 mg/0.2 ml, concentrate for solution for injection

1 vial of 0.2 ml (CIP: 34009 584 797 1 7)

Applicant: ALCON S.A.S

INN	ocriplasmin
ATC code (2013)	S01XA22 (other ophthalmologicals)
Reason for the request	**Inclusion**
List(s) concerned	**Hospital use** (French Public Health Code L.5123-2)
Indication(s) concerned	**"JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns."**

Actual Benefit	**The actual benefit of JETREA is:** **- substantial in patients with vitreomacular traction, isolated or associated with macular hole of ≤400 µm, the symptoms of which do not immediately necessitate vitrectomy,** **- insufficient, in the absence of clinical data, in patients with vitreomacular traction, isolated or associated with macular hole of ≤400 µm, the symptoms of which do immediately necessitate vitrectomy.**
Improvement in Actual Benefit	**Since:** **- the efficacy of JETREA has been studied only in patients with vitreomacular traction, isolated or associated with macular hole of diameter of less than or equal to 400 µm and the symptoms of which did not immediately justify vitrectomy, corresponding to patients who are not severely affected, i.e. a subpopulation of the Marketing Authorisation indication for JETREA.** **For these patients who are not severely affected,** **- it was expected that the administration of JETREA reduces or even eliminates the need for surgical vitrectomy which has a high success rate but is not free from risks, which has not been demonstrated,** **- the efficacy of JETREA, with follow-up limited to 6 months, is modest,** **the Committee believes that JETREA provides a minor improvement in actual benefit (IAB IV) in the management of a subpopulation of the Marketing Authorisation represented by patients with vitreomacular traction, isolated or associated with macular hole of diameter less than or equal to 400 µm and for whom the symptoms do not immediately necessitate vitrectomy.**
Therapeutic use	**JETREA is a 1st line treatment for vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm, the symptoms of which do not immediately necessitate use of vitrectomy.** **JETREA has not been studied in patients with vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm who are severely affected, for whom the current therapeutic strategy recommends vitrectomy without delay. JETREA does not, in the light of the current data, have any place in therapeutic use in this subpopulation.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Dated initiated (centralised procedure): 13 March 2013 Risk Management Plan including monitoring of "substantial risks (see 08.2 Adverse effects).
Prescribing and dispensing conditions / special status	List I Medicinal product reserved for hospital use Prescription restricted to ophthalmologists

ATC Classification	2013	
	S	Sensory organs
	S01	Ophthalmologicals
	S01X	Other ophthalmologicals
	S01XA	Other ophthalmologicals
	S01XA22	Ocriplasmin

02 BACKGROUND

The company is applying for the inclusion of JETREA, concentrate for solution for injection, the active ingredient of which is ocriplasmin, a medicine reserved for hospital use, on the list of medicines approved for use by hospitals.

Ocriplasmin, a truncated form of human plasmin produced by recombinant DNA technology, has proteolytic activity against the protein constituents of the vitreous humour and the vitreoretinal interface (for example laminin, fibronectin and collagen). It is intended to dissolve the protein matrix responsible for abnormal adhesion between the vitreous body and the macular region. The close bonding of protein components within the macular zone contributes to vitreomacular traction, leading to impaired vision or macular holes.

JETREA in injected into the vitreous humour of the affected eye, in a single administration which cannot be repeated.

03 THERAPEUTIC INDICATIONS

"JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns."

04 DOSAGE

“JETREA must be prepared and administered by a qualified ophthalmologist experienced in intravitreal injections. The diagnosis of vitreomacular traction (VMT) should comprise of a complete clinical picture including patient history, clinical examination and investigation using currently accepted diagnostic tools, such as optical coherence tomography (OCT).

Posology

The recommended dose is 0.125 mg (0.1 ml of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose. Each vial should only be used once and for the treatment of a single eye. Treatment with JETREA in the other eye is not recommended concurrently or within 7 days of the initial injection in order to monitor the post-injection course including the potential for decreased vision in the injected eye. Repeated administration in the same eye is not recommended.

Method of administration

Preoperative antibiotic drops may be administered at the discretion of the treating ophthalmologist.

Precautions to be taken before handling or administering the medicinal product:
The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include the use of surgical hand disinfection, sterile gloves, a sterile drape, a sterile eyelid speculum (or equivalent) and the availability of sterile paracentesis (if required). The periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia and a broad spectrum topical microbiocide should be administered prior to the injection according to standard medical practice.

The injection needle should be inserted 3.5-4.0 mm posterior to the limbus aiming towards the centre of the vitreous cavity avoiding the horizontal meridian. The injection volume of 0.1 ml is then delivered into the mid-vitreous.”

05 THERAPEUTIC NEED

Vitreomacular traction (VMT) is incomplete separation of the vitreous body at the level of the posterior pole with, in particular, persistence of vitreomacular attachment (anatomical signs), associated with more or less pronounced visual functional symptoms (metamorphopsia,[1] micropsia,[2] reduction in visual acuity and/or central scotoma). Vitreomacular traction may induce the formation of an epiretinal membrane,[3] which strengthens vitreomacular adhesion[4] and is often complicated by macular oedema. Untreated vitreomacular traction may lead to a macular hole or a full-thickness opening in the retinal tissue in the macular zone. Most of these holes are idiopathic (85% to 92%) or, more rarely, traumatic (8% to 15%).[5,6]
Vitreomacular traction, whether or not associated with macular hole, has a poor visual prognosis if it is not treated: progressive, or rapid in the case of a macular hole, decline in vision, worsening of visual symptoms and potentially irreversible retinal damage.
A diagnosis of vitreomacular traction, whether or not associated with macular hole, is made by means of questioning and a functional and anatomical assessment.[7,8] Optical coherence tomography is the reference diagnostic investigation; it can also be used to monitor developments by repeating the measurement of macular thickness.

Vitreomacular traction rarely regresses spontaneously.[9]

The development and prognosis of macular holes differ according to their stages:[10]
- Stage 1 or threat of macular hole regressing (50% of cases), full-thickness macular hole progressing (40% of cases), or progressing to lamellar holes in the innermost part of the retina with no full-thickness loss of substance (10% of cases).

- Stage 2 or full-thickness macular hole with retraction of the internal layers of the retina, ≤ 400 µm in diameter, recent, forming spontaneously in a few weeks (5 to 10% of cases) or progressing to stage 3 (about 75% of cases).

- Stage 3 or established full-thickness macular hole with an operculum and raised margins and stage 4 or full-thickness macular hole with posterior detachment of the entire vitreous body, generally of a diameter of > 400 µm, growing in 50% and 20% of cases respectively.

The objective of treatment is to eliminate adhesion between the vitreous body and the macula, which leads to traction, to make the visual symptoms regress (metamorphopsia, central scotoma), to improve visual acuity and, where appropriate, to make the macular hole close.

To date, the only treatment option for vitreomacular traction and macular hole (whatever the diameter) is surgical, by vitrectomy (ablation of the vitreous body).

[1] Distorted perception of straight lines and images.
[2] Distorted perception of objects and people which makes them seem smaller.
[3] Proliferative membrane at the level of the vitreoretinal interface which may shrink and cause thickening of the macula leading to a reduction in visual acuity and/or metamorphopsia.
[4] Areas of strong vitreoretinal adhesion at the level of the macula which can be explained by the presence of structures between the posterior part of the vitreous cortex and the internal basement membrane of the retina.
[5] McCannel CA et al. Population based incidence of macular holes. Ophthalmology 2009;116(7):1366-1369.
[6] McDonnell PJ et al. Clinical features of idiopathic macular cysts and holes. Am J Ophthalmol 1982;93:777-786.
[7] Brasseur G. Syndrome de traction vitréomaculaire.
J Fr Ophtalmol 2008;31(2):203-213
[8] Français-Maury C et al. Bilan actuel d'un syndrome de l'interface maculaire. J Fr Ophtalmol 2008;31(2):187-191
[9] Perol J et al. Trous maculaires. In: Cohen SY et Gaudric A, editors. Retine: Lavoisier, 2012.
[10] La Cour M, Friis J. Macular holes: classification, epidemiology, natural history and treatment. Acta Ophthalmol Scand 2002;80(6):579-587.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

No other medicinal product is indicated in the treatment of vitreomacular traction, particularly when associated with macular hole of diameter less than or equal to 400 µm.

06.2 Other health technologies

The only therapeutic option available is vitrectomy by means of a vitreotome which can be used to cut and aspirate the vitreous body, injecting physiological fluid as necessary to keep ocular volume and pressure constant. At the end of the procedure, balanced saline, silicone oil or gas is injected into the eye to replace the vitreous body and to re-establish normal intraocular pressure.[11,12]
The procedure is carried out under local or general anaesthesia. In the event of macular hole surgery, in the postoperative period it is recommended that the patient should keep his/her head bent forward (head facing down, parallel to the ground); this position should usually be held day and night for 5 to 8 days.
Because of its risks (retinal tear, haemorrhage, loss of vision), its complications (cataract, endophthalmitis, inflammation, acute changes in ocular pressure, etc.), and limitations, vitrectomy is indicated only case by case according to the degree of impact and/or visual disability, the diameter of the macular hole when there is one, or where there is a sudden worsening in symptoms, and before the occurrence of irreversible retinal damage.
The success rates of vitrectomy are approximately between 80% and 100%.[13]

◗ Conclusion

There is no pharmaceutical comparator for ocriplasmin. Surgery (vitrectomy) is at present the only relevant comparator depending on the symptoms of VMT, whether or not associated with macular hole:
- In the event of isolated VMT or with a threat of macular hole (stage 1), close medical monitoring is recommended until there is a stage of reduced visual acuity (generally a threshold below 0.4-0.5) which justifies vitrectomy.

- In the presence of macular hole:
    - ≤250 µm and of recent appearance, short-term, close medical monitoring may be suggested. If the macular hole has not closed after the specified period, vitrectomy is performed,
    - >250 µm, vitrectomy is usually carried out immediately.

