



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for ocriplasmin

Proprietary Product Name: Jetrea

Sponsor: Alcon Laboratories Australia Pty Ltd

November 2014

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<http://www.tga.gov.au>>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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List commonly used abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACSOM	Advisory Committee on the Safety Of Medicines
ADR	Adverse Drug Reaction
AE	Adverse Event
AMD	Age-related Macular Degeneration
ARTG	Australian Register of Therapeutic Goods
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
BSA	Body Surface Area
CER	Clinical Evaluation Report
CI	Confidence interval
C _{max}	Maximum concentration
CNS	Central Nervous System
DBP	Diastolic Blood Pressure
DLP	Data Lock Point
DSUR	Developmental Safety Update Report
EEA	European Economic Area
EMA	European Medicines Agency
EOS	End Of Study
ERG	ElectroRetinoGraphy or electroretinogram
ERM	Epiretinal Membrane
ES	Erosion Score
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FDA	United States Food and Drug Agency

Abbreviation	Meaning
ffERG	full-field electroretinography
FTMH	Full Thickness Macular Hole
GCP	Good Clinical Practice
IB	Investigator Brochure
ICH	International Conference on Harmonisation
ILM	Internal Limiting Membrane
INN	International Non-proprietary Names
IOP	Intraocular Pressure
ISCEV	International Society for Clinical Electrophysiology of Vision
IV	Intravenous
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mfERG	multifocal electroretinography
MH	Macular Hole
NOAEL	No observable adverse effect level
NOEL	No observable effect level
NRS	Numerical Rating Scale
PD	Pharmacodynamic
PDR	Proliferative Diabetic Retinopathy
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PPS	Per Protocol Set
PSUR	Periodic Safety Update Report
PT	Preferred Term
PVD	Posterior Vitreous Detachment
PVR	Proliferative Vitreoretinopathy
R{E	Retinal Pigment Epithelium

Abbreviation	Meaning
RMP	Risk Management Plan
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOC	System Organ Class
sVMA	Symptomatic vitreomacular adhesion
TGA	Therapeutic Goods Administration
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia
VMA	Vitreomacular Adhesion
VMT	Vitreomacular traction
w/v	Weight per volume

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	3 October 2014
<i>Active ingredient:</i>	Ocriplasmin
<i>Product name:</i>	Jetrea
<i>Sponsor's name and address:</i>	Alcon Laboratories Australia Pty Ltd 10/25 Frenchs Forest Road Frenchs Forest NSW 2086
<i>Dose form:</i>	Concentrated injection
<i>Strength:</i>	2.5 mg/mL
<i>Container:</i>	Glass vial
<i>Pack size:</i>	1s
<i>Approved therapeutic use:</i>	<i>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.</i>
<i>Route of administration:</i>	Intravitreal
<i>Dosage:</i>	Jetrea must be prepared and administered by a qualified ophthalmologist experienced in intravitreal injections. Single use vial is for intravitreal use only. 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. Administration to both eyes concurrently is not recommended. Repeated administration in the same eye is not recommended.
<i>ARTG number:</i>	206494

Product background

This AusPAR describes the application by the sponsor, Alcon Laboratories (Australia) Pty Ltd, to register a new chemical entity, ocriplasmin (Jetrea), a recombinant truncated form of the human serine protease, plasmin, proposed to be used for the treatment of symptomatic vitreomacular adhesion (sVMA) in adult patients including those associated with macular hole:

Initial proposal: Treatment of symptomatic vitreomacular adhesion (sVMA) including those associated with macular hole in adults

Subsequent Proposal: Treatment of vitreomacular traction (VMT) including when associated with macular hole of diameter less than or equal to 400 microns.

Ocriplasmin is produced by recombinant DNA technology in *Pichia pastoris* expression system. Ocriplasmin selectively cleaves peptide bonds located after a lysine or an arginine residue in many proteins, for example fibronectin, fibrinogen, collagen, laminin, gelatin, ocriplasmin, casein and pro-urokinase as well as synthetic peptides like S-2403 and S-2444.

With ageing, the vitreous physiologically liquefies and separates from the retina in a process called posterior vitreous detachment (PVD). On occasion, the vitreous can be abnormally adherent to the macula (vitreomacular adhesion; VMA). Vitreomacular traction occurs when VMA pulls on the macular surface. Continuous distortion of the macula can be associated with symptoms (symptomatic VMA), such as distorted vision, decreased visual acuity and central visual field defects. Intravitreal administration of ocriplasmin, a proteolytic enzyme, is intended to induce PVD by degrading the fibronectin, laminin and collagen containing extracellular matrix that adheres the vitreous to the internal limiting membrane (ILM) of the retina.

The proposed dose is a single dose of 0.125 mg (0.1 mL) administered by intravitreal (IVT) injection to the affected eye. Administration to both eyes concurrently (education material prepared by the sponsor defines it as concurrent or within 7 days of initial injection) is not recommended. Repeat administration in the same eye is not recommended.

Regulatory status

At the time the TGA considered this application, a similar application had been approved in multiple countries including the United States (US; 17 October 2012), the European Union (EU; 13 March 2013) and Canada (13 August 2013).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

II. Quality findings

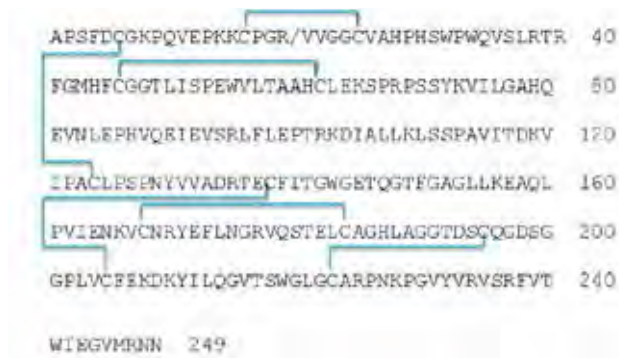
Drug substance (active ingredient)

Ocriplasmin is a protein of 249 amino acid residues. The protein consists of 2 peptide chains.

The first peptide is 19 amino acid residues long. The second is 230 amino acid residues long.

The peptides are linked together by 2 disulphide bonds between C6:C124 and C16:C24 residues according to the residue numbering presented in Figure 1.

Figure 1. Amino acid structure of ocriplasmin showing inter and intra disulphide bonds.



Drug product

Jetrea is proposed to be registered as a single strength and as a pack size of 1 vial.

It is presented as a solution for injection for intra-vitreous administration containing ocriplasmin as the active pharmaceutical ingredient at a concentration of 2.5 mg/mL.

The solution is clear, corresponding to European Pharmacopoeia (Ph. Eur) reference suspension I at maximum, with a colour less than or equivalent to Ph. Eur. reference solution B9 and practically free from visible particulate matter.

The product is sterilised by sterile filtration and aseptically filled in United States Pharmacopoeia (USP) and Ph. Eur. Type I glass vials.

Ocriplasmin drug product solution is to be diluted with an equal volume of 0.9% (w/v) sodium chloride (preservative-free) prior to use.

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Protect from light by storing in the original package until time of use.

The proposed shelf life is 18 months when stored frozen at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$. It has been proposed that the labelling of the product should use the recommended terminology of store below -18°C , deep freeze) from Therapeutic Goods Order No. 69D. This storage temperature is within the range supported by the stability data.

The sponsor has acknowledged that no transportation temperature excursions will be registered as acceptable

Current Good Manufacturing Practice clearances are in place for all appropriate steps of manufacture.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeia standards and relevant technical guidelines adopted by the TGA.

Minor labelling issues are yet to be resolved however this is unlikely to affect the final outcome of the evaluation as the sponsor has indicated they will submit revised and compliant artwork in the near future.

The quality evaluator recommends that Jetrea ocriplasmin (ryp) 2.5 mg per mL concentrated solution for intravitreal injection should be approved. As this is a New

Biological Entity, the Delegate is requested to include the following as a specific condition of registration:

- Batch Release Testing: As a minimum, the first five independent batches of Jetrea ocriplasmin (ryp) 2.5 mg per mL concentrated solution for intravitreal injection imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.

III. Nonclinical findings

Introduction

The submitted nonclinical data were generally in accordance with the relevant adopted guidelines.¹

Nonclinical data consisted of well reported and designed studies that were conducted in compliance with Good Laboratory Practice (GLP) requirements when required. The nonclinical dossier also contained published literature reports (non GLP) submitted in support of parts of the primary pharmacology section.

Carcinogenicity and reproductive toxicity studies were not conducted, which is acceptable given the proposed single use and/or lack of significant systemic exposure.

Pharmacology

Primary pharmacology

With ageing, the vitreous physiologically liquefies and separates from the retina in a process called posterior vitreous detachment (PVD). On occasion, the vitreous can be abnormally adherent to the macula (vitreomacular adhesion; VMA). Vitreomacular traction occurs when VMA pulls on the macular surface. Continuous distortion of the macula can be associated with symptoms (symptomatic VMA), such as distorted vision, decreased visual acuity and central visual field defects. Intravitreal administration of ocriplasmin, a proteolytic enzyme, is intended to induce PVD by degrading the fibronectin, laminin and collagen containing extracellular matrix that adheres the vitreous to the internal limiting membrane (ILM) of the retina.²

In vitro, ocriplasmin had a similar proteolytic activity profile to human plasmin. The kinetics of ocriplasmin against synthetic serine protease substrates were similar to that observed with human plasmin, while the relative potency of ocriplasmin towards natural substrates was variable depending on incubation time and substrate (ranging from equipotent [laminin and collagen] to 8 times lower in potency [fibronectin]).

IVT administration of ocriplasmin induced vitreous liquefaction and PVD in eyes from rats, rabbits, pigs and humans. Vitreal changes included altered morphological structure, loss of fibre integrity and reduced particle size corresponding to protein digestion. Complete PVD was characterised by an absence of fibronectin, laminin or collagen on the ILM. Vitreous concentrations of ocriplasmin inducing complete PVD in animals (34 to 60 µg/ mL) was similar to that seen in human eyes following IVT injection of 125 µg ocriplasmin (31 µg/ mL; assuming 4 mL vitreous fluid), thus lending support to the proposed indication and

¹ European Medicines Agency, 'ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)', June 2011.

² Tsui I, et al. (2012) *Ocriplasmin for vitreoretinal diseases*. J Biomed Biotechnol. 2012: 354979.

dose. The vitreolytic effect was not homogeneous throughout the eye, suggesting the activity was affected by viscosity and diffusion of the protein.

Secondary pharmacodynamics

As expected, based on its relationship to human plasmin, ocriplasmin had hydrolytic activity towards fibrin and fibrinogen and was shown to induce lysis of blood clots in vitro and in vivo.³ The concentration for 50% lysis of purified fibrin clots in 3 h was approximately equal to 100 nM ocriplasmin (2700 ng/ mL).⁴ Dogs that received greater than or equal to 1.5 mg/kg intravenous (IV) ocriplasmin had increased prothrombin time and significantly decreased fibrinogen levels. Thirty minutes after dosing, blood from dogs that received 15 mg/kg IV ocriplasmin did not coagulate. The No Observable Effect Level (NOEL) for coagulation effects was 0.15 mg/kg IV ocriplasmin (peak plasma concentration (C_{max}) approximately equal to 1500 ng/mL). Assuming a maximum possible human plasma concentration of 52 ng/ mL following IVT dosing with 125 µg ocriplasmin,⁵ the fibrinolytic activity of ocriplasmin is not expected to have a significant effect on the coagulation system during clinical use.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular and respiratory systems following IV dosing of ocriplasmin. These studies were GLP compliant and designed in accordance with guidelines for safety pharmacology studies for human pharmaceuticals.⁶

CNS function in rats (at less than or equal to 10 mg/kg; estimated C_{max} 5303 ng/ mL) and respiratory function in dogs (less than or equal to 15 mg/kg; maximum concentration (C_{max}) approximately equal to 121 600 ng/ mL) were unaffected by IV administration of ocriplasmin. P-wave amplitude and QTcV⁷ interval were increased in dogs that received 15 mg/kg IV ocriplasmin. A decrease in blood pressure was also evident in these dogs. The NOEL for cardiovascular effects was 10 mg/kg IV ocriplasmin (repeat dose toxicity study) (C_{max} approximately equal to 88,320 ng/mL). As peak plasma levels at the NOEL are estimated to be at least 100 times the maximum possible plasma levels in patients, no adverse CNS, cardiovascular, or respiratory effects are anticipated during clinical use.

³ Dommke C, et al. (2010) Thrombolytic efficacy of recombinant human microplasmin in a canine model of copper coil-induced coronary artery thrombosis. *J Thromb Thrombolysis* 30: 46-54; Nagai N, et al. (2003) Recombinant human microplasmin: production and potential therapeutic properties. *J Thromb Haemost.* 1: 307-313.

⁴ Dommke C, et al. (2010) Thrombolytic efficacy of recombinant human microplasmin in a canine model of copper coil-induced coronary artery thrombosis. *J Thromb Thrombolysis* 30: 46-54.

⁵ Calculated assuming 100% systemic bioavailability and a plasma volume of 2400 mL (48 mL/kg plasma in a 50 kg individual: Derelanko MJ, Hollinger MA. Eds. (1995) CRC Handbook of Toxicology. CRC Press Inc, Florida, USA).

⁶ European Medicines Agency, 'ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals, Step 5: Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (CPMP/ICH/539/00)', June 2001.

⁷ QT interval: In cardiology, the QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. A lengthened QT interval is a marker for the potential of ventricular tachyarrhythmias like torsades de pointes and a risk factor for sudden death. The QT interval is dependent on the heart rate (the faster the heart rate the shorter the R-R interval and QT interval) and may be adjusted to improve the detection of patients at increased risk of ventricular arrhythmia. Modern computer-based ECG machines can easily calculate a corrected QT (QTc). There are a number of different correction formulas.

Pharmacokinetics

Following IVT administration to porcine and human eyes, ocriplasmin underwent rapid inactivation with 20-30% of the initial activity detectable 4 h following injection. A similar rate of activity loss was seen in homogenised vitreous fluid. In porcine vitreous fluid, there was a concentration-dependent relationship with the rate of inactivation. Inactivation of ocriplasmin was also seen in buffer (pH 7.1-7.4) with a rate 2 to 3 times faster than that seen in vitreous fluid. The loss of activity was minimal in buffer at pH 3.1. Sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE) results indicated the degradation pattern of ocriplasmin was similar in buffer and porcine vitreous fluid, suggesting loss of activity in both of these media was due, at least in part, to autoproteolysis. Serine protease inhibitors, α 2-antiplasmin, antithrombin III and α 1-antitrypsin have been detected in the vitreous of human subjects at varying levels and may contribute to ocriplasmin inactivation.⁸ As with plasmin, ocriplasmin was shown to bind α 2-antiplasmin to form an inactive complex. The binding kinetics of ocriplasmin with α 2-antiplasmin indicated a slower rate of binding than plasmin, though the latter reaction is quite rapid. Based on the kinetics in human vitreous, it has been estimated that some activity may be seen for up to 42 days in patients,⁹ though for a significant portion of this time, the activity is expected to be quite low.

No systemic pharmacokinetic studies were conducted with ocriplasmin following IVT injection. Assuming 100% bioavailability following IVT injection, resulting in a theoretical plasma concentration of 1.93 nM (52 ng/mL), which is unlikely given the extent of inactivation in the vitreous, there should be a sufficient level of circulating α 2-antiplasmin (plasma concentration 1 μ M)¹⁰ to inactivate any ocriplasmin that may reach the circulation.

Toxicology

The ocular toxicity of ocriplasmin was assessed following a single IVT injection to rabbits, mini pigs, and Cynomolgus monkeys and two IVT injections (4 weeks apart) in Cynomolgus monkeys. The pivotal studies were conducted under GLP conditions. The dosing regimen and duration is acceptable for a single use product¹¹ and the duration of the observation periods (1 to 8 weeks) is acceptable. A formulation similar to the clinical formulation was used; balanced salt solution was used as a diluent rather than 0.9% saline. This difference is not expected to impact on the utility of the toxicity studies. The choice of species is acceptable given the common use of rabbits and monkeys to assess ocular toxicity and porcine anatomy shares many similarities with the human eye.¹² Systemic toxicity was assessed in IV studies in rats (single and repeat dose) and dogs (repeat-dose).

Relative exposure

Ocular exposure was calculated based on dose adjusted for species differences in vitreous volume (Table 1). Vitreous volumes were 1.06 mL for Dutch-belted rabbits,¹³ 2.0 mL for

⁸ De Smet MD, et al. (2009). Microplasmin: ex vivo characterization of its activity in porcine vitreous. *Invest Ophthalmol Vis Sci*. 50: 814-819.

⁹ De Smet MD, et al. (2009). Microplasmin: ex vivo characterization of its activity in porcine vitreous. *Invest Ophthalmol Vis Sci*. 50: 814-819.

¹⁰ Coughlin PB. (2005) Antiplasmin: the forgotten serpin? *FEBS J* 272: 4852-4857.

¹¹ European Medicines Agency, 'ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995)', December 2009.

¹² Bode G, et al. (2010) The utility of the minipig as an animal model in regulatory toxicology. *J. Pharmacol Toxicol Methods* 62: 196-220.

¹³ Iyer MN, et al. (2005). Intravitreal clearance of moxifloxacin. *Trans Am Ophthalmol Soc*. 103: 76-81.

mini-pigs,¹⁴ 3.2 mL for Cynomolgus monkeys¹⁵ and 4.0 mL for human subjects,¹⁶ plus an additional 50 µL to account for the injection volume. Vitreous concentrations achieved were high in rabbits but were only marginally higher than that expected clinically. Given the minimal ocular toxicity seen in mini-pigs, consideration should have been given to testing higher doses.

Table 1. Relative exposure in the IVT toxicity studies.

Species	Dose (µg/eye)	Vitreous concentration (µg/mL)	Exposure ratio [#]
Rabbit (Dutch-belted)	2.5	1.67	0.07
	50	33.3	1.5
	62.5	41.7	1.8
	125	83.3	3.6
	200	133	6
	885	590	26
Mini-pig (Göttingen)	5	2.5	0.08
	25	12.5	0.39
	50	25	0.79
	100	50	1.6
	125	62.5	2.0
Monkey (Cynomolgus)	1.5	0.47	0.01
	20	6.25	0.20
	25	7.81	0.25
	75	23.4	0.74
	125	39.1	1.2
	200	62.5	2.0
Human	125	31	–

(#) = animal: human vitreous concentration (µg/mL) based on the dose injected

¹⁴ Shafiee AT, et al. (2008). Experimental determination and allometric prediction of vitreous volume and retina and lens weights in Gottingen minipigs. *Veterinary Ophthalmology* 11: 193-196.

¹⁵ Short BG (2008) Safety evaluation of ocular drug delivery formulations: techniques and practical considerations. *Toxicol Pathol.* 36: 49.

¹⁶ Short BG (2008) Safety evaluation of ocular drug delivery formulations: techniques and practical considerations. *Toxicol Pathol.* 36: 49.

Major toxicities

Following intravitreal injection of ocriplasmin, the main ocular changes included retinal toxicity, inflammatory responses, lens subluxation and expected effects associated with the pharmacological action of ocriplasmin. The latter, which was seen in all species, consisted of changes in vitreous morphology, vitreous opacity and liquefaction of the vitreous. These are not considered adverse effects.

Retinal toxicity was observed in rabbits (at greater than or equal to 50 µg/eye; exposure ratio [ER], 1.5) and monkeys (greater than or equal to 20 µg/eye; ER, 0.2) and consisted of reductions of both a- and b-wave amplitudes in electroretinograms (ERGs) corresponding with a thinning or narrowing of retinal vessels and retinal atrophy. The ERG changes were reversible (showing signs of recovery by Day 8) and retinal atrophy was not evident in monkeys that received a single dose of 125 µg/eye (ER, 1.2) 4 weeks earlier. However, retinal atrophy was still evident in rabbits 8 weeks after treatment; the delay in recovery may be associated with the severity of the effect. Irreversible retinal detachment was observed in one monkey that received 75 µg/eye ocriplasmin (ER, 0.74) on 2 occasions. The NOEL for retinal toxicity was 2.5 µg/eye in rabbits (ER, 0.07), 125 µg/eye in mini-pigs (ER, 2) and 1.5 µg/eye in monkeys (ER, 0.01). Given the low exposure margins, transient effects on retinal function may be seen clinically. The risk of retinal detachment should also be considered as possible.

A mild and transient inflammatory response was observed in rabbits (greater than or equal to 50 µg/eye; ER, 1.5) and monkeys (greater than or equal to 1.5 µg/eye; ER, 0.01) and was characterised by vitreal cells, aqueous flare, mononuclear cell infiltration and macrophage accumulation in the vitreous. Transient swelling of the eye was seen in rabbits the day following the IVT injection. These inflammatory responses had resolved by Day 22 in rabbits and had markedly improved by Day 6 in monkeys. The NOEL for an inflammatory response was 2.5 µg/eye in rabbits (ER, 0.07), 125 µg/eye in mini-pigs (ER, 2.0) and < 1.5 µg/eye in monkeys (ER, 0.01 µg). Given the low margin, transient uveitis is possible during clinical use.

After a single IVT injection, irreversible lens subluxation was observed in all species: rabbits at greater than or equal to 62.5 µg/eye (ER, 1.8), mini-pigs at 125 µg/eye (ER, 2.0) and monkeys at 125 µg/eye (ER, 1.2). The incidence and severity of lens subluxation increased with a second injection, with all animals given two doses of greater than or equal to 75 µg/eye ocriplasmin having displaced lenses. Abnormal iris movement, secondary to the lens effect, was also seen in most of these animals. The onset of lens subluxation was several days following injection (21 to 42 days in rabbits, 28 days in mini-pigs and 6 days in monkeys) and may be associated with the pharmacological activity of ocriplasmin. The ciliary zonules form the suspensory ligament of the eye, being anchored between the lens and ciliary body. Substrates of ocriplasmin, collagen IV, laminin and fibronectin are located in the extracellular matrix coating the ciliary zonular fibres.¹⁷ Degradation of this coating may affect the placement and function of the lens. The NOEL for lens subluxation was a single dose of 50 µg/eye in rabbits (ER, 1.5), 100 µg/eye in mini-pigs (ER, 1.6) and 25 µg/eye in monkeys (ER, 0.25). Given the low margin, lens subluxation is possible during clinical use. The delay in onset of lens subluxation, suggests an extended follow-up period would be warranted to monitor for this effect in treated patients. As the incidence and severity of lens subluxation significantly increased with a second IVT dose, affecting all treated animals, a subsequent IVT dose or doses of ocriplasmin to the one eye, should be avoided.

Systemic effects in rats and dogs that received IV doses of ocriplasmin included reddening of several organs and haemorrhage; at greater than or equal to 20 mg/kg/day for 7 days in

¹⁷ Los, L I *et al.* (2004) Presence of Collagen IV in the Ciliary Zonules of the Human Eye: An Immunohistochemical Study by LM and TEM. *J Histochem Cytochem* **52**: 789–795.

rats and greater than or equal to 10 mg/kg/day IV for 7 days in dogs. Deaths were seen in rats that received a single IV dose of greater than or equal to 40 mg/kg, while severe clinical signs necessitated euthanasia in dogs given greater than or equal to 15 mg/kg/day IV ocriplasmin for 7 days. These deaths were likely associated with haemorrhage, an expected pharmacological effect of ocriplasmin on the clotting cascade. The No Observable Adverse Effect Level (NOAEL) for systemic effects was 10 mg/kg IV every second day in rats and 2 mg/kg every second day in dogs. These doses are 4000 and 800 times the clinical dose¹⁸ in rats and dogs respectively, resulting in plasma C_{max} values approximately equal to 100 and approximately equal to 245 times the maximum possible clinically.¹⁹

Genotoxicity

No genotoxicity tests were submitted. As large proteins do not cross cell membranes and are unlikely to interact with DNA or chromosomal material, further genetic toxicology tests are not typically required according to published guidelines.²⁰

Carcinogenicity

No carcinogenicity studies were conducted. This is acceptable given the nature of the drug and its proposed short term/single use.

