17 January 2013
EMA/CHMP/74766/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

JETREA

International non-proprietary name: Ocriplasmin

Procedure No. EMEA/H/C/002381/0000

Note

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

API	Active Pharmaceutical Ingredient
BSS-plus	Balanced Salt Solution plus
CE	European Community
CEP	Certificate of Suitability to the European Pharmacopeia
CEX	Cation Exchange Chromatography
CEX-HPLC	Cation Exchange Chromatography - High-Performance Liquid Chromatography
CIPC	Critical In-Process Controls
COP	Critical Operating Parameters
DNA	Deoxyribonucleic Acid
DP	Drug Product
EDQM	European Directorate for the Quality of Medicines
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
HPLC	High-Performance Liquid Chromatography
IPC	In-Process Controls
Ph. Eur.	European Pharmacopeia
RP-HPLC	Reversed phase High-Performance Liquid Chromatography
SE-HPLC	Size-Exclusion High-Performance Liquid Chromatography
SmPC	Summary of Product Characteristics
USP	US Pharmacopeia
UV	UltraViolet
VMA	Vitreomacular Adhesion
VMT	Vitreomacular Traction
WCB	Working Cell Banks
w/v	Weight/Volume

1. Background information on the procedure

1.1. Submission of the dossier

The applicant ThromboGenics NV submitted on 26 September 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for JETREA, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: treatment of symptomatic vitreomacular adhesion (VMA) including macular holes.

The legal basis for this application refers to:

Article 8(3) of Directive 2001/83/EC – complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) (P/267/2010) on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance ocriplasmin contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 January 2010. The Scientific Advice pertained to quality of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Ian Hudson Co-Rapporteur: Kristina Dunder

- The application was received by the EMA on 26 September 2011.
- The procedure started on 19 October 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 6 January 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 4 January 2012.
- During the meeting on 13-16 February 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 February 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 3 August 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 September 2012.
- During the CHMP meeting on 15-18 October 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 December 2012.
- During the meeting on 14-17 January 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to JETREA.

2. Scientific discussion

2.1. Introduction

With aging, the vitreous undergoes liquefaction and weakening of the adhesion between the posterior vitreous cortex and the internal limiting membrane (ILM) of the retina. Liquefied vitreous exits the vitreous body with volume displacement and the observed collapse of the vitreous body, leading to PVD (posterior vitreous detachment). PVD is often initially incomplete or partial, resulting in maintenance of vitreous adhesions to the retina, typically at the retinal periphery and the optic nerve head, but sometimes also at the macula giving rise to a vitreomacular adhesion (VMA). Subsequent shrinkage of the vitreous cortex away from the macular area results in a tangential traction. This results in the vitreomacular traction syndrome (VMT), which may cause decreased vision, metamorphopsia (distortion of images), and micropsia (shrinkage of images), and is a risk factor for the development of macular holes [Maumenee 1967, Gass 1988]. In 1988 Gass described the staging of macular holes as ranging from 1 to 4. In stage 1, intraretinal splitting at the fovea causes a pseudocyst or a foveal detachment. Stage 2 macular holes are full thickness breaks in the retina of less than 400 µm in size. Stage 3 holes are larger than 400 µm but retain partial vitreomacular traction or adhesion; this is lost in stage 4 which is characterised by the presence of a complete PVD.

The prevalence of VMT is unknown, but macular holes occur in around 1 in 3300 people usually in the 6th and 7th decades of life, and are more common in women. The prognosis of VMT is difficult to define, since many patients may be asymptomatic and undiagnosed, but a significant proportion can be expected to recover spontaneously. Persistent traction on the macular may cause cystoid macular oedema or may induce the formation of an epiretinal membrane (ERM). Both of these conditions are likely to result in decreased or distorted vision. 30-50% of stage 1 macular holes will arrest or resolve spontaneously, often with resolution of symptoms [Ezra 2001]. The remainder of stage 1 holes progress to FTMH, and while 10% of stage 2 holes may close spontaneously, the majority progress to stage 3 or 4 holes, with a resultant persistent defect in central vision.

Currently, there is no pharmacological treatment for symptomatic VMA. The only active treatment option available is surgery (vitrectomy), whereby the vitreous is removed and any adhesions are dissected from the macular surface. Vitrectomy, especially if it requires peeling of any pathological membranes, carries the risk of complications, including retinal tears (<5%), low intraocular pressure (0-25%), acute endophthalmitis (0.03-0.23%), progression of cataract (23-79%), retinal detachment (0-17%), recurrent macular oedema (10%), and recurrent vitreous haemorrhage (7-9%) [Recchia 2010]. Surgery is commonly performed under local anaesthesia. The post-vitrectomy patient may also have to undergo a period of 4-6 weeks without being able to work, out of which 7-14 days may be in a “head-down” position to enhance the success rate of the surgical procedure. This “head-down” posturing can be very inconvenient for the patient, and carries a significant burden of care to family or friends. Furthermore, the vision in the first days post-operatively is often reduced to hand movements only, due to the retina trauma and associated inflammatory changes. Therefore, surgery is only used as an intervention when patients have or are at risk of severe visual disturbance and/or central blindness.

Jetrea 0.5 mg/0.2 ml concentrate for solution for injection contains the active substance ocriplasmin and is formulated for intravitreal (IVT) use. Other names are microplasmin or recombinant truncated human plasmin. The term microplasmin has been used in literature and study reports. The target indication is the treatment of vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns. Ocriplasmin is supplied as an unpreserved solution in single use glass vials, and is to be diluted with sodium chloride solution before use. The recommended dose is 125µg (corresponding to 0.1mL of the diluted solution) administered by intravitreal injection to the affected eye once as a single dose.

Ocriplasmin (molecular weight 27.2kDa), a recombinant human protein derived from the yeast Pichia pastoris, is a truncated form of the human plasmin with retained protease activity. It demonstrates activity against substrates important in the vitreous structure and vitreoretinal interface, including collagen, fibronectin and laminin. Plasmin occurs naturally in the vitreous, and increases with age.

2.2. Quality aspects

2.2.1. Introduction

Jetrea drug product is a sterile, clear, colourless preservative-free concentrate for solution for intravitreal injection, containing 200 µl of ocriplasmin active pharmaceutical ingredient at a concentration of 0.5 mg / 0.2 mL. Jetrea is presented in a 2 mL single use Type I glass vials to

be stored at -20 °C. A carton secondary pack has been specifically developed for ocriplasmin drug product to ensure the vial is secured and kept upright. Due to the inherent auto-proteolytic activity of Ocriplasmin, Jetrea must be stored and transported frozen. The supply chain for ocriplasmin drug product consists of shipment on dry ice and storage at the distributions sites at -20 °C ± 5 °C. Immediately prior to use, the frozen drug product (200µl) is thawed at room temperature and is to be diluted with an equal volume of 0.9 % (w/v) sodium chloride to adjust tonicity. The recommended dose is 0.125 mg (125 µg) corresponding to 0.1mL of the diluted solution. Ocriplasmin belongs to the pharmacotherapeutic group of ophthalmologicals.

2.2.2. Active Substance

Ocriplasmin, the active substance of Jetrea, is a truncated form of human plasmin (a protein naturally occurring in the eye) with retained protease activity. Other names are microplasmin or recombinant truncated human plasmin.

Ocriplasmin is a protein of 249 amino acid residues and consists of two peptide chains. The first peptide is 19 amino acid residues long and the second is 230 amino acid residues long (the peptide bond between the 19th and 20th amino acid has been cleaved during the activation step in the downstream process). The peptides are linked together by two disulfide bonds. Ocriplasmin does not contain O- or N-glycosylation or other post-translational modifications and has a molecular weight of 27 kDa.

Ocriplasmin is a serine protease that selectively cleaves peptide bonds located after a lysine or an arginine residue. Ocriplasmin is capable of cleaving many proteins, for example fibronectin, fibrinogen, collagen, laminin and gelatin. The ocriplasmin activity measured with physiological substrates like fibronectin, fibrinogen, collagen, laminin and gelatin showed comparable results with the proteolytic activity of human plasmin.

Manufacture

The recombinant protein ocriplasmin is produced in a methylotrophic yeast (*Pichia pastoris*) production system in the form of the inactive zymogen precursor microplasminogen. The protein is recovered and purified by chromatography steps using orthogonal separation modes. Microplasminogen is then activated to an active protease (ocriplasmin). The purified ocriplasmin is formulated in the drug substance buffer, filtered, aliquoted in bottles and stored frozen.

The manufacturing process comprises several stages: The upstream process involves inoculum preparation , seed fermentation, production fermentation and dilution. The downstream process involves purification of microplasminogen by chromatography. These steps serve to reduce the levels of process and product related impurities, including host cell proteins and DNA, prior to the activation step. Following activation ocriplasmin is further purified before concentration The purified ocriplasmin is formulated, diluted and then filtered before final filtration) to ensure microbiological quality, aliquoted in bottles and stored frozen *MCB and WCB*

Establishment of the production cell line has been described in detail, including plasmid construction, transformation of the yeast strain and selection of the producer clone. The best producer was selected to produce a pre- Master Seed which is stored at ≤ -65°C and used to generate the Master Cell Bank.

A description of the preparation of the cell bank used and the results of its testing was provided. The concept of a 2-tiered cell bank system was developed, in which 1 Master Cell Bank is used

to generate Working Cell Banks (WCBs). The MCB and WCB characterization testing has confirmed identity, purity and suitability of the cell banks. The DNA sequence codes for the correct amino acid sequence were confirmed by DNA sequencing. No rearrangements, deletions, or insertions within the protein-coding DNA sequence were detected in the MCB, WCBs or in an extended *in-vitro* cell age from MCB thaw. A comprehensive characterization of the research cell, MCB and WCB is presented, and the procedure for qualification of future WCBs is defined. The genetic stability in the production of microplasminogen has been confirmed in the extended generation study and subsequent genetic consistency testing.

Manufacturing Process Controls

Process performance is controlled and evaluated by use of in-process controls (IPCs), critical in-process controls (CIPCs) and critical operating parameters (COPs). Data of critical and non-critical operational parameters and IPC monitoring has been shown for full scale conformance batches.

Process validation and/or Evaluation

Process validation and evaluation studies were conducted to determine optimized process parameters followed by the validation of the final intended ocriplasmin drug substance manufacture process. Initially, operational ranges for the ocriplasmin manufacturing process were claimed qualified according to design space principles. However, the process characterisation data, risk assessment approach and full scale process validation data were considered insufficient for such a claim. Moreover, the IPCs were, with a few exceptions, made on technical performance attributes only. Major objections were therefore raised against the design space claim and the control strategy. The applicant clarified that the use of the word design space in their dossier was misleading and that it had pursued a traditional approach to process control. Furthermore, a tighter control of quality attributes throughout the process has been implemented which resolved the major objection. Critical quality attributes have been appropriately appointed and outstanding concerns regarding the continued process verification protocol and IPCs have been addressed.

The Applicant has satisfactorily addressed concerns regarding microbiological control throughout the downstream process.

Characterisation

Biochemical characterization was made using batches of the various process versions of the drug substance manufacture. A series of biophysical and analytical characterization assays were performed to provide details of the structural and chemical properties of the protein. Parameters including protein sequence and disulphide bond formation, secondary structure and higher order conformation were characterised. Size properties, including the presence of cleaved or truncated variants and aggregates were determined. The extent of post-translationally modified forms including deamidated and oxidised species were determined and Ocriplasmin was shown to be non-glycosylated. In addition, the presence of process-related impurities has been determined.

Primary structure, Disulphide Bridge Sites, Secondary Structure, Higher-order Structure, Physicochemical Properties and Biological Activity were characterized by use of analytical methods that are considered state of the art.

Mass spectrometry and N-terminal sequencing were used for the structural determination. The expected primary structure could be confirmed for the main peak of the various analytical chromatography methods, however the data also revealed a great heterogeneity and

polydispersity of the substance. In general, the biochemical characterization, including elucidation of product related impurities is considered acceptable.

Biological activity

Ocriplasmin belongs to the serine protease family and its intended physiological action is to cleave proteins present in vitreous and vitreoretinal interfaces. Ocriplasmin cleaves the peptide bonds of proteins at the C-terminal side of lysine or an arginine residues. The proteolytic activity measurement is representative of the *in vivo* potency of the molecule. Proteolysis of the chosen substrate has been shown to correlate well with proteolysis measured with natural substrates. The biological activity of Ocriplasmin towards physiologically relevant and synthetic substrates (representing the in vivo potency) has been shown to be comparable with human plasmin.

Specification

The proposed release and stability specifications for Ocriplasmin drug substance comprise test attributes for:

- General Properties: appearance (by visual inspection), pH (Ph. Eur.) and osmolality
- Identity: Size and Epitope and Isoelectric Point;
- Purity and Impurities: Molecular Size Variants (by SDS-PAGE), Hydrophobic Molecular Variants (by RP-HPLC), Molecular Charge Variants (by CEX-HPLC) and Molecular Size Variants (by SE-HPLC);
- Process related impurities: Residual Host Cell Proteins, Residual Host Cell DNA ;
- Quantity: Protein Concentration (by UV 280 nm);
- Potency: Enzyme Kinetic properties;
- Other quality characteristics: Endotoxin (Ph. Eur.) and Microbiological quality / bioburden (Ph. Eur.).

Product related Purity and Impurities is assessed by quantitative limits for peaks of SDS-PAGE, SE-HPLC, RP-HPLC and CEX-HPLC. Thus, the heterogeneity is controlled by a variety of orthogonal analytical methods. The proposed commercial specifications are based on data from ocriplasmin batches utilising the mean±3 standard deviation approach. The proposed specifications have been tightened were appropriate

The analytical methods are described in sufficient detail adequately validated when necessary. In response to concerns raised regarding the validation of the potency assay at D120, the Applicant has changed the potency assay A major objection that was raised in relation to the new potency specifications (see drug product section) was resolved. Several other concerns regarding the potency assay validation have also been resolved.

Stability

Primary Stability results were obtained with the 3 Conformance batches of ocriplasmin drug substance using the commercial manufacturing process. The primary stability data is available up to 24 months storage at frozen storage conditions (-20°C±5°C) in addition to primary stability data at accelerated conditions In addition, the results of a photosensitivity study are available.

Ocriplasmin drug substance was shown to be quite stable at the proposed storage temperature of -20°C, up to 24 months.

Based on the primary stability data an expiry date of 24 months is supported for the drug substance when stored at -20°C±5°C.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Two standard approaches were considered in the development of the sterile injectable formulation i.e. a lyophilised sterile powder for reconstitution before injection and a sterile injectable solution for dilution immediate prior to injection. Either a lyophilized formulation or a solution for injection was used during the non-clinical and clinical development program. The lyophilized and liquid formulations both contain the same ingredients. In addition, the reconstituted lyophilized and the liquid formulations have the same quantitative composition. Therefore, all clinical and non-clinical studies were performed using the same qualitative and quantitative formulation. All Phase 2 and Phase 3 clinical studies were performed using the sterile solution for injection. The sterile solution for injection was also used for the primary stability batches.

The acceptability of the container closure system was supported by:

- Demonstration of the ocriplasmin drug product stability / compatibility with the primary packaging components
- Demonstration of the safety of the materials in direct contact with ocriplasmin drug product (compliance with USP and Ph. Eur. monograph requirements)
- Extractable study on rubber stoppers
- Demonstration of the suitability of the container closure system to guarantee container closure integrity.

Adventitious agents

TSE Compliance

A TSE declaration from the ocriplasmin drug substance manufacturer stating that no products of animal origin are directly used in the manufacturing of ocriplasmin drug substance is provided.

Viral Safety

Ocriplasmin drug substance is produced by a genetically modified yeast expression system, *Pichia pastoris* followed by separation of the active substance and purification through various chromatographic steps. Yeast fermentation does not support the propagation of viruses and therefore it is considered that there is no risk of contamination with viral adventitious agents as a result of the manufacturing process. Furthermore, there is no need to test the cell banks or the drug substance for contamination with mycoplasma species.

No raw materials of animal or human origin are used in the manufacture of ocriplasmin drug substance or drug product therefore it is considered that any risk of contamination with viral adventitious agents introduced by the raw materials or excipients can be excluded.

Manufacture of the product

The aseptic manufacturing process for Jetrea is a standard process consisting of compounding, in-line bioburden reduction and sterile filtration steps, aseptic vial filling, stoppering and capping.. All product contact materials in the ocriplasmin drug product manufacturing process are sterile and disposable. The process and equipment are well described. Critical steps are defined as those which have a direct impact on product quality attributes. Adequate in-process controls have been set and the process is appropriately controlled.

Process Validation and/or Evaluation

The data presented support the overall conclusion that product manufacturing process is robust and consistent. The process is acceptably validated.

Product specification

The proposed release and stability specifications for Jetrea comprise test attributes for:

- General Properties: appearance (by visual inspection), pH (Ph. Eur.), osmolality and Sub-Visible Particles (by particle count);
- Identity: Size and Epitope and Isoelectric Point;
- Purity and Impurities: Molecular Size Variants (by SDS-PAGE), Hydrophobic Molecular Variants (by RP-HPLC), Molecular Charge Variants (by CEX-HPLC) and Molecular Size Variants (by SE-HPLC);
- Quantity: Protein Concentration (by UV 280 nm);
- Potency: Enzyme Kinetic properties;
- Other quality characteristics: Uniformity of dosage unit (Ph. Eur.), Endotoxin (Ph. Eur.) and Sterility (Ph. Eur.).

The proposed drug product release and stability specifications are based on a statistical evaluation of the release and stability data for the drug product batches manufactured at the commercial manufacturing site using the mean±3 standard deviation approach. The analytical methods are described in sufficient detail and adequately validated when necessary.

The proposed specifications of product related Purity/Impurities are the same as for the drug substance, which reflects that ocriplasmin is stable Major objections were raised regarding the drug product specifications, which were set wider than the clinical batches. Specifications have now been narrowed as requested. A major objection was raised at Day 120, since the Applicant changed the potency assay. This major objection was cleared. Potency assay data from the clinical batches generated with the old method has been linked to the new method by side-by-side analyses. Specifications limits for the new potency assay have been set and justified by clinical qualification as well as on batch data, as requested.

The limits for sub-visible particles are set in accordance with the Ph. Eur. requirements for parenterals. However, considering that this product is intended for intra-vitreal administration, the applicant has, as requested, proposed new acceptance criteria for sub-visible particles

Extractable volume testing is not included in the drug product specification. This is acceptable, considering that the drug product will be diluted before use. The fill volume accuracy, which is of great importance to ensure accurate dosing, has been acceptably validated. Following dilution, the vials will contain 400µl for an IVT injection of 100µl. The potential risk for multiple dosing from one vial has been addressed in the SmPC, label and PIL. Moreover, trained user

testing has shown that it is not always possible to withdraw two 100µl doses. In conclusion, this potential problem has been acceptably addressed.

The reference standard used during routine control of ocriplasmin drug product is the same as that used for the routine control of ocriplasmin drug substance and is considered acceptable.

Stability of the product

The stability / compatibility of ocriplasmin drug product with the primary packaging components has been demonstrated through the stability program.

The applicant has supplied 18 months primary stability data. Primary stability data have been obtained for the three process validation batches of 2R ocriplasmin drug product manufactured using the commercial manufacturing process.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this medicinal product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

At the time of the CHMP opinion, there were no unresolved quality issues which could have an impact on the benefit/risk ratio of the medicinal product.

Non-clinical aspects

2.2.5. Introduction

Ocriplasmin, a recombinant human protein derived from the yeast *Pichia pastoris*, is a truncated form or fragment of human plasmin with retained protease activity.

Ocriplasmin is intended to release the VMA to attempt to restore normal anatomy with eventual recovery of visual function and relief of symptoms, using a minimally invasive and a less traumatic procedure compared to vitrectomy.

2.2.6. Pharmacology

There is no appropriate disease model for VMA which would allow investigating the non-clinical efficacy of ocriplasmin. The applicant has therefore presented a number of *in vitro, in vivo and ex vivo* publications and studies to support the use of ocriplasmin. The biochemical properties of ocriplasmin were investigated in vitro and the pharmacodynamic profile of ocriplasmin was evaluated in vivo and ex vivo in rat, guinea pig, rabbit, cat, porcine and human eyes.