[11] Perol J, Gualino V, Tadayoni R. Trous maculaires. In: Cohen SY et Gaudric A, editors. Retine: Lavoisier, 2012.
[12] Le Mer Y. La chirurgie du vitré évolue-t-elle ? J Fr Ophtalmol 2012;35:387-390.
[13] American Academy of Ophthalmology Retina Panel. Preferred Practice Pattern® Guidelines. Idiopathic Macular Hole. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: http://www.aao.org/ppp.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Marketing Authorisation	
	Date	**Indication(s)**
Canada	13 August 2013	JETREA is indicated in the treatment of symptomatic vitreomacular adhesion
European Union	13 March 2013	JETREA is indicated in adults for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns.
USA	17 October 2012	**"*JETREA is a proteolytic enzyme indicated for the treatment of symptomatic vitreomacular adhesion*".**

Country	Reimbursement	
	Status	**Scope**
England and Wales	NICE Opinion of 23 October 2013	*Ocriplasmin is recommended as an option for the treatment of VMT in adults, only if:* ***an epiretinal membrane is not present; and if they have a full-thickness, stage II macular hole with a diameter less than or equal to 400 microns and/or if they exhibit severe symptoms.***
Germany	Opinion of the Federal Joint Committee (G-BA) of 17 October 2013	*The benefit provided (medical improvement) by JETREA was recognized as:* *- a substantial improvement by comparison with close medical monitoring in patients with* ***VMT with mild symptoms,*** *- not demonstrated, in the absence of data, by comparison with vitrectomy in patients with* ***VMT with severe symptoms.***
Canada	Assessment in progress	Final decision expected in December 2013
Denmark	Yes* (27 May 2013)	Population of the indication in the European Marketing Authorisation
Scotland	No reimbursement: SMC Opinion of 9 September 2013	Not applicable
Ireland	Yes* (18 September 2013)	Population of the indication in the European Marketing Authorisation
Finland	Yes* (5 June 2013)	
Norway	Yes* (7 June 2013)	
Nether-lands	Yes (July 2013)	
Sweden	Yes* (27 May 2013)	
USA	Yes* (14 January 2013)	Population of the indication in the American Marketing Authorisation

**Reimbursed until Marketing Authorisation obtained and/or the medicinal product went on the market.*

08 ANALYSIS OF AVAILABLE DATA

In support of its application, the company submitted the results:

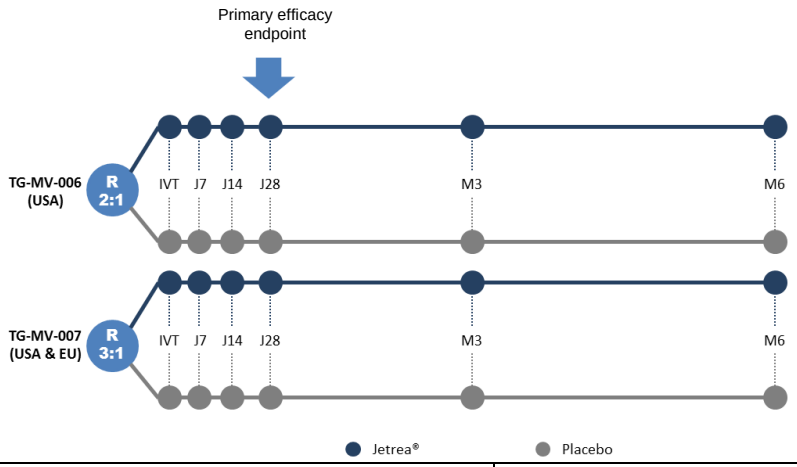
- of two phase III clinical studies[14] (TG-MV-006 (42 centres in the USA) and TG-MV-007 (48 centres in Europe[15] and the USA) with a common methodology, comparing the efficacy and safety of a single intravitreal injection of 125 µg of ocriplasmin with a single intravitreal injection of the excipient of JETREA in patients with vitreomacular traction, whether or not associated with macular hole of diameter less than or equal to 400 µm.

- of a pooled, planned and documented analysis of the results of the 2 aforementioned studies made before the code was broken, based on the similarity of the protocols; the differences concern the links between the JETREA/placebo randomisation and the geographical zones in which the studies were performed.

08.1 Efficacy: studies of ocriplasmin versus placebo

	Study TG-MV-006	Study TG-MV-007
Primary objective of the study	To assess the safety and efficacy of a single intravitreal injection of ocriplasmin in a dose of 125 µg in patients with vitreomacular traction, whether or not associated with macular hole less than or equal to 400 µm.	
Method	Randomised, double-blind, placebo-controlled study with a duration of six months.	
Inclusion criteria	- Men or women aged 18 or above, - Vitreomacular traction diagnosed in an eye examination by OCT, - Best corrected visual acuity (BCVA) of 20/25 or less in the eye studied, - BCVA of 20/800 or more in the other eye.	
Main exclusion criteria:	- Large diameter macular hole (> 400 microns; measured by OCT), - Severe myopia (spherical correction > 8 dioptres or axial length > 28 mm), - History of retinal detachment, - Zonular instability of the crystalline lens, - Proliferative diabetic retinopathy, - Ischaemic retinopathy, - Retinal venous occlusion, - Age-related macular degeneration (AMD), - Vitreous haemorrhage, - Recent eye surgery or intraocular injection (particularly laser treatment).	
Treatment groups	Ocriplasmin: 1 single intravitreal injection of 125 µg of ocriplasmin in 0.1 ml of solution. Placebo: 1 single intravitreal injection of 0.1 ml of the excipient of JETREA	
Course of the study	Patients received a single intravitreal injection of ocriplasmin in a dose of 125 µg or placebo (the excipient of JETREA) at the start of the study and were followed up for six months.	

[14] Stalmans P, et al. Enzymatic vitreolysis with ocriplasmin for vitreomacular traction and macular holes. N Engl J Med 2012; 367: 606-615.
[15] Germany, Belgium, Spain, Poland, Czech Republic, United Kingdom.

		
Number of patients included and randomisation ratio	326 patients included: • Ocriplasmin: 219 patients. • Placebo: 107 patients. Ratio 2:1 (ocriplasmin : placebo).	326 patients included: • Ocriplasmin: 245 patients. • Placebo: 81 patients. Ratio 3:1 (ocriplasmin : placebo).
Primary efficacy endpoint	Percentage of patients who had achieved nonsurgical resolution of vitreomacular adhesion (VMA) on the 28th day, determined by the centralised reading centre, based on the assessment by optical coherence tomography.	
Main secondary endpoints:	- Percentage of patients with total posterior vitreous detachment[16] (PVD) on the 28th day (determined by the investigator on the basis of standardised B mode ultrasound). - Percentage of patients with nonsurgical closure of the macular hole on the 28th day and at the 6th month. - Percentage of patients not requiring vitrectomy at the 6th month. - Percentage of patients with an improvement in BCVA with a gain of ≥ 2 lines or ≥ 3 lines (without vitrectomy and irrespective of vitrectomy) at the 6th month by comparison with baseline (measured using the ETDRS scale). - Mean change in BCVA (without vitrectomy and irrespective of vitrectomy) at the 6th month by comparison with baseline (measured using the ETDRS scale). - Mean change in the visual function score at the 6th month by comparison with baseline (measured using visual function questionnaire 25 (VFQ-25) of the National Eye Institute).	
Calculation of the number of people required	Assuming a success rate for the primary efficacy endpoint of 27.5% in the ocriplasmin group in a dose of 125 µg and of 10.0% in the placebo group, a sample of 320 patients for each study was expected to achieve a power of approximately 90% with a two-sided significance level of 0.05.	
Statistical analysis	The studies were analysed individually and in groups. The pooled analysis was planned and documented before the code was broken, based on the similarity of the protocols and the types of data collected (except for the randomisation ratios and the geographical zones in which the studies were performed). The differences between the treatments were assessed using Fisher's exact test (individual studies) or the Cochran-Mantel-Haenzel test, stratified by study (pooled data). For continuous variables, the differences between the treatments were assessed by means of an analysis of variance (ANOVA) with the study factor in the pooled analysis. Logistic regression analyses were carried out where necessary. The Breslow-Day test was used to test the hypothesis of the homogeneity of odds ratios between the studies.	

[16] Posterior vitreous detachment: detachment of the vitreous body which is normally bound to the retina (a physiological phenomenon linked to ageing of the eye). In the event of VMT, this detachment does not occur naturally.

	The comparison of the primary efficacy endpoint was made for a two-sided significance level of 0.05. The formal statistical test of the secondary endpoint of total PVD on the 28th day was assessed only if statistical significance ($p<0.05$) was achieved for the primary efficacy endpoint in both the ITT population and the modified ITT population. With the exception of the primary efficacy endpoint (resolution of VMA on the 28th day) and the secondary endpoint (total PVD on the 28th day), the analyses of the secondary endpoints were regarded as having a supporting or exploratory role. The results for these criteria are described with 95% confidence intervals. The missing data for the efficacy endpoints were replaced by the most recent observed value; the method of projecting the last observation was used to attribute any missing data.

8.1.1 Main characteristics of the patients included

The study populations are shown in Table 1.

Table 1: Study populations

	Study TG-MV-006	Study TG-MV-007	Pooled analysis
Randomised patients (n)	**326**	**326**	**652**
Ocriplasmin group (n)	***219***	245	464
Placebo group (n)	***107***	81	188
Patients who completed the study, n (%)	***298 (91%)***	309 (95%)	607 (93%)

The main characteristics of the patients included are shown in Table 2.

Study TG-MV-006
On inclusion, the characteristics of the patients were similar between the 2 groups, except for a lower percentage of women in the placebo group (placebo: 55.1%; ocriplasmin 67.6%) and of pseudophakic patients (with an artificial crystalline lens) (placebo: 27.1%; ocriplasmin: 41.6%). The mean age of the patients was 71.3 years. The mean score for best corrected visual acuity (BCVA) was 64.5 in the ocriplasmin group and 65.3 in the placebo group.

Study TG-MV-007
On inclusion, the demographic and ocular characteristics of the patients were similar between the groups. The mean age of the patients was 72.0 years. The mean scores for best corrected visual acuity (BCVA) were 64.9 in the ocriplasmin group and 63.4 in the placebo group.