Reproductive toxicity

No reproductive toxicity studies were submitted. This is acceptable, as ocriplasmin is expected to have extremely low systemic exposure in humans following intravitreal administration of 125 µg. Furthermore, the reproductive organs were not target organs for toxicity in the general toxicity studies.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.²¹ Given the absence of adequate animal reproductive toxicity studies, Category B2²² is considered more appropriate.

Local tolerance

Following a single paravenous injection of 1.2 mg (in 0.3 mL) to rabbits, there were no significant differences compared to the vehicle (control) injections. Local irritation was attributed to the injection procedure and the low pH of the vehicles (pH 3.1).

Immunogenicity (systemic)

Anti-drug antibodies were detected in rats and dogs that received repeated IV doses of ocriplasmin. Antibody production was not assessed in IVT studies. Given the single use of the drug and the expected low systemic exposure, the absence of such an assessment is considered acceptable.

¹⁸ Based on mg/kg in a 50 kg individual and assuming 100% systemic bioavailability

¹⁹ Based on data from Studies 662911 and 662314. Day 1 data for rats (C_{max} 5303 ng/ mL) and dogs (12 800 ng/ mL; average male/female data). Clinical C_{max} assumed to be 52 ng/ mL.

²⁰ European Medicines Agency, 'ICH guideline S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)', June 2011.

²¹ Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

²² Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Other toxicity studies

Impurities

In an abnormal behaviour study, no adverse effects were seen in rats following an IV dose of a placebo containing yeast proteins that co-purify with ocriplasmin.

Paediatric use

No specific studies in young animals were submitted.

Nonclinical summary and conclusions

- *In vitro*, ocriplasmin had a similar proteolytic activity profile to human plasmin, with catalytic activity towards collagen, laminin and fibronectin. IVT administration of ocriplasmin induced vitreous liquefaction and PVD in eyes from rats, rabbits, pigs and humans. Vitreous concentrations of ocriplasmin inducing complete PVD in animals (34 to 60 µg/ mL) was similar to that seen in human eyes following IVT injection of 125 µg ocriplasmin (31 µg/ mL).
- Ocriplasmin had hydrolytic activity towards fibrin and fibrinogen and affected or inhibited the clotting system in dogs but only at high IV doses (greater than or equal to 1.5 mg/kg IV). Effects on the clotting system are not expected during clinical use. CNS function in rats, and respiratory and cardiovascular function in dogs were unaffected at high IV doses (less than or equal to 10 mg/kg IV).
- Ocriplasmin undergoes autolysis in the vitreous. Minimal systemic exposure is expected but if any ocriplasmin reaches the circulation, it is expected to be rapidly inactivated by binding to α 2-antiplasmin.
- The ocular toxicity of ocriplasmin was assessed following a single IVT injection to rabbits, mini-pigs and Cynomolgus monkeys and two IVT injections (4 weeks apart) in Cynomolgus monkeys. The main findings included changes in vitreous morphology (associated with the desired pharmacological action), retinal toxicity (reduction of ERG wave amplitudes, thinning/narrowing of retinal vessels, retinal atrophy and retinal detachment), a mild and transient ocular inflammatory response, and irreversible lens subluxation. All of these effects occurred at low relative exposures (based on vitreous concentration). The onset of lens subluxation was several days following injection and lens subluxation was present in all monkeys that received two IVT doses of ocriplasmin.
- No genotoxicity, carcinogenicity or reproductive toxicity studies were submitted, which is considered acceptable.
- The pharmacology studies support the proposed indication and dose.
- Toxicities of potential clinical relevance include:
 - Effects on retinal function, and retinal toxicity: ERG changes and retinal atrophy (both of which were reversible), and retinal detachment;
 - A transient ocular inflammatory response;
 - Lens subluxation: The delay in onset of lens subluxation, suggests an extended follow-up period would be warranted to monitor for this effect in treated patients. A subsequent IVT dose or doses of ocriplasmin to one eye should be avoided as this will increase the likelihood of lens subluxation.
- Provided adequate monitoring is in place for lens subluxation and retinal detachment, and adequate treatment options are available, there are no objections on nonclinical grounds to the registration of Jetrea for the proposed indication.

- Amendments to the draft Product Information were recommended but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

VMA is now considered to be a distinct clinical entity and an ICD-9 code has recently been assigned to the condition (ICD-9-CM Diagnosis Code 379.27). The following brief outline of VMA, and the rationale for ocriplasmin as a pharmacological treatment for the proposed indication are primarily derived from the sponsor's letter of application and the sponsor's Clinical Overview, supported by relevant information from recent reviews and publications.²³

In the ageing eye, liquefaction and collapse of the vitreous can result in the formation of VMA when complete separation of the vitreous from the posterior retina fails to occur.²⁴ Persisting VMA can result in VMT, leading to tractional damage to the macular and symptoms such as decreased visual acuity, metamorphopsia (distorted vision), and central visual field defects. Furthermore, idiopathic lamellar and full thickness macular hole (FTMH), tractional cystoid macular oedema and the vitreomacular traction syndrome are caused directly by the tractional effects of early stage (perifoveal) posterior vitreous detachment (PVD) with VMA.²⁵

Compared with other retinal conditions, limited epidemiological data exist for the natural history of VMA despite the condition being first identified and histologically confirmed more than 40 years ago.²⁶ However, due to the advent of advanced imaging technology, most notably optical coherence tomography (OCT), the recognition of this condition and its progressive sight-threatening complications such as FTMH have increased in recent years. While many cases of VMT do not require treatment and maintain good visual acuity with minimal visual disturbance, vision in untreated VMT generally deteriorates over time and spontaneous separation of VMA with release of traction occurs infrequently. In a retrospective series of 53 consecutive patients (53 eyes) with VMT followed without treatment for a median of 60 months (range: 6, 110 months), complete spontaneous posterior vitreous detachment PVD (that is, spontaneous release of VMT) occurred in only

²³Carpinetio P et al. Diagnosing and treating vitreomacular adhesion. *European Ophthalmic Review* 2011; 5(1): 69-73). Bottos J et al. Vitreomacular traction syndrome. *J Ophthalmic Vis Res* 2012;7(2):148-161. Johnson ME. Editorial – How should we release vitreomacular traction: surgically, pharmacologically, or pneumatically? *Am J Ophthalmol* 2013;155:203-205. Rodrigues IA et al. Intravitreal injection of expansile perfluoropropane (C₃F₈) for the treatment of vitreomacular traction *Am J Ophthalmol* 2013;155:270-276.

²⁴Carpinetio P et al. Diagnosing and treating vitreomacular adhesion. *European Ophthalmic Review* 2011; 5(1): 69-73). Larsson L and Osterlin S. Posterior Vitreous Detachment. A Combined Clinical and Physiochemical Study. *Graefes Arch Clin Exp Ophthalmol* 1985;223:92-95. chino E, Uemura A and Ohba N. Initial Stages of Posterior Vitreous Detachment in Healthy Eyes of Older Persons Evaluated by Optical Coherence Tomography. *Arch Ophthalmol* 2001;119(10):1475-79.

Sebag J. Anomalous Posterior Vitreous Detachment: A Unifying Concept in Vitreo-Retinal Disease. *Graefes Arch Clin Exp Ophthalmol* 2004;242(8):690-98.

²⁵Johnson ME. Editorial – How should we release vitreomacular traction: surgically, pharmacologically, or pneumatically? *Am J Ophthalmol* 2013;155:203-205.

²⁶Reese AB, Jones IS, Cooper WC. Vitreomacular traction syndrome confirmed histologically. *Am J Ophthalmol* 1970;69:975-977.

11% of patients, while decreased visual acuity of 2 or more Snellen lines occurred in 64% of patients.²⁷

Unresolved VMA can lead to FTHM, which can result in central blindness. It has been estimated that FTHM has a prevalence of 1/3300, and usually occurs in the sixth and seventh decades of life.²⁸ In the Eye Disease Case Control Group study of idiopathic FTHM (that is, due to VMT) in 198 patients, FTHM was more common in patients aged greater than or equal to 55 years than in patients aged 45 to 54 years (97% versus 3%), and in women compared with men (72% versus 28%).²⁹ Studies investigating the natural history of FTHM, undertaken before vitrectomy became the standard of care show that the rate of spontaneous closure of FTHM is low and the size of the hole increases over time.³⁰ In Chew et al., 1999³¹, 198 patients were examined at baseline and 122 had follow-up examinations. Of all eyes with macular holes, 34.4% had an increase in hole size, and 45% had a decrease in VA of 2 lines, 27.8% had a decrease in VA of greater than or equal to 3 lines, and VA remained stable in 40.9%. Spontaneous regression of the macular hole occurred in 3 (8.6%) of 35 patients with a follow-up interval of 6 or more years, whereas no regression occurred in patients with a shorter follow-up. In Kim et al., 1996,³² the majority of eyes with of Stage 2 FTHM (71%; 15/21 eyes) randomly assigned to observation progressed to Stage 3 or 4 FTHM after 12 months, compared with 20% (3/15) of eyes randomized to vitrectomy. In addition, macular holes of greater than or equal to 2 years duration may be more difficult to close successfully with surgery than more recent macular holes, and visual improvement appears to be less favourable.³³

The current treatment of choice for many cases of symptomatic VMA is vitrectomy, particularly for those cases associated with poor visual acuity and progressive macular traction.²³ Improvement in visual acuity has been reported in 44% to 78% of cases of VMT syndrome treated with surgery.³⁴ However, vitrectomy surgery carries intra-operative risks such as iatrogenic retinal breaks (15%), including retinal detachment (1.2% to 6.6%), and intraocular haemorrhage.³⁵ In addition, post-operative risks include low intraocular pressure, infection, choroidal detachment, macular oedema and vitreous

²⁷Hikichi T, Yoshida A and Trempe CL. Course of Vitreomacular Traction Syndrome. *Am J Ophthalmol* 1995;119(1):55-61.

²⁸Ezra E. Idiopathic Full Thickness Macular Hole: Natural History and Pathogenesis. *Br J Ophthalmol* 2001;85:102-108.

²⁹The Eye Disease Case-Control Study Group. Risk Factors for Idiopathic Macular Holes: The Eye Disease Case-Control Study Group. *Am J Ophthalmol* 1994;118:754-61.

³⁰Morgan CM and Schatz H. Idiopathic Macular Holes. *Am J Ophthalmol* 1985;99(4):437-44. Akiba J, Yoshida A and Trempe CL. Risk of Developing a Macular Hole. *Arch Ophthalmol* 1990;108 (8):1088-90. Kim JW, Freeman WR, Azen SP, el-Haig W, Klein DJ and Bailey IL. Prospective Randomized Trial of Vitrectomy or Observation for Stage 2 Macular Holes. Vitrectomy for Macular Hole Study Group. *Am J Ophthalmol* 1996;121(6):605-14. Chew EY, Sperduto RD, Hiller R, Nowroozi L, Seigel D, Yanuzzi LA, Burton TC, Seddon JM, Gragoudas ES, Haller JA, Blair NP and Farber M. Clinical Course of Macular Holes: The Eye Disease Case-Control Study. *Arch Ophthalmol* 1999;117 (2): 242-46.

³¹Chew EY, Sperduto RD, Hiller R, Nowroozi L, Seigel D, Yanuzzi LA, Burton TC, Seddon JM, Gragoudas ES, Haller JA, Blair NP and Farber M. Clinical Course of Macular Holes: The Eye Disease Case-Control Study. *Arch Ophthalmol* 1999;117 (2): 242-46.

³²Kim JW, Freeman WR, Azen SP, el-Haig W, Klein DJ and Bailey IL. Prospective Randomized Trial of Vitrectomy or Observation for Stage 2 Macular Holes. Vitrectomy for Macular Hole Study Group. *Am J Ophthalmol* 1996;121(6):605-14.

³³Thompson JT, Sjaarda RN and Lansing MB. The Results of Vitreous Surgery for Chronic Macular Holes. *Retina* 1997;17(6):493-501.

³⁴Bottos J et al. Vitreomacular traction syndrome. *J Ophthalmic Vis Res* 2012;7(2):148-161.

³⁵Guillaubey A, Malvitte L, Lafontaine PO, Hubert I, Bron A, Berrod JP and Creuzot-Garcher C. Incidence of Retinal Detachment After Macular Surgery: A Retrospective Study of 634 Cases. *Br J Ophthalmol* 2007 Oct 91(10):1327-30. Epub 2007 May 23. Ramkissoon YD, Aslam SA, Shah SP, Wong SC and Sullivan PM. Risk of Iatrogenic Peripheral Retinal Breaks in 20-G Pars Plana Vitrectomy. *Ophthalmology* 2010;117(9):1825-30. Epub 2010 May 14. Rizzo S, Belting C, Genovesi-Ebert F and di Bartolo E. Incidence of Retinal Detachment after Small-Incision, Sutureless Pars Plana Vitrectomy Compared with Conventional 20- Gauge Vitrectomy in Macular Hole and Epiretinal Membrane Surgery. *Retina* 2010;30(7):1065-71.

haemorrhage³⁶, while the development of cataract is a long-term risk of vitrectomy.³⁷ In addition, the sponsor states that post vitrectomy patients may require 7-14 days in the 'head-down' position to enhance the success rate of the surgical procedure, and may be unable to return to work for 4-6 weeks. The prolonged 'head-down' position may be particularly difficult for elderly patients to tolerate. Therefore, in general, surgery is only used when patients have severe visual disturbance and/or central blindness or are at risk of developing these conditions. Consequently, 'watchful waiting' is adopted for many patients with surgery being undertaken if the condition deteriorates.

In view of the inherent limitations of vitrectomy for the treatment of VMT, there has been long standing interest in developing pharmacological methods for the nonsurgical treatment of the condition.²⁵ A recent editorial in the American Journal of Ophthalmology states that, theoretically, pharmacological vitreolysis represents an attractive alternative to surgery for the induction of clean and complete PVD.²⁵ Furthermore, the editorial comments that the advantages of pharmacological vitreolysis compared with surgery (that is, safer, easier, cheaper, possibly more effective as regards faster visual rehabilitation with optimal stable outcomes) '*could well allow earlier intervention in disease progression, before visual function has dropped to the level that would justify surgical risk*'.²⁵ The sponsor states that ocriplasmin offers the first pharmacological option for the treatment of symptomatic VMA and provides a treatment option for both those who are eligible for surgery and for those who are not candidates for surgery.

Comment: The sponsor's rationale for the submission is considered to be acceptable.

Contents of the clinical dossier

Scope of the clinical dossier

The clinical dossier documented a clinical development program for ocriplasmin administered by IVT injection for the treatment of sVMA consisting of limited clinical pharmacology data, clinical dose-finding studies and pivotal clinical efficacy and safety studies. The clinical dossier is considered adequate for evaluation of the submission for the proposed indication. The sponsor states that ocriplasmin was initially developed as an intravenous thrombolytic agent for the treatment of acute ischaemic stroke. The sponsor goes on to state that development of the product for this indication was terminated for commercial reasons unrelated to safety.

The submission contained the following clinical information:

- 3 reports of bioanalytical and analytical methods for human studies.
- 2 clinical pharmacology studies, both including pharmacokinetic data and 1 including pharmacodynamic data.
- 2 pivotal Phase III efficacy and safety studies.

³⁶Chen CJ. Glaucoma after Macular Hole Surgery. *Ophthalmology* 1998;105:94-100. Cheng L, Azen SP, El-Bradey MH, Scholz BM, Chaidhawangul S, Toyoguchi M and Freeman WR. Duration of Vitrectomy and Postoperative Cataract in the Vitrectomy for Macular Hole Study. *Am J Ophthalmol* 2001;132(6): 881-87. Park SS, Marcus DM, Duker JS, Pesavento RD, Topping TM, Frederick AR Jr and D'Amico DJ. Posterior Segment Complications After Vitrectomy for Macular Hole. *Ophthalmology* 1995;102:775-81. Thompson JT, Sjaarda RN, Glaser BM and Murphy RP. Increased Intraocular Pressure after Macular Hole Surgery. *Am J Ophthalmol* 1996;121(6):615-22. Recchia FM, Scott IU, Brown GC, Brown MM, Ho AC and Ip MS. Small-Gauge Pars Plana Vitrectomy: A Report by the American Academy of Ophthalmology. *Ophthalmology* 2010;117(9):1851-57.

³⁷Cheng L, Azen SP, El-Bradey MH, Scholz BM, Chaidhawangul S, Toyoguchi M and Freeman WR. Duration of Vitrectomy and Postoperative Cataract in the Vitrectomy for Macular Hole Study. *Am J Ophthalmol* 2001;132(6): 881-87.

- 3 dose-ranging studies.
- 2 other efficacy and safety studies.
- 10 other reports of planned studies, on-going studies, or studies for indications other than that proposed.
- Integrated summary of efficacy, Integrated summary of safety, Integrated summary of clinical retinal findings, Integrate summary of immunogenicity, 120-Day Safety Update Report, statistical plan for summary of clinical efficacy, statistical plan for summary of clinical safety and literature references.
- The sponsors quality overall summary, nonclinical overview, clinical overview, clinical summaries including, biopharmaceutic studies and associated bioanalytical methods, clinical pharmacology studies, clinical efficacy studies for the treatment of vitreomacular adhesion (VMA), clinical safety, literature references and synopses of individual studies.

Paediatric data

The sponsor provided a justification for not providing a paediatric program for Jetrea based on the fact that VMA with macular holes is primarily a disease of adults. The justification is considered to be acceptable.

Good clinical practice

All of the sponsor's studies were conducted in accordance with the ethical principles of Good Clinical Practice according to the relevant guideline³⁸.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no studies exploring the pharmacokinetics (PKs) of ocriplasmin following IVT injection in healthy subjects, as such studies were considered unethical.

The submission included two complete clinical study reports (CSRs) investigating the in vivo PKs of ocriplasmin in humans. Study TG-M-001 was the 'first-in-human' Phase I trial and formed part of the development program for ocriplasmin as an IV thrombolytic agent for the treatment of acute ischaemic stroke. The study investigated the systemic PKs of ocriplasmin in healthy males in an IV infusion dose-escalation trial investigating doses much higher than that being proposed for IVT injection. Study TG-MV-010 was a Phase II trial of the IVT PKs of ocriplasmin in patients scheduled to undergo pars plana vitrectomy (PPV) who had received a single IVT dose of ocriplasmin 125 µg at various times prior to planned surgery. The IVT injection study in patients is considered to provide pivotal ocriplasmin PK data for the proposed indication, while the IV infusion study in healthy males is considered to provide supportive ocriplasmin PK data only.

Clinical evaluator's overall conclusions on pharmacokinetics

There was one pivotal clinical PK study in humans investigating the IVT PKs of single-dose ocriplasmin (125 µg) administered by injection to patients with eye disease at varying times prior to planned PPV, and one supportive PK study investigating the IV PKs of ocriplasmin administered to healthy male volunteers in various dosing regimens.

³⁸ ICH Harmonized Tripartite Guideline (Topic E6): Good Clinical Practice

In the IVT PK study (TG-MV-010), the mean ocriplasmin activity level was 11,597.7 ng/mL in vitreous samples (n = 8) collected 5 to 30 minutes post-injection. As expected, mean ocriplasmin activity levels decreased with increasing time from injection to sample (8,108.7 ng/mL [31 to 60 minutes]; 2,610.6 ng/mL [2 to 4 hours]; and 496.5 ng/mL [24 plus/minus 2 hours]). In samples taken 7 plus/minus 1 day after the IVT injection (n = 4), ocriplasmin levels were below the lower limit of quantification (LLOQ) (< 272.37 ng/mL), and were comparable with the level in the control group. The mean ocriplasmin activity level in samples taken 2 to 4 hours after injection was 22.5% of the injected dose. This level is consistent that in the in vivo study (SR 10/mPl16/ItP) involving human vitreous fluid (that is, 16% of the initial actual concentrations of ocriplasmin at 5 hours following spiking with 125 µg).

In the IV PK study in healthy male volunteers (TG-M-001), $C_{max}(\text{obs})$ increased in a less than dose proportional manner, while area under the plasma concentration versus time curve from time 0 to a time t ($AUC_{(0-t)}$) increased in a greater than dose proportional manner. The results suggested saturation of ocriplasmin elimination at high systemic plasma concentrations. The mean terminal half-life varied from 3.5 to 8 hours, while the mean plasma clearance varied from 6.6 to 8.0 mL/h/kg.

There were no studies investigating distribution, metabolism, or elimination of ocriplasmin following IVT injection. However, it is likely that any ocriplasmin moving from the vitreous to the systemic circulation following IVT injection will enter the endogenous protein catabolism pathway, where it will be rapidly inactivated via the protease inhibitor $\alpha 2$ -antiplasmin or binding to $\alpha 2$ -macroglobulin.

There were no IVT PK studies involving ocriplasmin in patients with renal or hepatic impairment, nor were there IVT PK studies in other special populations (for example, gender, race, paediatrics/adolescents). There were no IVT or systemic drug-drug PK interaction studies involving ocriplasmin.

Overall, the limited PK data are considered to be adequate for ocriplasmin 125 µg administered as a single-dose IVT injection proposed for the treatment of sVMA.

Pharmacodynamics

Studies providing pharmacodynamic data

The 'first-in-human' Phase I study TG-M-001 in healthy males following IV infusion of various doses of ocriplasmin included PD data on $\alpha 2$ -antiplasmin activity (AAP) inhibition, prothrombin time (PT), partial thromboplastin time (APTT), fibrinogen, plasminogen, and fibrin/fibrinogen degradation products (FDP). The pharmacodynamic (PD) data from this IV infusion study in healthy males are considered not to be directly relevant to single-dose IVT injection in patients with sVMA. However, the PD data from Study TG-M-01 Part 1 (single IV infusion) and Part 3 (older subjects) have been briefly summarized in Attachment 2.

Clinical evaluator's overall conclusions on pharmacodynamics

There were limited data on the PDs of ocriplasmin in humans. The data from Study TG-M-001 in healthy male volunteers following IV infusion demonstrated that there was a dose dependent effect of ocriplasmin on AAP inhibition. As the dose of ocriplasmin increased, mean maximum AAP inhibition increased and the duration of AAP inhibition increased. Slight dose dependent prolongation of PT and APTT was observed. There were no notable differences in PD parameters between older and younger subjects following a total dose of 2.0 mg/kg, with the exception of a slightly greater decrease in mean fibrinogen concentrations in older compared with younger subjects.

Dosage selection for the pivotal studies

The submission included two, small, Phase II dose-ranging studies (TG-MV-003 and TG-MV-004) identified by the sponsor as supporting the choice of single-dose ocriplasmin 125 µg used in the pivotal Phase III studies. The two dose-ranging studies are considered to provide limited evidence supporting the selection of ocriplasmin 125 µg for the pivotal Phase III studies. In addition, the submission also included two exploratory Phase II dose-ranging studies that are considered to provide no meaningful dose-ranging data as regards the proposed indication (TG-MV-001 and TG-MV-002).