Primary pharmacodynamic studies

An appropriate disease model for VMA to investigate the non-clinical efficacy of ocriplasmin towards symptomatic VMA is not available. The applicant has therefore presented a number of *in vitro*, *in vivo* and *ex vivo* publications and studies. The biochemical properties of ocriplasmin were investigated *in vitro* and the pharmacodynamic profile of ocriplasmin was evaluated *in vivo* and *ex vivo* in rat, guinea pig, rabbit, cat, porcine and human eyes. A summary of the pharmacodynamics studies used to support the use of intravitreal ocriplasmin is provided in the Table below.

Overview on the Primary Pharmacodynamic Studies Conducted with Ocriplasmin

Study Type	Study Description	Reference
Biochemical characterization of ocriplasmin	Enzymatic activity of ocriplasmin towards synthetic substrates (S-2304, S-2444), fibrin, fibrinogen; inhibition by α_2-antiplasmin *in vitro*	R04-TX-002
	Enzymatic activity of ocriplasmin towards S-2304, fibrinogen, collagen type IV, gelatin, laminin and fibronectin *in vitro*	R04-TX-003
Vitreolytic properties of ocriplasmin on porcine vitreous fluid	Dynamic properties of vitreous following ocriplasmin administration (*ex vivo* and *in vitro* investigations)	(R04-TG-001)
	Molecular biology of vitreolysis by ocriplasmin *ex vivo*	(Sebag, 2005)
	Effects of ocriplasmin on the vitreous structure, protein degradation, and dye diffusion *ex vivo*	(Gad Elkareem *et al.*, 2010b)
Multispecies investigations of posterior vitreous detachment (PVD) induction by ocriplasmin	Interactions of microplasmin with fibronectin and laminin at the vitreoretinal interface in rats *in vivo*	(Chen *et al.*, 2009)[1]
	Vitreous oxygen levels as affected by ocriplasmin-induced PVD in the rat, guinea pig and cat *in vivo*	(Quiram *et al.*, 2007a)
	Increased lens nuclear pO_2 levels by ocriplasmin-induced PVD in the rat, guinea pig, rabbit and cat *in vivo*	(Giblin *et al.*, 2009)
	Short and long-term effects of ocriplasmin-induced PVD in rabbit eyes *in vivo*	(Sakuma *et al.*, 2005)
	Effects of ocriplasmin on the vitreoretinal interface in porcine eyes *ex vivo*	(De Smet *et al.*, 2009)
	Effects of ocriplasmin on the vitreoretinal interface in cats *in vivo* and in human donor eyes	(Gandorfer *et al.*, 2004)

Ocriplasmin was able to reduce particles in the vitreous; this has been demonstrated following application of ocriplasmin to the vitreous of the porcine eye. This led to a breakdown of vitreous macromolecules and to partial liquefaction and appears to be a dose-dependent vitreolytic effect (at a dose range of 12.5 to 800 µg/eye). The enzymatic effect of ocriplasmin on the vitreous was similar to that of plasmin, however its effect appears to be present for a longer period of time compared to plasmin and it is agreed that this may be due to a more rapid penetration because of the smaller size of protein (27 kDa) compared to plasmin (83 kDa).

The studies presented confirm that after an injection of microplasmin or ocriplasmin in rats, guinea pigs, rabbits, cats and post-mortem pig and post-mortem human eyes, that ocriplasmin can induce posterior vitreous detachment. Signs of continuing mild inflammation such as presence of vitreous cells were observed in rabbit and monkey studies. Considering the proposed mode of action (proteolytic activity against fibronectin, laminin, collagen) of ocriplasmin, the role of possible drug related inflammation in liquefaction was further discussed by the Applicant. It is suggested that fibronectin degradation products could secondarily contribute to posterior vitreous detachment (PVD) and / or liquefaction of the vitreous through the stimulation of inflammatory mediators and monocyte chemoattraction. Vitreous cells appear within days after administration of ocriplasmin, which is consistent with a possible

contribution of fibronectin degradation products. Although secondary effects of e.g. fibronectin degradation products cannot be ruled out the significance of these effects in clinical practice is difficult to conclude upon. In vivo pharmacodynamics has been adequately described.

The rationale of dose based on µg of protein was provided and summarised enzyme activity across various batches of ocriplasmin. Considering the use of µg protein for dosing and demonstrating comparable protein activity across batches, it is considered that this has been adequately addressed in the Applicant's response.

Secondary pharmacodynamic studies

The secondary pharmacology studies submitted in the application were performed to support the use of ocriplasmin for cardiovascular indications, and were considered by the CHMP as not relevant for this marketing authorisation application, due to the rapid degradation of ocriplasmin once intravitreally injected.

Safety pharmacology programme

A single GLP safety pharmacology study was performed with ocriplasmin that examined cardiovascular, respiratory and haematological endpoints. This study was conducted in compliance to ICH S7a and used male Beagle dogs. No changes were seen in the low dose group of animals (0.15 mg/kg). Prothrombin time was increased and fibrinogen was decreased in animals treated with 1.5 mg/kg and this was more significant in the high dose group (15 mg/kg). The high dose exceeds the anticipated active systemic dose of 4 mg/kg by 3.5 times and several haematological (increases in red blood cell count, haemoglobin, and haematocrit), cardiovascular (increase in Q-T interval, Q-TcV interval, heart rate and diastolic and systolic blood pressure) and respiratory (decreased tidal volume) effects are seen that demonstrate exaggerated pharmacology and doses administered are well in excess of the anticipated clinical exposure.

Intravenous administration of ocriplasmin at doses of 2, 6 or 10 mg/kg to male Sprague Dawley rats had no significant effects on the general behaviour of the male rat.

In two studies to examine the effect of ocriplasmin on the vitreoretinal interface in cats and rabbits revealed that intravitreal administered ocriplasmin was well tolerated at doses up to 9 µg/ml vitreous volume in feline eyes. In rabbit eyes there were transient ERG changes at doses of 60 and 119 µg/ml, however these were reversed (at 60 µg/ml after 14 days) or reversing (at 1189 µg/ml after 90 days).

No specific concerns are raised in safety pharmacology for the intravitreal use of ocriplasmin.

Pharmacodynamic drug interactions

Ocriplasmin **pharmacodynamic drug interactions** were studied in rabbits. There were no adverse effects, but an increase in initial retinal penetration of bevacizumab was observed by light microscopy. In addition, analyses of plasma from humans and animals revealed that ocriplasmin administrated intravenously at doses up to 4 mg/kg did not freely circulate in the blood due to the presence of serine protease inhibitors (as also discussed in the Clinical section). Consequently, any ocriplasmin in plasma is expected to be inactivated by serine protease inhibitor α2-antiplasmin at the clinical exposure dose, and systemic interactions are not anticipated.

Pharmacodynamic drug interactions between ocriplasmin and topical anaesthetic and antimicrobial agents administered as eye drops were not specifically investigated, as interaction of ocriplasmin with topical drugs is expected to be very limited: ocriplasmin is injected intravitreally, and it is expected that there would be minimal direct contact with topically administered drugs. In general, only a small amount of topically administered drugs are absorbed into the vitreous humour. It is also expected that due to the selectivity of ocriplasmin and given the chemical nature of anaesthetic, antimicrobial and antifungal therapies, or commonly used preservatives in eye drops, the pharmacodynamics of these drugs, even if injected intravitreally, are not expected to be affected by the presence of ocriplasmin (Packer et al., 2011; Riddell et al., 2011). The CHMP considered this acceptable.

2.2.7. Pharmacokinetics

The non-clinical pharmacokinetic (PK) profile of ocriplasmin was determined following intraocular and intravenous administration to rabbit and porcine eyes as well as to porcine and human vitreous fluid.

In vitro investigations of single administration of ocriplasmin in PBS and porcine and human homogenised vitreous fluid demonstrated that ocriplasmin undergoes rapid degradation i.e. auto-proteolytic degradation similar to that described for plasmin. Due to the rapid degradation, *in vivo* pharmacokinetic/toxicokinetic investigations to support the safety and efficacy profiling of ocriplasmin for single-dose intraocular treatment of symptomatic vitreomacular adhesion were not conducted. The applicant demonstrated a similar rate of ocriplasmin degradation in human and porcine vitreous fluid in a clinical study following intravitreal injection of 125 µg ocriplasmin in 40 patients undergoing vitrectomy (study TG-MV-010).

The assessment of toxicokinetics after intravenous administration of ocriplasmin was conducted as part of the systemic repeated dose toxicity studies in rats and dogs.
The biological activity of ocriplasmin after intravitreal injection was determined using a bioassay. Ocriplasmin and IgG antibodies to ocriplasmin were determined using ELISA assays. Methods of analysis were validated from samples obtained from rats and dogs. The methods were considered to be suitably validated.

There were no specific non-clinical in vivo studies conducted to examine absorption, distribution, metabolism or excretion of ocriplasmin. There is negligible systemic exposure assumed following IVT administration of ocriplasmin and as it is expected to enter the endogenous protein catabolism pathway, ocriplasmin is expected to be rapidly inactivated via its interactions with protease inhibitor α2-antiplasmin or α2-macroglobulin.

In vitro investigations of ocriplasmin in PBS, porcine and human vitreous fluid demonstrated that ocriplasmin was inactivated in 2 phases. There is an initial rapid decline phase followed by a secondary phase. Ocriplasmin undergoes a concentration dependent auto-proteolytic degradation similar to that described for plasmin. A similar result was obtained when ocriplasmin was injected intravitreally ex vivo in post-mortem porcine eyes.

There were no specific non-clinical studies conducted to examine potential pharmacokinetic drug interactions with ocriplasmin following IVT administration. No systemic pharmacokinetic drug interactions are expected following intravitreal administration with ocriplasmin due to the rapid degradation following IVT injection.

The pharmacokinetics of intravenous ocriplasmin have been briefly addressed in order to support interpretation of intravenous toxicity studies that were submitted as part of the

non-pivotal toxicology documentation. An immunologically based method was used to determine ocriplasmin in plasma from rat and dog. The package was limited but acceptable, in view of the type of product, the route of administration and the rapid degradation of ocriplasmin.

2.2.8. Toxicology

A comprehensive number of toxicology studies have been conducted to support the safety review of ocriplasmin. In the single and repeat dose studies the toxicity of ocriplasmin administered IVT has been examined in Cynomolgus monkey. Further single dose IVT studies have been conducted in Dutch belted rabbits and Gottingen Mini-Pigs. Studies have also been undertaken to examine systemic effects of ocriplasmin using IV administration (Sprague-Dawley rats and Beagle dog). A justification for the choice of the species in toxicological studies has been provided.

Single dose toxicity

Single dose toxicity was examined in Dutch belted rabbits in three GLP compliant studies. Due to the size of the rabbit eye, the applicant has not performed their pivotal studies in this species. An earlier development batch of ocriplasmin was used. Administered doses ranged from 2.5 to 885 µg/eye (equivalent to 2.3 to 797 µg/ml vitreous volume); the anticipated human equivalent dose is 125 µg/eye or 29 µg/ml vitreous.

Attenuation of retinal vessels was observed in all doses, including 2.5 µg/eye, though this resolved during the 8 week recovery period. At higher doses this effect showed some evidence of reversibility in a number of animals though was persistent in more than 2 animals treated with >62.5 µg/eye ocriplasmin, even after 8 weeks recovery.

ERG changes were observed in all treated eyes except for 2.5 µg and were persistent in animals treated with 125 and 200 µg/eye even following 8 week recovery.

Lens subluxation occurred in 2 of 12 treated eyes of animals of the 50 µg group (45µg/ml), 1 of 6 eyes treated with 62.5 µg and 3 of 6 eyes treated with 200 µg. There was cupping of the optic nerve seen in one animal treated with 200 µg ocriplasmin that may be attributed to damage to lens zonules or due to increase IOP.

Inflammation and infiltration of cells into the vitreous was observed in all treated eyes, though varied in extent, persistence and severity with increasing dose. Effect was slight and transient at 2.5 µg early in study that was absent at end of 8 week recovery.

Cyclitis was observed in the highest two doses, 200 and 885 µg/eye.

Transient swelling of the eye was seen in eyes treated with 62.5 µg ocriplasmin, though this was also seen in control eyes.

Histological changes: retinal atrophy was observed in all dosed animals >50 µg/eye, though severity increased with increased dosage. From 50 µg/eye (45 µg/ml), accumulation of macrophages in the vitreous body of ocriplasmin treated eyes was observed. This appeared to be dose-related. Rabbit eyes treated with 2.5 µg/eye (2.37 µg/ml vitreous) were unaffected in each aspect, although eyes treated with 50 µg/eye there were signs of toxicity, most showed signs of reversibility during the recovery period except for inflammation.

Single dose toxicity was examined in Cynomolgus monkeys in three GLP studies. The studies performed are considered pivotal due to their administration to a relevant animal species. An earlier development batch of ocriplasmin was used in two of the studies. The third study was conducted to bridge a change of the drug substance and drug product manufacturers. Administered doses ranged from 1.5 to 200 µg/eye (equivalent to 0.81 to 108 µg/ml vitreous volume).

ERG changes were observed in all treated eyes except for eyes treated with 1.5 µg. There was evidence of recovery at 20, 25 and 125 µg/eye, although this was only partial in the high dose 200 µg/eye animals.

Lens subluxation was seen in the batch comparability study (570256) in 2/6 treated eyes (125 µg/eye), although no effect was seen in the second batch tested at the same dose. The issue of lens subluxation is discussed further down in this paragraph.

Inflammation and cellular infiltration: 2/3 of the eyes that received 200 µg had a red/closed eye and a constricted pupil. Constricted pupils were also seen in eyes treated with 25 and 125 µg ocriplasmin (14 and 68 µg/ml vitreous volume respectively. Infiltration of cells into the vitreous was observed in all treated eyes, and this varied in extent, persistence and severity, independently to dose and resolved over time. Anterior uveitis was observed at 125 µg/eye on Day 2 post-dosing but this resolved/was resolving by termination of study. All eyes injected with 1.5, 25 or 125 µg of ocriplasmin (0.81, 14 or 68 µg/ml vitreous volume, respectively) showed a dose-related reduction in intraocular pressure as compared to pre-treatment values but normalised by end of study. It is agreed that subconjunctive haemorrhage observed in eyes treated with ocriplasmin are assumed to be caused by the injection procedure as they are also present in control eyes.

Histological changes: retinal lesions were not detected in any of the animals receiving a single administration of 1.5 µg to 200 µg ocriplasmin/eye. Monkey eyes treated with 1.5 µg/eye (0.81 µg/ml vitreous) were unaffected in each aspect, affects such as inflammatory cell in vitreous/ERG changes were seen in doses of 25/125 and 20 µg/eye respectively, although these showed sign of reversibility. Lens subluxation was seen in doses greater than 75 µg/eye (41 µg/ml vitreous). Due to effects seen in each treatment group in monkeys, no accurate NOAEL can be established.

Toxicity in Göttingen Mini-Pigs was examined in two GLP single dose studies. An earlier development batch of ocriplasmin was used in one study, the other used GMP-grade ocriplasmin. Administered doses ranged from 5 to 125 µg/eye (equivalent to 2.4 to 61 µg/ml vitreous volume). There was no evidence of systemic toxicity after administration to male mini-pigs. There were no treatment-related deaths or effects on body weight or food consumption and there were no significant gross observations at necropsy, ERG or histopathological changes in the eye. There was an instance of slight lens subluxation in 1 eye at the highest dose, 125 µg/eye. A NOAEL was determined to be 100 µg/eye ocriplasmin (49 µg/ml vitreous volume).

The applicant has provided a tabulated summary of the findings from the single-dose toxicity study in animals following intravitreal administration of ocriplasmin. The figure for lens subluxation in monkeys also includes data from the repeat-dose intravitreal study (570221), following the first administration of ocriplasmin to the eye. This dose is still above the anticipated clinical dose, however the highest dose at which lens subluxation is not observed is 25 µg/eye (equivalent to 14 µg/ml) and therefore lower than the dose to be given in the clinic. The applicant discusses the presence of glycoproteins in fibres of the lens zonules and of collagen IV and fibronectin in the extracellular matrix around the zonules that may be targeting

by ocriplasmin. This may explain the presence of this effect. Considering that in the animal studies, the highest dose at which lens subluxation is not observed is 25 µg/eye (equivalent to 14 µg/ml), the applicant was asked to comment further on the potential risks of lens subluxation seen in the animal studies, and whether the lack of an adequate safety margin would have an impact on the clinical use of ocriplasmin.

The CHMP considered acceptable the explanation proposed by the applicant on the incidence of lens subluxation seen in the animal studies:

1) The volume of vitreous humour, a collagen containing gel, might influence the time in which, as well as the quantities of, active ocriplasmin reaches the zonula.

2) The physical size of eye and length of injection needle may also influence delivery location of ocriplasmin to the eye. The correct injection site location for intravitreal injection is smaller in animal species with smaller eye size. Injections which are too posterior risk retinal breaks while those that are too anterior may damage the lens.

3) All intravitreal injections may not be the same: they may not diffuse evenly throughout the vitreous cavity because of its macromolecular gel structure. Injections are likely further affected by variations in individual vitreous composition, such as vitreous liquefaction and lacunae formation (Asami et al., 2012). It was also shown that the most significant vitreolytic effect after intravitreal injection of ocriplasmin is in the immediate area of enzyme contact. With increasing distance from the site of bolus delivery of enzyme, efficacy is reduced (Gad Elkareem et al., 2010).

The above considerations may help to explain the incidence of subluxation observed in the different animal species; incidence in the smaller eyes of rabbit and monkey is higher than the incidence observed in the larger pig eye as well as the apparent non-dose related occurrence of lens subluxation in rabbits and monkeys. The higher vitreous volume and size in humans may also have had an influence in the low incidence in human subjects (2 lens subluxations observed from 820 patients administered ocriplasmin).

Systemic single dose toxicity was examined in rats dosed with ocriplasmin via IV infusion, at doses of 10, 25 and 40 mg/kg to both males and females. There was clear evidence of toxicity at 40 mg/kg, with a number of deaths. There was subdued behaviour and staggering for up to 15min post dosing in animals treated with 25 mg/kg ocriplasmin. No mortality or dose-limiting toxicities occurred after administration of single doses of 10 mg/kg.

Repeat dose toxicity

A single repeat dose study examining IVT administration of ocriplasmin was performed. Two doses were selected, 75 µg and 125 µg/eye, corresponding to 41 and 68 µg/ml vitreous volume. These two dosages exceed the anticipated clinical vitreal exposure (125 µg/eye, 29 µg/ml). Following IVT administration with ocriplasmin the major ocular finding was that of lens subluxation. This effect was seen in the single dose studies with rabbits and monkeys where the lowest dose in which this change was seen was 125 µg/eye in the Cynomolgus monkey (study 570256) with a GMP-grade batch of ocriplasmin. In this study changes were seen in both doses of ocriplasmin, at 125 µg this was seen 6 days after the first dose, increasing in number and severity on Days 27, 33/34, 41, 57, 70 and 83. This effect was previously discussed in the single dose studies and the possible proteolytic activity of ocriplasmin on the lens zonules. To further clarify the apparent increased risk of lens subluxation seen the GMP grade of ocriplasmin, compared to another GMP grade Batch (study 570256), the Applicant has provided

a summary of the cross-species comparison of observations of lens subluxation. Susceptibility of lens subluxation with an early development ocriplasmin batch showed that rabbit sensitivity was increased and that this was most likely due to reduced vitreal volume compared to pig and monkeys. The largest vitreal volume is found in the mini-pig, which had a single case of lens subluxation at 61 µg/mL vitreous volume.