Pooled analysis of the 2 studies
The mean age of the patients was 71.7 years. The percentage of women was slightly smaller in the placebo group (61.2%) than in the ocriplasmin group (67.7%), as was the percentage of pseudophakic patients (placebo: 28.7%; ocriplasmin: 37.1%).The mean scores for best corrected visual acuity (BCVA) were 63.9 in the ocriplasmin group and 65.1 in the placebo group.

Table 2: Demographic and ocular eye characteristics on inclusion - (ITT population)

Study		TG-MV-006			TG-MV-007			Pooled analysis		
n(%)		Ocriplasmin (n = 219)	Placebo (n = 107)	Total (n = 326)	Ocriplasmin (n = 245)	Placebo (n = 81)	Total (n = 326)	Ocriplasmin (n =464)	Placebo (n = 188)	Total (n = 652)
Gender (%)	Male	71 (32.4)	48 (44.9)	119 (36.5)	79 (32.2)	25 (30.9)	104 (31.9)	150 (32.3)	73 (38.8)	223 (34.2)
	Female	148 (67.6)*	59 (55.1)	207 (63.5)	166 (67.8)	56 (69.1)	222 (68.1)	314 (67.7)	115 (61.2)	429 (65.8)
Age (years)	Mean (SD)	71.5 (10.3)	71.1 (10.0)	71.3 (10.2)	72.6 (7.6)	70.2 (10.9)	72.0 (8.5)	72.1 (8.9)	70.7 (10.4)	71.7 (9.4)
	Median	72.0	70.0	71.0	73.0	72.0	73.0	72.0	71.0	72.0
	Min, max	18, 93	24, 96	18, 96	23, 89	32, 97	23, 97	18, 93	24, 97	18, 97
Initial diagnosis[(a)] n (%)	VMT associated with MH	57 (26.0)	32 (29.9)	89 (27.3)	49 (20.0)	15 (18.5)	64 (19.6)	106 (22.8)	47 (25.0)	153 (23.5)
	Isolated VMT	162 (74.0)	75 (70.0)	237 (72.7)	196 (80.0)	66 (81.5)	262 (80.4)	358 (77.2)	141 (75.0)	499 (76.5)
Initial ocular characteristic[(b)] n (%)	ERM	86 (39.3)	35 (32.7)	121 (37.1)	98 (40.0)	33 (40.7)	131 (40.2)	184 (39.7)	68 (36.2)	252 (38.7)
	Pseudophakic	91 (41.6)*	29 (27.1)	120 (36.8)	81 (33.1)	24 (29.6)	105 (32.2)	172 (37.1)*	53 (28.2)	225 (34.5)
	DR[(f)]	12 (5.5)	7 (6.5)	19 (5.8)	18 (7.3)	8 (9.9)	26 (8.0)	30 (6.5)	15 (8.0)	45 (6.9)
Type (Ø) of focal VMA[(c)] n/N (%)	> 1500 µ	47/207 (22.7)	19/99 (19.2)	66/306 (21.6)	55/233 (23.6)	22/77 (28.6)	77/310 (24.8)	102/440 (23.2)	41/176 (23.3)	143/616 (23.2)
	≤ 1500 µ	145/207 (70.0)	74/99 (74.7)	219/306 (71.6)	169/233 (72.5)	49/77 (63.7)	218/310 (70.3)	314/440 (71.4)	123/176 (69.9)	437/616 (70.9)
	Could not be determined	15/207 (7.2)	6/99 (6.1)	21/306 (6.9)	9/233 (3.9)	6/77 (7.8)	15/310 (4.8)	24/440 (5.5)	12/176 (6.8)	36/616 (5.8)

Study n(%)		TG-MV-006			TG-MV-007			Pooled analysis		
		Ocriplasmin (n = 219)	Placebo (n = 107)	Total (n = 326)	Ocriplasmin (n = 245)	Placebo (n = 81)	Total (n = 326)	Ocriplasmin (n =464)	Placebo (n = 188)	Total (n = 652)
Vitrectomy considered if necessary[(d)] n (%)	Yes	174 (79.5)	85 (79.4)	259 (79.4)	222 (90.6)	67 (82.7)	289 (88.7)	396 (85.3)	152 (80.9)	548 (84.0)
	No	44 (20.1)	22 (20.6)	66 (20.2)	23 (9.4)	14 (17.3)	37 (11.3)	67 (14.4)	36 (19.1)	103 (15.8)
	Missing	1 (0.5)	0	1 (0.3)	0	0	0	1 (0.2)	0	1 (0.2)
Total initial PVD n (%)	Yes	1 (0.5)	0	1 (0.3)	0	0	0	1 (0.2)	0	1 (0.2)
	No	218 (99.5)	107 (100.0)	325 (99.7)	245 (100.0)	81 (100.0)	326 (100.0)	463 (99.8)	188 (100.0)	651 (99.8)
BCVA score (letters)	Mean (SD)	64.5 (10.9)	65.3 (9.8)	64.8 (10.5)	63.4 (13.7)	64.9 (11.6)	63.8 (13.2)	63.9 (12.4)	65.1 (10.6)	64.3 (11.9)
	Median	67.0	67.0	67.0	67.0	66.5	67.0	67.0	67.0	67.0
	Min, max	20, 85	38, 82	20, 85	8, 88	9, 82	8, 88	8, 88	9, 82	8, 88
Diameter of the macular hole[(e)] n/N (%)	> 250 µ	25/56 (48.2)	16/32 (50.0)	43/88 (48.9)	30/49 (61.2)	6/15 (40.0)	36/64 (56.3)	57/105 (54.3)	22/47 (46.8)	79/152 (52.0)
	≤ 250 µ	29/56 (51.8)	16/32 (50.0)	45/88 (51.1)	19/49 (38.8)	9/15 (60.0)	28/64 (43.8)	48/105 (45.7)	25/47 (53.2)	73/152 (48.0)

VMA: vitreomacular adhesion; PVD: posterior vitreous detachment; SD: standard deviation; BCVA: best corrected visual acuity; ERM: epiretinal membrane or epimacular membrane; DR: diabetic retinopathy; MH: macular hole; VMT: vitreomacular traction.

Note: one patient was randomised to the placebo group but was inadvertently treated with ocriplasmin instead of placebo.

** Statistically significant difference between the two treatment groups.*

[(a)] Based on a review by the centralised reading centre of the pre-treatment OCT examination. All cases other than cases of MT were regarded as cases of VMT.

[(b)] Patients could have more than one ocular characteristic on inclusion.

[(c)] The percentages are calculated from the number of patients in the ITT analysis with focal VMA on inclusion.

[(d)] Yes/No reply to the question asked by the investigator before randomisation: "if no improvement in the patient's condition was observed, do you think you would go ahead with vitrectomy?"

[(e] The diameter of the macular hole was not reported in one patient.

[(f] The 45 patients with diabetic retinopathy were all suffering from VMT that was not associated with macular hole.

In the pooled analysis, 499 patients (76.5%) had **isolated vitreomacular traction** (which could include the stage with threat of macular hole or stage 1) with:
- a best corrected visual acuity (BCVA) of less than 20/25 (0.8 (decimal fraction) or 80 letters (ETDRS traction)) and above the visual acuity threshold (generally 0.4-0.5) warranting surgical intervention. The median BCVA was 69 letters (about 0.5) and three quarters of the patients had a BCVA of less than or equal to 74 letters (about 0.6);
- a median time since diagnosis of about 2.4 months (72.0 days) and three quarters of patients with a time since diagnosis of less than or equal to about 8.4 months (mean about 8.9 months).
- 229 patients (46%) with an epiretinal membrane.
- 45 patients (9%) with diabetic retinopathy.

Later use of vitrectomy was considered by the investigator in 82% of cases if patients showed no clinical improvement.

A total of 153 patients (23.5%) had **vitreomacular traction associated with macular hole of diameter less than or equal to 400 microns** or stage 2, of which:
- 79 patients (52%) had a hole > 250 microns and 73 patients (48%) a hole ≤ 250 microns,
- 23 patients (16%) had an epiretinal membrane.
- no patients had diabetic retinopathy.

The median diameter of the macular hole was 261 microns and three quarters of patients had a diameter of less than or equal to 337 microns (with a mean of about 273 microns).
The median time since diagnosis was about 0.7 months and three quarters of patients had a time since diagnosis of less than or equal to about 1.6 months (with a mean of about 2.1 months).

Later use of vitrectomy was considered by the investigator in 92% of cases, if there was no clinical improvement in the patients.

8.1.2 Results for the primary efficacy endpoint

A statistically significant difference in favour of ocriplasmin by comparison with placebo was shown for the primary efficacy endpoint consisting in the nonsurgical resolution of vitreomacular adhesion on the 28th day with 26.5% resolution in the ocriplasmin group versus 10.1% in the placebo group for the pooled analysis [10.5; 22.3] (p< 0.001) (Table 3).

Table 3: Primary efficacy endpoint: nonsurgical resolution of vitreomacular adhesion on the 28th day (ITT population)

Study	Ocriplasmin n/N (%)	Placebo n/N (%)	Difference [95% CI]	p
TG-MV-006	61/219 (27.9)	14/107 (13.1)	14.8 [6.0; 23.5]	0.003
TG-MV-007	62/245 (25.3)	5/81 (6.2)	19.1 [11.6; 26.7]	< 0.001
Pooled analysis	123/464 (26.5)	19/188 (10.1)	16.4 [10.5; 22.3]	< 0.001

8.1.3 Results for secondary endpoints

Table 4 shows the results for the main secondary endpoints excluding BCVA.