In Study TG-MV-003, the proportion of patients with non-proliferative vitreoretinal disease achieving total PVD at the beginning of vitrectomy (primary efficacy endpoint) was higher in the pooled ocriplasmin group than in the placebo group following single IVT injections 7 days prior to planned PPV (21.3%, 20/94 versus 10.0%, 3/30, respectively; $p = 0.279$). The proportion of patients achieving total PVD following single IVT injections 7 days prior to planned PPV was higher in the ocriplasmin 125 µg group (31.3%, 10/32) than in the 25 µg group (13.8%, 4/29) and the 75 µg group (18.2%, 6/33). None of the pairwise comparisons between placebo and the ocriplasmin groups were statistically significant. There were numerous secondary efficacy endpoints and the results for the majority of these endpoints favoured ocriplasmin 125 µg over ocriplasmin 25 µg and 75 µg. In a secondary efficacy endpoint analysis of patients achieving either total PVD (using the primary endpoint definition) or prevention of need for vitrectomy through Day 180, the proportion of patients achieving the endpoint was statistically significantly higher in the ocriplasmin 125 µg group compared with placebo for all patients and for several subgroups (for example, patients with baseline VMT with or without MH; patient with baseline MH). However, all statistical pairwise comparisons for the secondary efficacy endpoints should be considered nominal rather than confirmatory due to no adjustments being made to account for multiple tests.

In Study TG-MV-004, the primary efficacy endpoint analysis failed to show a statistically significant difference between single-dose pooled ocriplasmin (all doses) and sham in the proportion of patients with VMT achieving total PVD at Day 14 as assessed by the Central Reading Center (CRC) (12.7%, 7/55 versus 0%, 0/11, respectively). Furthermore, there was no dose response for total PVD at Day 14, as assessed by the CRC with the proportion of patients achieving the endpoint being 18.2% (2/11), 13.6% (3/22), and 18.2% (2/11) for ocriplasmin 75 µg, 125 µg and 175 µg, respectively. There were a number of secondary endpoint analyses in which outcomes through to Day 28 were nominally higher in the ocriplasmin 125 µg treatment group (pooled Cohort 2 and 4) compared with the ocriplasmin 75 µg and 175 µg treatment groups (for example, total PVD, investigator assessment; resolution of VMT; resolution of index condition). The effect of repeated injection of ocriplasmin 125 mg on resolution of VMT was studied in a small number of patients who had not responded to single injections of ocriplasmin 125 µg or sham at Day 28. The data did not show a clear benefit of repeat-dose ocriplasmin compared with single-dose ocriplasmin but patient numbers in the repeat-dose analysis were small.

Overall, it is considered that no definite conclusions can be drawn from this exploratory study about the efficacy of ocriplasmin or the optimal dose. The study was not powered to detect statistically significant difference between treatment groups.

Efficacy

Studies providing efficacy data

The submission included two, pivotal, Phase III studies of similar design. In addition to separate analyses of the two pivotal Phase III studies, the submission included pre-specified integrated efficacy and safety analyses of the pooled data from the two pivotal

Phase III studies. Separate Statistical Analysis Plans (SAPs) were provided for each of the integrated analyses.

Three exploratory clinical studies (TG-MV-005, TG-MV-008 and TG-MV-009) and two investigator-initiated studies (JSEI-TG-AMD-001 and 10-EI-0186) were ongoing as of the data cut-off date of 31 March 2011.

In addition to the five on-going studies listed above, two Phase IIIb clinical studies sponsored by ThromboGenics and planned at the time of the data cut-off are also ongoing.

Evaluator's overall conclusions on clinical efficacy

The total number of patients included in the efficacy analyses in the two pivotal Phase III studies was 652 (188, placebo; 464, ocriplasmin). The mean (SD) age of the total population was 71.7 (9.39) years (range: 18, 97), and 92.3% were 'White' with most of the other patients being 'Black' (4.4%). The total population included a greater proportion of females than males (65.8% and 34.2%, respectively).

In addition to symptomatic VMA at baseline, almost all patients in both treatment groups had at least 1 objectively defined macular pathologic finding identified by OCT (98.9% in both treatment groups), and more than 1 objectively defined pathologic finding was defined in 94.1% of patients in the placebo group and 94.6% of patients in the ocriplasmin group had. The most common objectively defined macular pathologies were retinal deformity (91.0%, placebo; 90.7%, ocriplasmin 125 µg) and intraretinal cysts (83.5%, placebo; 85.3%, ocriplasmin 125 µg). In the total population, only 1 patient did not have total PVD (ocriplasmin 125 µg group). FTMH at baseline was reported in 23.5% of patients in the total population (25.0%, placebo; 22.8%, ocriplasmin 125 µg) and VMT (including diabetic retinopathy) was reported in 76.5% of patients in the total population (75.0%, placebo; 77.2% ocriplasmin).

It is considered that the submitted data adequately confirm the efficacy of ocriplasmin for the treatment of symptomatic vitreous macular adhesions (sVMA), as regards anatomical outcomes of resolution of VMA at Day 28 (primary efficacy endpoint) and total PVD at Day 28 (key secondary efficacy endpoint).

The primary efficacy endpoint in both pivotal Phase III studies was the proportion of patients achieving non-surgical VMA resolution at Day 28, without creation of an anatomical defect, as determined by masked CRC evaluation of OCT scans (FAS, LOCF). The proportion of patients meeting the primary efficacy endpoint was at least 2 times higher in the ocriplasmin group than in the placebo group in both pivotal studies, and the difference between the two treatment groups in both studies statistically significant favoured ocriplasmin compared with placebo (p less than or equal to 0.003). In both pivotal studies, the results of the secondary analyses in the Full Analysis Set (FAS) with VMA at Baseline (last observation carried forward (LOCF)) and in the Per Protocol (PP) set were consistent with the results for the primary analysis in the FAS (LOCF). The results for the integrated efficacy analysis (IEA) were consistent with those from the two pivotal, Phase III studies.

In both pivotal Phase III studies, the proportion of patients achieving VMA resolution was significantly greater in the ocriplasmin group compared with the placebo group at all post-injection time-points (Days 7, 14, 28 and Months 3, 6). The difference between the two groups occurred as early as on Day 7 (the first-time point), peaked at Day 28 and remained relatively constant from Day 28 through to Month 6. The results in the IEA were consistent with those from both pivotal studies.

In both pivotal Phase III studies, the key secondary efficacy endpoint was the proportion of patients achieving total PVD at Day 28, as determined by masked investigator assessment of B-scan ultrasound (FAS, LOCF). In both pivotal studies, the proportion of

patients meeting the key secondary efficacy endpoint was statistically significantly higher in the ocriplasmin group compared with the placebo group (p less than or equal to 0.104). The results for the primary analysis in the FAS (LOCF) from both pivotal studies were consistent with the results for the secondary analysis in the FAS with VMA at Baseline (LOCF), but only the results for Study TG-MV-007 were significant for the secondary analysis in the PP set. The results from the IEA (FAS, LOCF) were consistent with those from both pivotal studies, and the results from the IEA for the secondary analyses in the FAS with VMA at Baseline and in the 'PP' set were consistent with the primary analysis in the FAS (LOCF).

All other efficacy secondary endpoints in both pivotal Phase III studies were evaluated at the two-sided 5% level of significance but as no adjustments were made for multiplicity all p-values were considered to be nominal rather than confirmatory. The Statistical Analysis Plans (SAPs) for both pivotal studies stated that the *'results for the additional secondary endpoints will be of a supportive nature only and will be interpreted as such.'* The SAP for the IEA stated that *'no adjustments'* will be made for multiple comparisons as there is only one primary efficacy endpoint. All other analyses are secondary analyses or subset analyses. Based on the statements in the SAPs, it is considered that the results for the additional secondary efficacy endpoints are supportive and not confirmatory.

In both pivotal, Phase III studies, non-surgical full-thickness macular hole closure (FTMHC) in patients with sVMA and baseline FTMH (additional secondary efficacy endpoint) at Day 28 and Month 6 occurred in a numerically greater proportion of patients in the ocriplasmin group compared with placebo. However, the results for the two pivotal studies were inconsistent. In Study TG-MV-006, the difference between the ocriplasmin and placebo groups in the proportion of patients achieving FTMHC was similar at Day 28 and Month 6 (p-value nominally significant at both time-points) but in Study TG-MV-007 the difference between the ocriplasmin and placebo groups at Month 6 (p-value nominally non-significant) was 50% smaller than at Day 28 (p-value nominally significant). In the IEA, the difference between the ocriplasmin and placebo groups in the proportion of patients achieving FTMHC was similar at Day 28 and Month 6 (p-value nominally significant at both time points).

In both pivotal Phase III studies there was a numerically greater proportion of patients requiring vitrectomy by Month 6 (secondary efficacy endpoint) in the placebo group compared with ocriplasmin group and the p-value was nominally insignificant for the difference between the two groups in both studies. In the IEA there was a numerically greater proportion of patients requiring vitrectomy by Month 6 in the placebo group compared with the ocriplasmin group and the p-value was nominally significant for the difference between the groups.

In both, pivotal Phase III studies, there was a numerically greater proportion of patients in the ocriplasmin group compared with the placebo group with non-surgical improvements of greater than or equal to 2 lines and greater than or equal to 3 lines from baseline to Month 6. In Study TG-MV-006, the p-value was nominally significant for the difference between the two groups for improvement greater than or equal to 2 lines but not for improvement greater than or equal to 3 lines. In Study TG-MV-007, the p-value was nominally non-significant for the difference between the two groups for improvement greater than or equal to 2 lines but nominally significant for improvement greater than or equal to 3 lines. In IEA, the p-value was nominally significant for the difference between the two treatment groups for both improvement greater than or equal to 2 lines and greater than or equal to 3 lines.

In Study TG-MV-006, there was a numerically greater proportion of patients in the ocriplasmin group compared with the placebo group with non-surgical declines of greater than or equal to 2 lines and greater than or equal to 3 lines from baseline to Month 6, with all p-values being nominally non-significant for the differences between the two groups. In

Study TG-MV-007, there was a numerically identical proportion of patients with non-surgical declines of greater than or equal to 2 lines in the two treatment groups and a numerically greater proportion of patients with non-surgical declines of greater than or equal to 3 lines in placebo group compared with the ocriplasmin group, with all p-values being nominally non-significant for the differences between the two groups. In the IEA there was a numerically greater proportion of patients in the ocriplasmin group compared with the placebo with non-surgical declines of greater than or equal to 2 lines and greater than or equal to 3 lines from baseline to Month 6, with all p-values being nominally non-significant for the differences between the two groups. In the IEA the greatest difference between the two treatment groups was the numerically greater proportion of patients with non-surgical declines of greater than or equal to 2 lines and greater than or equal to 3 lines from baseline to Day 7 in the ocriplasmin group compared with the placebo group, with all p-values being nominally non-significant for the differences between the two treatment groups. The initial rapid decline in best corrected visual acuity (BCVA) following ocriplasmin is a safety issue.

In both pivotal Phase III studies and the IEA, improvements in BCVA mean letter scores (additional secondary efficacy endpoint) from baseline through to Month 6 were small and are considered to be of doubtful clinical significance. The differences between the two treatments groups were nominally non-significant for the change from baseline to Month 6 in both pivotal studies and the IEA.

In general, mean Visual Functioning Questionnaire 25 (VFQ-25) scores from baseline to Month 6 (additional secondary efficacy endpoint) in the IEA were numerically greater in the ocriplasmin group compared with the placebo group but the differences were small and of doubtful clinical significance. The p-values were nominally non-significant for most of the differences between the two treatment groups.

Safety

Exposure

The submitted safety data included a Summary of Clinical Safety (SCS) providing pooled safety data from the two pivotal Phase III studies, and integrated safety data from 7 completed clinical studies as of 31 March 2011. In addition, the submitted safety data included a 120-Day Safety Update Report for the period 1 April 2011 to 31 May 2012. The 120-Day Safety Report Update included information on deaths and serious adverse events that occurred over the period covered by the report.

The 120-Day Safety Update Report indicates that, as of 31 May 2012, 758 patients had been exposed to ocriplasmin by IVT injection in 8 completed clinical studies, and 243 patients had received control (placebo or sham). Furthermore, it was estimated that 215 patients had received ocriplasmin and 94 had received control (placebo or sham) in 5 clinical studies that were on-going during the reporting period 1 April 2011 to 31 May 2012, while 3 patients received ocriplasmin on a compassionate use basis, and 4 control patients did not receive any treatment. Overall, as of the 31 May 2012 it is estimated that total exposure from completed and on-going studies to ocriplasmin and control is 976 and 341 patients, respectively.

Of the 758 patients exposed to ocriplasmin as of 31 May 2012, 599 (79.0%) have been exposed to the proposed dose of 125 µg. Of the 758 patients exposed to ocriplasmin, 465 (61.3%) have been exposed to one single IVT 125 µg dose of ocriplasmin in the two pivotal Phase III studies (number 6 and number 7). The exposure data for the 8 completed clinical trials as of 31 May 2012 are summarized in Table 12 in Attachment 2.

In the CER, the evaluation focuses primarily on the data from the pooled safety set from the two pivotal Phase III studies provided in the SCS. The safety data for ocriplasmin from these two studies are considered to be pivotal as regards the proposed indication. The safety data from the individual CSRs of the two pivotal Phase III studies have also been examined.

Postmarketing experience

No data on postmarketing experience are available.

Evaluator's overall conclusions on clinical safety

Overall, the safety of single-dose ocriplasmin 125 µg administered by IVT injection for the treatment of VMA is considered to be satisfactory. The key safety data in the submission are considered to be from the two pivotal Phase III studies (TG-MV-006 and TG-MV-007). The two studies provide a double-masked comparison of patients with VMA randomized to treatment with either ocriplasmin 125 µg (the dose proposed for approval) or placebo. The two pivotal Phase III studies included a pooled safety set consisting of 465 patients treated with ocriplasmin 125 µg and 187 patients treated with placebo. The safety profile of ocriplasmin based on the pivotal Phase III studies is consistent with the safety profiles of the drug derived from the 7 completed studies combined (n = 741) up to 31 March 2011 (SCS), and on data from all completed and ongoing studies (n = 976) up to 31 May 2012. Based on the 'rule of three', 976 patients exposed to ocriplasmin (all doses) from the completed and ongoing studies up to 31 May 2012 provides a database of sufficient size to support detection of ADRs occurring with an upper 95% confidence interval (CI) greater than or equal to 0.31%.³⁹ The size of the database is insufficient to ensure detection of ADRs occurring at frequencies < 0.3%. The majority of patients in the pivotal Phase III studies treated with ocriplasmin were Caucasian (92.2%), and there are limited data on the safety of the drug in non-Caucasians.

In the pivotal Phase III studies, the proportion of patients with adverse events (AEs) (any) was higher in the ocriplasmin 125 µg group compared with placebo (76.6%, n = 356 versus 69.0%, n = 129; respectively). Most of the AEs in the two treatment groups were ocular AEs occurring in the study eye, and the proportion of patients with these events was notably higher in the ocriplasmin 125 µg group compared with placebo (69.7%, n = 324 versus 52.9%, n = 99; respectively). The proportion of patients with non-ocular AEs was similar in the ocriplasmin 125 µg and placebo groups (30.1%, n = 140 versus 28.3%, n = 53; respectively), as was the proportion of patients with ocular AEs in the non-study eye (13.1%, n = 61 versus 11.8%, n = 22; respectively).

In the pivotal Phase III studies, the most frequently reported ocular adverse drug reactions (ADRs) in the study eye in the ocriplasmin 125 µg group were consistent with pharmacologic vitreolysis and PVD (for example, vitreous floaters, photopsia), while other ADRs were due to inflammation/irritation resulting from either the injection procedure and/or the drug. The majority of ocular ADRs in the ocriplasmin 125 µg group were categorised as mild or moderate in intensity, and severe reactions occurred infrequently. Most of the ocular ADRs in the study eye in the ocriplasmin 125 µg group occurred within the first 7 days post-injection, and most had resolved by the end of the study.

In the pivotal Phase III studies, the most commonly reported ocular ADRs in the study eye occurring in greater than or equal to 5% of patients in the ocriplasmin 125 µg group (versus placebo) were: vitreous floaters (16.8% versus 7.5%); eye pain (13.1% versus 5.9%); photopsia (11.8% versus 2.7%); vision blurred (8.4% versus 3.2%); visual acuity reduced (6.2% versus 4.3%); visual impairment (5.4% versus 1.1%); and retinal oedema

³⁹ Jovanovic BD and Levy PS. A look at the rule of threes. *The American Statistician* 1997;51 (2): 137-139.

(5.4% versus 1.1%). All ADRs in the study eye occurring in greater than or equal to 5% of patients in the ocriplasmin 125 µg group were reported more commonly in the active group than in the placebo group.

In the pivotal Phase III studies, ocular ADRs in the study eye occurring in < 5% and greater than or equal to 1% of patients in the ocriplasmin 125 µg group and greater than or equal to 1% more frequently than in the placebo group were: macular oedema (4.1% versus 1.6%); anterior chamber cells (3.7% versus 2.7%); photophobia (3.7% versus 0%); ocular discomfort (2.8% versus 1.1%); vitreous detachment (2.6% versus 1.1%); iritis (2.6% versus 0%); dry eye (2.4% versus 1.1%); metamorphopsia (2.2% versus 0.5%); retinal degeneration (1.7% versus 0.5%); eyelid oedema (1.5% versus 0%); retinal pigment epitheliopathy (1.5% versus 0%); macular degeneration (1.3% versus 0.5%); miosis (1.1% versus 0%); scotomata (1.1% versus 0%); and corneal abrasion (1.1% versus 0%). There were no cases of endophthalmitis reported in either treatment group and there have been no cases of endophthalmitis reported with ocriplasmin in all completed and ongoing studies up to 31 May 2012.

In the pivotal Phase III studies, 5 deaths (1.1%) occurred in 465 patients in the ocriplasmin 125 µg group and no deaths occurred in 187 patients in the placebo group. The 5 deaths in the ocriplasmin 125 µg group all occurred in women aged greater than or equal to 76 years. Four (4) of the deaths were considered to be unrelated to treatment, while the relationship with treatment was described as 'remote' for 1 of the deaths (malignant lung neoplasm). In the completed and ongoing IVT injection studies there have been a total of 10 deaths (6 in the ocriplasmin group, 2 in the sham group and 2 treatment still masked), as of the database cut-off date of 31 May 2012. If it is assumed that in this database the masked treatment is ocriplasmin (worst case scenario) then the incidence of death in the ocriplasmin (all doses) group is 0.8% (8/976) compared with compared with 0.6% (2/341) in the control group. Overall, the reported deaths associated with ocriplasmin IVT injections do not give rise to concern.

In the pivotal Phase III studies, serious adverse events (SAEs) (any) occurred in a similar proportion of patients in the ocriplasmin 125 µg and placebo groups (13.3%, n = 62 versus 12.8%, n = 24; respectively). Most of the SAEs were ocular events occurring in the study eye and were reported more frequently in patients in the placebo group than in the ocriplasmin group (10.7%, n = 20 versus 7.7%, n = 36; respectively). The most commonly reported ocular SAE in the study eye was macular hole (includes progression of macular hole) and this event occurred more frequently in patients in the placebo group than in the ocriplasmin 125 µg group (8.6%, n = 16 versus 5.2%, n = 24; respectively). The only other ocular SAEs in the study eye occurring in greater than or equal to 1% of patients in either treatment group were vitreous adhesions (1.1%, n = 5, ocriplasmin versus 0.5%, n = 1, placebo), and retinal detachment (0.4%, n = 2, ocriplasmin versus 1.6%, n = 3, placebo). The additional SAE reports associated with ocriplasmin in the 120-Day Safety Update Report were consistent with previous reports.

In the pivotal Phase III studies, the majority of the SAEs (any) in both treatment groups were considered to be unrelated to the study drug. All SAEs considered to be drug-related were ocular events occurring in the study eye and were reported in the same proportion of patients in both the ocriplasmin 125 µg and placebo groups (3.2%, n = 15 versus 3.2%, n = 6). The 16 drug-related SAEs in the 15 patients in the ocriplasmin 125 µg group were macular hole (x9), retinal detachment (x2), vitreous adhesion (x2), visual acuity reduced (x2), and posterior capsule opacification (x1). The 6 drug-related SAEs in the 6 patients in the placebo group were macular hole (x4), macular oedema (x1) and vitreous adhesion (x1).

In the pivotal Phase III studies, withdrawal from the study due to AEs occurred in a small number of patients in both the ocriplasmin 125 µg and placebo groups (0.9%, n = 4 versus 1.1%, n = 2; respectively). The reason for the 4 withdrawals due to AEs in the ocriplasmin

125 µg group was death (unrelated to treatment) and the reasons for the 2 withdrawals in the placebo group were subcapsular cataract (possibly related to treatment) and spondylolisthesis (unrelated to treatment).

In the pivotal Phase III studies, ocular AEs in the study eye of special interest occurring in a greater proportion of patients in the ocriplasmin 125 µg group than in the placebo group, respectively were: vision alteration (20.2%, n = 94 versus 7.5%, n = 14); eye pain (15.9%, n = 74 versus 7.0%, n = 13); retinal/macular oedema (9.5%, n = 44 versus 2.7%, n = 5); intraocular inflammation (7.1%, n = 33 versus 3.7%, n = 7); retinal pigment change (2.4%, n = 11 versus 0.5%, n = 1); glaucoma (0.6%, n = 3 versus 0%); and colour vision/ERG abnormalities (0.6%, n = 3 versus 0%).

In the pivotal Phase III studies, ocular AEs in the study eye of special interest occurring in a greater proportion of patients in the placebo group than in the ocriplasmin 125 µg group, respectively, were: macular hole (9.6%, n = 18 versus 6.7%, n = 31); cataract (any) in phakic patients (11.9%; n = 16 versus 8.2%, n = 24); intraocular pressure increased (5.3%, n = 10 versus 4.1%; n = 19); intraocular haemorrhage (3.7%, n = 7 versus 2.4%, n = 11); and retinal breaks (4.3%, n = 8 versus 1.9%, n = 9).

There were no immunogenicity data in the pivotal Phase III studies, or in other IVT studies. Data from studies involving high doses of ocriplasmin administered by IV infusion suggest ocriplasmin antibodies and anti-staphylokinase antibodies following IVT injection are unlikely to be a frequent occurrence. In the pivotal Phase III studies, immune system disorders were reported in 9 (1.9%) patients in the ocriplasmin 125 µg group, including a total of 11 events (4 x seasonal allergy, 3 x drug hypersensitivity and 1 each for allergy to arthropod sting, contrast media allergy, hypersensitivity, and iodine sensitivity), but not in any placebo patients.

No clinical laboratory data or vital sign data were assessed in the pivotal Phase III studies. Clinical laboratory data from the pilot IVT Study TG-MV-001 and clinical laboratory AE data from the pivotal studies suggests that clinically significant laboratory abnormalities are unlikely to develop following single dose ocriplasmin (125 µg) administered by IVT injection. Scheduled ophthalmic assessments were undertaken of Intraocular Pressure (IOP), retinal changes, lens changes, intraocular inflammation, and vitreous haemorrhage. The findings from these assessments were consistent with those reported for ocular AEs for the individual assessed parameters.

Analyses of selected ocular AEs in the study eye in the pivotal Phase III studies, indicated a higher incidence of these disorders in female versus male patients, patients aged < 65 years versus greater than or equal to 65 years, patients aged < 75 years versus greater than or equal to 75 years, patients with baseline phakia versus pseudophakia, patients with baseline FTMH versus patients no FTMH, and patients with baseline ERM versus no ERM. VMA resolution at Day 28 was strongly associated with a higher incidence of the AE of vision alteration. Consistent with this, the other subgroups with higher incidence of the AE of vision alteration were generally those that achieved higher rates of VMA resolution.

In the 820 patients treated with ocriplasmin from completed and ongoing studies up to and including 31 March 2011, 6 patients (0.7%) developed serious and/or severe acute transient vision decreases with no alternative explanation. The severity of these events ranged from loss of visual acuity ranging from 20/200 to hand motions, and 50% of the patients reported transient visual field restriction. In the most severe cases, the onset was within 24 hours of injection and within 7 days for the less severe cases. The visual impairment generally resolved over days to weeks.