Although the effect of subluxation was only slight in the lower dose group following the first injection, further increased effect was seen during the course of the study and following the second dose. One animal with slight lens subluxation had marked retinal detachment with hypertrophy of the retinal pigment epithelium and severe retinal vacuolation. In clinical studies, subluxation of the lens or lens instability was reported in 3 patients. One was thought to be caused by forward pressure from the vitreous tamponading agent post-vitrectomy and not related to posterior capsule / zonular integrity. The other two were observed at the time of vitrectomy. One case of lens subluxation was reported in an at risk premature male infant with extremely low birth weight and significant medical and ophthalmic issues, although it is noted that a marked improvement in the anatomy of the retina with retinal reattachment was seen. The same patient was given a second dose of ocriplasmin in the other eye and suffered no reported lens subluxation. The smaller eye volume of the premature infant, the larger ocriplasmin dose and the possible access of study drug to the zonules due to injection were considered to be possible cause of this finding. In the last case a patient experienced an adverse event of 'lens luxation' that was non-serious, mild in intensity and due to intraocular lens displacement by pressure from tamponading agent and unrelated to zonule integrity. There was also a level of inflammatory response characterised as inflammatory cells in the anterior chamber, uveitis, miosis and hazy fundus view seen in most treated eyes. Due to these findings a third dose of 75 µg was not administered. A NOAEL could not be established for this study due to the presence of multiple findings following one or two administrations of ocriplasmin, and at both 75 and 125 µg doses. It is also considered that due to the proteolytic activity of ocriplasmin, a risk of subluxation of the lens cannot be ruled out though this would be low in adults, but may present as a higher risk in premature infants. This potential safety concern is raised in the RMP and is highlighted in sections 4.8 and 5.3 of the SmPC.

A range of systemic toxicity studies were performed in rats and dogs to support the development of ocriplasmin for the treatment of acute ischemic stroke, and so administered doses of ocriplasmin are well in excess of the anticipated intravitreal exposure. These studies are therefore considered as supportive in the safety assessment for ocriplasmin. Ocriplasmin was well tolerated when administered every second day at of 2, 7 and 10 mg/kg (7 administrations in total) via an initial IV loading dose of 1, 3.5 or 5 mg/kg followed by a 1h infusion of 1, 3.5 or 5 mg/kg to rats. In Beagle dogs, the intravenous administration of ocriplasmin at doses of 2, 7 and 10 mg/kg/day every other day for 7 administrations were well tolerated. Plasma ocriplasmin concentrations increased with the increasing dose and upon repeat dosing the systemic exposure to ocriplasmin also increased. Fibrinogen and α2-antiplasmin levels increased with repeat dosing at all doses due to the pharmacodynamic effect of exposure to ocriplasmin.

Genotoxicity

The range and type of genotoxicity studies that are routinely conducted for pharmaceuticals are generally not applicable for biotechnology-derived products as it is unlikely that the administration of large levels of proteins would yield any useful results. Ocriplasmin is also unlikely to interact with DNA or chromosomal material.

Carcinogenicity

Standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals. This is in line with ICH S6 (R1) guideline for preclinical safety evaluation of biotechnology-derived pharmaceuticals. There is a need for standard carcinogenicity studies for products expected to be used clinically for over 6 months, but ocriplasmin is intended for single administration only.

Reproduction Toxicity

The absence of reproductive and developmental toxicity studies is justified by ocriplasmin characteristics and intended use.

Toxicokinetic data

Maximum plasma levels and systemic exposure showed great variability in rat and dog studies. In dogs, recorded exposures were generally much higher in males than in females. At the tentative NOAELs identified in intravenous studies the margins of exposure to the maximum possible systemic dose after one intravitreal administration seem sufficiently high to conclude that no systemic effects are to be expected after intravitreal administration

Ocriplasmin levels in 14 day intravenous rat study

Dose (mg/kg)	Cmax (ng/ml) (M, F)			AUC(0-τ) (ngxhr/ml)			tmax (hr)		
2	Day 1	645.1	724.0	Day 1	1817	1831	Day 1	3.25	1.75
	Day13	466.8	470.7	Day13	978	945	Day13	5.25	5.25
7	Day 1	3766	4381	Day 1	7783	8470	Day 1	1.50	2.25
	Day13	5210	4720	Day13	15647	9216	Day13	1.50	1.75
10	Day 1	5454	5152	Day 1	13063	14810	Day 1	1.50	1.50
	Day13	10214	10162	Day13	24982	17316	Day13	2.25	1.50

Ocriplasmin levels in 14 day intravenous dog study

Dose (mg/kg)	Cmax (µg/ml) (M, F)			AUC(0-τ) (µgxhr/ml)			tmax (hr)		
2	Day 1	10.13	5.32	Day 1	15.36	10.23	Day 1	0.50	0.50
	Day13	12.03	5.13	Day13	15.59	10.45	Day13	0.50	0.75
7	Day 1	61.78	25.01	Day 1	155.3	53.51	Day 1	1.38	0.50
	Day13	66.71	26.43	Day13	178.7	54.03	Day13	0.63	0.50
10	Day 1	11.4	10.69	Day 1	37.53	37.61	Day 1	4.00	4.50
	Day13	20.52	41.57	Day13	74.03	102.6	Day13	0.63	0.75

Local Tolerance

Local tolerance was investigated in a dedicated study in New Zealand White rabbits, administered a single paravenous injection of ocriplasmin in vehicle at a dose of 0.9 mg. Three animals were sacrificed 48 h after injection and another three on day 8. There was no evidence of compound-related local reactions following injection with any of the treatments. There were incidents of local irritation observed after injection although this can be attributed to the injection procedure and the low pH of the control item, rather than effects due to ocriplasmin. These effects were greatest 48 h after injection and were cleared 7 days after injection.

Other toxicity studies

Immunogenicity

Non-human product-related impurities related to *P. pastoris* host cell proteins and staphylokinase have the potential to cause immunogenicity. A study was performed using batch of ocriplasmin not used in the pivotal non-clinical studies, or during clinical development to assess immunogenicity of host cell protein content at the time.

Immunogenicity has been evaluated as part of the systemic toxicity studies conducted in rats and dogs. No antibodies were found in the rat study, this may be due to the short period between administration and sampling (7 days). In the dog, one sample tested positive for anti-ocriplasmin antibodies, although no adverse effects have been attributed to the presence of antibodies to ocriplasmin. During intravitreal administration to Cynomolgus monkeys, no immunogenicity measurements were taken and only a post-hoc analysis was undertaken. An increased level of events associated with an increased immune response can be seen. Immunogenicity would be expected in the animal studies due to the difference in sequence homology, and so its relevance for a human product is limited. Although no specific concerns for immunogenicity are raised for this single administration product, the applicant should also provide the data for immunogenicity measurements that appear to have been taken during study 662911 (rat).

2.2.9. Ecotoxicity / environmental risk assessment

The applicant provided a suitable justification for not performing an Environmental Risk Assessment (ERA) in line with the guidance from the "Guideline on the Environmental Risk Assessment of the medicinal products for human use" (EMEA/CHMP/SWP/4447/00). Ocriplasmin is a recombinant protein and is unlikely to result in significant risk to the environment. No further evaluation of ocriplasmin has been provided and this was considered acceptable.

2.2.10. Discussion on non-clinical aspects

The nonclinical documentation was designed to evaluate the pharmacology, pharmacokinetics, and toxicology of ocriplasmin in support of clinical intravitreal (IVT) treatment of symptomatic vitreomacular adhesion (VMA) including macular holes.

Studies and submitted publications were conducted in vitro (PD), in vivo and ex vivo. The biochemical properties of ocriplasmin were investigated in vitro and the pharmacodynamic profile of ocriplasmin was evaluated in vivo and ex vivo in rat, guinea pig, rabbit, cat, porcine and human eyes, and the scope of the studies is considered to be extensive. Signs of continuing mild inflammation such as presence of vitreous cells were observed in rabbit and monkey studies. Considering the proposed mode of action (proteolytic activity against fibronectin, laminin, collagen) of ocriplasmin, the role of possible drug related inflammation in liquefaction has been adequately discussed also in view of temporal relationships of PVD and ocriplasmin activity. As ocriplasmin is a proteolytic protein, dosing based on µg protein is sufficient to ensure a standardised biological activity and therapeutic effect. In this respect further discussion was provided where proteolytic activity of ocriplasmin batches was seen to be comparable and thus this can be excluded as source for the noted differences in ocular toxicity in monkeys.

The potential concomitant effects of ocriplasmin have not been examined by the Applicant as intravitreal dose is expected to be rapidly neutralised in vivo, which would negate the need to examine this further. Interaction of ocriplasmin with topical drugs is expected to be very limited as the ocriplasmin is injected intravitreally, and therefore it is expected that there would be minimal direct contact with topically administered drugs. In general, only a small amount of topically administered drugs are absorbed into the vitreous humour. It is also expected that due to the selectivity of ocriplasmin and given the chemical nature of anaesthetic, antimicrobial and antifungal therapies, or commonly used preservatives in eye drops, the pharmacodynamics of these drugs, even if injected intravitreally, are not expected to be affected by the presence of ocriplasmin.

The non-clinical pharmacokinetic (PK) profile of ocriplasmin was determined following intraocular and intravenous administration to rabbit and porcine eyes as well as to porcine and human vitreous fluid. The change in active concentration profile over time of active ocriplasmin was investigated in vitro in phosphate buffered saline pH 7.4 (PBS), porcine and human vitreous fluid as well as ex vivo in post-mortem porcine eyes. One of the porcine studies was conducted in accordance with the OECD Principles of Good Laboratory Practice (GLP). There were no specific non-clinical studies conducted to examine absorption, distribution, metabolism or excretion of ocriplasmin. There is negligible systemic exposure assumed following IVT administration of ocriplasmin and as it is expected to enter the endogenous protein catabolism pathway, ocriplasmin is expected to be rapidly inactivated via its interactions with protease inhibitor α2-antiplasmin or α2-macroglobulin. In vitro investigations of ocriplasmin in PBS, porcine and human vitreous fluid demonstrated that ocriplasmin was inactivated in 2 phases. There is an initial rapid decline phase followed by a secondary phase. Ocriplasmin undergoes a concentration dependent auto-proteolytic degradation similar to that described for plasmin. A similar result was obtained when ocriplasmin was injected intravitreally ex vivo in post-mortem porcine eyes. The degradation of ocriplasmin after addition to the supernatant of homogenised vitreous fluid appeared much slower than after injection ex vivo followed by homogenisation and determination of ocriplasmin. Biochemical properties specific for post mortem eyes may indicate uncertainties as to extrapolation of the degradation profiles to clinical conditions. There are no data on the natural substrates for ocriplasmin 2 to 24 hours post mortem. Potassium and phosphorous concentrations are known to increase with time postmorten. Recovery of active enzyme was not significantly affected at least for 6 hours. Overall, while no specific data on degradation profile dependence is available, at least for the 6 first hours no major differences would be expected.

A comprehensive number of toxicology studies have been conducted to support the safety review of ocriplasmin. In the single and repeat dose studies the toxicity of ocriplasmin administered IVT has been examined (Cynomolgus monkey). Further single dose IVT studies has been conducted in Dutch belted rabbits and Gottingen Mini-Pigs. Studies have also been undertaken to examine systemic effects of ocriplasmin using IV administration (Sprague-Dawley rats and Beagle dog). Discussion for the exclusion of rabbits and the inclusion for pig eyes has been given, justification for using the Cynomolgus monkey as a relevant animal species has been provided.

The Applicant has provided a summary of the cross-species comparison of observations of lens subluxation. Issues were first raised in the batch comparability study in monkeys (Study 570256) with GMP grade batches of ocriplasmin, where a variation in incidence of lens subluxation appeared linked to the batch of product administered. Susceptibility of lens subluxation with an early development ocriplasmin batch showed that rabbit sensitivity was increased and that this was most likely due to reduced vitreal volume compared to pig and

monkeys. The largest vitreal volume is found in the mini-pig, which had a single case of lens subluxation at 61 µg/mL vitreous volume. The Applicant reanalysed the activity data in the ocriplasmin batches. Batch variability in terms of protein activity may not be a cause of the variability in the susceptibility of lens subluxation in the monkey although this has not been clearly demonstrated by the Applicant in their response. However it is accepted that reduced vitreal volume may lead to increased incidence of lens subluxation, and that this would be greatly reduced in clinical practice with the higher human vitreal volume.

2.2.11. Conclusion on the non-clinical aspects

Although the package is limited in parts, the CHMP concluded that, due to the nature of the product, the route of administration, and the single use, the nonclinical profile is adequately characterised.

The potential risk for lens subluxation is highlighted in sections 4.8 and 5.3 of the SmPC.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID, Location	Design	Study Posology	Status, total no. enrolled, population	Primary Endpoint
Pivotal Phase III studies				
TG-MV-006 USA	**Phase III** Placebo-controlled, double-masked 6-month study	125µg or placebo injection	**Completed** (n=326) Patients with symptomatic VMA	o proportion of patients with nonsurgical resolution of focal VMA at Day 28
TG-MV-007 Europe & USA	**Phase III** Placebo-controlled, double-masked 6-month study	125µg or placebo injection	**Completed** (n=326) Patients with symptomatic VMA	o proportion of patients with nonsurgical resolution of focal VMA at Day 28
Completed Phase II studies				
TG-MV-001 Europe	**Phase II** Uncontrolled, ascending dose/exposure time, 6-month	Dose/time before vitrectomy: 25µg/1h; 25µg/24h; 25µg/7d; 50µg/24h; 75µg/24h; or 125µg/24h	**Completed** (n=61) Patients with VMT maculopathy	o Grade of PVD preoperatively and release of vitreomacular traction o Ease of induction of PVD o Extent and speed of resolution of macular oedema o Post-operative BCVA at 1, 2 and 4 weeks and 3 and 6 months.
TG-MV-003 USA	**Phase II** Placebo-controlled, dose-range finding, 6-month	25µg, 75µg or 125µg or placebo in the study eye	**Completed** (n=125) Patients undergoing vitrectomy for treatment of non-proliferative vitreoretinal disease	o Proportion of patients who achieved total PVD without creation of an anatomical defect (i.e. retinal hole, retinal detachment)
TG-MV-004 Europe	**Phase II** Sham-injection controlled, dose-range finding, 6-month	75µg, 125µg or 175µg or sham	**Completed** (n=61) Patients with VMT maculopathy	o Proportion of patients with total PVD
TG-MV-010 Belgium	**Phase II (PK)** Open label, ascending exposure time, 7-week	Dose/time before vitrectomy: 125µg/5-30min; 125µg/31-60min; 125µg/2-4h; 125µg/24h; 125µg/7d; no ocriplasmin treatment	**Completed** (n=38) Patients scheduled for vitrectomy	o Ocriplasmin activity level in vitreous samples obtained at the beginning of vitrectomy o Time necessary to remove the vitreous from the eye

Study ID, Location	**Design**	Study Posology	**Status, total no. enrolled, population**	Primary Endpoint
Supportive Phase II studies (ongoing or in different patient population)				
TG-MV-002 Europe	**Phase II** Sham-injection controlled, dose-range finding, 12-month	25µg, 75µg or 125µg or sham in the study eye	**Completed** (n=51) Patients with diabetic macular oedema	o Proportion of patients with total PVD
TG-MV-005	**Phase II** Sham-injection controlled, 12-month	125µg	**Ongoing** (planned n=100) Patients with wet AMD	o Proportion of subjects with release of focal vitreomacular adhesion by day 28
TG-MV-008	**Phase II** Open label, 6-month	125µg	**Ongoing** (planned n=30) Patients with focal vitreomacular adhesion	o Proportion of subjects with non-surgical resolution of focal vitreomacular adhesion at day 28
TG-MV-009	**Phase II** Placebo-controlled, 6-month	175µg	**Ongoing** (planned n=24) Infants and children scheduled for vitrectomy	o Proportion of patients with total macular PVD at beginning of surgery o Assessment of vitreous liquefaction o Immediate post-operative retinal/macular reattachment o Presence of proliferative vitreoretinopathy on follow-up o ROP classification on follow-up

In addition to the above studies, 4 studies with i.v. administration of ocriplasmin have been performed in indications like peripheral arterial occlusion, stroke and deep vein thrombosis. These are briefly addressed in the pharmacokinetic and safety section as they are not relevant for evaluation of efficacy in the current indication.

2.3.2. Pharmacokinetics

Jetrea is a product intended for single IVT injection. For a locally administered, locally acting product, with no or very low systemic exposure expected, intended for single use, the pharmacokinetic information is mainly used descriptively. Neither dose adjustments based on pharmacokinetic variability nor pharmacokinetic drug-drug interactions are expected.

Clinical pharmacology analyses on ocriplasmin were initially performed after intravenous (IV) administration, as ocriplasmin was originally developed as a thrombolytic agent for intravascular use. The development as a thrombolytic agent was terminated for commercial reasons (unrelated to safety) and intravitreal administration was tested for the induction of posterior vitreous detachment.

Systemic PK studies were done in 2 clinical trials with intravenous administration (TG-M-001 and TG-M-004). These were IV multiple dose studies that investigated the thrombolytic effect of ocriplasmin. PK and PD analyses were part of these systemic administration trials and were

included to obtain information on the systemic effect and safety. IV doses given in studies TG-M-001 and -004 were between 50 and 2000 times higher than the dose to be administered intravitreally. In these PK studies the ocriplasmin levels that were measured reflect both 'free' and 'bound' ocriplasmin (bound to α2-antiplasmin, and inactivated).

Ocriplasmin vitreous PK data following intravitreal injection are available from one trial (TG-MV-010). A final PK study (SR 10/mPl16/ItP) investigated the inactivation profile of ocriplasmin in human vitreous fluid, obtained from random vitrectomy patients.

TG-MV-010 was a Phase 2, open-label, ascending-exposure-time, single centre study to evaluate the PK properties of 125µg ocriplasmin administered as a single intravitreal dose at different time points prior to planned primary pars plana vitrectomy (PPV). A control group with no ocriplasmin injection prior to PPV was also included. The mean ocriplasmin activity levels decreased with time from injection. By 24 hours after injection, levels were below the lower limit of detection (<272 ng/ml) in 2 of 4 subjects, and by 7 days after injection levels were undetectable in all subjects.

No human metabolism or excretion studies were conducted, as it is expected that ocriplasmin enters the endogenous protein catabolism pathway through which it is rapidly inactivated via its interactions with protease inhibitor α2-antiplasmin (in vitro study R04-TX-002) or α2-macroglobulin (Gyzander and Teger-Nilsson, 1980).

Due to the very low likelihood of systemic availability of ocriplasmin after a single dose intravitreal administration, no systemic biodistribution studies after intravitreal injection were conducted.

The pharmacokinetic package for ocriplasmin is limited, but this reflects the nature of the product and the route of administration. Plasmin is an endogenous substance within the eye, and levels have been shown to increase with age, to an approximate level of 1.2µg/eye in subjects over the age of 50 years (Vaughan-Thomas et al. 2000).

Absorption and Distribution

Ocriplasmin is injected intravitreally. The systemic bioavailability after intravitreal dosing has not been assessed, and is not known. Even if the systemic bioavailability of the intravitreal dose was 100%, a plasma concentration of 35ng/mL would be expected (based on data from TG-M-001); this was below the lower level of quantification in plasma (2.5µg/mL).

Initial preclinical testing was performed with a lyophilised formulation; however, in all human trials a solution for injection was used. Adjustments to the manufacturing method were made during the development process. After completion of the Phase 3 studies, the process was scaled up to commercial levels. This is further discussed in the Quality Assessment Report.

Metabolism and Elimination

Metabolism and elimination of ocriplasmin have not specifically been investigated, but data has been presented showing that ocriplasmin is inactivated when it complexes with α2-antiplasmin or α2-macroglobulin. Levels of α2-antiplasmin in the plasma (1 nmol/mL) are more than sufficient to inactivate any ocriplasmin that reaches the systemic circulation.

The results of TG-MV-010, a small human PK study, show that when a 125 µg dose of ocriplasmin is injected into the eye its activity is negligible at 24 hours and immeasurable at 7 days.

Study SR 10/mPl16/ItP, an in vitro PK study conducted with human vitreous fluid samples, has several limitations that affect interpretation of the results for clinical practice. Firstly the vitreous samples were homogenised and centrifuged, with the supernatant being used for the experiment. Secondly samples from different donors were pooled together. However, the results do show a similar pattern of inactivation of ocriplasmin to that seen in study TG-MV-010, and demonstrate that its inactivation is described by a second-order reaction.