Table 4: Main secondary endpoints (excluding BCVA) (ITT population)

	Total PVD 28th day	Nonsurgical closure of MH		Use of vitrectomy
		28th day	6th month	6th month
Study TG-MV-006				
Ocriplasmin n/N (%)	**36/219 (16.4%)**	**25/57 (43.9%)**	**26/57 (45.6%)**	**45/219 (20.5%)**
Placebo n/N (%)	**7/107 (6.5%)**	**4/32 (12.5%)**	**5/32 (15.6%)**	**31/107 (29.0%)**
Difference (95% CI)	**9.9 [3.1, 16.7]**	**31.4 [14.1, 48.6]**	**30.0 [11.9, 48.0]**	**-8.5 [-18.5, 1.7]**
p	**0.014**	**0.002**	**0.005**	NS
Study TG-MV-007				
Ocriplasmin n/N (%)	**26/245 (10.6%)**	**18/49 (36.7%)**	**17/49 (34.7%)**	**37/245 (15.1%)**
Placebo n/N (%)	**0/81 (0%)**	**1/15 (6.7%)**	**3/15 (20.0%)**	**19/81 (23.5%)**
Difference (95% CI)	**10.6 [6.4, 14.4]**	**30.1 [11.6, 48.5]**	**14.7 [-9.5, 38.9]**	**-8.4 [-18.6, 1.9]**
p	**< 0.001**	**0.028**	NS	NS
Pooled analysis				
Ocriplasmin n/N (%)	**62/464 (13.4%)**	**43/106 (40.6%)**	**43/106 (40.6%)**	**82/464 (17.7%)**
Placebo n/N (%)	**7/188 (3.7%)**	**5/47 (10.6%)**	**8/47 (17.0%)**	**50/188 (26.6%)**
Difference (95% CI)	**9.6 [5.5, 13.8]**	**30.0 [17.1, 42.8]**	**23.6 [9.3, 37.8]**	**-8.9 [-16.1, -1.7]**
p	**< 0.001**	**< 0.001**	**0.004**	**0.016**

PVD: posterior vitreous detachment; MH: macular hole.

- **Total posterior vitreous detachment (PVD)**

A statistically significant difference in favour of ocriplasmin by comparison with placebo was shown for total posterior vitreous detachment on the 28th day:
- Study TG-MV-006: 16.4% ocriplasmin versus 6.5% placebo (p=0.014).
- Study TG-MV-007: 10.6% ocriplasmin versus 0% placebo (p<0.001).
- Pooled analysis: 13.4% ocriplasmin versus 3.7% placebo (p<0.001).

- **Nonsurgical closure of macular hole (MH)**

A statistically significant difference in favour of ocriplasmin by comparison with placebo was shown for nonsurgical closure of MH:
- on the 28th day: **Study TG-MV-006:** 43.9% ocriplasmin versus 12.5% placebo (p=0.002), **Study TG-MV-007**: 36.7% ocriplasmin versus 6.7% placebo (p = 0.028), **Pooled analysis**: 40.6% versus 10.6% placebo (p<0.001).
- at the 6th month: **Study TG-MV-006:** 45.6% ocriplasmin versus 15.6% placebo (p = 0.005), **Pooled analysis**: 40.6% ocriplasmin versus 17.0% placebo (p=0.004).
On the other hand, at the end of study **TG-MV-007** (6th month), no statistically significant difference was seen for the endpoint nonsurgical closure of MH (34.7% in the ocriplasmin group versus 20.0% in the placebo group, NS).

- **Use of vitrectomy**

No statistically significant difference was revealed in the rate of use of vitrectomy during the study (6th month) between the 2 treatment groups:
- in **study TG-MV-006**: 20.5% (45/219) of the patients treated with ocriplasmin versus 29.0% (31/107) of the patients on placebo,
- in **study TG-MV-007**: 15.1% (37/245) of the patients treated with ocriplasmin versus 23.5% (19/81) of the patients on placebo,

Only the **pooled analysis** showed a statistically significant difference in favour of ocriplasmin (17.7%) by comparison with placebo (26.6%) in the use of vitrectomy at 6 months (p=0.016).

- **Best corrected visual acuity (BCVA) at the 6th month**

The results for BCVA at the 6th month are shown in Table 5.

Study TG-MV-006
A statistically significant difference in favour of the ocriplasmin group was shown by comparison with placebo in the endpoint "gain ≥ 2 lines (10 letters)" in the analyses of BCVA without vitrectomy (25.6% ocriplasmin versus 11.2% placebo, p=0.002) and irrespective of vitrectomy (30.1% ocriplasmin versus 16.8% placebo, p=0.010). No statistically significant difference between the two groups was seen in the endpoint "gain ≥ 3 lines (15 letters)".

Study TG-MV-007
A statistically significant difference in favour of the ocriplasmin group was shown by comparison with placebo for the endpoints:
- gain ≥ 2 lines (10 letters) in the analysis of BCVA without vitrectomy (22.0% ocriplasmin versus 11.1% placebo, p=0.035).
- gain ≥ 3 lines (15 letters) in the analyses of BCVA without vitrectomy (9.0% ocriplasmin versus 0% placebo, p=0.002) and irrespective of vitrectomy (11.8% ocriplasmin versus 3.8% placebo, p=0.049).

Pooled analysis
A statistically significant difference in favour of the ocriplasmin group was seen by comparison with placebo for the endpoints "gain ≥ 2 lines (10 letters)" and "gain ≥ 3 lines (15 letters)" in the analyses of BCVA without vitrectomy and irrespective of vitrectomy.

- **Improvement in visual function (VFQ-25 score) at the 6th month[17]**

Study TG-MV-006: A statistically significant difference in favour of the ocriplasmin group by comparison with the placebo group was observed on the subscales "overall vision" (ocriplasmin 7.1 (±16.0) points versus placebo 2.0 (±17.3) points, p=0.011) and "limitation of activities" (ocriplasmin 8.1 (±23,9) points versus placebo 2.4 (±22.1) points, p=0.040).
On the other hand, no difference was shown between the two groups in the composite score[18] (ocriplasmin 3.5 (±11.7) versus placebo 1.2 (±9.9)).

Study TG-MV-007: A statistically significant difference in favour of the ocriplasmin group by comparison with the placebo group was observed on the subscales "dependence" (ocriplasmin 2.1 (±19,2) points versus placebo -1.8 (±12.4) point, p=0.038), and "driving" (ocriplasmin 2.8 (±21.8) points versus placebo -5.1 (±21.3) points, p=0.023) and in the composite score[18] (ocriplasmin 33 (±12.0) points versus placebo -0.1 (±10.3) point, p=0.013).

Pooled analysis:
A statistically significant difference in favour of the ocriplasmin group by comparison with the placebo group was observed only on the subscale "overall vision" (ocriplasmin 6.1 points versus placebo 2.1 points, p=0.024). No difference was revealed between the two groups in the composite score.[18]

[17] The p value is based on a test of the sum of Wilcoxon rankings, comparing the change by comparison with baseline between placebo and ocriplasmin.
[18] The composite score was calculated as the mean of the 11 subscales concerning vision, excluding the subscale on general health.

Table 5: Proportion of patients with a change in BCVA at the 6th month by comparison with the initial visit without vitrectomy and irrespective of vitrectomy (ITT population)

	Analysis of BCVA without vitrectomy		Analysis of BCVA irrespective of vitrectomy			
Categories of change by comparison with initial vision	**Gain ≥ 2 lines**	**Gain ≥ 3 lines**	**Gain ≥ 2 lines**	**Gain ≥ 3 lines**	**Loss ≥ 2 lines**	**Loss ≥ 3 lines**
Study TG-MV-006						
Ocriplasmin (n = 219)	**56 (25.6%)**	**23 (10.5%)**	**66 (30.1%)**	**28 (12.8%)**	**22 (10.0%)**	**16 (7.3%)**
Placebo (n = 107)	**12 (11.2%)**	**7 (6.5%)**	**18 (16.8%)**	**9 (8.4%)**	**5 (4.7%)**	**2 (1.9%)**
Difference (95% CI)	**14.4 (6.0, 22.7)**	**4.0 (-2.2, 10.2)**	**13.3 (4.0, 22.7)**	**4.4 (-2.5, 11.2)**	**5.3 (-0.3, 11.0)**	**5.4 (1.1, 9.7)**
p	**0,002**	**NS**	**0.010**	**NS**	**NS**	**NS**
Study TG-MV-007						
Ocriplasmin (n = 245)	**54 (22.0%)**	**22 (9.0%)**	**64 (26.1%)**	**29 (11.8%)**	**14 (5.7%)**	**10 (4.1%)**
Placebo (n = 81)	**9 (11.1%)**	**0 (0%)**	**14 (17.5%)**	**3 (3.8%)**	**6 (7.5%)**	**4 (5.0%)**
Difference (95% CI)	**10.9 (2.3, 19.5)**	**9.0 (5.4, 12.6)**	**8.6 (-1.4, 18.6)**	**8.1 (2.3, 13.9)**	**-1.8 (-8.2, 4.7)**	**-0.9 (-6.3, 4.5)**
p	**0.035**	**0.002**	**NS**	**0.049**	**NS**	**NS**
Pooled study						
Ocriplasmin (n =464)	**110 (23.7%)**	**45 (9.7%)**	**130 (28.0%)**	**57 (12.3%)**	**36 (7.8%)**	**26 (5.6%)**
Placebo (n =181)	**21 (11.2%)**	**7 (3.7%)**	**32 (17.1%)**	**12 (6.4%)**	**11 (5.9%)**	**6 (3.2%)**
Difference (95% CI)	**12.5 (6.6, 18.5)**	**6.0 (2.2, 9.8)**	**10.9 (4.1, 17.7)**	**5.9 (1.3, 10.5)**	**1.9 (-2.3, 6.0)**	**2.4 (-0.9, 5.7)**
p	**< 0.001**	**0.008**	**0.003**	**0.024**	NS	NS

BCVA: best corrected visual acuity

8.1.4 Results of the additional, pre-specified subgroup analyses

- **Presence or not of a macular hole**

Ocriplasmin was more effective than placebo in resolving vitreomacular adhesion on the 28th day (results of the pooled analysis):

- in patients with MH (50.0% (53/106) in the ocriplasmin group versus 25.5% (12/47) in the placebo group (p=0.006),
- in patients without MH (19.6% (70/358) in the ocriplasmin group versus 5.0% (7/141) in the placebo group (p<0.001).

A similar result was shown for each of the two studies, except for study TG-MV-006 for which no difference was shown between the 2 groups for patients with TM.