In the 820 patients referred to in the above paragraph, dyschromatopsia occurred in 16 (2%) patients treated with ocriplasmin, and loss of BCVA greater than or equal to 10 letters by day 7 was reported in 44 (5.7%) patients treated with ocriplasmin (versus 3 [1.1%] out of 269 patients in the control group).

The incidence of ERG abnormalities in patients treated with ocriplasmin has not yet been determined.

First round benefit-risk assessment

First round assessment of benefits

The submitted data indicate that the benefits of treatment with ocriplasmin (single-dose IVT injection, 125 µg) in patients with symptomatic VMA relate primarily to improvements in non-surgical resolution of VMA at Day 28 without creation of an anatomical defect, and total PVD at Day 28. Improvement in non-surgical VMA resolution with ocriplasmin 125 µg was seen as early as on Day 7, with benefits peaking at Day 28 and being maintained through to Month 6. However, the benefits observed with ocriplasmin 125 µg for both VMA resolution and PVD at Day 28 were modest, as can be seen from the absolute difference between the two treatment groups and the number of patients needed to be treated for one patient to achieve a benefit (number needed to treat (NNT)).

In Study TG-MV-006, the primary efficacy endpoint of non-surgical VMA resolution at Day 28 was achieved in 27.9% (61/219) of patients in the ocriplasmin 125 µg group and 13.1% (14/107) of patients in the placebo group (difference 14.8% [95% CI: 6.0, 23.5]; $p = 0.003$). The absolute difference between the two treatment groups indicates that the NNT is 7 patients. In Study TG-MV-007, the primary efficacy endpoint of non-surgical VMA resolution at Day 28 was achieved in 25.3% (62/254) of patients in the ocriplasmin 125 µg group and 6.2% (5/81) of patients in the placebo group (difference 19.1% [95% CI: 11.6, 26.7]; $p < 0.001$). The absolute difference between the two treatment groups indicates that the NNT is 5 patients. The results for the two pivotal studies were consistent with the results from the IEA.

In Study TG-MV-006, the key secondary efficacy endpoint of total PVD at Day 28 was achieved in 16.4% (36/219) of patients in the ocriplasmin 125 µg group and 6.5% (7/107) of patients in the placebo group (difference 9.9% [95% CI: 3.1, 16.7]; $p = 0.014$). The absolute difference between the two treatment groups indicates that the NNT is 10 patients. In Study TG-MV-007, the key secondary efficacy endpoint of total PVD was achieved in 10.6% (26/245) of patients in the ocriplasmin 125 µg group and 0% (0/81) of patients in the placebo group (difference 10.6% [95% CI: 6.8, 14.5]; $p < 0.001$). The absolute difference between the two treatment groups indicates that the NNT is 9 patients. The results for the two pivotal studies were consistent with the results from the IEA.

Non-surgical FTMHC at Day 28 and Month 6 in patients with sVMA and baseline FTMH occurred in a numerically greater proportion of patients in the ocriplasmin 125 µg group than in the placebo group in both pivotal Phase III studies but all p -values for the differences between the two treatment groups were nominal. In Study TG-MV-006, the proportion of patients achieving FTMHC in the ocriplasmin and placebo groups at Day 28 was 43.9% (25/57) and 12.5% (4/32), respectively, (difference 31.4% [95% CI: 14.1, 48.6], $p = 0.002$), and at Month 6 was 45.6% (26/57) and 15.6% (5/32), respectively (difference 30.0% [95% CI: 11.9, 48.0], $p = 0.005$). In Study TG-MV-007, the proportion of patients achieving FTMHC in the ocriplasmin and placebo groups at Day 28 was 36.7% (18/49) and 6.7% (1/15), respectively, (difference 30.1% [95% CI: 11.6, 48.5], $p = 0.028$), and at Month 6 was 34.7% (17/49) and 20.0% (3/15), respectively (difference 30.0% [95% CI: 11.9, 48.0], $p = 0.354$). The results for the two pivotal studies were inconsistent. In Study TG-MV-006, the numerical benefit observed with ocriplasmin at Day 28 compared with placebo was maintained at Month 6 but in Study TG-MV-007 the numerical benefit observed with ocriplasmin at Day 28 compared placebo was halved at Month 6. The results from the IEA were consistent with those from Study TG-MV-006. There are no

confirmatory data establishing that treatment with ocriplasmin 125 µg results in FTMHC in patients with sVMA and baseline FTMH.

In both pivotal Phase III studies, there was a numerically greater proportion of patients requiring vitrectomy in the study eye by Month 6 in the placebo group compared with the ocriplasmin 125 µg group but the p-value was nominally insignificant for the difference between the groups in both studies. The data relating to improvements from baseline to Month 6 in BCVA (categorical and mean changes) and from baseline to Month 6 in VFQ-25 mean scores from both pivotal studies suggest that the limited benefits observed with ocriplasmin 125 µg compared with placebo for these functional outcomes are of doubtful clinical significance.

First round assessment of risks

The major risks associated with ocriplasmin 125 µg administered by IVT injection for the treatment of VMA relate to adverse drug reactions (ADRs) in the injected eye. There are no significant risks of systemic non-ocular AEs or ocular AEs in the non-injected eye. There is no increased risk of death associated with single-dose IVT injection of ocriplasmin 125 µg. However, the size of the ocriplasmin database from all completed and ongoing studies as of 31 May 2012 is insufficient to ensure detection of ADRs occurring at frequencies below 0.3%. The majority of patients in the pivotal Phase III studies treated with ocriplasmin were Caucasian (92.2%), and there are limited data on the safety of the drug in non-Caucasians.

The most commonly reported ocular ADRs in the study eye observed with ocriplasmin 125 µg were consistent with pharmacologic vitreolysis and PVD (for example, vitreous floaters, photopsia), while other ADRs were due to inflammation/irritation resulting from either the injection procedure and/or the drug. The majority of ocular ADRs in the study observed with ocriplasmin 125 µg were categorised as mild or moderate in intensity and severe reactions occurred infrequently. Most of the ocular ADRs in the study eye observed in patients in the ocriplasmin 125 µg group occurred within the first 7 days post-injection, and most had resolved by the end of the study.

In the pivotal Phase III studies, the most commonly reported ocular ADRs in the study eye occurring in greater than or equal to 5% of patients in the ocriplasmin 125 µg group (versus placebo) were: vitreous floaters (16.8% versus 7.5%); eye pain (13.1% versus 5.9%); photopsia (11.8% versus 2.7%); vision blurred (8.4% versus 3.2%); visual acuity reduced (6.2% versus 4.3%); visual impairment (5.4% versus 1.1%); and retinal oedema (5.4% versus 1.1%).

In the pivotal Phase III studies, ocular ADRs in the study eye occurring in < 5% and greater than or equal to 1% of patients in the ocriplasmin group and greater than or equal to 1% more frequently than in the placebo group were: macular oedema (4.1% versus 1.6%); anterior chamber cells (3.7% versus 2.7%); photophobia (3.7% versus 0%); ocular discomfort (2.8% versus 1.1%); vitreous detachment (2.6% versus 1.1%); iritis (2.6% versus 0%); dry eye (2.4% versus 1.1%); metamorphopsia (2.2% versus 0.5%); retinal degeneration (1.7% versus 0.5%); eyelid oedema (1.5% versus 0%); retinal pigment epitheliopathy (1.5% versus 0%); macular degeneration (1.3% versus 0.5%); miosis (1.1% versus 0%); scotomata (1.1% versus 0%); and corneal abrasion (1.1% versus 0%). There were no cases of endophthalmitis reported in either treatment group, and there have been no cases of endophthalmitis reported with ocriplasmin in all completed and ongoing studies up to 31 May 2012.

In the pivotal Phase III studies, the risk of ocular SAEs occurring in the injected eye was lower in patients treated with ocriplasmin 125 µg than with placebo (7.7% versus 10.7%, respectively), and risk of the most commonly reported SAE (macular hole) was lower in the ocriplasmin 125 µg group than in the placebo group (5.2% versus 8.6%, respectively).

The only other ocular SAEs in the injected eye occurring in greater than or equal to 1% of patients in either treatment group were vitreous adhesions (1.1%, n = 5, ocriplasmin versus 0.5%, n = 1, placebo), and retinal detachment (0.4%, n = 2, ocriplasmin versus 1.6%, n = 3, placebo). The proportion of patients with drug-related SAEs was 3.2% in each treatment group. The 16 drug-related SAEs in the 15 patients in the ocriplasmin 125 µg group were macular hole (x9), retinal detachment (x2), vitreous adhesion (x2), visual acuity reduced (x2), and posterior capsule opacification (x1). The 6 drug-related SAEs in the 6 patients in the placebo group were macular hole (x4), macular oedema (x1) and vitreous adhesion (x1).

Withdrawal from the study due to AEs was reported in a small number of patients in both the ocriplasmin 125 µg and placebo groups (0.9%, n = 4 versus 1.1%, n = 2; respectively). The reason for the 4 withdrawals due to AEs in the ocriplasmin 125 µg group was death (unrelated to treatment), and the reasons for the 2 withdrawals in the placebo group were subcapsular cataract (possibly related to treatment) and spondylolisthesis (unrelated to treatment).

In the pivotal Phase III studies, ocular AEs in the injected eye of special interest occurring in a greater proportion of patients in the ocriplasmin 125 µg group than in the placebo group, respectively were: vision alteration (20.2% versus 7.5%); eye pain (15.9% versus 7.0%); retinal/macular oedema (9.5% versus 2.7%); intraocular inflammation (7.1% versus 3.7%); retinal pigment change (2.4% versus 0.5%); glaucoma (0.6% versus 0%); and colour vision/ERG abnormalities (0.6% versus 0%). On the other hand, ocular AEs in the study eye of special interest occurring in a greater proportion of patients in the placebo group than in the ocriplasmin 125 µg group, respectively, were: macular hole (9.6% versus 6.7%); cataract (any) in phakic patients (11.9% versus 8.2%); intraocular pressure increased (5.3% versus 4.1%); intraocular haemorrhage (3.7% versus 2.4%); and retinal breaks (4.3% versus 1.9%).

There were no data from the pivotal Phase III studies assessing the risks of clinical laboratory abnormalities associated with ocriplasmin 125 µg administered by IVT injections. However, data from the pilot IVT study and clinical laboratory AE data from the pivotal studies suggests that clinically significant laboratory abnormalities are unlikely to develop following single dose ocriplasmin 125 µg IVT injection. There are no data the pivotal Phase III studies assessing the risk of vital sign changes (blood pressure, pulse rate, and temperature) or electrocardiogram (ECG) changes associated with ocriplasmin 125 µg IVT injections. However, there are no AE data from these studies suggesting that notable changes in vital sign and ECG parameters are associated with ocriplasmin 125 µg IVT injection. There are no immunogenicity data for ocriplasmin following IVT injection. However, there was no indication from the immune system AEs reported in the pivotal Phase III studies that ocriplasmin 125 µg is associated with clinical significant changes in this system.

Exploratory safety data from the pivotal Phase III study relating to selected frequently occurring ocular AEs in the injected eye suggest that females, patients younger than 65 years, phakic patients, patients with baseline FTMH, and patients with baseline might be at an increased risk of experiencing some and/or all of the assessed events. There are no safety data specifically assessing the effects of ocriplasmin 125 µg patients with hepatic impairment, renal impairment, or cardiovascular impairment. However, the totality of the provided safety suggests that patients in these groups are unlikely to be exposed to additional risks from single-dose ocriplasmin 125 µg IVT injection.

While colour vision/ERG abnormalities were reported in 0.6% of patients in the ocriplasmin 125 µg group (including 1 ERG abnormality) and no patients in the placebo group in the pivotal Phase III studies, the actual frequency of ERG abnormalities cannot be assessed from these studies since ERG assessments were not routinely undertaken. Furthermore, due to the absence of routine ERG testing in the majority of completed

clinical studies the incidence of ERG abnormalities following ocriplasmin administration cannot be calculated from the available data.

There is a small, uncommon (0.7%, 6/820) risk of serious and/or severe acute transient impairment of visual impairment occurring within the first 7 days following injection with ocriplasmin, with the most severe cases occurring in the first 24 hours. In these patients, visual impairment generally resolved over days to weeks.

There is a common (2.0%, 16/820) risk of mild, dyschromatopsia (generally described as yellowish vision) following ocriplasmin injection. Most cases occurred on the day of injection, and median time to resolution was 3 months (range: 1, 28 months) with resolution being reported in 14 of the 16 patients. One additional case was reported in the 120 Day Safety Update Report giving a total of 17 (1.7%) reported cases 976 patients exposed to ocriplasmin in completed and ongoing studies.

There is a common risk (5.4%, 44/820) of loss of BCVA of greater than or equal to 10 letters (that is greater than or equal to 2 lines) by Day 7 in patients treated with ocriplasmin (compared with 1.1%, 3/269, in patients treated with control). However, BCVA returned to within 1 line (5 letters) of baseline values during the study for all patients, except for 6/820 (0.7%) treated with ocriplasmin and 1/269 (1.1%) treated with control.

First round assessment of benefit-risk balance

The benefit risk balance of ocriplasmin 125 µg administered by single-dose IVT injection for the treatment of symptomatic VMA is favourable.

However, it is considered that the benefits of treatment are modest and are primarily related to beneficial anatomical outcomes of VMA resolution and creation of total PVD. It is considered that the benefits related to improvement in functional outcomes of BCVA and quality of life following administration of ocriplasmin are very modest and are of limited clinical significance.

The place of ocriplasmin relative to surgery for the treatment of VMA is uncertain. It would be treatment option for patients considered to be unsuitable for surgery or for patients who elect not to undergo surgery. However, in view of the modest treatment effect observed with ocriplasmin 125 µg in the pivotal Phase III studies it is considered unlikely that ocriplasmin would displace vitrectomy as the first treatment option for most patients with VMA.

The results of the pivotal Phase III studies are not applicable to patients excluded from the studies, including patients with large diameter macular holes (greater than 400 µm), high myopia, aphakia, history of retinal detachment, lens instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration and vitreous haemorrhage. The sponsor stated that patients with these conditions were excluded from the pivotal Phase III studies because it was considered that they were unlikely to benefit from treatment (based on clinical experience or literature), or were theoretically at a higher risk of complications due to the IVT injection procedure or the vitreolytic effect of ocriplasmin. Treatment in these patients is not recommended. Concurrent treatment of both eyes has not been investigated and is not recommended.

First round recommendation regarding authorisation

It is recommended that ocriplasmin be approved in adults for '*the treatment of symptomatic vitreomacular adhesion (sVMA)*'.

It is recommended that the wording of the sponsor's proposed indication be amended to exclude reference to patients with sVMA associated with macular hole. There is no confirmatory data demonstrating that FTMHC is achieved in patients with sVMA and FTMH at baseline. The data relating to the FTMHC in patients with sVMA and FTMH in the two pivotal Phase III studies is limited to additional secondary efficacy endpoint analyses in these subgroups in which all p-values were nominal. Furthermore, the results of the two pivotal Phase III studies were inconsistent. In Study TG-MV-006, the results suggest that FTMHC achieved at Day 28 can be maintained through to Month 6 but in Study TG-MV-007 the results suggest that FTMHC achieved at Day 28 cannot be satisfactorily maintained through to Month 6.

Clinical questions

Efficacy

The approved US and EU recommended indications for Jetrea differ. In the US label, no reference is made to patients with sVMA including those associated with macular hole. The indication simply states that Jetrea is indicated '*for the treatment of symptomatic vitreomacular adhesions*'. In contrast, the EU recommended indication states that Jetrea is indicated '*for the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns*'. Please account for the difference between the two indications with respect to treatment of patients with sVMA with macular holes.

Second round evaluation

The major issue raised in the sponsor's response (see Attachment 2) relates to whether reference to patients with sVMA associated with macular hole less than or equal to 400 µm in diameter should be included in the wording of the indication. The sponsor notes that patients with FTMH accounted for almost 25% of patients in the two pivotal Phase III studies, and that VMA resolution at Day 28 in patients with FTMH was higher than in patients with VMT only (50% versus 19.6%). The issue of whether the indication should include patients with FTMH was considered in the first round evaluation. Based on the first round evaluation of the submitted data it was concluded that specific reference to patients with FTMH should be excluded from the wording of the indication for the reasons outlined in the *First round benefit-risk assessment* (4th paragraph) of this CER. However, following consideration of the sponsor's response it is recommended that the indication for ocriplasmin in adults should be for the '*treatment of symptomatic vitreomacular adhesion (sVMA), including when associated with macular hole less than or equal to 400 microns in diameter*'. It is considered that the term sVMA should be used rather than VMT (as proposed by the sponsor), as this term is consistent with that used to describe the condition in the inclusion criteria for the two pivotal Phase III studies.

Review of the integrated efficacy analysis of the data from the two pivotal Phase III studies shows that 23.5% (153/652) of patients with sVMA had FTMH at baseline. Patients with baseline macular holes greater than 400 microns in diameter were excluded from the pivotal studies. Therefore, the pivotal study population included a 'substantial' number of patients with sVMA associated with baseline macular holes less than or equal to 400 microns in diameter. In patients with FTMH at baseline, VMA resolution was statistically significantly higher in the ocriplasmin group compared with placebo. The absolute difference between the two treatment groups was 24.5% (95% CI: 8.8, 40.2) in favour of ocriplasmin, and the odds ratio (PR) statistically significantly favoured ocriplasmin over placebo.

Second round benefit-risk assessment

Second round assessment of benefits

Following consideration of the sponsor's response to the clinical questions it is considered that the benefits of treatment with ocriplasmin have been satisfactorily established for patients with sVMA, including when associated with macular hole less than or equal to 400 microns in diameter.

The submitted data indicate that the benefits of treatment with ocriplasmin (single-dose IVT injection, 125 µg) in patients with symptomatic VMA relate primarily to improvements in non-surgical resolution of VMA at Day 28 without creation of an anatomical defect, and total PVD at Day 28. Improvement in non-surgical VMA resolution with ocriplasmin 125 µg was seen as early as on Day 7, with benefits peaking at Day 28 and being maintained through to Month 6. However, the benefits observed with ocriplasmin 125 µg for both VMA resolution and PVD at Day 28 were modest, as can be seen from the absolute difference between the two treatment groups and the number of patients needed to be treated for one patient to achieve a benefit (NNT).

In Study TG-MV-006, the primary efficacy endpoint of non-surgical VMA resolution at Day 28 was achieved in 27.9% (61/219) of patients in the ocriplasmin 125 µg group and 13.1% (14/107) of patients in the placebo group (difference 14.8% [95% CI: 6.0, 23.5]; $p = 0.003$). The absolute difference between the two treatment groups indicates that the NNT is 7 patients. In Study TG-MV-007, the primary efficacy endpoint of non-surgical VMA resolution at Day 28 was achieved in 25.3% (62/254) of patients in the ocriplasmin 125 µg group and 6.2% (5/81) of patients in the placebo group (difference 19.1% [95% CI: 11.6, 26.7]; $p < 0.001$). The absolute difference between the two treatment groups indicates that the NNT is 5 patients. The results for the two pivotal studies were consistent with the results from the IEA.

In Study TG-MV-006, the key secondary efficacy endpoint of total PVD at Day 28 was achieved in 16.4% (36/219) of patients in the ocriplasmin 125 µg group and 6.5% (7/107) of patients in the placebo group (difference 9.9% [95% CI: 3.1, 16.7]; $p = 0.014$). The absolute difference between the two treatment groups indicates that the NNT is 10 patients. In Study TG-MV-007, the key secondary efficacy endpoint of total PVD was achieved in 10.6% (26/245) of patients in the ocriplasmin 125 µg group and 0% (0/81) of patients in the placebo group (difference 10.6% [95% CI: 6.8, 14.5]; $p < 0.001$). The absolute difference between the two treatment groups indicates that the NNT is 9 patients. The results for the two pivotal studies were consistent with the results from the IEA.

The two pivotal studies included a substantial number of patients with sVMA associated with baseline FTMH (23.5% [153/652] in the IEA) but patients with baseline macular hole greater than 400 microns in diameter were excluded from both pivotal studies. In the IEA, VMA resolution at Day 28 was observed in a significantly greater proportion of patients in the ocriplasmin group than in the placebo group (25.5% [12/47] versus 50.0% [53/106], respectively, absolute difference = 24.5% [95% CI: 8.8, 40.2]). In addition, the odds ratio significantly favoured ocriplasmin over placebo in the analysis of patients with baseline FTMH (2.053 [95% CI: 1.126, 3.742]; $p = 0.019$).

In both pivotal Phase III studies, there was a numerically greater proportion of patients requiring vitrectomy in the study eye by Month 6 in the placebo group compared with the ocriplasmin 125 µg group but the p-value was nominally insignificant for the difference between the groups in both studies. The data relating to improvements from baseline to Month 6 in BCVA (categorical and mean changes), and from baseline to Month 6 in VFQ-25 mean scores from both pivotal studies suggest that the limited benefits observed with ocriplasmin 125 µg compared with placebo for these functional outcomes are of doubtful clinical significance.

Second round assessment of risks

The second round assessment of the risks of treatment with ocriplasmin in adults for sVMA, including when associated with macular holes less than or equal to 400 microns in diameter, remains largely unchanged from the first round assessment. However, the first Periodic Benefit-Risk Evaluation Report (PBRER) report indicates that there have been 8 spontaneous reports of pupillary reflex impairment following treatment with ocriplasmin (3.63 events/1000 dose distributed).

Second round assessment of benefit-risk balance

Following consideration of the sponsor's response to the first round clinical questions it is considered that the benefit-risk balance for ocriplasmin is favourable for the treatment of adults with sVMA, including when associated with macular hole less than or equal to 400 microns in diameter.

It is considered that the benefits of treatment are modest and are primarily related to beneficial anatomical outcomes of VMA resolution and creation of total PVD. It is considered that the benefits related to improvement in functional outcomes of BCVA and quality of life following administration of ocriplasmin are very modest and are of limited clinical significance.

The place of ocriplasmin relative to surgery for the treatment of VMA is uncertain. It could be a treatment option for patients considered to be unsuitable for surgery or for patients who elect not to undergo surgery. However, in view of the modest treatment effect observed with ocriplasmin 125 µg in the pivotal Phase III studies it is considered unlikely that ocriplasmin will displace vitrectomy as the first treatment option for most patients with VMA.

The results of the pivotal Phase III studies are not applicable to patients excluded from the studies, including patients with large diameter macular holes (greater than 400 µm), high myopia, aphakia, history of retinal detachment, lens instability, recent ocular surgery or intraocular injection (including laser therapy), proliferative diabetic retinopathy, ischaemic retinopathies, retinal vein occlusions, exudative age-related macular degeneration and vitreous haemorrhage. The sponsor stated that patients with these conditions were excluded from the pivotal Phase III studies because it was considered that they were unlikely to benefit from treatment (based on clinical experience or literature), or were theoretically at a higher risk of complications due to the IVT injection procedure or the vitreolytic effect of ocriplasmin. Treatment in these patients is not recommended. Concurrent treatment of both eyes has not been investigated and is not recommended.

Second round recommendation regarding authorisation

Following consideration of the sponsor's response to the first round clinical questions it is recommended that ocriplasmin be approved for the following indication:

Jetrea is indicated in adults for the treatment of symptomatic vitreomacular adhesion (sVMA), including when associated with macular hole less than or equal to 400 microns in diameter.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU-RMP Version 5, dated January 2013 with an Australian Specific Annex (undated, no version number) which was reviewed by the TGA.

The presentation of the submission is acceptable, except for the following:

- The Australian Specific Annex should be dated and have a version number assigned.
- The RMP contains a number of internal inconsistencies regarding the status of ongoing and proposed studies.

Summary of ongoing safety concerns

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 2.

Table 2. Summary of Ongoing Safety Concerns.