Dose proportionality and time dependencies

No information is available concerning dose proportionality of intravitreal administration of ocriplasmin, only the intended dose 125 µg has been studied.

In study **TG-M-001**, ocriplasmin was given intravenously at different dose levels. In the five groups receiving a fast infusion (15 minutes), the lowest dose group (0.1 mg/kg) resulted in drug levels below the level of quantitation, data for the other four groups indicated a more than dose proportional increase in AUC of the sum of free acriplasmin and acriplasmin/ α2-antiplasmin complex.

Infusion Dose [Ratio] ($mg.kg^{-1}$)	n	Adjusted Geometric Mean	
		Cmax [Ratio] ($ng.ml^{-1}$)	AUC(0-t) [Ratio] ($ng.h.ml^{-1}$)
F 0.5 [1]	4	12930 [1]	28190 [1]
F 1.0 [2]	4	28270 [2.19]	106900 [3.79]
F 1.5 [3]	4	30860 [2.39]	122100 [4.33]
F 2.0 [4]	4	42290 [3.27]	214100 [7.59]

Data presented in this table are located in Tables 14.2.2.1 and 14.2.2.2

The tendency to more than dose-proportional increase in exposure to the sum of ocriplasmin and acriplasmin/ α2-antiplasmin complex was observed, however, it is not relevant to the intravitreal route, where the dose is far below the doses studied intravenously.

The lack of dose-proportionality study of intravitreally administered ocriplasmin was considered acceptable since only one dose will be used for treatment.

- **Time dependency**

Not applicable since the product is for single administration.

Special populations

There is minimal information on the pharmacokinetics of ocriplasmin in special populations (ie, hepatic/renal impairment, elderly, different races), However, since the systemic exposure to ocriplasmin is negligible, this was considered acceptable.

Pharmacokinetic interaction studies

There is no information on systemic drug interactions. As the systemic exposure to ocriplasmin is negligible, this is acceptable.

The potential for local, ocular drug interactions is low, since only a single treatment is recommended, and ocriplasmin is likely to be active within the eye for little more than 24 hours.

2.3.3. Pharmacodynamics

Mechanism of action

Plasmin is a serine protease that mediates the fibrinolytic process and modulates the extracellular matrix. It hydrolyses a variety of glycoproteins, including laminin and fibronectin, both of which are present at the vitreoretinal interface and are thought to play a key role in vitreoretinal attachment. Plasmin does not degrade collagen type IV, a major component of basement membranes and the ILM.

Primary and Secondary pharmacology

Proof of concept studies were primarily performed in vitro or in animals. This was considered acceptable given the absence of biomarkers for an effect and the concerns with performing unnecessary intravitreal procedures in healthy volunteers. In several non-clinical studies plasmin and recombinant ocriplasmin were shown to be effective in inducing posterior vitreous detachment, resulting in a bare inner limiting membrane with few remaining collagen fibrils. These effects appeared to be dose-proportional.

No specific pharmacodynamic studies with ocriplasmin were performed. Three Phase II dose-ranging studies were performed; the results of these are discussed more fully in the efficacy section. Data regarding proof of concept from published studies in cadaveric human eyes were supplied by the applicant.

2.3.4. Discussion on clinical pharmacology

Clinical pharmacology data for intravitreal ocriplasmin are limited. In one study, intravitreal ocriplasmin was administered at various times prior to pre-planned vitrectomy. This study showed that the activity level of ocriplasmin in the vitreous decreased over time, becoming very low after 24 hours, and non measurable after 7 days. An in vitro study on human vitreous showed a comparable result.

The systemic bioavailability of intravitreal ocriplasmin is not known, but since the administered dose is low, and the product is rapidly inactivated both within the eye and in the systemic circulation, this was not considered of concern.

However, it cannot be excluded that ocriplasmin may target other intraocular structures containing fibronectin, laminin or collagen IV, e.g. the zonulae zinni of the lens as indicated in non-clinical studies as well as in patients with lens subluxation (see safety). It can also not be excluded that concomitant intraocular administration of other drugs may be affected by the enzymatic and proteolytic activity of ocriplasmin, and there could be a potential for direct interactions. However, the half-life of ocriplasmin is short and concerns would only be theoretical. Further, published data (see Non-Clinical section), indicated no direct effect on bevacizumab when administered IVT to rabbits one week after ocriplasmin-injections. On the other hand, an increased penetration of bevacizumab into the retina after intraocular injection of ocriplasmin, i.e. a potential for secondary interactions, was indicated from the preclinical studies. Since adhesion between the retina and vitreous often occurs in patients with age-related macular degeneration (AMD), the lack of data on concomitant use with VEGF-inhibitors is highlighted in section 4.4 of the SmPC. Vitreolysis may also lead to changes in the pharmacokinetic profile of other compounds given as IVT injections. However, neither

dose adjustments based on pharmacokinetic variability nor pharmacokinetic drug-drug interactions are expected.

The data in the dossier on the primary pharmacology of ocriplasmin are based mainly on published non-clinical studies, but do support the mechanism of action, hydrolisation of proteins at the vitreoretinal interface in a dose-dependent manner.

2.3.5. Conclusions on clinical pharmacology

The clinical pharmacology package for ocriplasmin, though limited, is sufficient to support the proposed mechanism of action and to demonstrate the pharmacokinetic profile after administration into the eye. The limited pharmacodynamic data raise no concern and no systemic interactions are expected due to the negligible systemic exposure. However, a risk for secondary proteolytic effects on other intraocular targets and a potential for secondary pharmacodynamic interactions due to this cannot be excluded.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

Three dose-response studies were performed in patients scheduled for vitrectomy with vitreomacular traction maculopathy or non-proliferative vitreoretinal disease, with doses of ocriplasmin ranging from 25 to 175µg.

TG-MV-001 was a small study which examined the effect of different doses of ocriplasmin given at different times prior to vitrectomy. Limited conclusions on the efficacy or dose-effect relationship of ocriplasmin could be drawn from this study, since the group sizes were small and the baseline characteristics of subjects varied widely. There was a suggestion of improved efficacy after longer exposure, with patients exposed to ocriplasmin for 7 days showing the highest response rate for induction of posterior vitreous detachment. Results for resolution of macular oedema and improvement in vision are difficult to interpret due to the differing baseline characteristics and the effects of surgery.

TG-MV-003 was a larger study (with approximately 30 patients per group) in patients scheduled for vitrectomy for non-proliferative vitreoretinal disease. Unfortunately, the baseline diagnosis varied widely amongst groups, with only half of patients in the 25µg group having VMT as opposed to nearly all in the 75µg group. Likewise the spread of macular holes was significantly different across the groups. However, with regard to the primary endpoint, a trend was observed for induction of PVD with increasing doses of ocriplasmin, suggesting a dose-effect relationship.

In study TG-MV-004 the effects of doses of ocriplasmin up to 175µg were assessed, with some patients in the 125µg group being exposed to two repeat doses.

In their initial assessment, the CHMP considered that the dose-response studies did not clearly show that the 125µg dose is the optimum dose level, since only 11 patients in a single study (TG-MV-004) received the higher dose of 175µg. In their answer, the applicant acknowledged the limited number of patients treated; however, the plateau of a dose-response relationship was found at 125µg and no further benefit for any of the outcome measures was observed with 175µg, with the potential of greater adverse events at this higher dose, as it was too close to the NOAEL in pigs. The CHMP therefore considered the choice of the 125 mg dose as acceptable.

2.4.2. Main studies

Two pivotal Phase III studies were conducted between December 2008 and June 2010. TG-MV-006 and -007 were multicentre, randomised, placebo-controlled, double-blind, 6-month studies investigating the safety and efficacy of a single intravitreal injection of 125 µg ocriplasmin in patients with symptomatic VMA.

The 2 trials were identical in design (except for allocation ratio of 2:1 in TG-MV-006 and 3:1 in TG-MV-007) and conduct (except for geography: TG-MV-006 conducted in the USA and TG-MV-007 conducted in the EU and USA).

Methods

Study Participants

Main Inclusion Criteria

- Male or female subjects aged ≥ 18 years
- Presence of symptomatic focal VMA (ie, central vitreal adhesion within 6 mm OCT 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 VA, or other visual complaint)
- BCVA of 20/25 or worse in study eye and 20/800 or better in the non-study eye

Main Exclusion Criteria

- Any evidence of proliferative retinopathy (including proliferative diabetic retinopathy (PDR) or other ischemic retinopathies involving vitreoretinal vascular proliferation) or exudative AMD or retinal vein occlusion in the study eye
- Subjects with any vitreous haemorrhage or any other vitreous opacification which precluded either of the following: visualisation of the posterior pole by visual inspection OR adequate assessment of the macula by either OCT and/or fluorescein angiogram in the study eye
- Subjects with MH diameter >400µm in the study eye
- Subjects with a history of rhegmatogenous retinal detachment in either eye
- Subjects who had laser photocoagulation to the macula, Aphakia , vitrectomy, uncontrolled glaucoma, high myopia (more than 8D) in the study eye at any time
- Subjects who had ocular surgery, laser photocoagulation treatment, or intravitreal injection(s) in the study eye in the prior 3 months
- Subjects with pseudo-exfoliation, Marfan's syndrome, phacodenesis or any other finding in the Investigator's opinion suggesting lens/zonular instability

Treatments

On Day 0, eligible subjects received a single intravitreal injection of 125µg ocriplasmin in the study eye using either a 30G or 27G size needle. Study drug was diluted with 0.75mL normal saline, and 0.1mL was injected into the mid-vitreous. The same dilution process was undertaken for subjects randomised to placebo injection.

Study drug was provided in glass vials containing 0.75mL of study drug (1.875mg ocriplasmin) as a frozen liquid. The quantitative composition of the product (1 vial) is provided in the table below. The placebo had the same components and concentrations, except that no ocriplasmin was included.

If at any point after 4 weeks from time of study drug injection, the underlying condition did not improve (ie, the adhesion was not relieved), the investigator could proceed to vitrectomy at his/her discretion. Additionally, if before this time, the BCVA in the study eye worsened by >2 lines, or the underlying condition worsened, the Investigator could proceed to vitrectomy at his/her discretion.

Although not ideal from an ethical view, from a methodological perspective, the CHMP considered that use of a placebo injection (rather than a sham injection) was acceptable, since it is possible that injection of a volume of 100µl fluid into the eye could cause detachment of the vitreous.

Objectives

The objective of these clinical studies was to evaluate the safety and efficacy of a single intravitreal injection of ocriplasmin 125µg in subjects with symptomatic VMA (ie, focal VMA leading to symptoms).

Outcomes/endpoints

The primary efficacy endpoint was the proportion of subjects with nonsurgical resolution of focal VMA at Day 28 post-injection, as determined by masked CRC OCT evaluation. The primary endpoint is also more simply referred to as VMA resolution at Day 28, since the CRC could not classify the response as a success unless VMA was completely absent. Any subjects who had a creation of an anatomical defect (ie, retinal hole, retinal detachment) that resulted in loss of vision or that required additional intervention were not counted as successes for the primary endpoint.

The applicant justified the choice of this endpoint as the objective of treatment of symptomatic VMA is to relieve tractional effects at the macula that may lead to loss of visual function. VMA resolution may also save the patient from the treatment burden of a vitrectomy. Vision might be restored if treatment is administered early enough (ie, before permanent damage ensues). VMA resolution focuses on the central 3mm radius around the macula, the most important part of the retina for sharp distance vision and close work. Advice was not sought within the EU on the choice of primary endpoint.

Secondary efficacy endpoints were:

- Proportion of subjects with total PVD at Day 28, as determined by masked Investigator assessment of B-scan ultrasound
- Proportion of subjects requiring vitrectomy
- Proportion of FTMHs that closed without vitrectomy as determined by CRC
- Achievement of $\geq$ 2 and $\geq$ 3 lines improvement in best corrected visual acuity (BCVA) without need for vitrectomy
- Improvement in BCVA

- Improvement in the National Eye Institute (NEI) 25-Item Visual Function Questionnaire (VFQ-25)

The effects of the following baseline characteristics were investigated in subgroup analyses: type of VMA (>1500µm versus ≤1500µm diameter), presence of ERM, presence of MH, width of MH (at level of retina and RPE), and vision.

Methods of Assessment

OCT

OCT was conducted at baseline in both eyes, and thereafter only in the study eye. The Stratus OCT (Zeiss Meditec) was mandatory for these studies. Spectral domain OCT (SD-OCT) machines (Cirrus or Spectralis) were used at selected investigative sites, in addition to the Stratus OCT. CRC assessment of VMA was based on Stratus OCT. However, at sites where SD-OCT was done in addition to Stratus OCT, subjects could be enrolled if VMA was clearly seen on SD-OCT but not on Stratus OCT. In these cases, the follow-up assessment was also performed using SD-OCT and success/failure of the primary endpoint was based on this assessment. OCT measurements were made by a certified assessor on subjects after dilation of the pupil. All OCT scans were submitted by the sites to the CRC, where all scans were evaluated using a set of categories. Focal VMA was defined by a subset of these categories. Success was defined as progression from any one of the categories in this first subset to any of the categories in another subset at Day 28.

OCT scans were also used to assess closure of FTMH.

Fluorescein angiography

Fluorescein angiography was conducted at baseline in both eyes, and at Month 6 in the study eye.

B-scan Ultrasound and PVD assessment

B-scan ultrasound was conducted at baseline in both eyes, and thereafter only in the study eye. B-scan ultrasounds were performed by a certified echographer after administration of anaesthetic drops in the subject's eye. The examination was performed directly on the conjunctiva. Transverse and longitudinal scans were taken to evaluate the fundus from the posterior pole to the limbus. Static images were obtained, and if appropriate equipment was available, video movies were also obtained for kinetic evaluation. Ultrasound images were assessed for the presence and grade of PVD. The assessments were documented on the following scale:

- 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

Visual Acuity

VA was evaluated at each study visit. VA was evaluated in both eyes at Baseline and in the study eye only at all other visits. Distance VA was measured using Precision Vision's (or equivalent) backlit Early Treatment Diabetic Retinopathy Study (ETDRS) charts set at 4 meters from the

subject. BCVA was reported as the number of letters read correctly by the subject on the ETDRS chart.

VFQ

The subject completed the VFQ-25 at Baseline and Post-Injection Month 6.

Sample size

Assuming a primary endpoint event rate of 27.5% in the 125µg dose group and 10% in the placebo group, a sample size of 320 subjects was planned to achieve over 90% power with a 2-sided alpha of 0.05.(according to the original randomisation ratio of 3:1).

Randomisation

Subjects were randomised centrally through a telephone-based IVRS to either ocriplasmin intravitreal injection or placebo. Study site personnel called the IVRS on the day of the subject's randomisation and were informed which vial number to use for the subject's injection. The original allocation ratio was 3:1 (ocriplasmin:placebo). This ratio was modified to 2:1 (ocriplasmin:placebo) in TG-MV-006 through Protocol Amendment 1.

Blinding (masking)

The Investigator, the study site personnel, representatives of ThromboGenics and Chiltern (contract research organisation) were masked to the study treatment throughout the study. Ocriplasmin and placebo were identical in appearance.

The randomised treatment for individual subjects was masked until after the final database lock. After all subjects completed or were withdrawn from the study, a masked medical review meeting was held to evaluate protocol violations and agree upon analysis populations. Subsequently, the database was locked, and unmasking was authorised.

Statistical methods

Analysis Sets

The Safety Set was the primary population for all safety analyses. It consisted of all subjects who received treatment with study drug (ocriplasmin and placebo).

The full analysis set (FAS) was the primary population for all analyses of Baseline/demographic and efficacy data. The FAS included all randomised subjects who received treatment with study drug (ocriplasmin and placebo). Data were analysed according to subject treatment group randomised, regardless of treatment actually received.

The population with second priority for assessment of the primary endpoint (VMA resolution at Day 28) was the modified FAS population, defined as all randomised subjects who received treatment with study drug and had symptomatic focal VMA to begin with at Baseline (ie, the FAS with exclusion of subjects with either no or undetermined focal VMA status at Baseline). Subjects without focal VMA at Baseline, by definition, had no possibility to be a success on the primary endpoint of VMA resolution. Therefore, this primary population was of secondary importance and was utilised to determine the most accurate point estimate of event rates in both the active and placebo groups.

The Per-Protocol Set included the FAS excluding subjects where a deviation was of sufficient concern to warrant exclusion. Decisions regarding data exclusion from the Per-Protocol Set were taken prior to unmasking the randomisation code (masked review) and documented appropriately.

Statistical Methodology

The primary endpoint was primarily evaluated using the FAS. The proportion of subjects meeting the endpoint was tabulated by randomised treatment group and the treatment groups were compared using Fisher's exact test. The two-sided 95% CIs for the difference between the 2 groups and the exact odds ratio were also calculated. In the event that statistical significance with $p<0.05$ was achieved for the primary endpoint for the FAS, the second priority was to determine the resolution of focal VMA in all randomised subjects who received treatment with study drug and had focal VMA at Baseline. This population was to be evaluated separately and excluded subjects with either no focal VMA or undetermined focal VMA status at Baseline.

The key secondary endpoint of this study was the proportion of subjects with total PVD at Day 28. The treatment groups were compared using Fisher's exact test. The two-sided 95% CI for the difference between the 2 groups and the exact odds ratio were also calculated. The analysis was performed with subjects with total PVD at Baseline included as failures (no total PVD) and repeated excluding subjects with total PVD at Baseline.

The formal statistical testing of the key secondary efficacy endpoint was to be evaluated if statistical significance ($p<0.05$) was achieved in the analysis of the primary efficacy endpoint for the entire FAS and the subset of the FAS with VMA at Baseline.

For each endpoint, the proportion of subjects meeting the endpoint was tabulated by randomised treatment group, and the treatment groups were compared using Fisher's exact test. The two-sided 95% CI for the difference between the 2 groups and the exact odds ratio were also calculated. The proportion of subjects with VMA resolution at Day 28 was also evaluated counting all cases as successes (not excluding subjects with retinal defects as specified in the analysis of the primary efficacy endpoint). The analysis was performed as specified for the primary analysis above.

The improvement from baseline in BCVA and VFQ-25 scores for treatment groups were compared using the Wilcoxon rank-sum test.

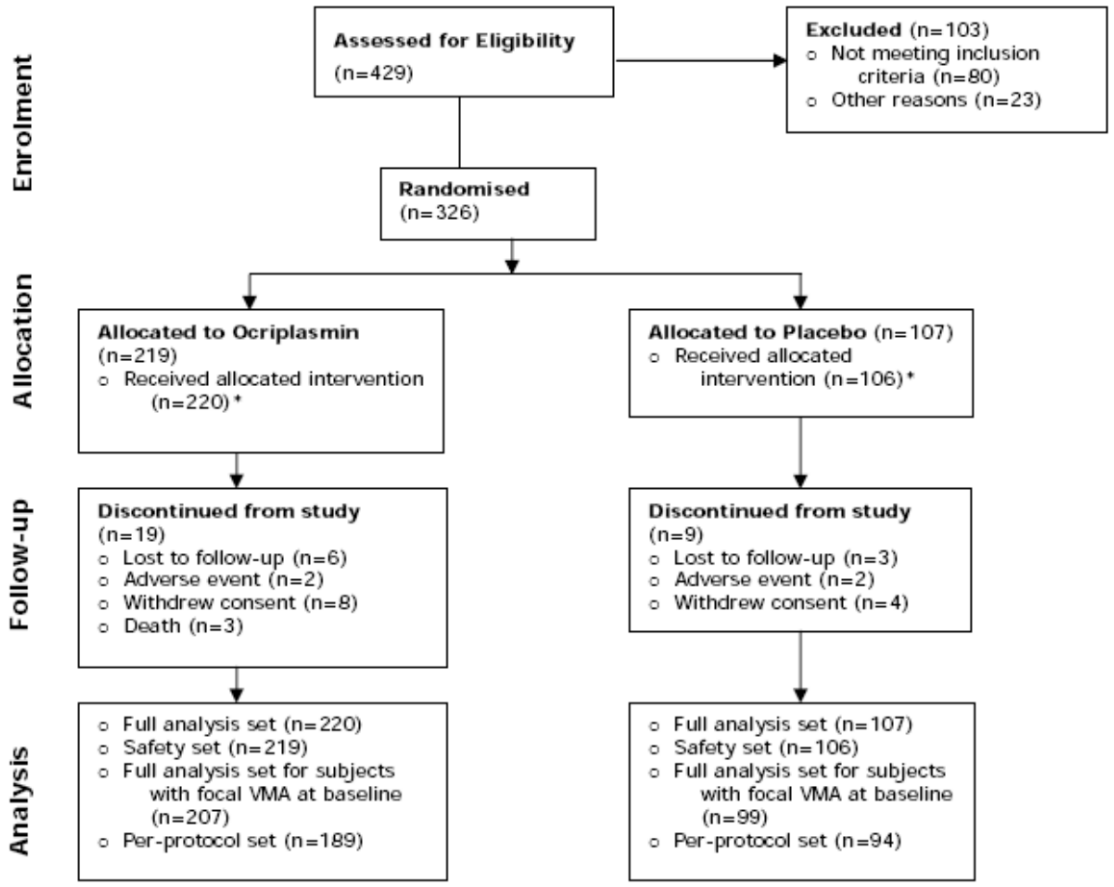
An interim analysis was not planned or performed. An independent DMC was used for evaluating potential safety issues regarding the study drug. The DMC reviewed masked data at pre-specified time points and as described in the DMC charter. There were no statistical analyses performed for the DMC.