- **Presence or not of an epiretinal membrane**

In the subgroup of patients with ERM, no statistically significant difference in terms of the resolution of VMA on the 28th day was seen between ocriplasmin and placebo: study TG-MV-006: 7.0% ocriplasmin versus 0.0% placebo (NS), study TG-MV-007: 10.2% ocriplasmin versus 3.0% placebo (NS). Only the pooled analysis showed a statistically significant difference in patients with ERM: ocriplasmin 8.7% (16/184) versus placebo 1.5% (1/68), p=0.046.

In the subgroup of patients without ERM, a statistically significant difference in favour of ocriplasmin in terms of the resolution of VMA at the 28th day was seen in:
- study TG-MV-006: 40.6% ocriplasmin versus 19.4% placebo, p=0.003.
- study TG-MV-007: 34.5% ocriplasmin versus 6.4% placebo, p<0.001.
- the pooled analysis: 37.4% (101/270) ocriplasmin versus 14.3% (17/119) placebo, p<0.001.

- **Diameter of vitreomacular adhesion (VMA)**

In the subgroup of patients with a VMA diameter of ≤ 1500 microns, a statistically significant difference in favour of ocriplasmin was seen in terms of the resolution of VMA on the 28th day: study TG-MV-006: 36.6% ocriplasmin versus 18.9% placebo (p=0.008), study TG-MV-007: 33.1% ocriplasmin versus 8.2% placebo, p<0.001, pooled analysis: 34.7% ocriplasmin versus 14.6% placebo, p<0.001.

On the other hand, in the subgroup of patients with a VMA diameter of > 1500 microns, no statistically significant difference was seen between the 2 groups in terms of the resolution of VMA on the 28th day in study TG-MV-006, study TG-MV-007 or the pooled analysis.

8.1.5 Post hoc analysis according to the diameter of the macular hole

More patients treated with ocriplasmin had nonsurgical closure of the MH than in the placebo group, whatever the diameter of the MH (results of the pooled analysis):
- in the 79 with a macular hole of diameter ≤ 250 microns, 58.3% of the patients treated with ocriplasmin versus 16.0% of the patients on placebo (difference in absolute terms of 42.3 points, p < 0.001),
- in the 73 with a macular hole of diameter > 250 microns, 24.6% of the patients treated with ocriplasmin versus 4.5% of the patients on placebo (difference in absolute terms of 20.1 points, p = 0.031).

08.2 Safety/Adverse effects

8.2.1 Safety data from clinical studies

Seven completed clinical studies, including the two phase III controlled studies versus placebo (TG-MV-006 & TG-MV-007), three phase II controlled studies versus placebo or simulated injection and two phase II non-controlled studies provide safety data for a follow-up period generally of six months (in one single clinical study (TG-MV-002), the follow-up period was one year).

- **Assignment of patients**

A total of 741 patients received an intravitreal injection of ocriplasmin, whatever the dose, of which 582 patients the dose recommended by the Marketing Authorisation of 125 µg. Except for 12 patients, all received a single intravitreal injection of ocriplasmin.

More than 90% of the patients completed the clinical studies. Since the treatment was given on a single occasion at the start of the study, patients who subsequently withdrew their consent, who had therefore received the whole of the planned dose, were included in the safety population.

Table 6: Patient distribution (safety population)

	Phase III studies		All completed studies	
	Placebo n (%)	Ocriplasmin 125 µg n (%)	Control[a] n (%)	Ocriplasmin in any dose n (%)
Safety population	187 (100.0%)	465[b] (100.0%)	247 (100.0%)	741 (100.0%)
Patients who completed the study	171 (91.4%)	436 (93.8%)	228 (92.3%)	701 (94.6%)
Patients who dropped out of the study	16 (8.6%)	29 (6.2%)	19 (7.7%)	40 (5.4%)
Reasons for the drop-outs				
• **Adverse event**	2 (1.1%)	4 (0.9%)[c]	2 (0.8%)[c]	7 (0.9%)[d]
• **Decision of the investigator**	1 (0.5%)	0	1 (0.4%)	0
• **Withdrawal of consent**	8 (4.3%)	13 (2.8%)	9 (3.6%)	17 (2.3%)
• **Lost to follow-up**	5 (2.7%)	8 (1.7%)	5 (2.0%)	10 (1.3%)
• **Death[e]**	0	4 (0.9%)	2 (0.8%)	5 (0.7%)
• **Other**	0	0	0	1 (0.1%)

[a] *Patients assigned to treatment with placebo, simulated injection or no treatment.*

[b] *One patient in study TG-MV-006 was randomised to the placebo group but was inadvertently treated with ocriplasmin instead of placebo. For the safety analysis, this patient was included in the ocriplasmin group.*

[c] *One patient dropped out of the study because of an adverse event (metastatic brain cancer, unconnected with ocriplasmin) and died of this disease more than 30 days after dropping out of the study. This patient was included in the "adverse event" line rather than in the "death" line.*

[d] *Reasons for dropping out were given as "other" for one patient and "decision of the investigator" for another patient. A review of these cases led to a change in the reason for dropping out for these two patients to "adverse event"; each patient was included just once in the "adverse event" line.*

[e] *The deaths were due to non-ocular adverse events and were regarded as unconnected with the study treatment.*

- **Profile of adverse events**

In the phase III clinical studies, 76.6% of the patients who had received ocriplasmin and 69.0% of those who had received an intravitreal injection of placebo had at least one adverse event (AE). The proportion of patients with an adverse event linked to treatment was 40.0% in the ocriplasmin group and 21.4% in the placebo group.

Most of the adverse events were of mild to moderate intensity. The adverse events observed in the ocriplasmin group and in the placebo group were as follows in terms (Table 7):

- of severe AEs (8.4% ocriplasmin versus 7.5% placebo),
- of serious AEs (13.3% ocriplasmin versus 12.8% placebo),
- of serious AEs linked to the treatment (3.2% in both groups),
- of AEs which led to withdrawal from the study (0.9% ocriplasmin versus 1.1% placebo).

Table 7: Adverse events (safety population)

Patients n (%)	Phase III studies		All completed studies	
	Placebo (n = 187)	Ocriplasmin 125 µg (n = 465)	Control[(a)] (n = 247)	Ocriplasmin any dose (n = 741)
≥ 1 adverse event	129 (69.0%)	356 (76.6%)	180 (72.9%)	593 (80.0%)
Ocular adverse event	99 (52.9%)	317 (68.2%)	141 (57.1%)	529 (71.4%)
Adverse event linked to the treatment	40 (21.4%)	186 (40.0%)	50 (20.2%)	263 (35.5%)
Serious adverse event	24 (12.8%)	62 (13.3%)	34 (13.8%)	100 (13.5%)
Serious ocular adverse event	20 (10.7%)	36 (7.7%)	22 (8.9%)	57 (7.7%)
Severe adverse event	14 (7.5%)	39 (8.4%)	23 (9.3%)	62 (8.4%)
Severe ocular adverse event	11 (5.9%)	23 (4.9%)	13 (5.3%)	33 (4.5%)
Serious adverse event linked to the treatment	6 (3.2%)	15 (3.2%)	6 (2.4%)	16 (2.2%)
Adverse event that led to withdrawal from the study[(b)]	2 (1.1%)	4 (0.9%)	2 (0.8%)	7[(c)] (0.9%)
Adverse event with fatal outcome[(d)]	0	5[(b)] (1.1%)	2 (0.8%)	6[(b)] (0.8%)

(a) Patients assigned to treatment with placebo, simulated injection or no treatment.

(b) One patient dropped out of the study because of an adverse event (metastatic brain cancer, unconnected with ocriplasmin) and died of this disease more than 30 days after dropping out of the study. This patient was included in two lines: "adverse event that led to withdrawal from the study" and "adverse event with fatal outcome".

(c) Reasons for dropping out were given as "other" for one patient (ocriplasmin 25 µg) and "decision of the investigator" for another patient (ocriplasmin 50 µg). A review of these cases led to a change in the reason for dropping out for these two patients to "adverse event"; each patient was included just once in the "adverse event that led to withdrawal from the study" line.

(d) All adverse events with fatal outcome were non-ocular adverse events and were regarded as not connected with the study treatment.

The non-ocular adverse events reported in at least 2% of patients were nausea, bronchitis and headaches.

In the phase III clinical studies, **ocular adverse events** were reported in 68.2% of patients treated with ocriplasmin, compared with 52.9% of the patients in the placebo group. These events were of mild to moderate intensity. The ocular adverse events regarded as potentially linked to the treatment in the ocriplasmin group were vitreous floaters (16.8%), eye pain (13.1%), photopsia (11.8%), blurred vision (8.4%), reduced visual acuity (6.2%) (Table 8).

Table 8: Ocular adverse events potentially linked to the treatment, reported in at least 2% of the patients (safety population)

Patients n (%)	Phase III studies		All completed studies	
	Placebo (n = 187)	Ocriplasmin 125 µg (n = 465)	Control[(a)] (n = 247)	Ocriplasmin any dose (n = 741)
Vitreous floaters	14 (7.5%)	78 (16.8%)	18 (7.3%)	119 (16.1%)
Eye pain	11 (5.9%)	61 (13.1%)	19 (7.7%)	90 (12.1%)
Photopsia	5 (2.7%)	55 (11.8%)	7 (2.8%)	66 (8.9%)
Blurred vision	5 (3.2%)	39 (8.4%)	7 (2.8%)	47 (6.3%)
Reduced visual acuity	8 (4.3%)	29 (6.2%)	8 (3.2%)	41 (5.5%)
Visual impairment	2 (1.1%)	25 (5.4%)	2 (0.8%)	27 (3.6%)
Retinal oedema	2 (1.1%)	25 (5.4%)	2 (0.8%)	32 (4.3%)
Macular oedema	3 (1.6%)	19 (4.1%)	10 (4.0%)	43 (5.8%)
Anterior chamber cells	5 (2.7%)	17 (3.7%)	12 (4.9%)	57 (7.7%)
Photophobia	0	17 (3.7%)	0	25 (3.4%)
Eye irritation	2 (1.1%)	13 (2.8%)	4 (1.6%)	17 (2.3%)
Vitreous detachment	2 (1.1%)	12 (2.6%)	2 (0.8%)	13 (1.8%)
Iris inflammation	0	12 (2.6%)	0	12 (1.6%)
Dry eye	2 (1.1%)	11 (2.4%)	2 (0.8%)	14 (1.9%)
Metamorphopsia	1 (0.5%)	10 (2.2%)	1 (0.4%)	14 (1.9%)
Retinal degeneration	1 (0.5%)	8 (1.7%)	1 (0.4%)	11 (1.5%)
Eyelid oedema	1 (0.5%)	7 (1.5%)	8 (3.2%)	22 (3.0%)
Retinal pigment epitheliopathy	0	7 (1.5%)	4 (1.6%)	24 (3.2%)
Macular degeneration	1 (0.5%)	6 (1.3%)	1 (0.4%)	13 (1.8%)
Ocular hyperaemia	1 (0.5%)	4 (0.9%)	1 (0.4%)	14 (1.9%)

[(a)] *Patients assigned to treatment with placebo, simulated injection or no treatment.*

The rate of **serious ocular adverse events** was 7.7% in the ocriplasmin group and 10.7% in the placebo group. The most commonly reported ocular adverse events were:
- in the ocriplasmin group: macular holes (5.2%) and vitreous adhesion (1.1%),
- in the placebo group: macular holes (8.6%) and retinal detachment (1.6%).