Important Identified Risks	<ol style="list-style-type: none"> 1. Visual impairment 2. Dyschromatopsia 3. ERG abnormalities 4. Retinal detachment 5. Intraocular pressure increased 6. Intraocular haemorrhage 7. Intraocular inflammation 8. Increased vitreomacular traction 9. Development of new macular hole or progression of macular hole size 10. Retinal / macular oedema 11. Lens subluxation 12. Endophthalmitis
Important Potential Risks	<ol style="list-style-type: none"> 13. Immunogenicity (including hypersensitivity / allergic reactions) 14. Off-label use 15. Interactions with other intraocular medications 16. Medication errors 17. Traumatic cataract
Important Missing Information	<ol style="list-style-type: none"> 18. Safety and efficacy information for ocriplasmin in populations other than Caucasians 19. Safety and efficacy of repeat dosing 20. Use in younger adults 21. Use in severe renal impairment 22. Use in severe hepatic impairment

Evaluator's comments

Pursuant to the evaluation of the clinical aspects, the above summary of the Ongoing Safety Concerns is considered acceptable, except for the following:

1. Retinal tear should be listed individually in the ongoing safety concerns for the following reasons:
 - a. A retinal tear does not always involve retinal detachment and therefore this risk is not adequately captured under the term 'retinal detachment'.
 - b. Retinal tear is a known risk with intraocular injections.
 - c. There is also a theoretical risk for retinal tear with pharmacologic vitreolysis. This may occur as traction is exerted on the retina as the vitreous gel pulls loose.

- d. It is noted that the occurrence of retinal tears was lower in the ocriplasmin treated patients compared to placebo in the pivotal trials (0.2% versus 0.5%). However, retinal tears would have contributed to multiple other adverse events such as retinal detachment and the size of the database makes it difficult to accurately quantify the magnitude of risks with low frequencies.
2. The sponsor should provide justification for the exclusion of the following serious risks that are listed as suspected ADR's for ocriplasmin but not captured in the list of ongoing safety concerns. These are:
 - a. Retinal pigment epitheliopathy (1.5% for ocriplasmin and 0% for placebo).
 - b. Macular degeneration (1.3% for ocriplasmin and 0.5% for placebo).
 - c. Retinal degeneration (1.7% for ocriplasmin and 1.5% for placebo).
3. For completeness, Use in pregnant and lactating women should be listed as important missing information.

Proposed pharmacovigilance activities

The sponsor proposes routine and additional pharmacovigilance activities (latter detailed below).

Additional pharmacovigilance activities

Additional Study TG-MV-014 (ongoing study) for safety concerns:

- Visual impairment
- Dyschromatopsia
- ERG abnormalities
- Increased vitreomacular traction
- Development of new macular holes or progression of macular hole size.

Additional Study TG-MV-017 Drug Utilisation Study (planned study) for safety concerns

- Retinal detachment
- Intraocular haemorrhage
- Increased vitreomacular traction
- Development of new macular holes or progression of macular hole size
- Lens subluxation
- Endophthalmitis
- Off-label use including paediatric use
- Medication errors
- Safety and efficacy of repeat dosing

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all important identified risks and important potential risks and important areas of missing information except:

- 'Safety and efficacy information for ocriplasmin in populations other than Caucasians'
- 'Use in younger adults'.

Additional risk minimisation activities are also proposed for:

- Visual impairment
- Retinal detachment
- Intraocular pressure increased
- Intraocular haemorrhage
- Increased vitreomacular traction
- Development of new macular holes or progression of macular hole size
- Lens subluxation
- Endophthalmitis

Patient information pack

The sponsor states '*A patient information pack will be provided in printed and in audio format, containing the following key elements:*

- *Patient information leaflet*
- *How to prepare for Jetrea treatment*
- *How is Jetrea treatment administered*
- *What are the steps following treatment with Jetrea*
- *Key signs and symptoms of serious adverse events*
- *When to seek urgent attention from the health care provider'*

The sponsor will implement this educational plan nationally, prior to marketing, and as agreed with the Competent Authorities in the Member States.

The sponsor states that '*Measurement criteria for the success of the educational materials are currently under evaluation, for inclusion in a specific survey to be conducted as an integrated part of the Drug Utilisation Study. These criteria will be outlined in the protocol for the Drug Utilisation Study.*' The sponsor has committed to reporting the success rates of the educational materials as part of the final report of the Drug Utilisation Study.

Specialist training campaign

The sponsor states the following: '*when launched to the Australian market, vitreomacular specialists will be targeted in a training campaign including:*

- *Dear Dr Letters*
- *Representative visits*
- *A CME based program*
- *Education sessions at symposia/conferences*
- *Provision of CMI. The EU RMP refers to patient education leaflet, in Australia the CMI is comparable.*

As the program is developed, material will be presented to the TGA in the form of an updated RMP. Once the program is in place a corresponding monitoring plan will be developed. This will be communicated to the TGA.'

Reconciliation of issues outlined in the RMP report

The section below summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Retinal tear should be listed individually in the ongoing safety concerns.

Sponsor's response

The sponsor acknowledges the reviewer's comment that a retinal tear does not always involve a retinal detachment. However, the sponsor presents both as one important Identified Risk in the RMP as:

- In the context of ocriplasmin administration, the two events are results of a common underlying mechanism, with retinal detachment being the more severe expression;
- Contemplated separately, retinal detachment would not have fulfilled the criteria for inclusion as Important Identified Risk, as observed frequencies in the clinical trial dataset for this event are slightly lower in ocriplasmin recipients than in comparators.

The sponsor therefore conservatively included retinal tears under the term 'retinal detachment' as the more severe identified risk, as no common Medical Dictionary for Regulatory Activities (MedDRA⁴⁰) Preferred Term (PT) for the two events is existing.

The need for changes to this risk in the RMP will be evaluated regularly and implemented as appropriate with subsequent RMP updates in accordance with emerging new data from clinical trials or postmarketing pharmacovigilance reporting

Evaluator's comment

This is acceptable.

Recommendation #2 in RMP evaluation report

The sponsor should provide justification for the exclusion of the following serious risks that are listed as suspected ADR's for ocriplasmin but not captured in the list of ongoing safety concerns. These are:

- Retinal pigment epitheliopathy (1.5% for ocriplasmin and 0% for placebo).
- Macular degeneration (1.3% for ocriplasmin and 0.5% for placebo).
- Retinal degeneration (1.7% for ocriplasmin and 1.5% for placebo).

Sponsor's response

As per the guideline on good pharmacovigilance practices (Module V), safety concerns should include important identified and important potential risks identified since the last submission of the RMP. The evidence accrued in the clinical trial program on ocriplasmin was adequate for discussing Retinal pigment epitheliopathy, macular degeneration or retinal degeneration as Suspected Adverse Drug Reactions but not for considering them as important identified risks, due to the relative weakness of the corresponding safety signal. Indeed, although their previously described observation after natural VMT resolution suggests some amount of biological plausibility for a causal relationship with ocriplasmin administration and although there is a numerically higher incidence in the ocriplasmin as compared to the comparator groups in the completed clinical trials, the overall numbers remain low and the many of the cases in the ocriplasmin groups were confounded by intercurrent vitrectomy, which is also a recognised cause for these events. The details

⁴⁰A clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

described below are cited from the Integrated Summary of Clinical Retinal Findings, which was provided as an attachment to the sponsor's response.

Evaluator's comment

The evaluator acknowledges the sponsor's comments regarding these risks. However, based on the data presented, these risks should be listed in the ongoing safety concerns and thus given specific focus within PSURs.

Recommendation #3 in RMP evaluation report

It is recommended that all study reports and updates that are submitted to the EU, also be submitted to Australia with the same timelines.

Sponsor's response

PBRER, Clinical Study Report for Study TG-MV-009 and Periodic Update Safety Report (PSUR) are included with this response.

Evaluator's comment

The sponsor is requested to clarify if all study reports and updates that are submitted to the EU, will also be submitted to Australia with the same timelines.

Recommendation #4 in RMP evaluation report

A targeted questionnaire for ERG abnormalities is listed as part of the EU pharmacovigilance plan. It is recommended that this questionnaire be made available to Australian treating physicians. A copy of this questionnaire should be provided to the TGA for review prior to market authorisation of ocriplasmin.

Sponsor's response

All reports of dyschromatopsia, ERG abnormalities and visual acuity loss will be followed up with targeted follow-up questionnaires to collect the relevant data for the assessment of these reports.

Alcon will provide TGA a copy of the questionnaire which will be rolled out globally as soon as it is approved by the European Medicines Agency (EMA) expert committee (Pharmacovigilance Risk Assessment Committee, PRAC). In order to ensure consistency in the collection and subsequent analysis of data it is desirable that the questionnaire used is the same in all countries.

Evaluator's comment

This is acceptable.

Recommendation #5 in RMP evaluation report

Additional pharmacovigilance activities are recommended for the important identified risk of 'intraocular pressure increased'.

Sponsor's response

Transient increases in intraocular pressure (IOP) can be expected after intraocular injection as there are volumetric constraints in a self-contained organ such as the eye.

In the pivotal trials, there were no differences between ocriplasmin and placebo in acute changes from baseline in IOP overall.

Special warnings and precautions for use in the proposed Australian PI recommend post injection monitoring with particular emphasis on increases in intraocular pressure. Transient increases in IOP including transient blindness and non-perfusion of the optic nerve have been seen within 60 minutes of injection of Jetrea. Monitoring for increases in IOP may consist of a check for perfusion of the optic nerve head immediately after the

injection and tonometry within 30 minutes following the injection. Alcon will roll out a physician's educational material in Australia at the time of Jetrea launch where recommendations regarding IOP will be addressed.

Evaluator's comment

This is acceptable.

The sponsor has agreed to include this risk in the educational material (additional risk minimisation). The ASA should be amended accordingly.

Recommendation #6 in RMP evaluation report

It is recommended that the sponsor clarify the exclusion of the following from additional risk minimisation such as the specialist training campaign:

- a. Dyschromatopsia
- b. ERG abnormalities
- c. Intraocular inflammation
- d. Retinal/macular oedema
- e. Immunogenicity
- f. Medication errors
- g. Traumatic cataract

Sponsor's response

The specialist training campaign is not part of any additional risk minimization measures discussed in the RMP.

Alcon confirms that a physician's educational material will be rolled out to Australian physicians at the time of Jetrea launch in Australia, which would cover the risks of dyschromatopsia, ERG abnormalities, intraocular inflammation, retinal/macular oedema, immunogenicity, medication errors and traumatic cataract, as recommended by the TGA.

Evaluator's comment

This is acceptable.

Physician education materials are classified as additional risk minimisation, The ASA should be amended accordingly.

Recommendation #7 in RMP evaluation report

In regards to the important potential risk of '*medication error*', it recommended that additional risk minimisation activities be applied due to the issues raised.

Sponsor's response

As discussed in the RMP actions proposed as minimization activities are: Routine Pharmacovigilance (PSUR reporting dates, unless new safety signals arise that may impact the benefit-risk balance of the product) and in addition, this risk will be further characterised in a Drug Utilization Study (TG-MV-017). Those measures should be considered sufficient given that Jetrea is reserved for use by specialised ophthalmologists and specific draft Australian PI wording has been included to provide detailed instructions for appropriate storage, handling and administration of Jetrea to mitigate this risk.

Additionally, Alcon will roll out in Australia a physician's educational material at the time of Jetrea launch with specific recommendations to prevent medication errors.

Evaluator's comment

This is acceptable.

The sponsor has agreed to include this risk in the educational material (additional risk minimisation). The ASA should be amended accordingly.

Recommendation #8 in RMP evaluation report

It is recommended that the sponsor provide details of the transport and extreme cold chain handling process within Australia, including the companies selected to transport the product and details of how the sponsor plans to manage this process.

Sponsor's response

Using a validated shipment container (temperature and time) that utilizes dry ice to maintain a controlled internal frozen environment, Jetrea will be shipped from the manufacturing site (Alcon Puurs) directly to the specialist ophthalmologist, clinic or hospital. Each container can hold up to 10 vials of Jetrea at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$ for up to 120 h. Alcon Australia are currently evaluating the service, capabilities and performance of select international transportation companies that can deliver pharmaceuticals by air freight to Australia and provide transportation from domestic airports directly to the ophthalmologist clinic or hospital. Deliveries to Australia will occur on specific days of the week, typically Monday to Wednesday, to optimize delivery accuracy. Where a clinic or hospital has a validated/monitored ultra-freezer it is envisaged that Jetrea will be removed from the validated shipment container by the ophthalmologist and stored in the ultra-freezer until patient use. Where an ultra-freezer is not available, Jetrea will be kept in its validated shipment container up to 120 hours until patient use. A quality agreement would link the chosen transportation company and Alcon Australia. Alcon Australia, utilizing specific education material and medical science liaison personnel will educate and train each prescribing ophthalmologist on the correct handling, storage and injection of Jetrea. Alcon Australia has not finalised the warehousing of Jetrea in Australia. In any event this would require an authorised warehouse with a validated ultra-freezer for storage. Delivery from the warehouse to the ophthalmologist clinic or hospital would utilise an approved transportation company utilizing the above mention validated shipment container. A quality agreement would link the chosen transportation company and Alcon Australia.

'Duty of care' release will be performed by the quality control team at Alcon Australia for each shipment of Jetrea in conjunction with the Australian clinic or hospital, utilising:

- Data from the shipment time and/or temperature probes
- The product's batch specific certificate of analysis
- Physical check of the exterior shipment container.

Evaluator's comment

This is acceptable.

Recommendation #9 in RMP evaluation report

Patient education:

- h. The sponsor should clarify if this information pack will be available for Australian patients.
- i. The naming of the patient educational material should be consistent. It is recommended that this risk minimisation activity be consistently referred to as a 'patient booklet' throughout the RMP.
- j. The patient booklet should contain a statement regarding the risk of temporary visual disturbances affecting the ability to drive. The statement should be to the effect of 'the Jetrea treatment procedure may induce a significant, but transient loss of visual acuity and visual disturbances, which may affect the ability to

drive or use machines. This is most likely to occur during the first week after the injection due to the release of vitreomacular traction. Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.'

- k. The sponsor claims that the 'information pack' will also be provided in audio format. The sponsor should provide an assurance that the contents of the audio materials are identical to the printed education materials.

Sponsor's response

Alcon confirms that the 'Jetrea patient booklet' will be rolled out to Australian patients at the time of Jetrea launch in Australia. Alcon does confirm that the recommendations a-to-d will be addressed in this document. Alcon also confirms that the contents of the audio material are identical to the printed educational materials.

INJECT Jetrea Registry:

Alcon is implementing a global registry on up to 3,000 patients treated with ocriplasmin. The aim of this registry is to evaluate safety, clinical effectiveness, and HRQoL (Health-Related Question of Life) outcomes in a real world setting among a large population of patients exposed to ocriplasmin across different countries according to country's approved indications. Patients will be followed for 12 months following injection. The study is ongoing in Europe and sites are expected to be activated in Australia following product registration.

In addition to the ocriplasmin registry, Alcon proposes running in Australia a sub-study survey to evaluate the Jetrea patient booklet given to the patients prior to the treatment. This survey would be designed at the same basis of the European survey and will run as a separate/parallel study. Australian patients enrolled in the Jetrea registry will be invited to complete a survey, 7 to 14 days after Jetrea injection to assess their knowledge about the product and procedure provided through the Jetrea patient booklet.

Evaluator's comment

This is acceptable, however, should this application be approved, these documents should be submitted to the TGA prior to supply of ocriplasmin in Australia.

Recommendation #10 in RMP evaluation report

The specialist training campaign:

- l. Some activities in the 'specialist training campaign' may be linked with promotional activities. The sponsor should provide justification for their inclusion in the ASA, including how these activities will be separated from promotional activities.
- m. The proposed 'Dear Dr letters' and the 'CME based program' should be submitted to the TGA for review prior to market authorisation of ocriplasmin. Furthermore, details of the proposed monitoring plan for the effectiveness of these activities should also be submitted to the TGA for review prior to market authorisation.

Sponsor's response

Alcon confirms that the proposed 'Dear Dr letters and the 'CME based education program(s)' will be submitted to the TGA for review prior to market authorisation of ocriplasmin. In addition, Alcon also confirms that 'CME based education program(s)', although not yet designed, will not be promotional and will be coordinated /conducted by the Scientific Affairs department at Australia.

Evaluator's comment

This is acceptable.

Recommendation #11 in RMP evaluation report

It is recommended that a preparation and administration guide also be developed to enhance safe use of ocriplasmin. This guide should include the following key elements:

- a. Assessing patient suitability, including exclusion of patients with active or suspected ocular or periocular infections/inflammation.
- b. Appropriate pre-treatment communication including provision of the 'patient booklet' and antibiotic eye drops.
- c. Appropriate storage of ocriplasmin, including statements regarding the instability of ocriplasmin at temperatures greater than -20°C and the importance of discarding any product exposed to higher temperatures during storage.
- d. Preparation steps including pictures
- e. Post-procedure care, including the appropriateness of antibiotic therapy, timing of follow-up visits, communication of common ADR's and advice on driving.
- f. Statements regarding the lack of data with repeated administration of Jetrea in the same eye and that treatment with Jetrea in the other eye is not recommended concurrently or within 7 days of the initial injection, in order to monitor post-injection course including the potential for decreased vision in the injected eye (as stated in the EU Summary of Product Characteristics (SmPC)), overdose and its management, including monitoring of intraocular pressure.
- g. Over dosage and its management, including monitoring of intraocular pressure.

Sponsor's response

Alcon confirms that a physician's educational material will be rolled out to Australian physicians at the time of Jetrea launch in Australia. Alcon does confirm that all the recommendations from a-to-g will be addressed in this document.

Evaluator's comment

This is acceptable, however, should this application be approved, these documents should be submitted to the TGA prior to supply of ocriplasmin in Australia.

Recommendation #12 in RMP evaluation report

In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft PI document as follows:

- h. Under 'Indications' the TGA will be seeking advice from the Advisory Committee on the Safety Of Medicines (ACSOM) committee to assist the Delegate regarding:
 - i. The evidence for the safe use of ocriplasmin for macular hole >400 µm.
 - ii. The evidence for the safe use of ocriplasmin for the broader indication of 'symptomatic adhesion' compared to the term 'vitreomacular traction'.

Sponsor's response

With reference to the draft indication proposed in Australia, Alcon would support, based on the limited number of patients who received ocriplasmin and who had a macular hole > 400 µm, clarification of patients with macular hole to include '≤ 400 µm'.

With reference to the draft indication proposed in Australia, Alcon would support, based on the interchangeability of sVMA and VMT, the replacement of 'symptomatic VMA' with 'vitreomacular traction (VMT)'. With consideration of patients with macular hole, Alcon

would support the indication stating ‘Treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns’.

Evaluator’s comment

This is acceptable.

Recommendation #13 in RMP evaluation report

It is recommended that the table shown on page 5 of the EU SmPC⁴¹ be included in the proposed Australian PI to enhance understanding of the safety profile of ocriplasmin.

Sponsor’s response

Alcon Australia are in agreement with TGA’s request that the table shown on page 5 of the EU SmPC be included in the proposed Australian PI to enhance understanding of the safety profile of ocriplasmin.

Evaluator’s comment

This is acceptable.

Recommendation #14 in RMP evaluation report

The statement regarding overdose should be strengthened to include a statement regarding the importance of monitoring intraocular pressure.

Sponsor’s response

Alcon Australia are in agreement with TGA’s request that the statement regarding overdose should be strengthened to include a statement regarding the importance of monitoring intraocular pressure.

Evaluator’s comment

This is acceptable.

Recommendation #15 in RMP evaluation report

The statement regarding driving should be strengthened to the effect of ‘the Jetrea treatment procedure may induce a significant, but transient loss of visual acuity and visual disturbances, which may affect the ability to drive or use machines. This is most likely to occur during the first 7 days after the injection due to the release of vitreomacular traction. Patients who experience these signs must not drive or use machines until these temporary visual disturbances subside.’

⁴¹ Table from page 5 of EU SmPC:

Eye disorders	Very common Vitreous floaters, eye pain, conjunctival haemorrhage
	Common Visual acuity reduced*, visual impairment, vision blurred, retinal haemorrhage, vitreous haemorrhage, retinal tear*, retinal detachment*, intraocular pressure increased, macular hole*, macular degeneration, retinal degeneration, macular oedema, retinal oedema, retinal pigment epitheliopathy, metamorphopsia, vitreous adhesions*, conjunctival oedema, eyelid oedema, vitritis, anterior chamber cell, anterior chamber flare, iritis, photopsia, conjunctival hyperaemia, ocular hyperaemia, vitreous detachment, retinogram abnormal*, eye irritation, dry eye, foreign body sensation in eyes, eye pruritus, ocular discomfort, photophobia, chromatopsia
	Uncommon Transient blindness, lens subluxation*, scotoma, visual field defect, diplopia, hyphaema, miosis, pupils unequal, corneal abrasion, anterior chamber inflammation, eye inflammation, conjunctival irritation

* see section ‘Description of selected adverse reactions’

Sponsor's response

Alcon Australia is in agreement with TGA's request. The statement regarding driving should be strengthened as proposed by the TGA.

Evaluator's comment

This is acceptable.

Recommendation #16 in RMP evaluation report

Due to the diverse multicultural population in Australia, it is recommended that statement be added to the Australian PI to the effect of 'experience is limited in groups other than Caucasians'. This is in line with the EU SmPC.

Sponsor's response

Alcon Australia is in agreement with TGA's request.

Evaluator's comment

This is acceptable.

Recommendation #17 in RMP evaluation report

A statement should be added suggesting the use of pre and post-operative antibiotic drops (at the discretion of the treating ophthalmologist and according to local guidelines). This is in line with other intraocular injections and the EU SmPC for ocriplasmin.

Sponsor's response

Alcon Australia is in agreement with TGA's request.

Evaluator's comment

This is acceptable.

Recommendation #18 in RMP evaluation report

Under 'Preparation for Administration', the figures should be placed with the associated preparation step to avoid confusion. This is in line with the presentation shown in the US PI.

Sponsor's response

Alcon Australia is in agreement with TGA's request.

Evaluator's comment

This is acceptable.

Recommendation #19 in RMP evaluation report

Under 'Presentation and Storage' further information should be added regarding the importance of discarding the product if exposed to higher temperatures (above -20°C) during storage. An additional statement would be appropriate stating that after dilution the product cannot be stored and must be used immediately. This is in line with the EU SmPC.

Sponsor's response

Alcon Australia is in agreement with TGA's request.

Evaluator's comment

This is acceptable.

Recommendation #20 in RMP evaluation report

Under 'Paediatric Use' the statement should be strengthened to include a warning regarding use in retinopathy of prematurity and stating that use in children is not recommended.

Sponsor's response

Alcon Australia is in agreement with TGA's request.

Evaluator's comment

This is acceptable.

Recommendation #21 in RMP evaluation report

The sponsor proposes risk minimisation activities in the form of a patient information booklet and a specialist training campaign (including dear Dr Letters and a CME based program). In light of the unique storage, preparation and administration procedures, plus the high risk of medication error, transmission of infectious agents and serious ADR's with ocriplasmin, the evaluator has recommended the addition of an 'administration guide' to the risk minimisation plan.

Sponsor's response

Alcon confirms that the 'Jetrea patient booklet' will be rolled-out to Australian patients at the time of Jetrea launch in Australia. Alcon does confirm that all TGA's recommendations will be addressed in this document. Alcon also confirms that the contents of the audio material are fully consistent but not identical to the printed education material.

Alcon also confirms that a physician's educational material will be rolled-out to Australian physicians at the time of Jetrea launch in Australia and that all TGA's recommendations to this document will be addressed.

Evaluator's comment

This is acceptable.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Ocriplasmin is a protein molecule of 249 amino acids from 2 peptide chains. The first peptide has 19 amino acids and the second has 230 amino acids. The two peptide chains are linked by disulphide bonds between C6 & C124 and C16 & C24.