The pivotal Phase 3 studies were analysed both individually and as an integrated dataset

Results

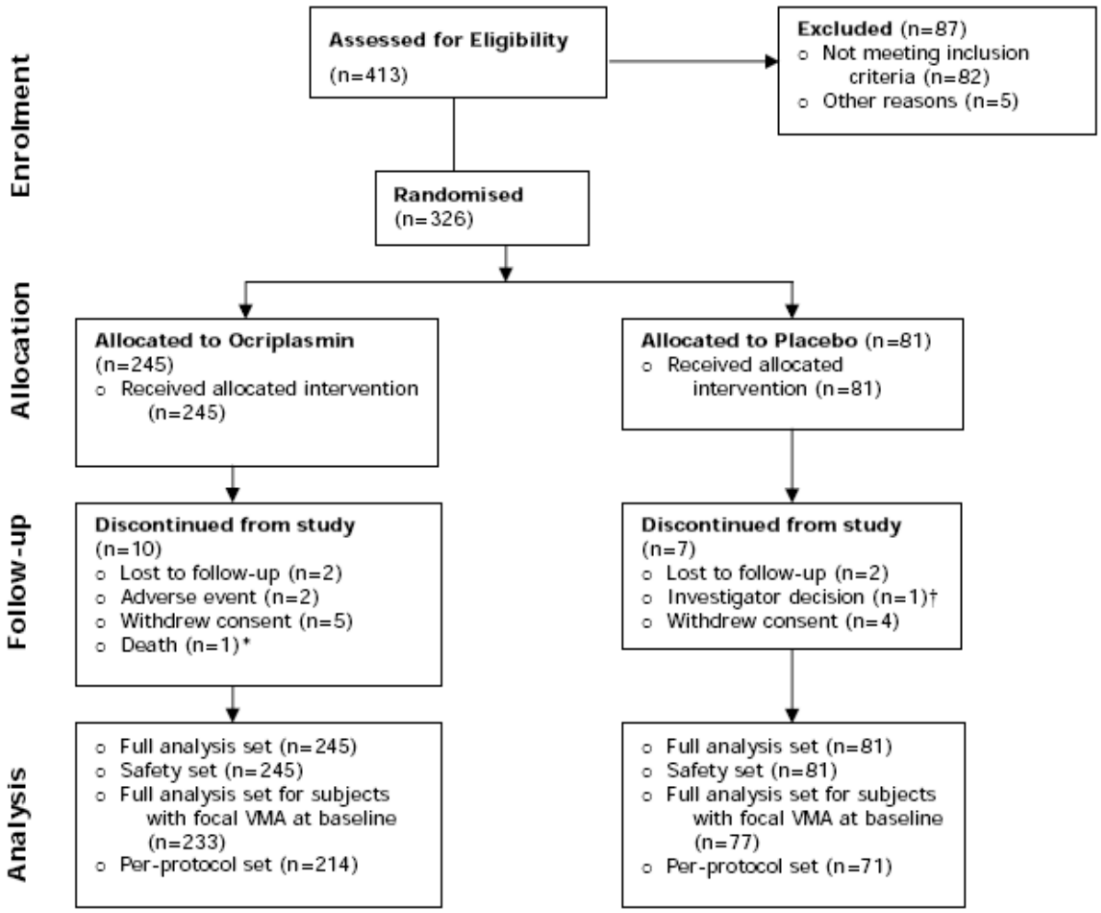
Participant flow

Participant flow TG-MV-006



* One subject inadvertently received study drug instead of the placebo allocated via randomisation

Participant flow TG-MV-007



* One subject discontinued the study due to metastatic brain cancer and subsequently died after study discontinuation. The subject is not counted as discontinuing due to death in this table.

† One subject withdrawn by investigator after vitrectomy

Reasons for discontinuation and screen failures, other than inclusion/exclusion criteria were provided within the clinical study report appendices, and did not raise any specific concerns.

The total amount of missing data is in general small. For TG-MV-006, the proportion of patients who withdrew and the reasons for withdrawal are the same across arms. For TG-MV-007 there were proportionally more withdrawals on placebo but as the numbers were small this was not a concern.

Recruitment

TG-MV-006: The first patient's first visit was on 23 December 2008, and the last patient's last visit was on 4 March 2010.

TG-MV-007: The first patient's first visit was on 22 December 2008, and the last patient's last visit was on 15 June 2010.

Conduct of the study

TG-MV-006

There was one protocol amendment applicable to all study sites (dated 29 Jan 2009):

- adjustment of the randomisation ratio from 3:1 to 2:1following discussion with the FDA (as a consequence, 55 subjects were randomised at 3:1 and 271 subjects were randomised at 2:1);
- requirement for reporting of all SAEs instead of just study drug-related SAEs to the DMC on an ongoing basis;
- amendment of fluorescein angiogram instructions to allow for alternate camera setting in cases where initially stated setting is not applicable.

TG-MV-007

There was one protocol amendment applicable to all study sites (dated 31 Jan 2009):

- Addition of exclusion criteria for women who were breast feeding
- To add "progression of the disease" as a potential withdrawal criterion
- To adjust the fluorescein angiogram instructions to allow for alternate camera setting in cases where initially stated setting is not applicable
- To document a minor change in procedure for sending images of fundus photography and fluorescein angiography exams

These changes to the protocols did not significantly affect the design or conduct of the studies.

Baseline data

Baseline Demographics and Disease Characteristics TG-MV-006

Characteristic	Treatment Group		
	Placebo (N=107)	Ocriplasmin (N=219)	Total (N=326)
Gender, n (%)			
Male	48 (44.9)	71 (32.4)	119 (36.5)
Female	59 (55.1)	148 (67.6)	207 (63.5)
Age (yrs)			
Mean (SD)	71.1 (10.04)	71.5 (10.25)	71.3 (10.17)
Median	70.0	72.0	71.0
Min, Max	24, 96	18, 93	18, 96
Race, n (%)			
White	97 (90.7)	195 (89.0)	292 (89.6)
Black	4 (3.7)	13 (5.9)	17 (5.2)
Asian	2 (1.9)	6 (2.7)	8 (2.5)
Other	4 (3.7)	5 (2.3)	9 (2.8)
Ethnicity, n (%)			
Non-Hispanic	98 (91.6)	204 (93.2)	302 (92.6)
Hispanic	9 (8.4)	15 (6.8)	24 (7.4)
Baseline Diagnosis, n (%) [a]			
FTMH	32 (29.9)	57 (26.0)	89 (27.3)
Vitreomacular Traction (Including DR)	75 (70.0)	162 (74.0)	237 (72.7)

Baseline Ocular Characteristics, n (%) [b]			
Epiretinal Membrane	35 (32.7)	86 (39.3)	121 (37.1)
Pseudophakic	29 (27.1)	91 (41.6)	120 (36.8)
Type (Diameter) of Focal VMA, n/N (%) [c]			
>1500µm	19/99 (19.2)	47/207 (22.7)	66/306 (21.6)
≤1500µm	74/99 (74.7)	145/207 (70.0)	219/306 (71.6)
Could Not Determine	6/99 (6.1)	15/207 (7.2)	21/306 (6.9)
Expected Need for Vitrectomy, n (%) [d]			
Yes	85 (79.4)	174 (79.5)	259 (79.4)
No	22 (20.6)	44 (20.1)	66 (20.2)
Missing	0	1 (0.5)	1 (0.3)
Total PVD at Baseline, n (%)			
Yes	0	1 (0.5)	1 (0.3)
No	107 (100.0)	218 (99.5)	325 (99.7)
BCVA (Letter Score)			
Mean (SD)	65.3 (9.83)	64.5 (10.86)	Not available
Median	67.0	67.0	
Min, Max	38, 82	20, 85	

Baseline Demographics and Disease Characteristics TG-MV-007

Characteristic	Treatment Group		
	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)
Gender, n (%)			
Male	25 (30.9)	79 (32.2)	104 (31.9)
Female	56 (69.1)	166 (67.8)	222 (68.1)
Age (yrs)			
Mean (SD)	70.2 (10.85)	72.6 (7.56)	72.0 (8.54)
Median	72.0	73.0	73.0
Min, Max	32, 97	23, 89	23, 97
Race, n (%)			
White	77 (95.1)	233 (95.1)	310 (95.1)
Black	2 (2.5)	10 (4.1)	12 (3.7)
Asian	2 (2.5)	2 (0.8)	4 (1.2)
Other	0	0	0
Ethnicity, n (%)			
Non-Hispanic (USA)	32 (39.5)	103 (42.0)	135 (41.4)
Hispanic (USA)	4 (4.9)	8 (3.3)	12 (3.7)
Not specified (non-USA)	45 (55.6)	134 (54.7)	179 (54.9)
Baseline Diagnosis, n (%) [a]			
FTMH	15 (18.5)	49 (20.0)	64 (19.6)
Vitreomacular Traction (Including DR)	66 (81.5)	196 (80.0)	262 (80.4)
Baseline Ocular Characteristics, n (%) [b]			
Epiretinal Membrane	33 (40.7)	98 (40.0)	131 (40.2)
Pseudophakic	24 (29.6)	81 (33.1)	105 (32.2)
Type (Diameter) of Focal VMA [c]			
>1500µm	22/77 (28.6)	55/233 (23.6)	77/310 (24.8)
≤1500µm	49/77 (63.6)	169/233 (72.5)	218/310 (70.3)
Could Not Determine	6/77 (7.8)	9/233 (3.9)	15/310 (4.8)
Expected Need for Vitrectomy, n (%) [d]			
Yes	67 (82.7)	222 (90.6)	289 (88.7)
No	14 (17.3)	23 (9.4)	37 (11.3)
Total PVD at Baseline, n (%)			
Yes	0	0	0
No	81 (100.0)	245 (100.0)	326 (100.0)
BCVA (Letter Score)			
N	80	245	Not available
Mean (SD)	64.9 (11.58)	63.4 (13.69)	
Median	66.5	67.0	
Min, Max	9, 82	8, 88	

BCVA=best-corrected visual acuity; DR=diabetic retinopathy; ETDRS=Early Treatment Diabetic Retinopathy Study; FTMH=full thickness macular hole; PVD=posterior vitreous detachment; SD=standard deviation; VMA=vitreomacular adhesion

[a] Based on Reading Center review of pre-treatment OCT. All cases other than FTMH were considered to be vitreomacular traction.

[b] Subjects could have had >1 baseline ocular characteristic.

[c] Percentages are based on subjects in the Full Analysis Set for subjects with focal VMA at Baseline.

[d] Yes/no answer for the question asked of the Investigator prior to randomization: "If no improvement in this patient's condition, do you think you would proceed to vitrectomy?"

The gender distribution of patients in both studies was consistent with the higher incidence of macular hole and PVD in women. The mean age of patients in both studies is 71-72 years. Literature data support an average age of late 60s, therefore the average age of subjects in the pivotal studies appears to be representative.

Although the condition has no known racial predilection, the overwhelming majority of subjects in both trials were white, probably representing the racial demographics of subjects in the regions of assessment. Section 4.2 of the SmPC contains a warning that experience is limited in groups other than Caucasians, and the RMP lists safety and efficacy information in populations other than Caucasians as 'Missing information', to ensure that the benefit-risk balance in these groups is discussed future PSURs.

The baseline mean visual acuity was similar between the studies and across the treatment groups, at around 65 letters (equating to 20/50 or 6/15). The expected need for vitrectomy differs by 9 percentage points between TG-MV-006 and -007, and notably in TG-MV-007 placebo-treated subjects were disproportionately more likely not to be expected to require vitrectomy, suggesting that they may have had significantly less severe disease. Given the unequal randomisation of 3:1 in this study, this may affect the power of this study to demonstrate an effect of active treatment over placebo. In keeping with this observation is the proportion of full thickness macular holes at baseline which was notably higher in patients in TG-MV-006 (particularly those in the placebo group). These findings limited the reliability of integrating the analysis of the results across the studies.

Numbers analysed

Analysis population: randomised subjects TG-MV-006

Data Set	Treatment Group		
	Placebo	Ocriplasmin	Total
Safety Set (N)	106 [a]	220 [a]	326
Full Analysis Set (N)	107 [a]	219 [a]	326
Full Analysis Set for Subjects with Focal VMA at Baseline, n (%)	99 (92.5)	207 (94.5)	306 (93.9)
Per-Protocol Set, n (%)	94 (87.9)	189 (86.3)	283 (86.8)

[a] One subject (Subject 631002) inadvertently received ocriplasmin instead of placebo. Therefore, the Safety Set deviates from the Full Analysis Set.
Note: Percentages for the analysis populations are based on the number of subjects randomized in each group.

Analysis population: randomised subjects TG-MV-007

Data Set	Treatment Group		
	Placebo (N=81)	Ocriplasmin (N=245)	Total (N=326)
Safety Set (N)	81	245	326
Full Analysis Set (N)	81	245	326
Full Analysis Set for Subjects with Focal VMA at Baseline, n (%)	77 (95.1)	233 (95.1)	310 (95.1)
Per-Protocol Set, n (%)	71 (87.7)	214 (87.3)	285 (87.4)

Outcomes and estimation

Primary endpoint: Proportion of Subjects with VMA Resolution in the Study Eye at Day 28

*Proportion of Subjects with VMA Resolution in the Study Eye at Day 28 without Creation of an Anatomical Defect (**TG-MV-006**)*

	Treatment Group		Difference (95% CI) [a]	p-value [b]
	Placebo	Ocriplasmin		
Full Analysis Set				
N	107	219		
n (%)	14 (13.1)	61 (27.9)	14.8 (6.0, 23.5)	0.003
Full Analysis Set for Subjects with Focal VMA at Baseline				
N	99	207		
n (%)	14 (14.1)	61 (29.5)	15.3 (6.1, 24.6)	0.004
Per-Protocol Set				
N	94	189		
n (%)	14 (14.9)	58 (30.7)	15.8 (6.0, 25.5)	0.004

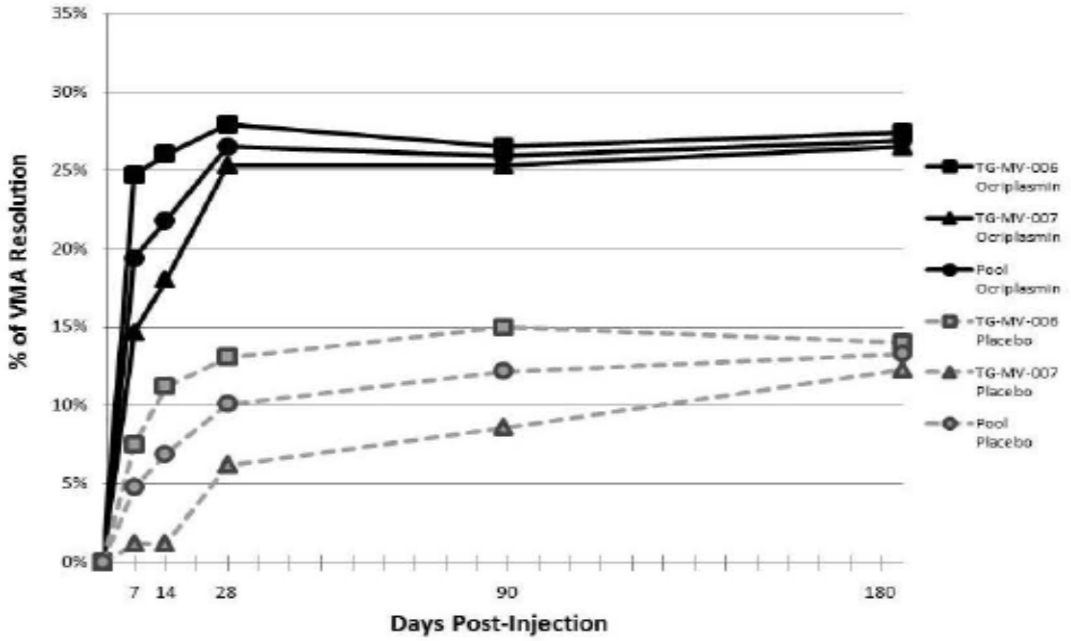
*Proportion of Subjects with VMA Resolution in the Study Eye at Day 28 without Creation of an Anatomical Defect (**TG-MV-007**)*

	Treatment Group		Difference (95% CI) [a]	p-value [b]
	Placebo	Ocriplasmin		
Full Analysis Set				
N	81	245		
n (%)	5 (6.2)	62 (25.3)	19.1 (11.6, 26.7)	<0.001
Full Analysis Set for Subjects with Focal VMA at Baseline				
N	77	233		
n (%)	5 (6.5)	62 (26.6)	20.1 (12.2, 28.0)	<0.001
Per-Protocol Set				
N	71	214		
n (%)	4 (5.6)	56 (26.2)	20.5 (12.6, 28.5)	<0.001

[a] The (absolute) difference and CIs between treatment groups are based on the percentage of successes.
[b] p-value is from Fisher's exact test, comparing placebo and ocriplasmin.

Sensitivity analyses conducted using worst case and observed case approaches for handling missing data showed similar results.

Proportion of Patients with VMA Resolution in the Study Eye (TG-MV-006, TG-MV-007 and Integrated Studies



A statistically significant difference was shown, in both studies, between ocriplasmin and placebo in the proportion of subjects achieving resolution of vitreomacular adhesion at Day 28.

This represents a surrogate endpoint for the prevention of the deterioration of vision. Its clinical relevance is not certain, but in this development programme it has been supported by the results on BCVA (see further discussion).

It is also noted that the placebo response rate was over twice as high in study TG-MV-006 than in study TG-MV-007. The explanation offered by the applicant for this is that subjects in TG-MV-006 had higher rates of macular hole, lower rates of ERM, and a higher proportion had VMA diameter ≤1500 µm at baseline (all factors which might enhance VMA resolution). Also, the response to treatment in TG-MV-007 was much slower than in TG-MV-006. The applicant argumented that placebo-treated patients in TG-MV-007 had baseline characteristics that made them less likely to achieve VMA resolution at Day 28 (i.e. lower proportion of patients in each of the following categories: age < 65 years, presence of FTMH, phakic lens status, absence of ERM, type (diameter) of VMA ≤ 1500µm). This finding, coupled with the small absolute number of placebo-treated patients in TG-MV-007 who achieved VMA resolution at Day 28 (n=5), likely contributed to the observed delay in time to effect in this treatment group.

These explanations were accepted by CHMP, but may imply that the characteristics of the patients in the two studies were different enough to limit the reliabilityof an integrated analysis of the results.