All other serious ocular adverse events were reported in fewer than 1% of patients in the two treatment groups.

The rate of severe ocular adverse events was 4.9% in the ocriplasmin group and 5.9% in the placebo group. Reduced visual acuity was the only event possibly linked to the treatment reported as severe in the two treatment groups (0.6% for ocriplasmin versus 0.5% for placebo).

The two phase III clinical studies were the subject of an extension phase with a median follow-up period of two years (study TG-MV-012) for a limited sample of 24 patients. The safety profiles observed for the two treatment groups were similar to those observed in the phase III clinical studies. Vitrectomy was performed in 2 of the 5 patients (40.0%) in the placebo group and 4 of the 19 patients (21.1%) in the ocriplasmin group during the long-term follow-up period. The limited size of the sample means that these results are exploratory in nature.

8.2.2 SPC data

The SPC states in particular that “all adverse reactions were ocular. The most commonly reported were vitreous floaters, eye pain and photopsia, as well as conjunctival haemorrhage resulting from the injection procedure. Most of the adverse reactions occurred within the first week after the injection. The majority of these reactions were non-serious, mild in intensity and resolved within 2 to 3 weeks.
The incidence of serious adverse reactions that occurred in all clinical studies was 2.2% in JETREA treated patients and 2.4% in control patients.”

8.2.3 Risk Management Plan

The risk management plan for JETREA, including a risk minimisation plan, provides for the monitoring of the following “substantial” risks:

- **identified risks:** visual impairment, dyschromatopsia, abnormalities in the electroretinogram (ERG), retinal detachment, increased intraocular pressure (IOP), intraocular haemorrhage, intraocular inflammation, progression of vitreomacular traction, new appearance or progression of a macular hole, retinal and macular oedema, subluxation of the crystalline lens, endophthalmitis.

- the **potential risks** include immunogenicity (including hypersensitivity and allergic reactions), off-label use (including in the paediatric population), drug interactions with other medicines used via the intravitreal route, medication errors and traumatic cataract.

Additional risk minimisation measures will be proposed, including making available educational material for patients. Two studies, TG-MV-014 (in progress) & TG-MV-017 (planned) will make it possible to monitor certain risks identified as substantial plus proper use of the medicinal product (see section 08.4 Planned studies). A targeted follow-up questionnaire will complement the RMP through the intensified follow-up of spontaneous reports of adverse events involving abnormalities in the electroretinogram (ERG).

08.3 Summary & discussion

Two randomised, double-blind clinical studies with similar methodologies compared a single intravitreal injection of 125 µg ocriplasmin (JETREA) with a single intravitreal injection of a placebo containing the excipient of JETREA.
The primary efficacy endpoint was the **resolution of vitreomacular adhesion (VMA) on the 28th day**, assessed using optical coherence tomography.
The company has analysed each of the 2 studies and, in addition, has made a pooled analysis of the data from the 2 studies which included a total of 652 patients, of which:
- 77% (n=499/652) with isolated vitreomacular traction (including stage 1),
- 23% (n=153/652) with VMT associated with macular hole ≤ 400 µm (stage 2), of which 79 patients with a hole > 250 µm and 74 patients with a hole ≤ 250 µm. The median diameter of the macular hole was 261 µm, the mean diameter 273 µm and three quarters of the patients had a diameter of ≤ 337 µm,

- 38.7% (n=252/652) with an epiretinal membrane.[19]
-70.9% (n=437/652) with focal VMA ≤1500 µ.

The median time since diagnosis was about 0.7 months and in three quarters of the patients it was less than or equal to 1.6 months (mean 2.1 months).

Patients could be included even with a modest loss of BCVA of 20/25 (0.8 (decimal fraction) or 80 letters (ETDRS score)). Patients with severe myopia (spherical correction > 8 dioptres or axial length > 28 mm), a history of retinal detachment, age-related exudative macular degeneration, recent eye surgery or intraocular injection (particularly laser treatment) were excluded.
The mean age of the patients was 71.7 years. The mean score for best corrected visual acuity (BCVA) was 63.9 letters in the ocriplasmin group and 65.1 letters in the placebo group.

The symptoms of the patients with isolated VMT or VMT associated with MH ≤ 400 µm did not immediately warrant vitrectomy, but justified close monitoring.

The **resolution of vitreomacular adhesion (VMA) on the 28th day** was more common with ocriplasmin than with placebo in the 2 studies: 27.9% versus 13.1%; p=0.003 (TG-MV-006) and 25.3% versus 6.2%; p<0.001 (TG-MV-007) (primary efficacy endpoint).

Total posterior vitreous detachment on the 28th day was more common in patients treated with ocriplasmin than in those in the placebo group: 16.4% versus 6.5%; p=0.014 (TG-MV-006) and 10.6% versus 0%; p<0.001 (TG-MV-007) (secondary endpoint).

Non-surgical closure of the macular hole (in the subpopulation of 153 patients with macular hole) was more common with ocriplasmin than with placebo (exploratory secondary endpoint):
- on the 28th day: 43.9% versus 12.5%; p=0.002 (TG-MV-006) and 36.7% versus 6.7%; p=0.028 (TG-MV-007).
- in the 6th month only in one of the 2 studies: 45.6% versus 15.6%; p = 0.005 (TG-MV-006). On the other hand, in study TG-MV-007, no statistically significant difference was seen in this endpoint (34.7% versus 20.0%, NS).

Use of vitrectomy in the 6th month was no different between ocriplasmin and placebo, 20.5% versus 29.0% (TG-MV-006) and 15.1% versus 23.5% (TG-MV-007) (exploratory secondary endpoint). Only the pooled analysis of the two studied showed a lower rate of use of vitrectomy with ocriplasmin than with placebo (17.7% vs 26.6%; p=0.016).

The **composite score for improvement in visual function (VFQ-25 score) at the 6th month** did not differ between ocriplasmin and placebo in study TG-MV-006 and in the pooled analysis. It was higher with ocriplasmin than with placebo in study TG-MV-007.

The resolution of vitreomacular adhesion in the 6th month was more common with ocriplasmin than with placebo in the subgroup of patients with MH (50.0% versus 25.5%; p = 0.006) and in the subgroup of patients without MH (19.6% versus 5.0%; p < 0.001) (results of the pooled analysis).

In the subgroup of patients with epiretinal membrane, resolution of vitreomacular adhesion on the 28th day did not differ between ocriplasmin and placebo in each of the 2 studies but was more common with ocriplasmin in the pooled analysis: 8.7% (16/184) versus 1.5% (1/68); p = 0.046.
In the subgroup of patients without epiretinal membrane, resolution of vitreomacular adhesion on the 28th day was more common with ocriplasmin than with placebo in the 2 studies.

[19] The epiretinal membrane strengthens vitreomacular adhesion and is most often complicated by macular oedema.

In the subgroup of patients with VMA diameter ≤ 1 500 microns, resolution of vitreomacular adhesion on the 28th day was more common with ocriplasmin than with placebo in the 2 studies: 36.6% versus 18.9%; p=0.008 (study TG-MV-006) and 33.1% versus 8.2%; p<0.001 (study TG-MV-007).
On the other hand, in the subgroup of patients with a VMA diameter > 1 500 microns, resolution of vitreomacular adhesion on the 28th day did not differ between ocriplasmin and placebo in the 2 studies and in the pooled analysis.

In the absence of stratification as a function of the various endpoints (presence or not of macular hole, presence or not of epiretinal membrane, diameter of vitreomacular adhesion) on randomisation, the results observed in the different subgroups are subject to interpretation and are merely exploratory in nature.

In the 2 clinical studies, at least one adverse event (AE) was reported by 76.6% of the patients who had received ocriplasmin and 69.0% of those who had received an injection of placebo. An adverse event linked to the treatment was reported by 40.0% of the patients who had received ocriplasmin and by 21.4% of those who had received placebo. Most were of mild to moderate intensity.

The rates observed in the ocriplasmin group and in the placebo group were as follows:
- Severe AEs: 8.4% versus 7.5%,
- Serious AEs: 13.3% versus 12.8%,
- Serious AEs linked to the treatment: 3.2% in both groups,
- AE that led to withdrawal from the study: 0.9% versus 1.1%

Almost all the AEs were ocular in nature. The commonest AEs potentially linked to the treatment in the two clinical studies in the ocriplasmin group and the placebo groups were as follows:
- vitreous floaters 16.8% versus 7.5%
- eye pain 13.1% versus 5.9%
- photopsia 11.8% versus 2.7%
- blurred vision 8.4% versus 3.2%
- reduced visual acuity 6.2% versus 4.3%
- visual impairment 5.4% versus 1.1%,
- retinal oedema 5.4% versus 1.1%
- conjunctival haemorrhage resulting from the injection procedure 14.6% versus 12.8%.