The production of ocriplasmin involves fermentation of recombinant *Pichia pastoris*, followed by multistep chromatographic purification. An activation step converts microplasminogen to the active ocriplasmin. Its proteolytic activity is stated to be comparable to the human plasmin.

The manufacture of ocriplasmin drug substance during the course of its development has involved 3 different processes. Nonclinical, Phase I and Phase II studies were conducted using ocriplasmin drug substance derived from Process 1. Ocriplasmin drug substance produced from Process 2 was subsequently used in Phase II and Phase III clinical trials and non-clinical studies. Process 3 is a further scaled up process to produce ocriplasmin drug substance in commercial quantities.

The real time stability data submitted support a shelf life of 30 months for the drug substance when stored at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$.

The drug product (Jetrea) is a sterile solution with no preservatives. The drug formulation has excipients mannitol (0.75 mg/0.2 mL) as cryoprotectant, citric acid monohydrate (0.21 mg/0.2 mL) as buffer, sodium hydroxide for pH adjustment to 3.1 ± 0.1 and water (to volume 0.2 mL).

The proposed shelf life of the finished drug product is 18 months when stored frozen at $-20^{\circ}\text{C} \pm 5^{\circ}\text{C}$. It is proposed that the labelling should use the recommended terminology of store below -18°C , deep freeze based on the labelling order (TGO 69). This storage temperature is within the range supported by the stability data. It is understood that any temperature excursions during transportation are considered unacceptable (also see discussion of extreme cold chain handling procedures in the RMP).

Nonclinical

Initial preclinical testing was done with a lyophilized formulation. However, subsequently and in all human trials, a solution for injection was used. The following summary findings were noted by the nonclinical evaluators.

In vitro ocriplasmin has proteolytic activity similar to human plasmin, with catalytic activity towards collagen, laminin and fibronectin. The IVT administration of ocriplasmin induced vitreous liquefaction and Posterior Vitreous Detachment (PVD) in eyes from rats, rabbits, pigs and humans. Vitreous concentrations of ocriplasmin inducing complete PVD in animals (34 to 60 $\mu\text{g}/\text{mL}$) were similar to that seen in human eyes following IVT injection of 125 μg ocriplasmin (31 $\mu\text{g}/\text{mL}$).

Ocriplasmin showed hydrolytic activity towards fibrin and fibrinogen and affected or inhibited the clotting system in dogs but only at high IV doses ($\geq 1.5 \text{ mg}/\text{kg IV}$). The CNS function in rats, and respiratory and cardiovascular function in dogs were unaffected at high IV doses ($\leq 10 \text{ mg}/\text{kg IV}$).

Ocriplasmin undergoes autoprolysis in the vitreous. Thus minimal systemic exposure is expected. Any ocriplasmin reaching the systemic circulation is expected to be rapidly inactivated by binding to $\alpha 2$ -antiplasmin.

The ocular toxicity of ocriplasmin was assessed following a single IVT injection to rabbits, mini-pigs and Cynomolgus monkeys and two IVT injections (4 weeks apart) in Cynomolgus monkeys. The main findings included changes in vitreous morphology (the intended pharmacological action), retinal toxicity (reduction of ERG wave amplitudes, thinning/narrowing of retinal vessels, retinal atrophy and retinal detachment), a mild and transient ocular inflammatory response, and irreversible lens subluxation. All of these effects occurred at low relative exposures (based on vitreous concentration). The ERG changes and retinal atrophy appeared to be reversible. The onset of lens subluxation was delayed several days following injection and was present in all monkeys that received two IVT doses of ocriplasmin.

No genotoxicity, carcinogenicity or reproductive toxicity studies were submitted. This was considered acceptable.

There are no nonclinical objections to the approval of the proposed product intended as single use, IVT administration. The nonclinical evaluators recommend extended follow up and monitoring for the risk of occurrence of lens subluxation and retinal detachment.

Clinical

As noted earlier, the manufacturing process was scaled up after completion of the Phase III trials. It is stated that data demonstrating comparability between drug product used in the pivotal trials and drug product intended for commercial supply have been provided. However, no clinical pharmacokinetic studies were undertaken to compare the 2 products.

The clinical dataset consists of 2 PK/PD studies, 3 dose finding studies, 2 pivotal efficacy trials and 1 supporting efficacy/safety study. The findings and conclusions are summarised below. Please see the Extract from the Clinical Evaluation Report (CER) in Attachment 2 for details.

Pharmacokinetics (PK)/Pharmacodynamics (PD)

Study TG-M-001 was 'first in human' randomised, double-blind, placebo-controlled trial (10 treatment groups of 6 subjects each) of ocriplasmin to assess systemic PK of ocriplasmin in adult healthy male volunteers in an IVI dose-escalation trial (0.1, 0.5, 1.0, 1.5 and 2.0 mg/kg) during the earlier developmental Phase for use in ischaemic stroke, including administration of single dose, two doses and fast (15 minutes)/slow (60 minutes) IVI administration.

The C_{max} was shown to increase in a less than dose proportional manner, and $AUC_{(0-t)}$ increase in greater than dose proportional manner. The mean elimination half-life ranged from 3.5 to 8 hours, while the mean plasma clearance varied from 6.5 to 8.0 mL/h/kg. No notable age effect was demonstrated.

The study also demonstrated PD effects of ocriplasmin on $\alpha 2$ -antiplasmin activity (dose dependent inhibition), prothrombin time (small, dose dependent prolongation), activated partial thromboplastin time (small, dose dependent prolongation), fibrinogen (no meaningful effect), plasminogen (small increase in activity with maximum effect plateauing at 1 mg/kg dose) and fibrin/fibrinogen degradation products (no meaningful effect).

Study TG-MV-010 was a Phase II, open label trial (N = 38) to assess local (that is IVT) PK of ocriplasmin in VMA patients who were given a single IVT dose of ocriplasmin 125 μ g (that is in vivo) at various times (5 to 30 minutes, 31 to 60 minutes, 2 to 4 hours, 1 day or 7 days) prior to scheduled vitrectomy. A vitreous sample (0.5 mL) was obtained at the beginning of vitrectomy for measuring ocriplasmin activity in vitreous fluid.

The mean ocriplasmin activity level was 11,597.7 ng/ mL in vitreous samples (n=8) collected at 5 to 30 minutes post injection. The mean ocriplasmin activity decreased with increasing time from injection to sampling (8,108.7 ng/ mL [31 to 60 minutes]; 2,610.6 ng/ mL [2 to 4 hours]; 496.5 ng/ mL [24 \pm 2 hours that is approximately 4% of level at 5 to 30 minutes]). In samples taken 7 \pm 1 days after the IVT injection (N = 4), ocriplasmin levels were below the lower limit of quantification (LLOQ) (< 272.37 ng/ mL) and were comparable with the level in the control group. The mean ocriplasmin activity level in samples taken 2 to 4 hours after injection was 22.5% of the injected dose. This level is consistent that in a separate in vitro study (SR 10/mPI16/ItP) in which 16% of the initial concentrations of ocriplasmin in vitreous fluid was reported at 5 hours after spiking with 125 μ g.

No data on absolute bioavailability, absorption, distribution, metabolism or mass balance studies for IVT administration were available. Ocriplasmin is expected to enter the endogenous protein catabolism pathway to be rapidly inactivated (in seconds) by protease inhibitor $\alpha 2$ -antiplasmin or binding to $\alpha 2$ -macroglobulin.

Dose finding

Study TG-MV-001

This study, in VMA patients (N = 60), investigated four single doses of ocriplasmin (25, 50, 75 and 125 µg) with IVT administration at various times before scheduled vitrectomy. The release of VMA, at the time of vitrectomy, was reported in the cohort with the longest exposure time (25 µg/7 days) and in cohorts with the highest doses (75 µg/24 h and 125 µg/24 h). The differences between the doses were not significant.

Study TG-MV-002

This was a dose-ranging study of IVT ocriplasmin (25, 75 and 125 µg) for non-surgical induction of total PVD in patients with diabetic macular oedema and failed to show clinical effect in comparison with sham injection.

Study TG-MV-003

This placebo controlled study (N = 125) assessed the effect of 3 single IVT doses of ocriplasmin (25, 75, and 125 µg) compared with placebo when administered 7±1 days prior to vitrectomy for treatment of non-proliferative vitreoretinal disease without evidence of PVD over macula and with BCVA of 20/400 or better in the non-study eye. Total PVD without an anatomical defect (macular hole; retinal tear), as assessed by surgeon prior to planned surgery was achieved by 10%, 13.8%, 18.2% and 31.3% patients in placebo, 25 µg, 75 µg and 125 µg ocriplasmin treatment groups respectively.

Study TG-MV-004

This was a sham-injection controlled, dose finding study (N=61; mean age 70 years) of single IVT ocriplasmin injection (75, 125 and 175 µg), administered mid vitreous, for non-surgical resolution of VMT/induction of PVD at 14 days post-injection. The studied population was adults with a partial central PVD but with vitreous still attached on the foveal area causing secondary macular oedema, no evidence of complete macular PVD in the study eye, BCVA of 20/40 or worse in study eye and BCVA of 20/400 or better in the non-study eye. Non responders at Day 28 in the 125 µg cohort and among sham injection patients also received up to two repeat injections (125 µg) at one monthly interval (cohort 4). The response rate (excluding repeat dosing data), with respect to Central Reading Centre (CRC) assessed total PVD at Day 14, was 0%, 18.2%, 15.3% and 18.2% in the sham injection, 75, 125 and 175 µg ocriplasmin groups respectively and lack of statistical discrimination between doses as shown in Table 3.

Table 3. Study eye, proportion of subjects with total PVD at post-injection Day 14 (CRC assessment) cohorts 1, 2 and 3; FAS.

Sham (Group 1)	Ocriplasmin 75µg (Group 2)	Ocriplasmin 125µg (Group 3)	Ocriplasmin 175µg (Group 4)	Total All patients	p-value (Chi-square)
0% (0/9)	18.2% (2/11)	15.3% (2/13)	18.2% (2/11)	13.6% (6/44)	0.61
	p = 0.4789 vs Group 1	p = 0.4935 vs Group 1	p = 0.4789 vs Group 1		
	p = 1 vs Group 3	p = 1 vs Group 4			
	p = 1 vs Group 4				

The CRC and the investigator assessed (both masked) results were at variance with each other especially with respect to the 75 µg dose at Days 14 and 28 as shown below in the two tables (repeat dose data in non-responders included) (Tables 4 and 5).

Table 4. Proportion of patients with total PVD (CRC assessment); FAS.

Time-point	Sham ^a n/N (%)	Ocriplasmin 75 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 175 µg n/N (%)
Day 3	0/12 (0.0)	1/12 (8.3)	2/13 (15.4)	3/25 (12.0)	0/11 (0.0)
Day 7	0/12 (0.0)	1/12 (8.3)	2/12 (16.7)	3/23 (13.0)	1/11 (9.1)
Day 14	0/11 (0.0)	2/11 (18.2)	2/13 (15.4)	3/22 (13.6)	2/11 (18.2)
Day 28	0/11 (0.0)	2/12 (16.7)	2/11 (18.2)	4/20 (20.0)	1/11 (9.1)
Day 90	0/9 (0.0)	2/12 (16.7)	2/13 (15.4)	N/A	1/11 (9.1)
Day 180	0/9 (0.0)	3/12 (25.0)	2/12 (16.7)	N/A	1/10 (10.0)

a = Sham includes sham patients from cohorts 1, 2, 3, and 4 up to and including Day 28, and sham patients from cohorts 1, 2, and 3 only for Day 90 and Day 180.

b = Includes ocriplasmin 125 µg patients from cohort 2.

c = Includes ocriplasmin 125 µg patients from cohorts 2 and 4.

Table 5. Proportion of patients with total PVD (investigator assessment); FAS.

Time-point	Sham ^a n/N (%)	Ocriplasmin 75 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 175 µg n/N (%)
Day 3	0/12 (0.0)	0/12 (0.0)	2/13 (15.4)	4/25 (16.0)	0/11 (0.0)
Day 7	1/12 (8.3)	0/12 (0.0)	1/13 (7.7)	4/25 (16.0)	3/11 (27.3)
Day 14	1/12 (8.3)	0/12 (0.0)	2/13 (15.4)	5/25 (20.0)	3/11 (27.3)
Day 28	1/12 (8.3)	0/12 (0.0)	2/13 (15.4)	6/25 (24.0)	3/11 (27.3)
Day 90	0/9 (0.0)	1/12 (8.3)	6/13 (46.2)	N/A	4/11 (36.4)
Day 180	1/9 (11.1)	1/12 (8.3)	6/13 (46.2)	N/A	4/11 (36.4)

a = Sham includes sham patients from cohorts 1, 2, 3, and 4 up to and including Day 28, and sham patients from cohorts 1, 2, and 3 only for Day 90 and Day 180.

b = Includes ocriplasmin 125 µg patients from cohort 2.

c = Includes ocriplasmin 125 µg patients from cohorts 2 and 4.

The results for investigator assessed resolution of VMT using Optical Coherence Tomography (OCT) were as shown in Table 6 and appeared to support the 125 µg dose.

Table 6. TG-MV-004: proportion of patients with resolution of VMT; FAS.

Time-point	Sham ^a n/N (%)	Ocriplasmin 75 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 175 µg n/N (%)
Day 3	0/12 (0.0)	2/12 (16.7)	4/13 (30.8)	7/25 (28.0)	3/11 (27.3)
Day 7	1/12 (8.3)	2/12 (16.7)	4/13 (30.8)	8/25 (32.0)	3/11 (27.3)
Day 14	1/12 (8.3)	3/12 (25.0)	5/13 (38.5)	10/25 (40.0)	3/11 (27.3)
Day 28	1/12 (8.3)	3/12 (25.0)	6/13 (46.2)	11/25 (44.0)	3/11 (27.3)
Day 90	1/9 (11.1)	4/12 (33.3)	7/13 (53.9)	N/A	5/11 (45.5)
Day 180	2/9 (22.1)	4/12 (33.3)	7/13 (53.9)	N/A	5/11 (44.5)

a = Sham includes sham patients from cohorts 1, 2, 3, and 4 up to and including Day 28, and sham patients from cohorts 1, 2, and 3 only for Day 90 and Day 180.

b = Includes ocriplasmin 125 µg patients from cohort 2.

c = Includes ocriplasmin 125 µg patients from cohorts 2 and 4.

The results with respect to closure of macular hole (in patients with macular hole at baseline) were as shown in Table 7 but there were too few patients in each group.

Table 7. TG-MV-004: proportion of patients with closure of macular hole; FAS.

Time-point	Sham ^a n/N (%)	Ocriplasmin 75 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 175 µg n/N (%)
Day 14	1/5 (20.0)	2/3 (66.7)	1/2 (50.0)	3/8 (37.5)	0/3 (0.0)
Day 28	1/5 (20.0)	2/3 (66.7)	1/2 (50.0)	3/8 (37.5)	0/3 (0.0)
Day 180	0/3 (0.0)	2/3 (66.7)	1/2 (50.0)	N/A	0/3 (0.0)

[a] = Sham includes sham patients from cohorts 1, 2, 3, and 4 up to and including Day 28, and sham patients from cohorts 1, 2, and 3 only for Day 90 and Day 180. [b] = Includes ocriplasmin 125 µg patients from cohort 2. [c] = Includes ocriplasmin 125 µg patients from cohorts 2 and 4.

The results for resolution of (any) index condition supported the use of 125µg dose as shown in Table 8.

Table 8. Proportion of patients with resolution of index condition at Day 28 and Day 180; FAS.

Time-point	Sham ^a n/N (%)	Ocriplasmin 75 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 125 µg n/N (%)	Ocriplasmin 175 µg n/N (%)
Day 28	1/12 (8.3)	2/12 (16.7)	5/13 (38.5)	8/25 (32.0)	1/11 (9.1)
Day 180	2/9 (22.1)	3/12 (25.0)	6/13 (46.2)	N.A	2/11 (18.2)

a = Sham includes sham patients from cohorts 1, 2, 3, and 4 up to and including Day 28, and sham patients from cohorts 1, 2, and 3 only for Day 90 and Day 180.

b = Includes ocriplasmin 125 µg patients from cohort 2.

c = Includes ocriplasmin 125 µg patients from cohorts 2 and 4.

No vitrectomies were performed up to the post-injection Day 28. From Day 28 to 180, one patient (8.3%) in 75 µg group, one patient (7.7%) in 125 µg group, 3 patients (27.3%) in 175 µg group and 3 patients (33.3%) in the sham injection group required vitrectomy.

Overall, the study failed to show statistically significant dose response among the tested doses including the 125 µg proposed for registration. On qualitative basis, the higher dose of 175 µg does not appear to result in improved efficacy and there is some support for 125 µg dose as the optimum dose especially based on VMT resolution and closure of macular hole rather than achievement of Total PVD. Although testing of 75 µg and 125 µg doses may have been appropriate in the Phase III trials, the decision to test only one dose level (125 µg) may be considered reasonable due to the relatively uncommon nature of target population.

Clinical efficacy

Two Phase III efficacy studies provide pivotal clinical data supporting this submission. The Study TG-MV-006 was conducted in the US whereas the Study TG-MV-007 was a multinational study (not including Australia). Both were similarly designed, randomised, double blind, placebo controlled, two parallel treatment arms studies. An integrated efficacy analysis (IEA) that is pooled results of Studies 006/007 was also provided. Both studies are considered together below:

Both trials investigated single 125 µg ocriplasmin IVT dose against placebo (vehicle) in adult patients with symptomatic vitreomacular adhesion (sVMA). The decision to use IVT placebo injection as control is reported to have involved agreement with the overseas regulators. The primary efficacy was assessed at post-injection Day 28 with period of observation to post-injection Month 6. The report of uncontrolled Study TG-MV-008 (uncontrolled study; N = 17) included in the dossier is relevant to safety data only.

The study population in the 2 pivotal trials (006/007) consisted of patients with symptomatic focal VMA that is central vitreal adhesion within 6 mm OCT (Optical Coherence Tomography) field surrounded by elevation of the posterior vitreous cortex that in the opinion of the investigator was related to decreased visual function such as metamorphopsia, decreased visual acuity (VA) or other visual complaint. Both eyes were examined and the eye with the worst BCVA was to be treated ('study eye'). The BCVA could be no better than 20/25 in the study eye and no worse than 20/800 in the non-study eye.

The main exclusion criteria (abbreviated) were proliferative retinopathy (including proliferative diabetic retinopathy or other ischaemic retinopathies involving vitreoretinal vascular proliferation), exudative Age-related Macular Degeneration, retinal vein occlusion, vitreous haemorrhage or opacification, macular hole > 400 µm diameter, aphakia, high myopia, history of ocular surgery, laser photocoagulation or intravitreal injection in the preceding 3 months, laser photocoagulation to the macula at any time,

history of vitrectomy or uncontrolled glaucoma in the study eye and history of rhegmatogenous retinal detachment or conditions causing lens instability in either eye.

Both main efficacy outcomes were surrogate in nature that is resolution of VMA without creation of anatomical defect (macular hole; retinal tear/detachment) at post-injection Day 28 and achievement of Total Posterior Vitreous Detachment (PVD) at post-injection Day 28.

VMA resolution was the primary efficacy outcome. Baseline and subsequent VMA status was assessed by (masked) Central Reading Center (CRC) using 1 of 7 categories on Optical Coherence Tomography (OCT) as shown below in Table 9.

Table 9. Categories on Optical Coherence Tomography (OCT)

0	1	2	3	4	5	6	7
No visible vitreous separation	Vitreous attached from fovea to ON; separated elsewhere	Vitreous attached at fovea and ON and separated between, may be separated outside	Vitreous attached only at ON or at ON and elsewhere, but not attached at fovea	Vitreous attached only at Fovea	Vitreous visible with complete separation and no attachment	Vitreous separation visible somewhere but unable to determine state of separation	Unable to determine state of separation

Focal VMA was defined by 3 of the 7 categories (Categories 1, 2 and 4). The assessments were based on Stratus OCT but Spectral domain OCT (SD-OCT, Cirrus or Spectralis) was also used at selected sites. Success that is VMA resolution was defined as progression of categories as below:

Baseline to Day 28:	Baseline to Day 28:	Baseline to Day 28:
1 to 0	2 to 0	4 to 0
1 to 3	2 to 3	4 to 3
1 to 5	2 to 5	4 to 5

The classification was devised internally by the sponsor and although not independently validated, appears to be clinically reasonable.

Total PVD was the main secondary outcome and was assessed using B-scan ultrasound, performed by (masked) certified echographer. The examination was performed directly on the conjunctiva. Transverse (cross-sectional) scans were taken in all quadrants. Longitudinal (radial section) scans were taken to evaluate the fundus from the posterior pole to the limbus. Ultrasound images were used to assess the presence and the grade of PVD (Grade 0: No PVD; Grade 1: Partial PVD with attachment at the optic disc and elsewhere in the posterior pole; Grade 2: Partial PVD with attachment at either the optic disc or elsewhere in the posterior pole; Grade 3: Total PVD without disc attachment). This also appears to be an internally developed scale.

Full ophthalmologic examination (visual acuity on Early Treatment Diabetic Retinopathy Study (ETDRS) charts, manifest refraction, IOP, slit lamp examination and dilated fundus examination), OCT and B-scan were done on both eyes at baseline and then at every visit (injection day, post-injection Days 7, 14, 28, Months 3 and 6) on the study eye. Other tests included Fundus photography and Fluorescein angiography at baseline and at last visit.

The clinical outcomes included Visual Acuity (VA) and quality of life (QoL) measurement using the National Eye Institute 25-item Visual Function Questionnaire (VFQ-25).

The eligible patients were randomised to ocriplasmin or placebo groups and received a single IVT injection of ocriplasmin 125µg or placebo in the study eye. If the underlying condition did not improve that is VMA was not relieved, the investigator could proceed to vitrectomy after 4 weeks of observation at his/her discretion. In addition, if BCVA in the study eye worsened by >2 lines or the underlying condition worsened at any time, the investigator could proceed to vitrectomy at his/her discretion.

A total of 464 patients were randomised to ocriplasmin treatment group (219 and 245 in studies 006 and 007 respectively) and 188 to placebo treatment group (107 and 81 in studies 006 and 007 respectively).

The groups were generally balanced with respect to baseline features. Overall (that is pooled 006/007 studies; both treatment groups), nearly 2/3 participants were females, and overall mean age of participants was 72 years. The proportions with various features at baseline were as follows: Baseline diagnosis (Full Thickness Macular Hole (FTMH) 23.5%, VMA 76.5%); Baseline ocular features (Epiretinal membrane (ERM) 38.7%, Pseudophakic 34.5%, non proliferative Diabetic Retinopathy (DR) 6.9%); diameter of focal VMA (>1500µm 23.2%; ≤1500µm 70.9%; undetermined 5.8%); physician assessed need for vitrectomy at baseline (yes 84%; no 15.8%); Total PVD at baseline (one patient in ocriplasmin group in Study 006). Overall, the mean baseline BCVA letter score was 64.3 ± 11.94 (median 67; range 8 to 88). Further baseline OCT findings in the 2 groups were as shown in Table 10.

Table 10. OCT findings at baseline (integrated pivotal studies).