Resolution of VMA could also be in part attributable to the intravitreal injection procedure itself as indicated by the shape of the placebo response curves, which being non-linear. This suggests that the injection of vehicle caused a higher rate of VMA resolution (an objective, anatomic measure that should by its nature be free from a 'placebo effect') than would be expected in an untreated population. This is biologically plausible too, since the manipulation during the injection of fluid into the vitreous could be expected to increase the likelihood of posterior vitreous detachment and resolution of VMA.

The CHMP noted that the number of subjects with VMA resolution in the active group of TG-MV-006 decreased from 61 at Day 28 to 58 at Day 90. A similar occurrence is observed in the placebo group between Days 90 and 180. The applicant's response evidenced that the number of subjects initially classified as having VMA resolution and subsequently reclassified as a failure was larger than initially apparent. Resolution of VMA at Day 28 that is subsequently followed by a reclassification due to either technical error or vitrectomy for macular hole cannot be regarded as success. For ocriplasmin and placebo-treated subjects, the numbers reclassified in TG-MV-006 were 20 and 10, respectively. In TG-MV-007 the figures were 13 and 1, respectively. Most of these reclassifications were due to patients who initially had a resolution of their VMA, but subsequently underwent a vitrectomy for macular hole, and were therefore classified as failures. In the remaining cases (n=15), the reason for reclassification was due to technical limitations of the reading centre. A sensitivity analysis of those subjects who were not reclassified from success to failure during the study, resulted in a treatment difference of 14.5% at Day 28. This result is statistically significant, and of similar magnitude with regard to clinical relevance as compared with the result of the original analysis.

The Applicant also presented a reanalysis of the baseline OCT scans showing that the vast majority of subjects had objective evidence of macular pathology, most notably 'retinal deformity' or intraretinal cysts. Nearly 40% of subjects had an epiretinal membrane. This provided reassurance that the subjects in the study did have a pathological condition which could be shown objectively to be causing a disruption of the macula. The indication initially applied for (*"treatment of symptomatic vitreomacular adhesion (VMA)")* was therefore amended to: *"treatment of vitreomacular traction (VMT)"*. This indication is more consistent with the results of the pivotal studies, which primarily demonstrated resolution of traction rather than resolution of symptoms.

Secondary endpoints

- Proportion of subjects with total PVD at Day 28

The proportion of subjects achieving total PVD by Day 28 after ocriplasmin injection was around 10 percentage points higher than the proportion receiving placebo. Although the p-value for this is low, demonstrating a statistically significant difference between ocriplasmin and placebo, the effect size is not particularly large, ranging between 8 and 11%.

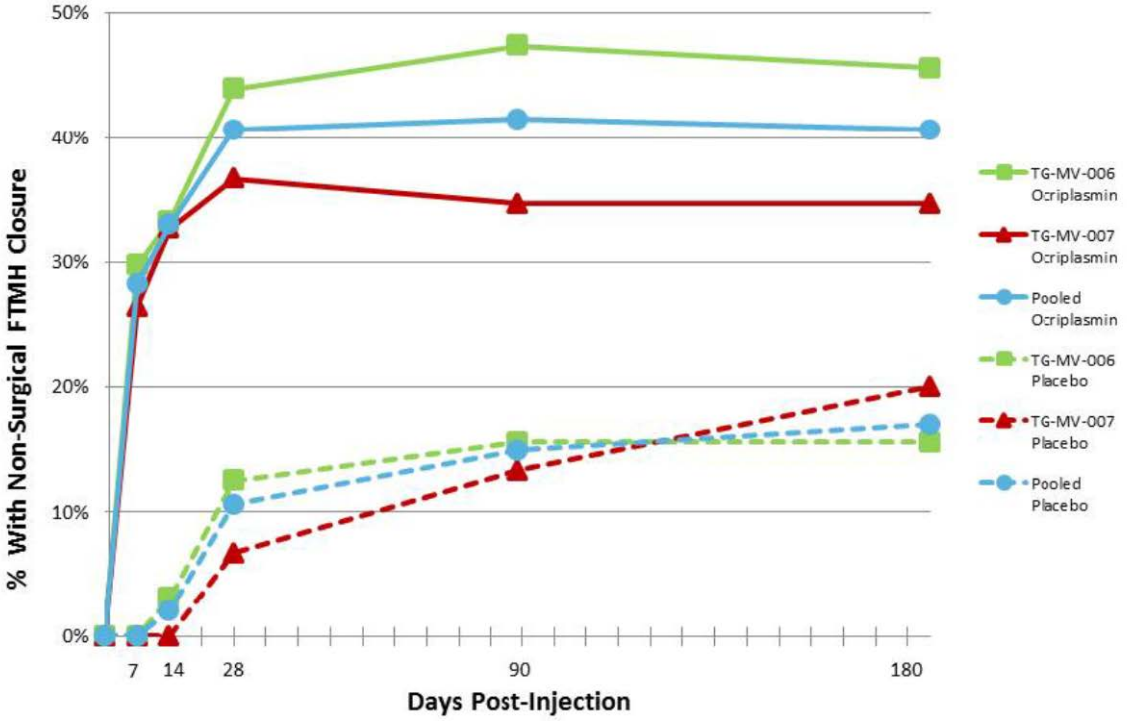
- Proportion of subjects receiving vitrectomy

In both studies the proportion of subjects requiring vitrectomy was lower in the ocriplasmin group than in the placebo group. However in neither study was this difference statistically significant, and the difference itself was small at about 8 percentage points.

The expected need for vitrectomy at baseline was higher in study TG-MV-007, particularly in the group assigned to ocriplasmin. However the proportion of subjects who ended up having a vitrectomy was, in fact, lower in this study. In particular, in the ocriplasmin-treated group 91% of subjects were expected to need a vitrectomy at baseline, but only 15% had undergone one by the end of the study.

The results for proportion of subjects receiving vitrectomy are to be viewed with caution, however, since vitrectomy was performed at the discretion of the treating ophthalmologist with no pre-specified criteria, and there may have been occasions where investigators deferred surgery until after the study. This could have introduced a bias.

- Proportion of Patients with FTMH at Baseline with Non-Surgical FTMHC by Study Visit

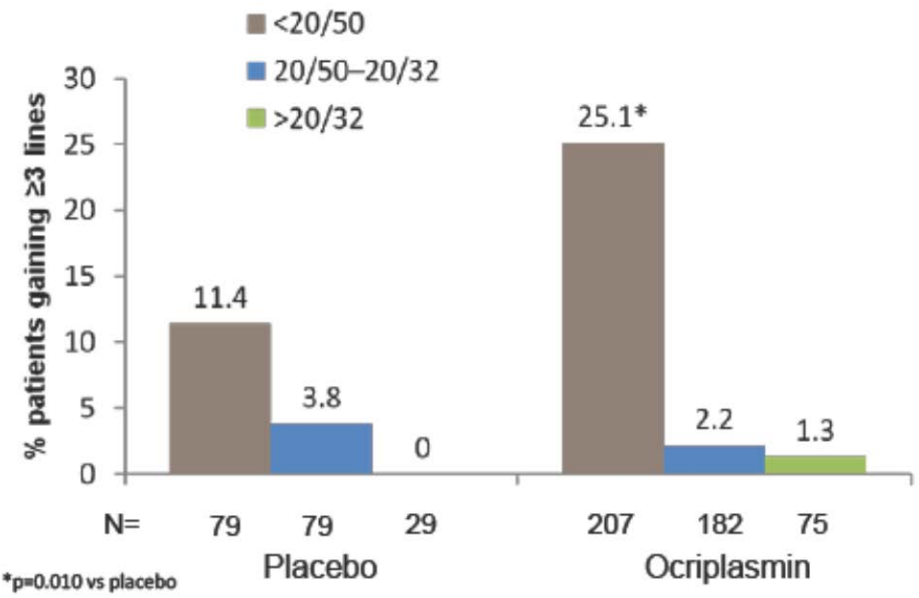


The proportion of subjects achieving non-surgical closure of their FTMH by Month 6 ranged between 35 to 45% in the two studies. This compares to closure rates of around 90% after vitrectomy with inner limiting membrane peeling. A difference of 30 percentage points was observed in both studies between ocriplasmin and placebo in the proportion of subjects achieving closure by Day 28. In study TG-MV-007 the statistical significance of this result is not clear (since there was no accounting for multiplicity in the secondary endpoints) and the difference becomes less impressive at Month 6 in study TG-MV-007, mainly due to an increase in the placebo response rate, and smaller group sizes. In the per protocol set the difference is comparable.

- Achievement of ≥2 and ≥3 lines improvement in best corrected visual acuity (BCVA) without need for vitrectomy

The CHMP considered that the endpoint "proportion gaining ≥2 or 3 lines of vision" is to be treated with some caution, since the mean level of vision at baseline was fairly good in both studies and so the potential to gain 2 or 3 lines of vision was limited. The proportion of subjects gaining 1, 2, and 3 lines of vision in the two studies (irrespective of whether they underwent vitrectomy) were analysed. The differences were small, however at month 6 a higher proportion of ocriplasmin-treated subjects had gained vision than those receiving placebo.

Proportion of Patients With ≥ 3-Line Improvement in BCVA at Month 6 Irrespective of Vitrectomy by Baseline BCVA (integrated studies)



The figure shows results for both studies together stratified by baseline vision; those with poorer baseline vision (<20/50, or <65 letters) appear to respond better to treatment with ocriplasmin, with a quarter gaining at least 3 lines of vision. The average visual acuity at baseline was around 65 letters.

- Improvement in BCVA

The results for the endpoint of mean change in vision from baseline are small, with subjects in both studies gaining only 2 to 3 letters after treatment, and no difference observed between active treatment and placebo. As mentioned above, however, this is not considered to be a particularly sensitive endpoint, since subjects generally had only a mild loss of vision at baseline.

Concerning the change in vision from baseline in the subsets of patients who achieved resolution of focal VMA (ie, success in the primary endpoint), or underwent a vitrectomy, in the ocriplasmin group, mean improvement from baseline in BCVA at Month 6 among patients who achieved VMA resolution was 8.8 letters in TG-MV-006 and 6.7 letters in TG-MV-007, compared to 1.4 and 2.6 letters among those who failed the endpoint. Improvement in visual acuity did correlate well with resolution of VMA which provides support for the clinical relevance of success in the primary endpoint, and suggested that those patients achieving resolution of vitreomacular adhesion at 1 month go on to benefit from improved vision at 6 months. Other symptoms of vitreomacular adhesion, such as metamorphopsia and micropsia, were not, however, assessed during follow-up.

In both studies the improvement in vision of subjects treated with ocriplasmin who did not undergo vitrectomy was in favour of ocriplasmin.

- VFQ-25

Ocriplasmin-treated subjects in both studies generally achieved numerically larger changes from baseline in subscale and composite scores of the VFQ-25.

Ancillary analyses

Subgroup analyses of the primary and selected secondary outcome variables were conducted by various baseline factors. Results for the primary endpoint are shown below.

Proportion of Subjects with VMA Resolution at Day 28 without Creation of an Anatomical Defect by Subgroup (**TG-MV-006**)

Subgroup	Placebo		Ocriplasmin		Difference (95% CI) [a]	p-value [b]
	N	n (%)	N	n (%)		
Age						
≥65 years	81	6 (7.4)	171	35 (20.5)	13.1 (4.7, 21.4)	0.010
<65 years	26	8 (30.8)	48	26 (54.2)	23.4 (0.7, 46.1)	0.086
Baseline ERM Status						
ERM present	31	0	80	6 (7.5)	7.5 (1.7, 13.3)	0.183
ERM absent	68	14 (20.6)	122	52 (42.6)	22.0 (9.0, 35.0)	0.002
Type (Diameter) of Focal VMA at Baseline						
>1500µm	19	0	47	4 (8.5)	8.5 (0.5, 16.5)	0.316
≤1500µm	74	14 (18.9)	145	53 (36.6)	17.6 (5.8, 29.5)	0.008
Baseline ERM Status and Type (Diameter) of Focal VMA						
ERM present with focal VMA >1500µm	12	0	30	0	0.0 (0.0, 0.0)	Not available
ERM present with focal VMA ≤1500µm	15	0	40	5 (12.5)	12.5 (2.3, 22.7)	0.308
ERM absent with focal VMA >1500µm	7	0	15	4 (26.7)	26.7 (4.3, 49.0)	0.263
ERM absent with focal VMA ≤1500µm	59	14 (23.7)	103	46 (44.7)	20.9 (6.4, 35.4)	0.011
ERM at Site of Focal VMA						
ERM present at site of VMA	25	0	65	5 (7.7)	7.7 (1.2, 14.2)	0.317
ERM absent at site of VMA	10	0	21	1 (4.8)	4.8 (-4.3, 13.9)	>0.999
FTMH Status at Baseline						
FTMH present	28	9 (32.1)	53	27 (50.9)	18.8 (-3.1, 40.7)	0.158
FTMH absent	71	5 (7.0)	154	34 (22.1)	15.0 (6.2, 23.9)	0.005
Expected Need for Vitrectomy at Baseline						
Vitrectomy expected	78	10 (12.8)	166	50 (30.1)	17.3 (7.1, 27.5)	0.004
Vitrectomy not expected	21	4 (19.0)	40	10 (25.0)	6.0 (-15.5, 27.4)	0.753

Proportion of Subjects with VMA Resolution at Day 28 without Creation of an Anatomical Defect by Subgroup (TG-MV-007)

Subgroup	Placebo		Ocriplasmin		Difference (95% CI) [a]	p-value [b]
	N	n (%)	N	n (%)		
Age						
<65 years	17	2 (11.8)	32	12 (37.5)	25.7 (3.0, 48.4)	0.096
≥65 years	64	3 (4.7)	213	50 (23.5)	18.8 (11.1, 26.5)	<0.001
Baseline ERM Status						
ERM present	31	1 (3.2)	93	10 (10.8)	7.5 (-1.3, 16.4)	0.289
ERM absent	45	3 (6.7)	135	49 (36.3)	29.6 (18.7, 40.5)	<0.001
Type (Diameter) of Focal VMA at Baseline						
>1500µm	22	0	55	2 (3.6)	3.6 (-1.3, 8.6)	>0.999
≤1500µm	49	4 (8.2)	169	56 (33.1)	25.0 (14.5, 35.4)	<0.001
Baseline ERM Status and Type (Diameter) of Focal VMA						
ERM present with focal VMA>1500µm	14	0	41	2 (4.9)	4.9 (-1.7, 11.5)	>0.999
ERM present with focal VMA ≤1500µm	14	1 (7.1)	47	7 (14.9)	7.8 (-9.1, 24.7)	0.668
ERM absent with focal VMA>1500µm	8	0	14	0	0.0 (0.0, 0.0)	----
ERM absent with focal VMA ≤1500µm	34	2 (5.9)	117	46 (39.3)	33.4 (21.6, 45.3)	<0.001
ERM at Site of Focal VMA						
ERM present at site of VMA	28	1 (3.6)	78	8 (10.3)	6.7 (-2.9, 16.3)	0.440
ERM absent at site of VMA	5	0	20	2 (10.0)	10.0 (-3.1, 23.1)	>0.999
FTMH Status at Baseline						
FTMH present	14	3 (21.4)	44	26 (59.1)	37.7 (11.7, 63.6)	0.029
FTMH absent	63	2 (3.2)	189	36 (19.0)	15.9 (8.8, 22.9)	0.002
Expected Need for Vitrectomy at Baseline						
Vitrectomy expected	63	4 (6.3)	210	57 (27.1)	20.8 (12.3, 29.3)	<0.001
Vitrectomy not expected	14	1 (7.1)	23	5 (21.7)	14.6 (-7.0, 36.2)	0.376

Several subgroup analyses were performed, e.g. evaluations of treatment effect by baseline characteristics and by success of endpoints. These analyses confirmed a reasonable consistency in most subgroups and there was generally a consistency in favour of ocriplasmin.

Subgroup analyses examining the effect of age on the primary and secondary outcome variables show that the efficacy in younger patients may be different, with much lower point estimates in both placebo and ocriplasmin arms in Study TV-MG-006 and higher rates in TG-MV-007. However there is still a clear separation from placebo for both age subgroups, and it is entirely plausible this was due to chance. CHMP concluded that the product is efficacious in both groups.

The effectiveness of ocriplasmin in inducing resolution of VMA or total PVD was markedly reduced in cases in which an ERM was present or the diameter of the focal VMA was >1500µm.

It was accepted that the group sizes were small, and that limited conclusions can be made on the statistical significance of these results. Given that the alternative for these patients is vitrectomy, which is also more complicated in these subgroups, that the risks of treating such patients with ocriplasmin do not appear greater than in the overall population, and that a single injection of ocriplasmin need not delay a subsequent vitrectomy if required, restricting use to patients without an ERM or with only small diameter adhesions did not appear warranted. Clinicians should, however, be adequately warned of this reduction in effect. A warning was added to Section 4.4, and a summary of efficacy data from subjects with an ERM or VMA diameter >1500µm was included in Section 5.1.

In patients who were expected at baseline to require a vitrectomy the effects of ocriplasmin on resolution of VMA were both numerically and statistically superior to placebo in both studies. Likewise, in those patients with a FTMH at baseline the effect size was greater.

It was demonstrated that success with regards to anatomical endpoints (VMA resolution, PVD and closure of macular holes) – independent of treatment arm - resulted in an increased VA, but differences between treatment arms were small.

The analyses also suggest that patients who are likely to require a vitrectomy (but not for an ERM), who have a smaller diameter focal VMA, a FTMH, and poorer baseline vision may benefit the most from ocriplasmin.

An analysis was conducted to compare the outcome of the main efficacy endpoints for the US and EU regions, and is tabulated below. In the studies, there were clear regional differences. With regards to non-surgical closures of FTMHs up to month 6, in the US centres, 44 and 15% of patients had macular hole closures in the active and placebo groups, respectively (difference 29%, 95% CI: 14.0; 44.9, p=0.001). In the EU centres, 2/7 (28%) and 7/25 (29%) had the corresponding closures in the ocriplasmin and placebo treatment groups (95% CI: -38.4; 37.2, p=0.977). Thus, there was no difference between groups from the EU region. However, this was due to a spontaneous closure in two patients in the placebo group and the limitations due to the small number of patients concerned are recognised.

Main efficacy outcomes by region. Studies TG-MV-006 (US) and TG-MV-007 (US and EU). FAS/LOCF

	US		EU	
	Placebo	**Ocriplasmin**	**Placebo**	**Ocriplasmin**
Primary endpoint - Non-Surgical resolution of VMA day 28 Table 2.1.1.7				
n/N (%)	17/143 (11.9)	92/330 (27.9)	2/45 (4.4)	31/134 (23.1)
Difference (95% CI), p	16.0 (8.8, 23.2), <0.001		18.7 (9.4, 28.0), 0.005	
Proportion of subjects with total PVD at Day 28 Table 2.2.1.2				
n/N (%)	7/143 (4.9)	53/330 (16.1)	0/45	9/134 (6.7)
Difference (95% CI), p	11.2 (5.9, 16.5), <0.001		6.7 (2.5, 11.0), 0.075	
Proportion of subjects requiring vitrectomy any time during study Table 2.3.7				
n/N (%)	43/143 (30.1)	61/330 (18.5)	7 (15.6)	21 (15.7)
Difference (95% CI), p	-11.6 (-20.2, -3.0), 0.007		0.1 (-12.1, 12.4), 0.985	
Proportion of baseline FTMHs that closed without vitrectomy day 28 Table 2.4.1.7				
n/N (%)	5/40 (12.5)	35/81 (43.2)	0/7	8/25 (32.0)
Difference (95% CI), p	30.7 (15.8, 45.6), <0.001		32.0 (13.7, 50.3), 0.089	
Improvement of ⩾2 lines in BCVA during study irrespective of vitrectomy Table 2.6.9				
Day 28, n/N (%)	13/143 (9.2)	62/330 (18.8)	3/45 (6.7)	17/134 (12.7)
Difference (95% CI), p	9.6 (3.3, 16.0), 0.009		6.0 (-3.2, 15.2), 0.269	
Month 6, n/N (%)	26/143 (18.3)	99/330 (30.0)	6/45 (13.3)	31/134 (23.1)
Difference (95% CI), p	11.7 (3.6, 19.7), 0.009		9.8 (-2.4, 22.0), 0.161	

The Applicant explained the differences in response rates between the EU and US regions, in terms of regional differences in baseline characteristics, characteristics that should be predictors of the outcome. To identify the predictors, the Applicant performed a number of multivariate logistic regression analyses. Even though some of these analyses seemed to support the Applicant's view, sufficiently firm conclusions could only be drawn if the predictors had been previously recognised to influence the outcome in the clinical setting(e.g. as macular holes leading to a higher risk of loss of vision), and not only on the basis of the study datasets (without much support from any external source).