The period of follow-up on ocriplasmin is limited to 6 months. Only exploratory data in a small population of 24 patients are available 2 years after the administration of ocriplasmin. The safety profile observed during this follow-up is similar to that of the phase III clinical studies.

There is no pharmaceutical comparator for ocriplasmin. The only other therapeutic option is surgical vitrectomy, which is not indicated automatically but case by case according to the symptoms of VMT, whether or not associated with macular hole. Where the patients included were at a stage which did not necessitate surgical vitrectomy immediately, no clinically relevant comparator was available. The choice of comparator could have been for a simulated intravitreal injection instead of an injection of the excipient of JETREA which itself could potentially have had an effect on vitreomacular adhesion by a hydrodynamic mechanism and is not free from adverse effects.

JETREA has not been studied in patients with vitreomacular traction, either isolated or associated with macular hole of diameter ≤ 400 microns, in a severe form, for whom the current therapeutic strategy recommends vitrectomy without delay, or in patients with vitreomacular traction associated with macular hole of diameter >400 microns.[20]

[20] According to the SPC, treatment with JETREA is not recommended in patients with MH of large diameter (>400 microns).

08.4 Planned studies

The studies in the risk management plan,[21] TG-MV-014 (in progress) & TG-MV-017 (planned) will allow the monitoring of certain risks identified as substantial in the RMP and proper use of the medicinal product.

The phase IIIb clinical study (TG-MV-014), conducted at 30 centres in the USA, is a randomised, double-blind, controlled study versus simulated injection, of a duration of two years, the objective of which is to assess the anatomical and functional results of a single intravitreal injection of JETREA in a dose of 125 µg. It is planned to include 210 patients with symptomatic VMA/VMT associated with macular hole, with a BCVA of 20/32 or less in the affected eye and to exclude patients with epiretinal membrane. The patients randomised (in a ratio of 2:1) will be stratified according to the presence or otherwise of macular hole on inclusion. As for the 2 pivotal phase III studies, the primary efficacy endpoint is the resolution of vitreomacular adhesion (VMA) on the 28th day, assessed using optical coherence tomography. The secondary endpoints include the percentage of patients with nonsurgical closure of macular hole at 2 years and the percentage of patients requiring vitrectomy at 2 years. As part of the risk management plan, the study will assess the links between resolution of VMA and best corrected visual acuity (BCVA) with microperimetry and full-field electroretinogram (ffERG). The study report is expected for the 3rd quarter of 2015.

The objectives of the European observational study are to document the real-life conditions for use of JETREA (in particular compliance with the Marketing Authorisation and the conditions of administration) and the characteristics of the patients treated. It is planned to include about 600 patients. Recruitment of the first patient to the study on proper use of the medicinal product (TG-MV-017) will occur approximately 6 to 12 months after launch in the first country. Recruitment of the last patient will occur approximately 36 months after recruitment of the first patient. Submission of the study report is scheduled for 12 months after the last patient's visit.

[21] Risk Management Plan. Jan 2013, version 5c.

09 THERAPEUTIC USE

- **Current therapeutic strategy:**

In cases of isolated VMT or with threat of macular hole (stage 1), the current therapeutic strategy consists in **close medical monitoring** until the stage of reduced visual acuity (generally a threshold below 0.4-0.5) which justifies surgical vitrectomy. [22,23]
Vitrectomy depends on the extent of the deterioration in visual acuity (generally a threshold below 0.4-0.5) and the worsening of visual symptoms (metamorphopsia, central scotoma), or on the rapid worsening of symptoms, but before irreversible retinal damage occurs. The right time for surgical vitrectomy is still difficult to determine, and must be assessed case by case given that, if it is left too late, recovery of function is likely to be modest in terms of visual acuity and that, if surgery is performed too early, the risks associated with surgery may outweigh the potential recovery of function. The decision is multifactorial, taking account in particular of the imaging examinations, the functional impact for the patient, the patient's case history and general condition, and the postoperative prognosis.

With a stage 2 macular hole:

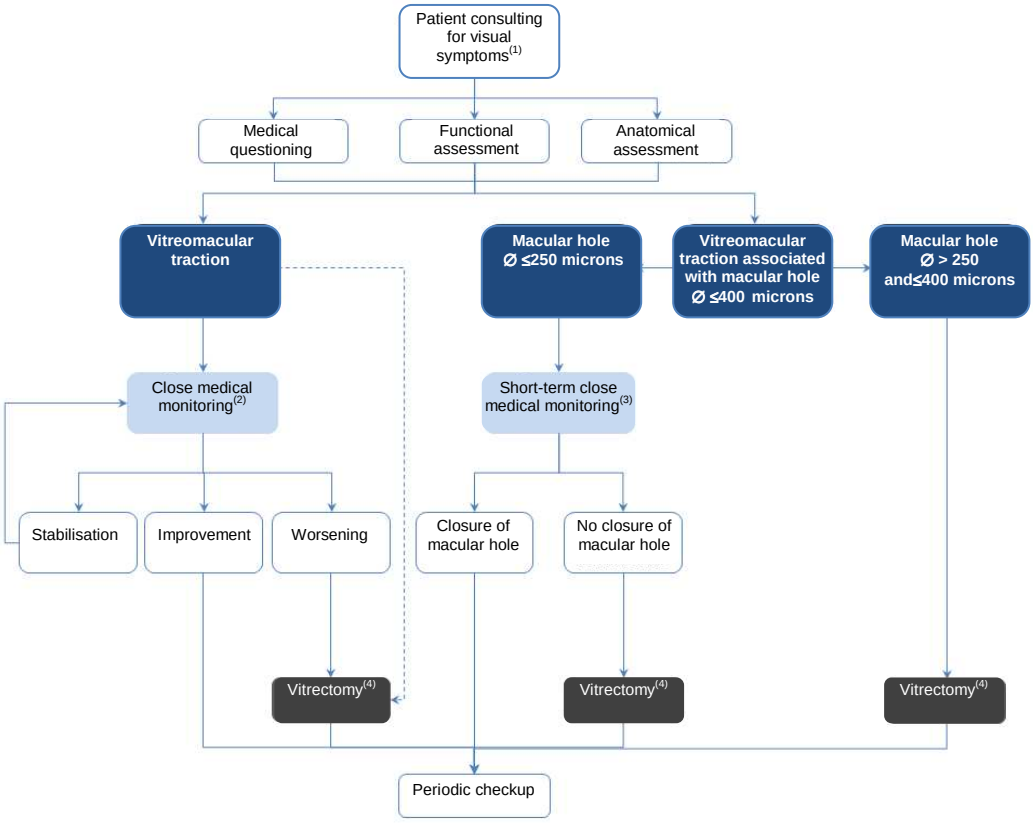
- **of diameter ≤250 µm which has appeared recently, close medical monitoring,** for about two to three months, may be suggested. If the macular hole has not closed after the specified period, vitrectomy is performed.

- of **diameter >250 µm and ≤400 µm, vitrectomy is usually performed without delay.**[24]

The data suggest that the longer the symptoms last, the worse the prognosis when surgical treatment is given.

[22] Creuzot-Garcher C. Syndrome de traction vitréo-maculaire. In: Cohen SY et Gaudric A, editors. Retine: Lavoisier, 2012.
[23] Berrod JP, Poirson A. Quelles sont les membranes épimaculaires qu'il faut opérer ? J Fr Ophtalmol 2008;31:192-199.
[24] Perol J, Gualino V, Tadayoni R. Trous maculaires. In: Cohen SY et Gaudric A, editors. Retine: Lavoisier, 2012.

Figure 1: Current algorithm for the treatment of vitreomacular traction, whether or not associated with macular hole of diameter less than or equal to 400 microns



OCT: optical coherence tomography; VA: visual acuity; ∅: diameter.

(1) Metamorphopsia, reduction in visual acuity and/or central scotoma (negative).

(2) Visit every 6 months, if there is no worsening of symptoms. Rapid return if new symptoms appear.

(3) Visit 2 to 3 months after the appearance of the macular hole, if there is no worsening of symptoms. Rapid return if new symptoms appear.

(4) Visit 1-2 days after the procedure (checkup), then 1 week and 1 month after the procedure. The frequency of and schedule for subsequent visits vary according to the result of the surgery and the patient's symptoms.

--- Vitrectomy may be suggested immediately in the event of poor visual acuity (threshold below 0.4-0.5).

- **Place of JETREA in therapeutic use:**

In the 2 clinical studies available, JETREA was studied in a population of patients most of whom (76.5%) were suffering from **isolated vitreomacular traction** (including the stage with threat of macular hole or stage 1) and 23.5% of patients had **VMT associated with macular hole less than or equal to 400 µm.** The median diameter of the macular hole was 261 microns and three quarters of patients had a diameter of less than or equal to 337 µm (with a mean of about 273 µm). 38.7% (n=252/652) of the patients had epiretinal membrane and 70.9% (n=437/652) had focal VMA ≤1500 µ.

The median time since diagnosis was about 0.7 months and three quarters of patients had a time since diagnosis of less than or equal to about 1.6 months (with a mean of about 2.1 months).

Patients could be included even with a modest loss of best corrected visual acuity (BCVA) of 20/25 (0.8 (decimal fraction) or 80 letters (ETDRS score)). In the pooled analysis of the 2 studies, the mean BCVA score was 63.9 letters in the ocriplasmin group.

It should be noted that, in these 2 studies, patients with severe myopia (spherical correction > 8 dioptres or axial length > 28 mm), a history of retinal detachment, age-related exudative macular degeneration, recent eye surgery or intraocular injection (particularly laser treatment) were not included.

JETREA was studied in a population of patients with vitreomacular traction, isolated or associated with macular hole of less than or equal to 400 µm whose symptoms warranted not automatic vitrectomy but close monitoring, corresponding to a category of patients who are not severely affected.

The period of follow-up on ocriplasmin is limited to 6 months.

JETREA has not been studied in patients with vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm who are severely affected, for whom the current therapeutic strategy recommends vitrectomy without delay. In the light of the current data, JETREA has no place in therapeutic use in this subpopulation.