Characteristic	Placebo (N=188) n (%)	Ocriplasmin (N=464) n (%)
At least 1 objectively-defined macular pathology	186 (98.9)	459 (98.9)
Presence of retinal deformity	171 (91.0)	421 (90.7)
Presence of intraretinal cysts	157 (83.5)	396 (85.3)
Baseline retinal thickness ≥ 275 µm	75 (39.9)	221 (47.6)
Presence of ERM	68 (36.2)	184 (39.7)
Presence of subretinal fluid	68 (36.2)	173 (37.3)
ERM at site of VMA	53 (28.2)	143 (30.8)
FTMH	47 (25.0)	106 (22.8)
Presence of retinal schisis	31 (16.5)	69 (14.9)
More than 1 objectively-defined macular pathology	177 (94.1)	439 (94.6)

Reference: Table 2.7.3.7-1, Table 2.7.3.7-4, Table 2.7.3.7-5
ERM=epiretinal membrane; FTMH=full thickness macular hole; OCT=VMA+vitreomacular adhesion

The study drug was provided in glass vials containing 1.875 mg ocriplasmin in 0.75 mL frozen liquid. After thawing, the drug was diluted with equal volume (0.75 mL) of Normal saline and 0.1 mL that is 0.125 mg was injected into the mid-vitreous using 30G or 27G needle. The same process was undertaken for placebo injection (0.1 mL).

The results, based on Full Analysis Set (FAS) at Day 28 and at End of Study (Month 6), are provided and briefly described below. Note no adjustment for multiplicity has been done.

VMA resolution

The treatment differences began to appear by post-injection Day 7. At Day 28, VMA resolution (pooled data) was achieved in 26.5% ocriplasmin patients versus 10.1% placebo patients. The treatment difference was 16.4% (95%CI 10.5%, 22.3%).

By Month 6, VMA resolution (pooled data) was achieved in 26.9% ocriplasmin patients versus 13.3% placebo patients. The treatment difference was 13.6% (95%CI 7.3%, 20.0%).

Total PVD

At Day 28, Total PVD (pooled data) was achieved in 13.4% ocriplasmin patients versus 3.7% placebo patients. The treatment difference was 9.6% (95%CI 5.5%, 13.8%).

The Month 6 results for Total PVD could not be located. The sponsor is requested to provide these data, pooled as well as individual, in its Pre Advisory Committee on Prescription Medicines (ACPM) response.

Non-surgical closure of FTMH

At Day 28, non-surgical closure of FTMH, in the subset of patients with macular hole at baseline, was obtained (pooled data) in 40.6% ocriplasmin patients versus 10.6% placebo patients. The treatment difference was 29.9% (95%CI 17.1%, 42.8%).

By Month 6, non-surgical closure of FTMH, in the subset of patients with macular hole at baseline, was obtained (pooled data) in 40.6% ocriplasmin patients versus 17.0% placebo patients. The treatment difference was 23.5% (95%CI 9.3%, 37.8%).

Surgical vitrectomy

At Day 28 (pooled data), 0.6% ocriplasmin patients versus 1.1% placebo patients required surgical vitrectomy. The treatment difference was -0.4% (95%CI -2.1%, 1.2%).

By Month 6 (pooled data), 17.7% ocriplasmin patients versus 26.6% placebo patients required surgical vitrectomy. The treatment difference was -8.9% (95%CI -16.1%, -1.7%).

Clinical outcomes***Improvement in BCVA (≥ 2 lines)***

At Day 28 (pooled data), 17.0% ocriplasmin patients versus 8.6% placebo patients had at least 2 lines improvement in BCVA. The treatment difference was 8.5% (95%CI 3.2%, 13.7%).

At Month 6 (pooled data), 23.7% ocriplasmin patients versus 11.2% placebo patients had at least 2 lines improvement in BCVA. The treatment difference was 12.5% (95%CI 6.6%, 18.5%).

Improvement in BCVA (≥ 3 lines)

At Day 28 (pooled data), 6.0% ocriplasmin patients versus 3.7% placebo patients had at least 3 lines improvement in BCVA. The treatment difference was 2.3% (95%CI -1.2%, 5.8%).

At Month 6 (pooled data), 9.7% ocriplasmin patients versus 3.7% placebo patients had at least 3 lines improvement in BCVA. The treatment difference was 6.0% (95%CI 2.2%, 9.8%).

Worsening of BCVA (≥ 2 lines)

At Day 7 (pooled data), 8.4% ocriplasmin patients versus 2.1% placebo patients had 2 or more lines deterioration in BCVA. The treatment difference was 6.3% (95%CI 3.0%, 9.5%).

At Day 28 (pooled data), 2.8% ocriplasmin patients versus 2.7% placebo patients had 2 or more lines deterioration in BCVA. The treatment difference was 0.1% (95%CI -2.6%, 2.9%).

At Month 6 (pooled data), 4.7% ocriplasmin patients versus 2.7% placebo patients had 2 or more lines deterioration in BCVA. The treatment difference was 2.1% (95%CI -0.9%, 5.1%).

Worsening of BCVA (≥ 3 lines)

At Day 7 (pooled data), 3.2% ocriplasmin patients versus 0.5% placebo patients had 3 or more lines deterioration in BCVA. The treatment difference was 2.7% (95%CI 0.8%, 4.6%).

At Day 28 (pooled data), 1.1% ocriplasmin patients versus 0.5% placebo patients had 3 or more lines deterioration in BCVA. The treatment difference was 0.5% (95%CI -0.9%, 1.9%).

At Month 6 (pooled data), 3.0% ocriplasmin patients versus 1.6% placebo patients had 3 or more lines deterioration in BCVA. The treatment difference was 1.4% (95%CI -1.0%, 3.8%).

Quality of life

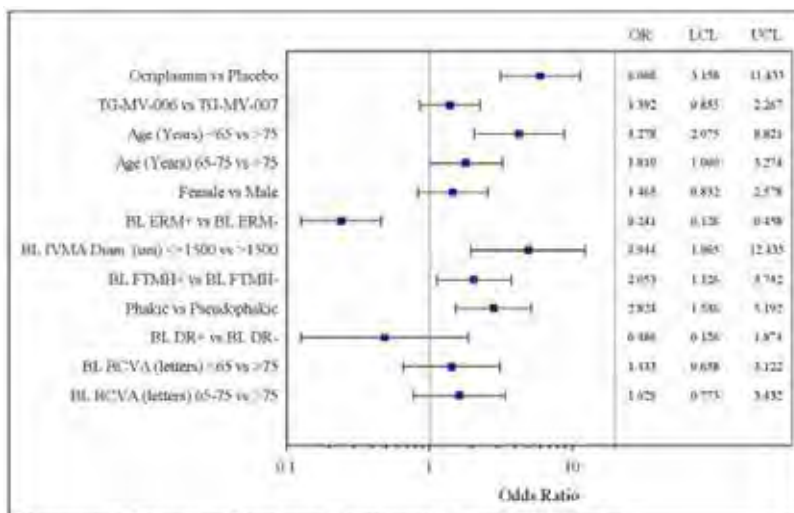
The results for the overall VFQ-25 composite score were as shown below in Table 11 and generally consistent with its component domains indicating lack of any meaningful effect on QoL.

Table 11. Results for overall VFQ-25 composite score

VFQ-25 Pooled 006/007 data		Placebo		Ocriplasmin		p-value
		n	Score	n	Score	
Composite score	Baseline	187	82.0 (12.15)	462	77.1 (15.91)	0.079
	Month 6	174	82.6 (13.68)	430	80.5 (16.37)	
	Change from B/L	173	0.7 (10.04)	428	3.4 (11.85)	

For some subgroup analyses of interest within individual studies with respect to selected outcomes. However, pooled analysis with data from both studies showed the following significant interactions with respect to VMA resolution at Day 28 (Figure 2).

Figure 2. VMA resolution at Day 28 (pooled 006/007 data): significant interactions.



Abbreviations: LCL=lower confidence limit; OR=odds ratio; UCL=upper confidence limit

The interactions indicate poorer prognosis upon ocriplasmin treatment with respect to VMA resolution in subgroup of patients with baseline epiretinal membrane or (possibly) diabetic retinopathy and relatively favourable prognosis in patients with baseline FTMH versus without FTMH, baseline focal VMA diameter $\leq 1500 \mu\text{m}$ versus $> 1500 \mu\text{m}$ and in phakic versus pseudophakic patients. Note proliferative diabetic retinopathy and aphakia were exclusion factors. The interaction with respect to the baseline epiretinal membrane may warrant exclusion of these patients from the proposed ocriplasmin use.

Clinical safety

A total of 599/758 patients (8 studies in this dossier including 17 patients from uncontrolled Study 008) were exposed to the proposed dose of IVT ocriplasmin 125 μg , including 465 in the two pivotal efficacy studies (006/007). In addition, 215 patients have received ocriplasmin in ongoing studies. There were reports of compassionate use in 3 patients. Thus, total available experience with IVT ocriplasmin consists of 976 patients.

The overall safety profile was similar in the 2 pivotal placebo-controlled studies and all completed studies combined. In the 2 pivotal studies, AEs were reported as shown in Table 12.

Table 12. Overall safety profile.

Studies 006/007	Placebo (N=187)		Ocriclasmin 125 µg (N=465)	
	n	%	n	%
Any AE	129	69.0%	356	76.6%
Any ocular AE	106	56.7%	324	69.7%
Any non-ocular AE	53	28.3%	140	30.1%
Study eye AE	99	52.9%	317	68.2%
Non-study eye AE	22	11.8%	61	13.1%

In the 2 pivotal studies, the ocular AEs reported with at least 2% frequency (ocriclasmin versus placebo respectively) were: vitreous floaters (16.8% versus 7.5%), conjunctival haemorrhage (14.6% versus 12.8%), eye pain (13.1% versus 5.9%), photopsia (11.8% versus 2.7%), vision blurred (8.4% versus 3.2%), macular hole (6.7% versus 9.6%), visual acuity reduced (6.2% versus 4.3%), visual impairment (5.4% versus 1.1%), retinal oedema (5.4% versus 1.1%), macular oedema (4.1% versus 1.6%), intraocular pressure increased (3.9% versus 5.3%), anterior chamber cells (3.7% versus 2.7%), photophobia (3.7% versus 0%), ocular discomfort (2.8% versus 1.1%), vitreous detachment (2.6% versus 1.1%), iritis (2.6% versus 0%), cataract (2.4% versus 4.3%), dry eye (2.4% versus 1.1%), conjunctival hyperaemia (2.2% versus 2.1%) and metamorphopsia (2.2% versus 0.5%).

In the 2 pivotal studies, non-ocular AEs were reported in 30.1% ocriclasmin patients versus 28.3% placebo patients. Non-ocular AEs occurring in $\geq 2\%$ of patients (ocriclasmin versus placebo respectively) were bronchitis (2.8% versus 1.6%), nausea (2.6% versus 0.5%) and headache (2.6% versus 2.1%). The organ systems reported affected (ocriclasmin versus placebo respectively) were Hepatobiliary disorder (none in either group), Renal and urinary disorders (0.9% versus 0.5%), Blood and lymphatic disorders (0.4% versus 1.1%), Cardiac disorders (1.3% versus 0.5%), vascular disorders (0.9% versus 1.1%) and Skin and subcutaneous tissue disorders (1.9% versus 2.6%).

In the 2 pivotal efficacy studies, AEs associated with intravitreal injection procedure (intraocular haemorrhage, intraocular inflammation and IOP increase) occurred in 46.5% ocriclasmin patients versus 28.3% placebo patients. The respective rates in all studies combined data were 50.2% versus 34.0% for ocriclasmin and control groups respectively.

In the 2 pivotal studies, serious AEs (SAEs) were reported in 62/465 (13.3%) ocriclasmin patients versus 24/187 (12.8%) placebo patients. In the completed 7 clinical studies, SAEs were reported in 100/741 (13.5%) ocriclasmin patients versus 34/247 (13.8%) control patients.

In the 2 pivotal studies, ocular SAEs (study eye) were reported in 37/465 (8.0%) ocriclasmin patients versus 20/187 (10.7%) placebo patients. In the completed 7 clinical studies, ocular SAEs were reported in 59/741 (8.0%) ocriclasmin patients versus 22/247 (8.9%) control patients. In the 2 pivotal studies, the most commonly reported ocular SAEs in the study eye were (ocriclasmin versus placebo respectively) macular hole (including progression of macular hole; 5.2% versus 8.6%), vitreous adhesions (1.1%, n=5, versus 0.5%, n=1), visual acuity reduced (0.6%, n=3, versus 0.5% n=1) and retinal detachment (0.4%, n=2, versus 1.6%, n=3). For the 7 completed studies combined, the pattern was similar.

In the 2 pivotal studies, 16 SAEs were considered drug-related by the sponsor were in 15 ocriclasmin patients (macular hole 9; retinal detachment 2; vitreous adhesion 2; visual acuity reduced 2; posterior capsule opacification 1), whereas 6 SAEs considered drug-

related were in 6 placebo patients (macular hole 4; macular oedema 1; vitreous adhesions 1). As of 31 March 2011, 12 patients were reported with SAEs in the ongoing trials and the sponsor considered 5 to be treatment-related. All were in ocriplasmin groups and included 2 cases of visual acuity reduced/retinal detachment and one of transient blindness, visual acuity reduced and lens dislocation each.

The 120-Day Safety Update Report included further information on 39 SAEs reported in 30 patients in on-going studies for the period 1 April 2011 to 31 May 2012. The most commonly reported SAEs were progression of pre-existing macular hole (6), intraocular pressure increased (3), retinal detachment (3), visual acuity reduced (3) and vitreous adhesions (3). Among these, 14 SAEs from 10 patients were considered treatment-related by the sponsor. These were visual acuity reduced (3), macular hole (2), intraocular pressure increased (2), and one event each of blindness transient, lens dislocation, impaired pupillary reflex, retinal detachment, retinal toxicity, retinal vasculitis and vitreous adhesions.

In the 2 pivotal studies, 5 deaths (1.1%) occurred in 465 ocriplasmin treated patients versus none in 187 placebo patients. All deaths were in women aged ≥ 76 years. In the completed and ongoing IVT ocriplasmin studies, a total of 10 deaths (6 in ocriplasmin groups, 2 in sham injection groups and 2 in groups still masked), as of the cut-off date of 31 May 2012. If the masked treatment is assumed to be ocriplasmin then the incidence of death in the ocriplasmin groups (all doses) is 0.8% (8/976) versus 0.6% (2/341) in control groups.

VMA resolution at Day 28 was strongly associated with a higher incidence of the AE of vision alteration. Consistent with this, the other subgroups with higher incidence of the AE of vision alteration were generally those that achieved higher rates of VMA resolution.

Immunogenicity data were not collected in the IVT ocriplasmin studies. Data from IV ocriplasmin studies suggest the risk to be low. In the 2 pivotal studies, immune system disorders were not reported in any placebo patient and in 9 (1.9%) ocriplasmin patients.

Please see CER for details of ocular AEs of special interest (functional retinal findings and anatomical findings) and for review of PBRER.

Based on the data cut-off date of 31 March 2011, a total of 16/820 (1.9%) patients reported dyschromatopsia ('yellowish vision'). Most cases occurred on the day of injection, and most are reported to have resolved. Median time to resolution was 3 months (range 1, 28 months). Eight out of these 16 patients also had ERG abnormalities.

A total of 10/820 patients (1.2%) had ERG abnormalities. The median time to onset of abnormal ERGs was 1 week (range 1 week to 1 month). In 6 out of 10 cases, the abnormalities were reported to have resolved. The median time to resolution was 6 months (range 3 to 6 months).

As of 31 May 2012, 177 patients have been treated in the ongoing Study 014. Of the 177 patients (still masked), dyschromatopsia was reported in 34 (19.2%), clinically significant ERG abnormalities in 11 (6.2%) and both dyschromatopsia and clinically significant ERG abnormalities in 4 (2.6%) patients. One serious case of 'photoreceptor toxicity' was reported. There has also been one report serious acute transient vision decrease in the ongoing exudative AMD Study 005. Transient vision decreases with no alternative explanation were reported in 9/976 (0.9%) patients who received ocriplasmin in completed and ongoing studies.

An 'Integrated Summary of Clinical Retinal Findings' identified 6/820 patients (0.73%) who developed temporary, but significant (serious or severe) visual impairment within 24 hours of injection without an alternative explanation on full ophthalmologic examination. Visual acuity ranged from 20/200 to hand motions only, and was associated with transient visual field constriction in 3 patients. In addition, 7 ocriplasmin patients in uncontrolled

Study 008 developed dyschromatopsia ('yellowish vision') and ERG changes, and 2 more patients had ERG changes but no dyschromatopsia. In a separate, uncontrolled Study 010, 4 additional cases of dyschromatopsia have been reported.

A retrospective analysis of retina-related data concluded that patients should be informed that in rare cases a temporary decrease in vision may occur, even if the macular hole closes or the vitreomacular traction is released.

The data search for BCVA decrease of ≥ 10 letters from baseline within 7 days of treatment, with no alternative explanation for the change and irrespective of whether or not a vision-related AE, in the completed and ongoing studies identified 44/820 (5.4%) ocriplasmin patients and 3/269 (1.1%) placebo patients. BCVA returned to within 1 line (5 letters) of baseline values during the study for all patients, except in 6/820 (0.7%) ocriplasmin patients and 1/269 (0.4%) placebo patient. The most commonly reported AEs occurring within 7 days of injection in the ocriplasmin patients included vitreous floaters (12/44, 27.3%) and photopsia (8/44, 18.2%), while subretinal fluid was noted in 6 (13.6%) patients. None of these events was reported in the 3 placebo patients.

A review of 25 of 49 ocriplasmin treated patients who experienced an unexplained ≥ 3 line loss in BCVA at any time during the 2 pivotal efficacy studies was done. The majority of vision losses were considered to be due to vitreomacular traction and/or macular hole progression. It was postulated that ocriplasmin treatment may lead to additional traction from incomplete enzymatic cleavage of the adhesion between the posterior vitreous cortex and the internal limiting membrane. In some cases, this may lead to enlargement or development of new macular holes.

As noted before, in the two pivotal studies, retinal/macular oedema was reported in 9.5% ocriplasmin patients versus 2.7% placebo patients. Retinal oedema was reported in 5.4% ocriplasmin patients versus 1.1% placebo patients. Macular oedema was reported in 4.1% ocriplasmin versus 1.6% placebo patients. Retinal pigment epitheliopathy was reported in 1.5% ocriplasmin patients versus none in placebo. Macular hole was reported in 6.7% ocriplasmin versus 9.6%, placebo patients.

Retinal breaks included the terms retinal tears and retinal detachments. In the 2 pivotal studies, retinal breaks were reported in 1.9% ocriplasmin patients versus 1.9% placebo patients. The reported rate in the 7 completed studies was 4.5% in each group.

The updated data and the risks identified with ocriplasmin treatment based on cumulative data in the first PBRER are as shown in Table 13.

Table 13. Updated data and the risks identified with ocriplasmin treatment, based on cumulative data in the first PBRER.

	Cumulative incidence reported in clinical trials	Spontaneous reports Per 1000 doses distributed
Visual impairment	15.8%	9.98
Dyschromatopsia	1.7%	3.63
ERG abnormalities	Could not be estimated	Nil report
Retinal detachment/retinal tear	1.9%	1.36
IOP increased	4.1%	0.45
Intraocular haemorrhage	2.4%	Nil report
Intraocular inflammation	7.1%	0.45
Increased VMT	1.5%	Nil report
New MH or progression of MH size	6.7%	1.36
Retinal and/or macular oedema	9.5%	0.91
Lens subluxation	Could not be estimated	0.45
Endophthalmitis	Nil reported	Nil report

The PBRER identified 8 spontaneous reports of pupillary reflex impairment following treatment with ocriplasmin (3.63 events/1000 dose distributed). In the 2 pivotal studies, pupillary reflex impairment was observed in 4/465 (0.9%) ocriplasmin patients and 1/187 (0.4%) placebo patients. In all studies combined dataset, pupillary reflex impairment was observed in 5/741 (0.7%) ocriplasmin patients and 1/274 (0.4%) placebo patient.

After the data lock for the PBRER, report of a patient, who developed full thickness macular hole with visual acuity decrease and 'damaged photoreceptor outer segments' 2 reports of abnormal retinal angiograms, including narrowed blood vessels were reported. One additional instance of abnormal retinal angiogram has been reported from the ongoing Study 014.

The ACSOM noted the ongoing Study 014 in which data on vision, colour vision, ERG changes and microperimetry is collected to assess anatomical and functional outcomes following ocriplasmin administration. There were 10 patients with an abnormal ERG. ACSOM advised that there were 4 areas of concern regarding ocriplasmin use that is potential ERG abnormalities, increased vitreomacular traction, progression of macular hole; and a 2 fold increase in macular oedema compared to placebo. ACSOM also advised that this study was the first in which saline injection was used as placebo and that the difference in benefit for treatment (25%) versus placebo (10% to 15%) for the relief from vitreomacular adhesion was not significant. However, ocriplasmin was more effective in closing small macular holes (41% versus 11% respectively).

Risk management plan

The EU-RMP version 5, dated January 2013 with Australian Specific Annex and any changes negotiated by the TGA Office of Product Review, apply to this submission. The sponsor has indicated that a global ocriplasmin registry study is being conducted aiming to include up to 3000 patients with 12 months follow up and outcomes data on safety, effectiveness and quality of life. It is also confirmed that the Australian sites will be included if the drugs becomes available here.

Advice from ACSOM was also obtained. The Committee noted that the term 'symptomatic adhesion' and 'vitreomacular traction' were used inconsistently in the study papers and advised that the term 'traction' more specifically indicated a band of vitreous seen with

Spectral Domain Optical Coherence Tomography (SD-OCT) within 6 mm of the central retinal vein field with surrounding elevation of the vitreous cortex. If the band of vitreous is outside this area, it is not symptomatic. ACSOM advised that the use of the term 'vitreomacular traction' was preferable and that it was important that a measurable reduction in visual acuity should be observed prior to ocriplasmin being prescribed.

The ACSOM also noted that epiretinal membrane (ERM) was a measure of chronicity of the condition and the efficacy was shown to be poorer in the presence of ERM. The Committee recommends listing ERM as a contraindication.

Risk-benefit analysis

Delegate's considerations

Ocriplasmin is a recombinant truncated human plasmin produced in the yeast cells. The drug substance is obtained by fermentation and purification. The drug formulation is solution for intravitreal injection (ocriplasmin 0.5 mg/0.2 mL) requiring deep freeze for storage. It requires thawing and dilution with equal volume of Normal saline immediately prior to use resulting in 0.5 mg/0.4 mL. The recommended dose is 0.1 mL volume containing 0.125 mg ocriplasmin of this prepared solution by single intravitreal route. The vial proposed for registration thus has the potential to be used for > 1 dose. The ACPM has previously recommended that this is not desirable. The sponsor is requested to provide comment in its Pre-ACPM response for consideration by the ACPM.

The drug molecule has proteolytic activity comparable to human plasmin. The molecule, being a simple polypeptide, has uncomplicated metabolism. There are no toxicology issues. The animal data indicated risk of lens subluxation on repeat dosing. The IVT drug is not expected to escape to systemic circulation. Hence, there are no concerns regarding systemic anti-thrombolytic effect.

The choice of dose selection (0.125 mg) is considered acceptable, although the dose response between 0.75 mg, 0.125 mg and 0.175 mg doses was not shown. In the relevant dose selection Study 004, the effect was particularly evident with respect to VMA resolution and closure of macular hole than for Total PVD. This pattern was later apparent also in the pivotal efficacy trials.

The pivotal efficacy studies (006/007) were based on surrogate/anatomical endpoints (VMA resolution, Total PVD, closure of macular hole), although clinical endpoints (BCVA, surgical vitrectomy, quality of life assessment) were also examined as secondary outcomes. The primary timepoint was 28 days post-injection. Follow up data up to 6 months are currently available.

For VMA resolution, placebo-corrected treatment difference (pooled studies 006/007) in favour of ocriplasmin (0.125 mg IVT) of 16.4% (95%CI 10.5%, 22.3%) at Day 28 and 13.6% (95%CI 7.3%, 20.0%) at Month 6 was observed. The results for Total PVD were less pronounced (9.6%, 95%CI 5.5%, 13.8% at Day 28; Month 6 results not provided). The results for macular hole closure favoured ocriplasmin versus placebo at Day 28 (29.9%, 95%CI 17.1%, 42.8%) and were maintained at Month 6 (23.5%, 95%CI 9.3%, 37.8%). The number of surgical (fewer) vitrectomies numerically favoured ocriplasmin at Day 28 (-0.4%, 95%CI -2.1%, 1.2%) becoming statistically significant by Month 6 (-8.9%, 95%CI -16.1%, -1.7%).