However, as other than for the endpoint of need for vitrectomy, a modest but consistent treatment effect was shown for ocriplasmin in both studies and both regions, the CHMP considered this point solved

Summary of main studies

The following table summarises the efficacy results from the main studies supporting the present application. It should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trials TG-MV-006 & TG-MV-007

Title: Ocriplasmin: Investigation of Efficacy and Safety in Non Surgical Treatment Of Focal Vitreomacular Adhesion		
Study identifier	TG-MV-006, TG-MV-007	
Design	Randomised, double-blind, placebo controlled. TG-MV-006 USA; TG-MV-007 Europe & USA.	
	Duration of main phase: 6 Months	
Hypothesis	Superiority	
Treatments groups	Placebo	Placebo injection of vehicle, single dose, subjects randomised TG-MV-006 107, TG-MV-007 81
	Ocriplasmin	Injection of 125 µg ocriplasmin, single dose, subjects randomised TG-MV-006 219, TG-MV-007 245
Endpoints and definitions	Primary endpoint	Proportion of subjects with nonsurgical resolution of focal VMA at Day 28
	Secondary endpoint	Proportion of subjects with total PVD at Day 28
	Secondary endpoint	Proportion of subjects not requiring vitrectomy
	Secondary endpoint	Proportion of FTMHs that closed without vitrectomy
	Secondary endpoint	Achievement of ≥2 and ≥3 lines improvement in best corrected visual acuity
	Secondary endpoint	Improvement in BCVA
	Secondary endpoint	Improvement in VFQ-25
Database lock	TG-MV-006: 13 April 2010 TG-MV-007: 7 July 2010	

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat, Full analysis set				
Descriptive statistics and estimate variability	Treatment group	TG-MV-006		TG-MV-007	
		Placebo	Ocriplasmin	Placebo	Ocriplasmin
	Number of subjects	107	219	81	245
	Proportion of subjects with nonsurgical resolution of focal VMA at Day 28	13.1%	27.9%	6.2%	25.3%
	Difference (95% CI) p-value	-	14.8 (6.0, 23.5) p=0.003	-	19.1 (11.6, 26.7) p<0.001
Analysis description	**Secondary Analyses**				

Analysis population and time point description	Intent to treat, Full analysis set				
Descriptive statistics and estimate variability	Treatment group	TG-MV-006		TG-MV-007	
		Placebo	Ocriplasmin	Placebo	Ocriplasmin
	Number of subjects	107	219	81	245
	Proportion of subjects with total PVD at Day 28	6.5%	16.4%	0	10.6%
	Difference (95% CI)	-	9.9 (3.1, 16.7)	-	10.6 (6.8, 14.5)
	Proportion of subjects who received a vitrectomy (by end of study)	29.0%	20.5%	23.5%	15.1%
	Difference (95% CI)	-	-8.4 (-18.5, 1.7)	-	-8.4 (-18.6, 1.9)
	Proportion of FTMHs that closed without vitrectomy (by end of study)	15.6%	45.6%	20.0%	34.7%
	Difference (95% CI)	-	30.0 (11.9, 48.0)	-	14.7 (-9.5, 38.9)
	Achievement of ≥2 improvement in best corrected visual acuity (by end of study)	16.8%	30.1%	17.5%	26.1%
	Difference (95% CI)	-	13.3 (4.0, 22.7)	-	8.6 (-1.4, 18.6)
	Achievement of ≥3 improvement in best corrected visual acuity (by end of study)	8.4%	12.8%	3.8%	11.8%
	Difference (95% CI)	-	4.4 (-2.5, 11.2)	-	8.1 (2.3, 13.9)
	Improvement in BCVA from baseline (by end of study)	2.8	3.5	2.1	3.6
	Improvement in VFQ-25 composite score from baseline (by end of study)	1.2	3.5	-0.1	3.3

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant conducted an integrated analysis of pooled data from the pivotal studies. However, as discussed above, differences in the disease characteristics of subjects in the two studies at baseline suggest that an integrated analysis has some limitations. The conclusions of this assessment are based on the analysis of the two pivotal trials.

Primary and key secondary/supportive outcomes. Pooled Studies TG-MV-006 and TG-MV-007 (FAS)

Placebo	Ocriplasmin	Difference (95% CI)[a]	p-value[b]
N=188	N=464		
Primary endpoint: Nonsurgical Resolution of Focal VMA at Day 28			
19 (10.1)	123 (26.5)	16.4 (10.5, 22.3)	<0.001
Key secondary endpoint: Proportion of subjects with total PVD at Day 28			
7 (3.7)	62 (13.4)	9.6 (5.5, 13.8)	<0.001
Proportion of Patients who received a Vitrectomy in the Study Eye by Month 6			
50 (26.6)	82 (17.7)	−8.9 (−16.1, −1.7)	0.016
Non-surgical improvement of ⩾2 lines in BCVA during study Month 6[c]			
21 (11.2)	110 (23.7)	12.5 (6.6, 18.5)	<0.001

Clinical studies in special populations

No specific studies were carried out in special populations. Subgroup analyses for the primary and secondary efficacy variables investigated the effects of age, and are discussed above. The effects of hepatic and renal impairment, and race were not investigated in the pivotal studies.

Since the systemic exposure to ocriplasmin is negligible, the CHMP concluded that hepatic and renal impairment are not likely to affect its efficacy. The effects of race have not been considered, and further data collection is requested as part of the RMP.

Supportive study

The applicant has submitted the results of a dose-ranging study in patients with diabetic macular oedema (TG-MV-002).

Methods

This was a multicentre, randomised, sham-injection controlled, double-masked, dose-range finding study evaluating the safety and preliminary efficacy of single intravitreal injections of ocriplasmin 25µg, 75µg and 125µg over a 12-month period in patients with diabetic macular oedema.

The study was conducted between December 2006 and January 2010 at 11 centres in Belgium, the Netherlands, Italy, Spain and the UK.

- **Study Participants**

Participants were patients with diabetic macular oedema involving the centre of the macula with a macular thickness (in the central subfield on OCT) of greater than 275 microns in the study eye, no evidence of complete macular PVD, and BCVA of 20/32 or worse. Patients were excluded if there was evidence of macular fibrocellular proliferation or proliferative retinopathy.

- **Treatments**

In three successive cohorts patients received either an injection of 25, 75 or 125 µg ocriplasmin or a sham injection.

In total, 51 patients were treated; 8 patients were administered 25 µg, 15 patients were administered 75 µg, and 15 patients were administered 125 µg ocriplasmin; 13 patients received a sham injection.

- **Outcomes/endpoints**

Efficacy variables included the proportion of patients with total PVD, macular oedema resolution, change in BCVA, proportion gaining ≥2 or ≥3 lines of vision, and need for alternative therapy.

Results

- **Baseline data**

32 patients were male and 19 female. The average age was 64 years in the ocriplasmin groups and 70 years in the sham group. 78% of subjects had insulin dependent diabetes, and mean duration of diabetes was between 10 and 18 years. Regarding other baseline characteristics, subjects in the 125 µg group had notably better mean vision and lower macular thickness than those in the other groups.

- **Outcomes and estimation**

This small supportive study in patients with diabetic macular oedema failed to show a benefit of ocriplasmin over sham-injection at inducing PVD, reducing macular thickness, or improving vision. The applicant noted that a limitation of this study was the inconsistency in the evaluation of the B-scan ultrasound results by the central reading centre for the rating of PVD, potentially due to the fact that dynamic imaging was available to the local echographers but not to the CRC, i.e. the CRC only reviewed still images of the ultrasound findings.

This led to a different approach in TG-MV-006/ TG-MV-007. Since dynamic imaging of B-scan ultrasound is more reliable than still pictures read by a CRC, in the pivotal studies PVD assessment grading was determined by masked local echographers / Investigators using B-scan US machines, which allowed them to view the ultrasound images dynamically.

Discussion on clinical efficacy

The clinical efficacy program for ocriplasmin included three small Phase II dose response studies in patients scheduled to undergo vitrectomy for vitreomacular traction or non-proliferative vitreoretinal disease. TG-MV-001 showed evidence of an exposure-response relationship for ocriplasmin, with patients exposed to ocriplasmin for 7 days showing the highest response rate for induction of posterior vitreous detachment. TG-MV-003 and TG-MV-004 demonstrated a dose-response relationship, but provide only limited support for the 125 µg dose taken forward to Phase III, since only 11 patients in a single study received a higher dose of 175 µg.

Two pivotal Phase III studies with almost identical protocols have been presented to support the efficacy of ocriplasmin in the proposed indication of symptomatic vitreomacular adhesion including macular holes. The included population was fairly representative of the target population, however it would have been reasonable to include only subjects with an anticipated need for vitrectomy since a non-surgical resolution of the VMA is aimed for. In addition, it is not unlikely that VMA has a role in other retinal disease as in wet age related macular degeneration (AMD) and diabetic proliferative disease. These patients were excluded from the trial, however, a study in subjects with wet AMD is ongoing.

Initial concerns with the methodology of these studies, which may have limited the conclusions of efficacy have been resolved. Data presented during review of the application demonstrate that the patients recruited to the studies had objective evidence of macular disruption on OCT, in the form of intraretinal cysts in over three-quarters and an epiretinal membrane in over a third. Analyses presented by the Applicant provide reassurance that anatomical resolution of vitreomacular traction relates to an improvement in visual acuity. However, the absolute response to treatment was modest, with only around a quarter of subjects achieving resolution

of VMT. A range of secondary endpoints were assessed, including visual acuity, but no adjustments were made to control for multiplicity, so assessment of the statistical significance of these endpoints is limited. The statistical methodology is otherwise generally acceptable.

An appreciable number of patients (6%, 36/652), who were enrolled and treated, did not have evidence of focal VMA on the assessment of the OCT by the CRC at baseline, despite being diagnosed with VMT by the Investigator. It is a concern that potential recipients of ocriplasmin could be treated unnecessarily with an invasive procedure, which is widely accepted to carry a 1 in 1000 risk of site threatening complications. In order to minimise the potential for inappropriate treatment, section 4.2 of the SmPC advises clinicians on how to optimise diagnosis and avoid unnecessary treatment: " *The diagnosis of vitreomacular traction (VMT) should comprise of a complete clinical picture including patient history, clinical examination and investigation using currently accepted diagnostic tools, such as optical coherence tomography (OCT). "*

In both trials 326 patients were randomised to treatment with ocriplasmin or placebo, in a 2:1 ratio in TG-MV-006 and a 3:1 ratio in TG-MV-007. Subject retention was adequate. However, there were a large number of screen failures, the vast majority attributed to not meeting inclusion criteria. The average age of participants was in the early 70s and the vast majority of subjects were white, despite there being no known racial predilection in macular hole or vitreomacular traction syndrome. This probably reflects the racial mix of the trial centres. Participants in the two studies were broadly similar, though a higher proportion of patients in TG-MV-006 had a macular hole.

Both trials were successful with regard to the primary endpoint. The difference to placebo in the proportion of ocriplasmin-treated subjects with VMA resolution at Day 28 was 15 percentage points in TG-MV-006 and 19 percentage points in TG-MV-007. The placebo response rate was over twice as high in study TG-MV-006 than in study TG-MV-007, suggesting that the characteristics of the patients in the two studies differed, limiting the reliability of an integrated analysis of the results. Furthermore the response rate was markedly different between the two studies at time-points prior to Day 28. These findings appear to be related to differences in baseline prognostic factors between participants in the two studies.

A smaller difference between ocriplasmin and placebo was observed in the endpoints of proportion achieving total PVD by Day 28 (10 percentage points) and proportion receiving vitrectomy (-8 percentage points). Even though 80-90% of subjects had an expected need for vitrectomy at baseline, it is surprising that less than 30% of placebo-treated patients received vitrectomy during the study. The primary outcome appears to overestimate the clinical benefit of treatment when this is translated into a need for vitrectomy: 11 patients need to be treated to avoid a single vitrectomy. However, it does not appear that treatment with ocriplasmin prior to vitrectomy has a negative impact on the functional outcome of surgery, and since treatment with ocriplasmin does not seem to delay the time to vitrectomy, this modest effect can be regarded as acceptable.

A larger effect of ocriplasmin over placebo was shown for the endpoint of nonsurgical closure of full thickness macular hole by Day 28: 31 percentage points (p=0.002) in TG-MV-006, and 30 percentage points (p=0.028) in TG-MV-007. By the end of the study however, this difference had reduced to 15 percentage points in TG-MV-007 mainly due to an increase in the placebo response rate. This has been related to differences in baseline prognostic factors between the participants. Macular hole is an important reason for visual loss and a driver for vitrectomy in the targeted population and it is evident, even though few subjects were concerned, that more

subjects had FTMH closures without vitrectomy and fewer such subjects required vitrectomy in the ocriplasmin-treatment groups.

Visual acuity was measured both as a categorical change from baseline (proportion gaining ≥2 and ≥3 lines) and a mean change from baseline. The categorical change from baseline should be treated with some caution, since the mean level of vision at baseline was fairly good in both studies and so the potential to gain 2 or 3 lines of vision was limited. Nonetheless, the proportion gaining vision in both studies was in favour of ocriplasmin, though the statistical significance of these results is unclear. With regard to mean change in vision from baseline, subjects in both studies gained only 2 to 3 letters after treatment, and no difference was observed between active treatment and placebo. However, this is unlikely to have been a particularly sensitive endpoint, since subjects generally had only a mild loss of vision at baseline. Improvement in visual acuity did correlate well with resolution of VMA however, which provides some support for the clinical relevance of success in the primary endpoint. Other symptoms of vitreomacular adhesion, such as metamorphopsia and micropsia, were not, however, assessed during follow-up.

Ocriplasmin-treated subjects in both studies generally achieved numerically larger changes from baseline in subscale and composite scores of the VFQ-25, though once again, the statistical significance of these results is unclear.

Subgroup analyses with various baseline characteristics suggest that the effects of ocriplasmin are only marginally better than placebo in patients with an epiretinal membrane, but that patients who have a smaller diameter focal VMA, a FTMH, and poorer baseline vision will benefit the most from ocriplasmin. In the evaluation of treatment effect by region, it was clear that there were regional differences. Although a comparable proportion of ocriplasmin-treated patients experienced non-surgical VMA in the EU and US regions (23 and 28%, respectively), in the placebo groups, the corresponding figures were 4 and 12%. In the US centres (pooled studies), 5 and 16% of patients had a total PVD in the placebo and active groups, respectively, while in the EU centres, a much lower proportion (0 and 7 % in the respective treatment groups) had a total PVD. In the US centres, 30 and 18% of patients underwent vitrectomy in the placebo and active groups, respectively (difference 12%, p=0.007). In the EU centres, 16% in each treatment group had surgery (p=0.985). Although a similar proportion of ocriplasmin-treated subjects had vitrectomy in the EU as in the US, few placebo-treated subjects required vitrectomy in EU. Thus, from the EU physician's perspective, there was no effect of ocriplasmin in reducing the need for surgery. In both treatment groups, a lower proportion of subjects from the EU region had a ≥2 line gain in VA although all cases irrespective of vitrectomy were included. Given that treatment with ocriplasmin need not delay vitrectomy should surgery be considered appropriate, the modest effect (in the pooled studies) with regard to this endpoint is considered acceptable.

Taken together, it appears that a difference in effect was observed in the EU region as compared to the US region. This has been attributed to differences in baseline prognostic factors; however, other than for the endpoint of need for vitrectomy, a modest but consistent treatment effect has been shown for ocriplasmin in both studies and both regions.

2.4.3. Conclusions on the clinical efficacy

Both main studies demonstrate statistical success in the primary endpoint; resolution of vitreomacular traction has been shown to confer an improvement in visual acuity. Although the number of subjects with a full thickness macular hole at baseline was small, a convincing effect

of treatment has also been shown with regard to closure rate. Results for the secondary endpoints of induction of PVD, and avoidance of vitrectomy were not fully convincing. However, in the context of a treatment that is administered only once, and that would be unlikely to significantly delay alternative treatment (ie, observation, followed by vitrectomy), this level of efficacy can be regarded as satisfactory.

2.5. Clinical safety

Safety data in support of this application come from the pooled results of 7 completed clinical trials with intravitreal ocriplasmin. Three other studies sponsored by the applicant (and two investigator-sponsored studies) were ongoing at the data cut-off date (31 March 2011). In addition, 5 studies to evaluate intravascular ocriplasmin were either completed or terminated at the data cut-off date.

In the animal studies with intravitreal ocriplasmin the following ocular signals were detected:

- inflammatory response and transient ERG changes in rabbits and Cynomolgus monkeys (but no such changes in minipigs, even at the highest doses)
- lens subluxation was observed in all species at ocriplasmin concentrations at or above 41µg/mL vitreous (a concentration above the intended clinical concentration of 29µg/mL)
- gross pathological changes related to intraocular haemorrhage in rabbits and Cynomolgus monkeys (however, it is unclear if this haemorrhage is related to the injection procedure itself or administration of ocriplasmin).

No systemic toxicity was observed after intravitreal administration of ocriplasmin to Dutch-belted rabbits, Cynomolgus monkeys and mini-pigs.

Patient exposure

The exposure to ocriplasmin in completed studies is summarised in the table below.

Table 1. Patient exposure intravitreal administration (cut off)

	Patients enrolled	**Patients exposed**	**Patients exposed to the proposed dose range**	**Follow up time**
Placebo-controlled	777	559	497	6 months
Active -controlled	112	88	42	12 m (002) 6 m(004)
Open studies	99	94	43	6 m (001) 6 w (010)
Post marketing				
Compassionate use	3	3	3	
Total	991	744	585	

Duration of follow-up was 6 months, except for TG-MV-010 (6 weeks), and TG-MV-002 (12 months). The total number of unique patients exposed to ocriplasmin in completed studies is 738. Three patients each participated in 2 clinical studies as permitted by the respective protocols and in the process received ocriplasmin in separate eyes in different studies. An additional 9 patients received more than 1 dose of ocriplasmin at monthly intervals in the same eye in study TG-MV-004 as per protocol. Specifically, 7 patients in study TG-MV-004, Cohort 4

who received ocriplasmin 125µg and 2 patients who received sham injection in the controlled period of the study each subsequently received 2 injections of ocriplasmin 125µg in the open period of the study. In TG-MV-007, 1 patient received an injection of undiluted investigational drug, a dose of ocriplasmin 250µg. This patient was counted in the ocriplasmin 125µg group. Since 3 patients received ocriplasmin in more than 1 study as described above, the total number of unique patients exposed to ocriplasmin in completed studies is 738. All but the 12 patients described above received a single injection of ocriplasmin.

In addition, 97 subjects have been exposed to ocriplasmin (0.1-5 mg/kg) via intravascular administration in studies TG-M-001 - -005. These studies are of low relevance for this application and safety outcomes are only briefly addressed below.