On the basis of the available data, for patients with VMT, isolated or associated with macular hole of diameter ≤400 µm, whose symptoms do not automatically justify vitrectomy, a single intravitreal injection of JETREA on diagnosis and/or the first symptoms of the disease allows early therapeutic management with the objective of avoiding the progression and worsening of the disease (deterioration of vision and/or worsening of visual symptoms).

Because of its invasive nature, its risks, its complications and the constraints for patients, vitrectomy is still a treatment for use after pharmacological treatment, the need for which is diagnosed according to the extent of its impact and/or the visual disability, the diameter of the macular hole if there is one, or in the event of a rapid worsening of symptoms, and before irreversible retinal damage occurs.

Thus, if the improvement is not considered sufficient, patients treated with JETREA may be offered 2nd line vitrectomy, without prejudice to the anatomical or functional results.

JETREA is a 1st line treatment for vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm and the symptoms of which do not immediately necessitate use of vitrectomy.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

- Vitreomacular traction, isolated or associated with macular hole of diameter less than or equal to 400 µm, is a progressive disease of the vitreoretinal interface characterised by visual symptoms (metamorphopsia and/or central scotoma) and a continuous and progressive deterioration in vision (or abrupt onset in the event of a macular hole) which can ultimately jeopardize the patient's sight.
The repercussions of the disease may lead to incapacity (in reading, driving, recognising faces), leading to functional disability, loss of independence and a marked deterioration in quality of life.

- This medicinal product is intended as curative therapy.

- The efficacy/adverse effects ratio is modest in vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm where the symptoms do not immediately necessitate the use of vitrectomy.

- There is no pharmacological treatment alternative. The only therapeutic option is a surgical technique, vitrectomy, which is not indicated automatically but case by case according to the symptoms of VMT, whether or not associated with macular hole. Patients with a macular hole of a diameter greater than 250 µm are usually operated on without delay.

- JETREA is a 1st line treatment for vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm where the symptoms do not immediately necessitate use of vitrectomy.

JETREA has not been studied in patients with vitreomacular traction, isolated or associated with macular hole of diameter ≤400 µm who are severely affected, for whom the current therapeutic strategy recommends vitrectomy without delay. JETREA does not, in the light of the current data, have any place in therapeutic use in this subpopulation.

- Public health benefit:
The public health burden of patients with vitreomacular traction, isolated or associated with macular hole of diameter less than or equal to 400 µm, may be considered low.
The reduction of visual impairment is a public health need which is an established priority (priorities of the GTNDO[25]).
In view of the data available with 6 months' follow-up, an impact of the medicinal product JETREA in terms of the promotion of visual acuity (BCVA) and a reduction in the frequency of the later use of vitrectomy is expected, but is at best low. The transferability of the results of studies to practice is in principle acceptable given the method of administration as a single intravitreal injection.
Consequently, JETREA is not expected to benefit public health in this indication.

[25] Groupe Technique National de Définition des Objectifs [National Technical Group for the Definition of Public-Health Objectives] (DGS [Directorate-General for Health]-2003)

Taking account of these points, the Committee considers that the actual benefit of JETREA is:

- substantial in patients with vitreomacular traction, isolated or associated with macular hole of ≤400 µm, the symptoms of which do not immediately necessitate vitrectomy,

- insufficient, in the absence of clinical data, in patients with vitreomacular traction, isolated or associated with macular hole of ≤400 µm, the symptoms of which do immediately necessitate vitrectomy.

010.2 Improvement in actual benefit (IAB)

Since:

- the efficacy of JETREA has been studied only in patients with vitreomacular traction, isolated or associated with macular hole of diameter less than or equal to 400 µm and the symptoms of which did not immediately justify vitrectomy, corresponding to patients who are not severely affected, i.e. a subpopulation of the Marketing Authorisation indication for JETREA.

For these patients who are not severely affected,
- it was expected that the administration of JETREA reduces or even eliminates the need for surgical vitrectomy with a high success rate but not freedom from risks, which has not been demonstrated,
- the efficacy of JETREA, with follow-up limited to 6 months, is modest,

the Committee believes that JETREA provides a minor improvement in actual benefit (IAB IV) in the management of a subpopulation of the Marketing Authorisation represented by patients with vitreomacular traction, isolated or associated with macular hole of diameter less than or equal to 400 µm and for whom the symptoms do not immediately necessitate vitrectomy.

010.3 Target population

The target population of JETREA is qualitatively defined as adult patients with vitreomacular traction, isolated or associated with threat of macular hole of diameter less than or equal to 400 µm, the symptoms of which do not immediately necessitate vitrectomy.

Macular hole and vitreomacular traction most commonly affect persons aged 60 to 70 years, but cases have been reported in younger persons. Women are three times more affected than men.[26,27,28]

Estimates of the annual number of new patients take account of recent epidemiological data on the incidence of macular holes (from 0.0078%[26] in the general population to 0.03%[29,30] in the 43 to 84 year age group per year), the distribution of the stages of macular holes (33% for stage 1 and 20% for stage 2[31,32]), projections of the demographic data according to age groups in the population of metropolitan France (INSEE, 2012), the theory of a frequency of vitreomacular traction of the order of three to four times that of macular holes (whatever their diameter),[33,34,35] the theory of the consistent presence of vitreomacular traction in patients with a stage 2 macular hole.

The epidemiological data on prevalence are taken from a Spanish cohort, observational, prospective, single-centre study conducted between April 2001 and December 2004, in patients with symptomatic, incomplete posterior vitreous detachment.[36]

The estimated annual prevalence in patients with incomplete, symptomatic posterior vitreous detachment was used as an indicator for an indirect measurement of the prevalence if vitreomacular traction syndrome, i.e. a rate of 0.66%.

Estimate/conclusion

Table 9 summarises the lower and upper estimates of the subpopulations with vitreomacular traction in terms of new patients (prospective incidence) and of current patients (prospective prevalence).

[26] McCannel CA et al. Population based incidence of macular holes. Ophthalmology 2009;116(7):1366-1369.
[27] Schwab C et al. Prevalence of early and late stages of physiologic PVD in emmetropic elderly population. Acta Ophthalmol 2011;90(3):e179-e184.
[28] La Cour M, Friis J. Macular holes: classification, epidemiology, natural history and treatment. Acta Ophthalmol Scand 2002;80(6):579-587.
[29] Klein R et al. The Beaver Dam Eye Study: visual acuity. Ophthalmology 1991;98:1310-1315.
[30] Klein R, Klein BE, Wang Q, et al. The epidemiology of epiretinal membranes. Trans Am Ophthalmol 1994;92:403-425.
[31] Hikichi T et al. Natural outcomes of stage 1, 2, 3, and 4 idiopathic macular holes. Br J Ophthalmol 1995;79(6):517-520.
[32] Yacoubi Y et al. Résultats de la chirurgie des trous maculaires idiopathiques de plus de 400 µm. Medical Thesis, Faculty of Medicine Nancy, 2009;52p.
[33] Perol J, Gualino V, Tadayoni R. Trous maculaires. In: Cohen SY et Gaudric A, editors. Retine: Lavoisier, 2012.
[34] Haouchine B, Massin P, Gaudric A. Foveal pseudocyst as the first step in macular hole formation: a prospective study by optical coherence tomography. Ophthalmology 2001;108:15-22.
[35] Chan A, Duker JS, Schman JS, Fujumoto JG. Stage 0 macular holes: Observations by optical coherence tomography. Ophthalmology 2004; 111(11):2027-2032.
[36] Carrero JL. Incomplete posterior vitreous detachment: prevalence and clinical relevance. Am J Ophthalmol 2012;153(3):497-503.

Table 9: Lower and upper estimate of subpopulations with vitreomacular traction

Subpopulation	Annual number of new patients (n) (prospective incidence)		Current number of patients (n) (prospective prevalence)	
	Lower limit	Upper limit	Lower limit	Upper limit
Subpopulation 1 **Patients with vitreomacular traction**	**17,700**	**29,700**	**72,600**	
Patients with isolated vitreo-macular traction (not associated with macular hole of any size)	***16,100***	***27,000***	***60,600***	***46,100***
Patients with vitreomacular traction associated with threat of macular hole (stage 1 macular hole)	***1600***	***2700***	***12,000***	***26,500***
Subpopulation 2 **Patients with vitreomacular traction associated with macular hole of diameter less than or equal to 400 µm (stage 2 macular hole)**	**1000**	**1700**	**7300**	**16,100**
Target population	**18,700**	**31,400**	**79,900**	**88,700**

The target population of adult patients with vitreomacular traction, whether or not associated with macular hole of diameter ≤ 400 µm, is estimated to be between **18,700 and 31,400 new cases per year**.

The current number of adult patients with vitreomacular traction, whether or not associated with macular hole of diameter ≤ 400 µm, is estimated to be between **79,900 and 88,700 cases.**

There are no data that can be used to give an accurate estimate of the target population for JETREA, which is limited to patients whose symptoms do not immediately necessitate use of vitrectomy, among the 79,900 to 88,700 adult patients with vitreomacular traction, whether or not associated with macular hole of diameter ≤ 400 µm.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee gives the following Opinion:

- it recommends inclusion on the list of medicines approved for hospital use in adults in the treatment of vitreomacular traction (VMT), isolated or associated with macular hole of diameter ≤ 400 µm, when the symptoms do not immediately necessitate vitrectomy and in the dosages of the Marketing Authorisation,

- it does not recommend inclusion on the list of medicines approved for hospital use in adults in the treatment of vitreomacular traction (VMT), isolated or associated with macular hole of diameter ≤ 400 µm, when the symptoms immediately necessitate vitrectomy.

◗ Packaging

It should be noted that JETREA, concentrate for solution for injection, must be stored in a freezer at a temperature of -20°C ± 5°C.

The packaging is appropriate for the prescription conditions in terms of indication, dosage and treatment duration.

◗ Request for data

The Committee asks to be informed of the results of study TG-MV-014, the objective of which is to assess the anatomical and functional results of a single intravitreal injection of JETREA in a dose of 125 µg in patients with symptomatic VMA/VMT associated with macular hole and of study TG-MV-017 on proper use of the medicinal product.