Clinical outcomes favoured ocriplasmin treatment but the proportions of patients were small and did not correlate well with the anatomical outcomes.

Improvement in BCVA (ocriplasmin-placebo difference; pooled data) ≥ 2 lines was achieved by 8.5% patients (95%CI 3.2%, 13.7%) at Day 28 and 12.5% patients (95%CI

6.6%, 18.5%) at Month 6. Improvement in BCVA (ocriplasmin-placebo difference; pooled data) ≥ 3 lines was achieved by 2.3% patients (95%CI -1.2%, 5.8%) at Day 28 and 6.0% patients (95%CI 2.2%, 9.8%) at Month 6.

However, worsening in BCVA was also reported. Worsening of BCVA ≥ 2 lines (ocriplasmin-placebo difference; pooled data) was reported in 6.3% patients (95%CI 3.0%, 9.5%) 7 days post injection. This initial effect appeared to stabilise by Day 28 (pooled data; ocriplasmin-placebo difference 0.1%, 95%CI -2.6%, 2.9%) but was reversing by Month 6 (pooled data; ocriplasmin-placebo difference 2.1%, 95%CI -0.9%, 5.1%). The results for BCVA Worsening ≥ 3 lines (pooled data; ocriplasmin-placebo difference) were similar (Day 7: 2.7%, 95%CI 0.8%, 4.6%); Day 28: 0.5%, 95%CI -0.9%, 1.9%; Month 6: 1.4% (95%CI -1.0%, 3.8%).

Quality of life measured on VFQ-25 (pooled results; overall composite) was not statistically significant but numerically favoured ocriplasmin treatment.

A large proportion of patients in pivotal studies reported AEs (>50%) in both groups. About 13% patients reported SAEs in both groups. Mortality was similar in the two groups. Most AEs were ocular, occurred in the injected eye and were more frequent in the first 7 days post injection. Most appear to be related to the IVT injection procedure and the intended pharmacological vitreolysis by the drug. All ocular AEs were more common with ocriplasmin than with placebo and some such as floaters may be related to effectiveness of treatment. Macular hole, macular oedema, increased intraocular pressure was reported more commonly in placebo group in the 2 pivotal studies. There are no important systemic adverse effects of concern including risk of immunogenicity. There remain unresolved concerns related to long term effect on visual acuity, retinal effects (tear, detachment), retinal vascular effects, dyschromatopsia, ERG abnormalities, and pupillary reflex impairment. As noted above, ACSOM has expressed concern with respect to potential ERG abnormalities, increased vitreomacular traction and progression of macular hole in some cases and a 2 fold increase in macular oedema compared to placebo in ongoing Study 014.

The results indicate potential use of IVT ocriplasmin in patients who currently require vitrectomy in VMA, although this cannot be claimed as ocriplasmin and vitrectomy have not been compared. The effect of treatment on visual acuity, especially long term, is unclear.

Based on the reported data, the Delegate is of the opinion that use in the 'treatment of vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter $\geq 400\mu\text{m}$ ' may be considered. The VMT term is adopted in agreement with comments made by ACSOM.

Furthermore, it is proposed that a description of the diagnostic criteria may be included with the indication such that 'Patients with symptomatic focal VMA that is central vitreal adhesion within 6 mm Optical Coherence Tomography field surrounded by elevation of the posterior vitreous cortex that in the opinion of the investigator is related to decreased visual function such as metamorphopsia, decreased visual acuity or other visual complaint'.

It is also proposed that the excluded patient groups be listed in detail in the PI. The Delegate agrees with the ACSOM that presence of epiretinal membrane at baseline may be included as a contraindication based on the significant adverse interaction in the subgroup analysis.

The inclusion criteria in the 2 pivotal efficacy trials included, among others, BCVA 20/25 or worse in the study eye and 20/800 or better in the non-study eye. Overall, the mean sample BCVA letter score at baseline was 64.3 ± 11.94 (median 67; range 8, 88). The sponsor is requested to provide baseline visual acuity in terms of BCVA line score for study and non-study eyes as it may be appropriate for inclusion in the PI.

The long term effect of treatment on visual acuity is unclear. The sponsor is requested to indicate whether 12 months data from Study 012 which was to follow the patients treated in the Studies 006/007 are available. If available, these may be appropriately reviewed before finalisation of the submission. In addition, the ongoing Study 014 is of regulatory interest and the sponsor should indicate when the results, including interim results, will be made available. Note ACSOM has commented on lower efficacy in the (still unreported) ongoing Study 014 which used saline placebo.

The proposed injected volume is 0.1 mL, which is at the upper limit of volume considered safe for IVT administration. Also note that 0.75 mL volume appears to have been used in the 2 pivotal clinical studies. The sponsor is requested to confirm this (and the volume of placebo (vehicle) injected in the pivotal studies).

The sponsor is requested submit annotated copy of the PI, using PI at the time of lodgement of application as the base document, and annotate all changes/recommendations from various areas of the TGA including those in this overview. Extensive revision of the PI is anticipated following consideration by the ACPM.

The ACPM is requested for advice.

Delegate's proposed action

The Delegate has no reason to say, at this time, that this application for should not be approved for registration, subject to further information to be provided by the sponsor in its Pre-ACPM response and the advice received from the ACPM.

Delegate's request for ACPM advice

The ACPM is requested to provide advice on the following issues:

1. Whether sufficient data are available to support the requested use. Advice is requested regarding the therapeutic indication which might optimise clinical benefit with respect to the intended disease (diagnostic features) and the patient population (inclusions, exclusions).
2. The Committee is requested advice on any further aspect of market surveillance in Australia beyond that foreseen in the RMP.

The ACPM is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

- *Issue 1: It is proposed that the labelling should use the recommended terminology of store below -18°C, deep freeze based on the labelling order (TGO 69).*

Response

The long-term storage conditions of Jetrea drug product were established in primary stability studies according to International Conference on Harmonisation (ICH) guidelines as $-20 \pm 5^\circ\text{C}$. Although the -15°C to -25°C temperature range covers the proposed upper limit of -18°C , the lower limit remains undefined. Therefore, the sponsor proposes to maintain all drug product labelling consistent with the validated long-term storage conditions of $-20 \pm 5^\circ\text{C}$. Alcon awaits TGA feedback on our previous response to this question.

- *Issue 2: The vial proposed for registration has the potential to be used for greater than 1 dose. The ACPM has previously recommended that this is not desirable. The sponsor is requested to provide comment in its Pre-ACPM response for consideration by the ACPM.*

Response

The package instructions (PI) include the following instructions:

6. Using aseptic technique, **withdraw all of the diluted solution** using an appropriate sterile needle (slightly incline the vial to ease withdrawal) (**Figure 5**) and discard the needle after withdrawal of the vial contents. Do not use this needle for the intravitreal injection.
7. Replace the needle with an appropriate sterile needle, **carefully expel the air from the syringe and adjust the dose to the 0.1 ml mark on the syringe** (corresponding to 0.125 mg ocriplasmin).
8. Inject 0.1 mL of the diluted solution without delay into the mid-vitreous as it contains no preservatives.
9. Discard the vial and any unused portion of the diluted solution after single use.

These instructions clearly specify that any unused portion of the diluted Jetrea product should be discarded immediately when preparing for the injection. Health care providers are responsible for following these instructions carefully.

In addition, a benchmark analysis of fill volume/injection volume ratio of currently marketed ophthalmology products for IVT injection in Australia was performed, and the results are provided in Table 14. A 400 µL final volume for Jetrea translates into a fill volume/injection volume ratio of 4. Benchmark analysis of current registered ophthalmology products reveals that the current Jetrea presentation is significantly better than Lucentis and Eylea. This analysis demonstrates that the Jetrea fill volume poses less risk of multiple doses from a single vial than other currently approved medicines for IVT injection in Australia.

Table 14. Fill Volume/Injection Volume Ratio For Registered Ophthalmology Products.

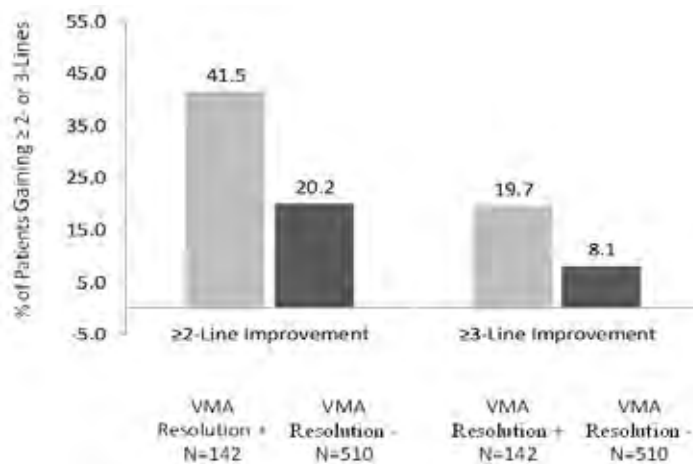
Product:	Eylea	Lucentis	Jetrea
Fill volume (µL):	278	230	400 (after 1:1 dilution with normal saline)
Volume/Injection (µL):	50	50	100
Fill volume / Injection volume ratio	5.6	4.6	4

- Issue 3: Clinical outcomes favoured ocriplasmin treatment but the proportions of patients were small and did not correlate well with the anatomical outcomes.

Response

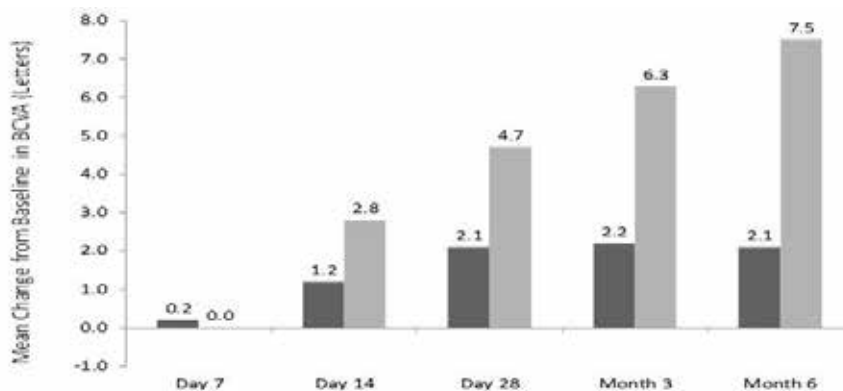
Alcon refers to its response to issue #4 that was raised in TGA's clinical evaluation report where clinical outcomes did in fact correlate with anatomical outcomes. The relevant correlations are summarised again below.

A statistically significant association was observed between achieving VMA resolution at Day 28 and ≥ 2 -line improvement in BCVA at Month 6, with improvement being significantly better in patients who achieved VMA resolution ($p=0.006$; odds ratio [OR]=2.079 [95% CI: 1.232, 3.509]). The proportion of patients with a ≥ 2 -line improvement in BCVA at Month 6 was 2-fold higher among patients who achieved VMA resolution at Day 28 (41.5%) compared with those who failed the endpoint (20.2%) (Figure 3).

Figure 3. Categorical Change from Baseline in BCVA by Status of VMA Resolution.

In addition, the proportion of patients with a ≥ 3 -line improvement in BCVA at Month 6 was higher among patients who achieved VMA resolution at Day 28 (19.7% versus 8.1%).

These results were also supported by the multi-factorial ANOVA that showed a statistically significant effect for outcome of VMA resolution on mean improvement in BCVA at Month 6 ($p < 0.001$). For all patients, mean improvement from baseline in BCVA was notably greater at each time point among patients who achieved VMA resolution compared with those who failed the endpoint. At Month 6, mean improvement from baseline in BCVA was 7.5 letters among patients who achieved VMA resolution and 2.1 letters among those who failed the endpoint (Figure 4), which corresponds to a 1-line difference on the ETDRS chart.

Figure 4. Mean Change from Baseline in BCVA by Status of VMA.

Note: Light bar = success for VMA resolution at Day 28 (N=142); dark bar = failure for VMA resolution at Day 28 (N=510).

The beneficial anatomical outcome of VMA resolution, if achieved, therefore translates into a clinically significant improvement of vision.

- *Issue 4: There remain unresolved concerns of long term effect on visual acuity, retinal effects (tear, detachment), retinal vascular effects, dyschromatopsia, ERG abnormalities, pupillary reflex impairment, increased vitreomacular traction, progression of macular hole, and macular oedema compared to placebo in ongoing Study 014.*

Response

Alcon acknowledges the ongoing concerns listed above. These important identified risks have been communicated in the product labelling, EU-RMP, and PBRER. Table 15 provides a summary of ongoing safety concerns as listed in the current PBRER.

Table 15. Summary of Risks of Ocriplasmin.

Safety Concern	Estimated Frequency	Actions Taken / Suggested ¹	
		Specific to Risk	Common to Risks
Visual Impairment (Including Visual acuity reduced)	13.8% ² 18.40 per 1000 doses distributed ⁵	Visual impairment and related terms listed as adverse reactions in USPI and SmPC Targeted Follow-up Questionnaire for spontaneous cases of Vision loss	Clinical Study TG-MV-014: long term visual function and safety Routine risk minimisation / pharmacovigilance activities Risk minimization/communication: patient information pack including patient information leaflet and patient/health care provider educational material
Dyschromatopsia	1.7% ³ 3.91 per 1000 doses distributed ⁵	Dyschromatopsia listed as adverse reactions in USPI and SmPC Targeted Follow-up Questionnaire for spontaneous cases of Dyschromatopsia	
ERG Abnormalities	Cannot be estimated ⁴ 0.43 per 1000 doses distributed ⁵	ERG changes listed as adverse reaction in USPI and SmPC Targeted Follow-up Questionnaire for spontaneous cases of ERG abnormalities	
Retinal detachment	1.9% ² 2.75 per 1000 doses distributed ⁵	Retinal detachment listed as adverse reaction in USPI and SmPC	
Increased Vitreomacular Traction	1.5% ² 0.14 per 1000 doses distributed ⁵	Advisement to closely monitor progression of condition in the USPI Listed as an adverse reaction seen in clinical trials and additional info. in SmPC	
Safety Concern	Estimated Frequency	Actions Taken / Suggested ¹	
		Specific to Risk	Common to Risks
Development of new macular hole or progression of macular hole size	6.7% ² 4.01 per 1000 doses distributed ⁵	Inclusion of event 'macular hole' in USPI and specific wording in SmPC which mentions this event and also the risk for occurrence of new or enlarged macular holes as a result of increase in tractional forces	
Retinal and / or Macular Oedema	9.5% ² 2.32 per 1000 doses distributed ⁵	Inclusion in USPI / SmPC or 'retinal and macular oedema' as an adverse reactions seen in clinical trials	

¹ The Drug Utilisation Study (TG-MV-017) has not started yet. The protocol was finalised as of 04 Nov 2013.

² Based on pivotal CTs data

³ Based on CT data as presented in PBRER#1

⁴ After no safety signal was concluded upon for study treatment-induced ERG abnormalities in clinical trials TG-MV-001 and TG-MV-002, ERG measurements were not scheduled in subsequent studies, but after initial reports of dyschromatopsia and ERG abnormalities in Study TG-MV-008 (an uncontrolled single-centre open-label clinical study in which most of the intravitreal injections were administered by the same investigator), an amendment to the protocol was made that specified ERG measurements must be performed for all subsequent patients participating in this study. Therefore, the overall frequency cannot be calculated. ERG changes were reported in at least half of the dyschromatopsia cases in the pivotal trials (estimated frequency of 2%)

⁵ Spontaneous Reports based on DLP for PBRER#2, Table 15 Section 16.4

With respect to the incidence of macular edema in ongoing Study TG-MV-014, it is important to note that the comparator is a sham injection and that the study is still masked to treatment. Therefore, the incidence of macular edema in the ocriplasmin treated patients compared to the incidence in sham treated patients is currently unconfirmed in clinical Study TG-MV-014.

- *Issue 5: The results indicate potential use of IVT ocriplasmin in patients who currently require vitrectomy in VMA, although this cannot be claimed as ocriplasmin and vitrectomy have not been compared. The effect of treatment on visual acuity, especially long term, is unclear.*

Furthermore, it is proposed that a description of the diagnostic criteria may be included with the indication such that 'Patients with symptomatic focal VMA that is central vitreal adhesion within 6mm Optical Coherence Tomography field surrounded by elevation of the posterior vitreous cortex that in the opinion of the investigator is related to decreased visual function such as metamorphopsia, decreased visual acuity or other visual complaint.'

It is also proposed that the excluded patient groups be listed in detail in the PI.

The sponsor is requested to provide baseline visual acuity in terms of BCVA line score for study and non-study eyes as it may be appropriate for inclusion in the PI.

Response

The effect of ocriplasmin treatment on visual acuity depends on whether VMA resolution is achieved or not (see response to *Issue 3*). It is acknowledged that follow-up data beyond 6 months are currently very limited. However, the mean changes in BCVA by status of VMA resolution show an increase in visual acuity over time for patients with VMA resolution (see Figure 3 in response to *Issue 3*). There were patients with VA loss at 6 months in pivotal Studies 006/007; however, the majority of the losses were due to alternative explanations such as presence of underlying conditions, disease progression, and vitrectomy, and not attributable to ocriplasmin. Follow-up data from Study 012 show, on average, visual stability at 1 year (see response to *Issue 6* below).

Alcon believes that the proposed diagnostic information is best located in the Clinical Trials section and it has been added preceding the description of efficacy results from the pivotal clinical studies. This would ensure that the prescriber is fully apprised of the relevant clinical trial data.

In the sponsor's opinion the results of the two placebo-controlled Phase III studies 006/007 do not justify the inclusion of epiretinal membrane (ERM) as a contraindication in the PI. Even in patients with ERM at baseline there was a 7.2% (95% CI: 2.2, 12.2) difference in VMA resolution rate in favour of ocriplasmin. The magnitude of the treatment effect is certainly less in the patients with the more pejorative baseline characteristics such as ERM, but the consistency of effect in all subgroups across endpoints suggests a real clinical benefit, irrespective of baseline characteristics. So, on this basis, it seems justified to offer ocriplasmin to these patients first, since the benefit of a potential response to ocriplasmin outweighs the relatively minor risks of treatment and is certainly preferable to the risks of a suboptimal vitrectomy. Based upon a review of adverse event characteristics reported among ERM and non-ERM patients, there were no safety issues that would preclude exposing these patients to ocriplasmin. Therefore, in the absence of an identifiable safety issue among ERM patients, it would be more appropriate to state under Precautions that *'The effect of Jetrea in inducing resolution of VMA or causing total PVD is reduced in subjects with an epiretinal membrane.'* This proposal is consistent to both the European SPC and US PI labelling.

The above-mentioned mean sample BCVA letter score at baseline refers to the study eyes. The mean baseline BCVA letter score for the non-study eyes was 74.5 ± 16.12 (median 79; range 4, 99).

- *Issue 6: The long term effect of treatment on visual acuity is unclear. The sponsor is requested to indicate whether 12 months data from Study 012 which was to follow the patients treated in the studies 006/007 are available. In addition, the ongoing Study 014 is of regulatory interest and the sponsor should indicate when the results, including interim results, will be made available*

Response

The data from Study 012 are available and the report was attached to the sponsor's response. The study included a total of 24 patients who had participated in studies

006/007. Of these, 19 had been treated with ocriplasmin and 5 with placebo. Compared with the EOS visit in Studies 006/007, the 5 placebo-treated patients showed a decrease in mean BCVA from 70.8 to 65.6 letters at the Month 12 visit while mean BCVA remained stable in the 19 ocriplasmin-treated patients (increase from 67.3 letters at 006/007 EOS to 68.1 letters at Month 12).

Study 014 is scheduled to be completed at the end of 2014. The report will become available in 2015. There will be no interim analysis.

- *Issue 7: 0.75 mL volume appears to have been used in the 2 pivotal clinical studies. The sponsor is requested to confirm this (and the volume of placebo (vehicle) injected in the pivotal studies).*

Response

The volume of injection for both ocriplasmin and placebo in the pivotal clinical trials TG-MV-006 and TG-MV-007 was 0.1 mL.

- *Issue 8: The sponsor is requested submit annotated copy of the PI.*

Response

The annotated PI was provided to the TGA with this response.

- *Issue 9: The 6 month results for Total PVD could not be located. The sponsor is requested to provide these data, pooled as well as individual, in its Pre ACPM response.*

Response

The 6 months results for Total PVD were included with this response to the TGA.

Advisory committee considerations

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Jetrea concentrated solution for injection containing 2.5 mg/mL of ocriplasmin to have an overall positive benefit-risk profile for the amended indication:

Treatment of vitreomacular traction (VMT) in adult patients including when associated with a macular hole of diameter less than or equal to 400 microns

In making this recommendation, the ACPM:

- Noted ACSOM advice that epiretinal membrane (ERM) was a measure of chronicity of the condition and the efficacy was shown to be poorer in the presence of ERM. The ACPM recommended that this should be explicitly noted in the clinical trials results section of the PI.
- Expressed concern that while clinical outcomes in the two pivotal trials favoured ocriplasmin treatment, the proportions of patients were small and did not correlate well with the anatomical primary endpoint outcomes. However; the ACPM noted that chemical vitrectomy offered by ocriplasmin did not prejudice subsequent surgical vitrectomy.
- Noted the reported heat sensitivity of the product and hence storage sensitivities, these should be prominent in the PI and in labelling.
- Noted the volume of the proposed presenting vial compared to the maximum injection dose proposed and expressed concern over the potential for more than one use from an individual vial. This is an on-going concern of the ACPM's.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA's Office of Product Review,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.
- Submission of the global registry study report when it becomes available

Specific advice

1. *Whether sufficient data are available to support the requested use. Advice is requested regarding the therapeutic indication which might optimise clinical benefit with respect to the intended disease (diagnostic features) and the patient population (inclusions, exclusions).*

The ACPM agreed with the Delegate that, based on the available data, use in the treatment of vitreomacular traction (VMT) in adults, including when associated with macular hole of diameter less than or equal to 400 µm, is appropriate for registration.

The ACPM were of the view that inclusion of a description of the diagnostic criteria with the indication: patients with symptomatic focal VMA, that is, central vitreal adhesion within 6 mm Optical Coherence Tomography field surrounded by elevation of the posterior vitreous cortex, that in the opinion of the investigator is related to decreased visual function such as metamorphopsia, decreased visual acuity or other visual complaint, was warranted.

It is also reasonable to list the exclusion criteria in detail in the PI.

2. *The Committee is requested to advise on any further aspect of market surveillance in Australia beyond that foreseen in the RMP.*

The ACPM advised that the RMP supporting the product and the changes negotiated were appropriate.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Jetrea ocriplasmin (ryp) 0.5 mg/0.2 mL concentrated solution for (intravitreal) injection vial indicated for:

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.

Specific conditions of registration applying to these goods

1. With all outstanding issues resolved, the implementation in Australia of the Jetrea (ocriplasmin) EU Risk Management Plan (RMP), version 5 dated January 2013 with an Australian Specific Annex (undated, no version number), and any subsequent revisions, as agreed with the TGA.

2. Batch Release Testing: As a minimum, the first five independent batches of Jetrea (ocriplasmin [ryp]) concentrated solution for (intravitreal) injection imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA.

Attachment 1. Product Information

The Product Information approved for Jetrea at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <<http://www.tga.gov.au/hp/information-medicines-pi.htm>>.

Attachment 2. Extract from the Clinical Evaluation Report

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