Patient Disposition (Safety Set)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo N=187		Ocriplasmin 125µg N=465		Control[a] N=247		Ocriplasmin Any Dose N=741	
	n	(%)	n	(%)	n	(%)	n	(%)
Safety set	187	(100.0%)	465	(100.0%)	247	(100.0%)	741	(100.0%)
Completed study	171	(91.4%)	436	(93.8%)	228	(92.3%)	701	(94.6%)
Discontinued from study	16	(8.6%)	29	(6.2%)	19	(7.7%)	40	(5.4%)
Reasons for discontinuation								
Adverse event	2	(1.1%)	4[b]	(0.9%)	2	(0.8%)	5	(0.7%)
Investigator decision	1	(0.5%)	0		1	(0.4%)	1	(0.1%)
Withdrew consent	8	(4.3%)	13	(2.8%)	9	(3.6%)	17	(2.3%)
Lost to follow-up	5	(2.7%)	8	(1.7%)	5	(2.0%)	10	(1.3%)
Death[c]	0		4	(0.9%)	2	(0.8%)	5	(0.7%)
Other	0		0		0		2	(0.3%)

[a] Patients allocated to placebo, sham injection, or no treatment

Baseline characteristics were well balanced between placebo-treated and ocriplasmin-treated patients in pivotal and all studies combined except for previous cataract surgery. In the ocriplasmin group of pivotal studies, 33.5% of patients had had a cataract operation compared to 24.6% of patients in the placebo group.

Ocular medical history: Study eye conditions reported for ≥ 10% of patients treated with ocriplasmin in pivotal placebo-controlled studies (Safety Set)

	Pivotal Placebo-Controlled Studies				All Studies Combined			
	Placebo (N=187)		Ocriplasmin 125µg (N=465)		Control[a] N=247		Ocriplasmin Any Dose (N=741)	
	n	(%)	n	(%)	n	(%)	n	(%)
Vitreous adhesions	183	(97.9%)	462	(99.4%)	211	(85.4%)	600	(81.0%)
Cataract	114	(61.0%)	284	(61.1%)	149	(60.3%)	404	(54.5%)
Maculopathy	74	(39.6%)	167	(35.9%)	89	(36.0%)	205	(27.7%)
Cataract operation	46	(24.6%)	156	(33.5%)	64	(25.9%)	192	(25.9%)
Macular hole	64	(34.2%)	151	(32.5%)	86	(34.8%)	321	(43.3%)
Macular degeneration	40	(21.4%)	113	(24.3%)	47	(19.0%)	128	(17.3%)
Macular oedema	40	(21.4%)	93	(20.0%)	58	(23.5%)	213	(28.7%)
Cataract nuclear	30	(16.0%)	65	(14.0%)	33	(13.4%)	74	(10.0%)
Vitreous detachment	28	(15.0%)	58	(12.5%)	32	(13.0%)	82	(11.1%)

[a] Patients allocated to placebo, sham injection, or no treatment.

Adverse events

Overview of adverse events

	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control[a] N=247			Ocriplasmin Any Dose N=741		
Number of Patients:	n	%	E	n	%	E	n	%	E	n	%	E
With at least one AE	129	(69.0%)	349	356	(76.6%)	1274	180	(72.9%)	596	593	(80.0%)	2346
With related AE	40	(21.4%)	61	186	(40.0%)	406	50	(20.2%)	92	263	(35.5%)	542
With severe AE	14	(7.5%)	16	39	(8.4%)	46	23	(9.3%)	30	62	(8.4%)	82
With serious AE	24	(12.8%)	28	62	(13.3%)	78	34	(13.8%)	44	100	(13.5%)	141
With related serious AE	6	(3.2%)	6	15	(3.2%)	16	6	(2.4%)	6	16	(2.2%)	17
With AEs leading to withdrawal[b]	2	(1.1%)	2[c]	4[d]	(0.9%)	4[c]	2	(0.8%)	2[c]	5[d]	(0.7%)	5[c]
With AE with fatal outcome[e]	0		0	5[b]	(1.1%)	5	2	(0.8%)	2	6[b]	(0.8 %)	6

In the pivotal placebo-controlled studies, the percentage of patients experiencing at least 1 adverse event (AE) was higher in the ocriplasmin group than in the placebo group (76.6% vs 69.0%), as was the percentage of patients with at least 1 drug-related AE (40.0% vs 21.4%). AEs of severe intensity were reported for 39 (8.4%) ocriplasmin-treated patients and 14 (7.5%) placebo-treated patients.

Ocular Adverse Events

Study Eye Adverse Events Reported for at Least 2% of Patients Treated with Ocriplasmin 125µg in the Pivotal Placebo-Controlled Studies (Safety Set)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control[a] N=247			Ocriplasmin Any Dose N=741		
Number of adverse events	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Any event	129	(69.0%)	349	356	(76.6%)	1274	180	(72.9%)	596	593	(80.0%)	2346
Any non-ocular event	53	(28.3%)	90	140	(30.1%)	288	82	(33.2%)	151	255	(34.4%)	490
Any ocular event	106	(56.7%)	259	324	(69.7%)	986	149	(60.3%)	445	538	(72.6%)	1856
Study eye event	99	(52.9%)	229	317	(68.2%)	900	141	(57.1%)	408	529	(71.4%)	1715
Non-study eye event	22	(11.8%)	30	61	(13.1%)	86	29	(11.7%)	37	101	(13.6%)	141
Eye disorders												
Any event	101	(54.0%)	240	321	(69.0%)	940	142	(57.5%)	411	518	(69.9%)	1718
Study eye event	95	(50.8%)	214	314	(67.5%)	859	135	(54.7%)	379	510	(68.8%)	1592
Non-study eye event	20	(10.7%)	26	57	(12.3%)	81	26	(10.5%)	32	90	(12.1%)	126
Study eye AEs												
Vitreous floaters	14	(7.5%)	15	78	(16.8%)	85	18	(7.3%)	19	119	(16.1%)	131
Conjunctival haemorrhage	24	(12.8%)	24	68	(14.6%)	69	49	(19.8%)	49	129	(17.4%)	140
Eye pain	11	(5.9%)	11	61	(13.1%)	68	19	(7.7%)	22	90	(12.1%)	103
Photopsia	5	(2.7%)	5	55	(11.8%)	60	7	(2.8%)	7	66	(8.9%)	71
Vision blurred	6	(3.2%)	7	39	(8.4%)	41	7	(2.8%)	8	47	(6.3%)	49
Macular hole	18	(9.6%)	18	31	(6.7%)	34	19	(7.7%)	19	50	(6.7%)	58
Visual acuity reduced	8	(4.3%)	8	29	(6.2%)	30	8	(3.2%)	8	41	(5.5%)	42
Retinal oedema	2	(1.1%)	2	25	(5.4%)	28	2	(0.8%)	2	32	(4.3%)	35
Visual impairment[b]	2	(1.1%)	2	25	(5.4%)	27	2	(0.8%)	2	27	(3.6%)	29
Macular oedema	3	(1.6%)	4	19	(4.1%)	19	10	(4.0%)	12	43	(5.8%)	47
Intraocular pressure increased	10	(5.3%)	10	18	(3.9%)	20	17	(6.9%)	17	65	(8.8%)	72
Anterior chamber cell	5	(2.7%)	5	17	(3.7%)	18	12	(4.9%)	13	57	(7.7%)	66
Photophobia [c]	0		0	17	(3.7%)	17	0		0	25	(3.4%)	25
Ocular discomfort	2	(1.1%)	2	13	(2.8%)	13	4	(1.6%)	4	17	(2.3%)	17
Vitreous detachment	2	(1.1%)	2	12	(2.6%)	13	2	(0.8%)	2	13	(1.8%)	14
Iritis	0		0	12	(2.6%)	13	0		0	12	(1.6%)	13
Cataract	8	(4.3%)	8	11	(2.4%)	11	12	(4.9%)	12	34	(4.6%)	36
Dry eye	2	(1.1%)	2	11	(2.4%)	11	2	(0.8%)	2	14	(1.9%)	14
Conjunctival hyperaemia	4	(2.1%)	4	10	(2.2%)	10	6	(2.4%)	6	25	(3.4%)	25
Metamorphopsia	1	(0.5%)	1	10	(2.2%)	10	1	(0.4%)	1	14	(1.9%)	14

[a] Patients allocated to placebo, sham-injection or no treatment.

[b] The verbatim term entopic phenomena (as can occur in setting of PVD) was conservatively coded to the preferred term (PT) visual impairment instead of floaters/photopsia in the appendix tables and in-text tables.

Adverse events were reported with a similar frequency in the pivotal studies compared to the entire safety set. In the pivotal studies the most frequently reported ocular treatment-emergent adverse events (TEAEs) were vitreous floaters, conjunctival haemorrhage, eye pain, photopsia (sensation of flashing lights) and blurred vision. All of these were more frequently reported in ocriplasmin-treated subjects than those receiving placebo. Photopsia occurred twice as frequently in ocriplasmin-treated subjects in TG-MV-006 than in TG-MV-007, perhaps due to the higher rate of PVD in this study. 14 of the 17 events of photophobia in the pivotal studies occurred in TG-MV-006. Three of these events were severe.

Non-Ocular Adverse Events

Non-ocular Adverse Events Reported for ≥2% of Patients (Safety Set)

System Organ Class Preferred Term Category	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control[a] N=247			Ocriplasmin Any Dose N=741		
	n	%	E	n	%	E	n	%	E	n	%	E
Number of Adverse Events												
Any event	129	(69.0%)	349	356	(76.6%)	1274	180	(72.9%)	596	593	(80.0%)	2346
Any non-ocular event	53	(28.3%)	90	140	(30.1%)	288	82	(33.2%)	151	255	(34.4%)	490
Bronchitis	3	(1.6%)	4	13	(2.8%)	14	5	(2.0%)	6	16	(2.2%)	17
Influenza	2	(1.1%)	3	5	(1.1%)	5	3	(1.2%)	4	14	(1.9%)	14
Nausea	1	(0.5%)	1	12	(2.6%)	14	3	(1.2%)	3	22	(3.0%)	24
Nasopharyngitis	5	(2.7%)	5	9	(1.9%)	10	9	(3.6%)	9	21	(2.8%)	22
Headache	4	(2.1%)	4	12	(2.6%)	14	11	(4.5%)	12	32	(4.3%)	40

[a] Patients allocated to placebo, sham injection or no treatment.

Rates of non-ocular TEAEs were similar in subjects treated with ocriplasmin and placebo.

Adverse Drug Reactions

AEs considered suspected adverse drug reactions (ADRs, ie, there was a reasonable possibility that these events were treatment related) were selected by applying a series of criteria (detailed in the clinical assessment report). The ADRs listed in section 4.8 of the SmPC are based on suspected ADRs. None of the systemic AEs were considered suspected ADRs.

Vitreous floaters were the only suspected ADR with a clear dose relationship. The 125 µg ocriplasmin dose was associated with a higher incidence of AEs related to visual function and sign of inflammation compared to lower doses of ocriplasmin.

In ocriplasmin-treated patients, >50% of adverse events of vitreous floaters, conjunctival haemorrhage, eye pain, photopsia, vision blurred, visual acuity reduced, retinal oedema, visual impairment, anterior chamber cell, photophobia, conjunctival hyperemia, ocular discomfort, iritis, metamorphopsia and anterior chamber flare were reported within 7 days of ocriplasmin administration.

The majority of adverse events of macular hole, cataract, maculopathy, retinal degeneration and retinal pigment epitheliopathy were reported from day 8 until end of study.

Overall, the time to onset of vitreous floaters and photopsia and anterior chamber cell was about half as long in ocriplasmin-treated patients compared to placebo-treated patients. Also the time to onset of vision blurred and visual acuity reduced, retinal and macular oedema and time to occurrence of retinal detachment was shorter for ocriplasmin-treated patients.

Suspected adverse drug reactions in Study eye by time to onset : No/Pre-vitrectomy or During/Post-vitrectomy : Pivotal placebo-controlled studies (Safety Set)

	Pivotal Placebo-Controlled Studies No / Pre-Vitrectomy						Pivotal Placebo-Controlled Studies During / Post-Vitrectomy					
	Placebo N=187			Ocriplasmin 125µg N=465			Placebo N=50			Ocriplasmin 125µg N=82		
Preferred Term	n	%	E	n	%	E	n	%	E	n	%	E
Vitreous floaters	13	(7.0%)	14	76	(16.3%)	83	1	(2.0%)	1	2	(2.4%)	2
Eye pain	7	(3.7%)	7	51	(11.0%)	55	4	(8.0%)	4	11	(13.4%)	13
Photopsia	4	(2.1%)	4	54	(11.6%)	57	1	(2.0%)	1	3	(3.7%)	3
Vision blurred	6	(3.2%)	7	35	(7.5%)	36	0		0	4	(4.9%)	5
Visual acuity reduced	6	(3.2%)	6	29	(6.2%)	30	2	(4.0%)	2	0		0
Visual impairment	1	(0.5%)	1	25	(5.4%)	27	1	(2.0%)	1	0		0
Retinal oedema	2	(1.1%)	2	24	(5.2%)	27	0		0	1	(1.2%)	1
Macular oedema	2	(1.1%)	2	11	(2.4%)	11	2	(4.0%)	2	8	(9.8%)	8
Anterior chamber cell	2	(1.1%)	2	14	(3.0%)	14	3	(6.0%)	3	4	(4.9%)	4
Photophobia	0		0	16	(3.4%)	16	0		0	1	(1.2%)	1
Ocular discomfort	2	(1.1%)	2	11	(2.4%)	11	0		0	2	(2.4%)	2
Vitreous detachment	2	(1.1%)	2	12	(2.6%)	13	0		0	0		0
Iritis	0		0	11	(2.4%)	11	0		0	1	(1.2%)	2
Dry eye	2	(1.1%)	2	9	(1.9%)	9	0		0	2	(2.4%)	2
Metamorphopsia	1	(0.5%)	1	7	(1.5%)	7	0		0	3	(3.7%)	3
Retinal degeneration	0		0	6	(1.3%)	6	1	(2.0%)	1	2	(2.4%)	2
Eyelid oedema	0		0	2	(0.4%)	2	1	(2.0%)	1	5	(6.1%)	5
Retinal pigment epitheliopathy	0		0	3	(0.6%)	3	0		0	4	(4.9%)	4
Macular degeneration	1	(0.5%)	1	4	(0.9%)	4	0		0	2	(2.4%)	2
Miosis	0		0	5	(1.1%)	5	0		0	0		0
Scotoma	0		0	4	(0.9%)	4	0		0	1	(1.2%)	1
Corneal abrasion	0		0	5	(1.1%)	5	0		0	0		0
Ocular hyperaemia	1	(0.5%)	1	4	(0.9%)	4	0		0	0		0
Conjunctival irritation	0		0	4	(0.9%)	4	0		0	0		0
Diplopia	0		0	3	(0.6%)	3	0		0	1	(1.2%)	1
Visual field defect	0		0	2	(0.4%)	2	1	(2.0%)	1	1	(1.2%)	1
Pupils unequal	0		0	3	(0.6%)	3	0		0	0		0

In the pivotal studies, 4.9% of ocriplasmin treated patients and 5.9% of placebo treated patients had a suspected ADR of severe intensity. For suspected ADRs, visual acuity reduced was the only preferred term reported as severe for both ocriplasmin 125µg (0.6%) and placebo (0.5%).

In the ocriplasmin 125µg group, suspected ADRs of severe intensity also included photophobia (0.6%), visual impairment (0.2%), vitreous detachment (0.2%) and visual field defect (0.2%). All 3 events of photophobia of severe intensity recovered without sequelae within 6 days of onset. Visual field defect resolved 1 day after onset and visual impairment and vitreous detachment were ongoing at the last study visit.

In the placebo group, suspected ADRs of severe intensity included macular oedema (0.5%) and macular degeneration (0.5%). At onset (Day 34), the Investigator considered macular oedema to be of moderate intensity. When the intensity increased to severe on Day 146, vitrectomy was performed with recovery 3 days later. Macular degeneration was ongoing at the last study visit.

In the ocriplasmin 125µg group, the suspected ADRs most frequently considered by the Investigators to be drug-related were vitreous floaters (13.8%), photopsia (9.0%) and vision blurred (5.2%). In the placebo group, vitreous floaters (4.8%) was the suspected ADR most frequently considered by the Investigator to be drug-related. None of these reactions were severe.

Taken together, analysis of adverse event reports demonstrated that adverse events mainly were confined to the study eye. The most frequently reported adverse events were vitreous floaters, eye pain and photopsia. Adverse events related to intraocular inflammation such as anterior chamber cell, iritis, photophobia and ocular discomfort were reported. Adverse event with relation to alteration of visual function were frequently reported. In the majority of cases, adverse events were mild to moderate and resolved without sequelae.

Serious adverse events and deaths

Eight deaths were reported in completed or ongoing studies with ocriplasmin. Two occurred in subjects receiving sham injections. In the pivotal studies TG-MV-006 and TG-MV-007 there were five reports with fatal outcome. All of these occurred in ocriplasmin-treated patients. Following analysis, the Applicant concluded that each death was probably due to a pre-existing medical condition and none of these events appeared to be causally related to ocriplasmin or the injection procedure. The conclusion by the Applicant is endorsed, especially since systemic exposure to ocriplasmin is expected to be insignificant.

Patients who died during or after study pariticipation (All patients)

Treatment	Study / Patient Number	Age (y)	Gender	Race	Injection Date	Date of Death	AE Resulting in Death	Relationship
Sham injection	TG-MV-002 / 011-301	74	male	white	10-Dec-2008	01-Aug-2009	cardiac arrest	unrelated
Sham injection	TG-MV-002 / 081-102	82	male	white	30-Mar-2007	25-Apr-2007	intestinal obstruction	unrelated
Ocriplasmin 75µg	TG-MV-003 / 101-021	75	male	white	21-Mar-2008	20-Jun-2008	myocardial infarction	unrelated
Ocriplasmin 125µg	TG-MV-006 / 603-008	81	female	white	22-Apr-2009	04-Jul-2009	cerebral haemorrhage	unrelated
Ocriplasmin 125µg	TG-MV-006 / 622-012	84	female	white	08-May-2009	29-Aug-2009	lung neoplasm malignant	unrelated
Ocriplasmin 125µg	TG-MV-006 / 632-008	83	female	white	22-Jul-2009	21-Nov-2009	cardiac failure congestive	unrelated
Ocriplasmin 125µg	TG-MV-007 / 721-008	76	female	white	16-Sep-2009	11-Dec-2009	brain cancer metastatic	unrelated
Ocriplasmin 125µg	TG-MV-007 / 775-003	88	female	white	11-Jun-2009	11-Nov-2009	lung neoplasm malignant	remote

In all, there were 6 cases that were serious and/or severe vision-related adverse events. Additionally, one patient, which was inadvertently given an ocriplasmin dose of 250 µg due to a dilution error, had a decrease in BCVA of 21 letters from baseline but no vision-related AEs were reported. The BCVA returned to within 9 letters of baseline.

The six patients mentioned experienced rapid decline in VA following ocriplasmin administration. In two patients in whom ERG was performed, abnormal findings were observed. ERG remained abnormal at up to 1 year. Two patients experienced macula-off retinal detachment which was treated with vitrectomy. One additional patient (TG-MV-006) experienced a dark spot in the vision with onset at day 2. At day 7, BCVA decreased by 6 letters and at day 14 BCVA increased 4 letters from baseline. At the day 28 visit, severe AE VMT progression from baseline was reported with BCVA decreased by 34 letters from baseline. The patient underwent vitrectomy on the same day. No subsequent assessments of study visits were performed as the patient withdrew consent from the study.

Serious adverse events in the Study Eye (Safety Set)

	Pivotal Placebo-Controlled Studies						All Studies Combined					
	Placebo N=187			Ocriplasmin 125µg N=465			Control[a] N=247			Ocriplasmin Any Dose N=741		
Preferred Term	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**	**n**	**%**	**E**
Number of ocular SAEs	20	(10.7%)	24	37	(8.0%)	41	22	(8.9%)	28	59	(8.0%)	74
Study eye	20	(10.7%)	24	36	(7.7%)	39	22	(8.9%)	28	57	(7.7%)	71
Non-study eye	0		0	2	(0.4%)	2	0		0	3	(0.4%)	3
Study eye SAEs by Preferred Term												
Macular hole	16	(8.6%)	16	24	(5.2%)	25	16	(6.5%)	16	35	(4.7%)	39
Vitreous adhesions	1	(0.5%)	1	5	(1.1%)	5	2	(0.8%)	2	5	(0.7%)	5
Visual acuity reduced	1	(0.5%)	1	3	(0.6%)	3	1	(0.4%)	1	3	(0.4%)	3
Retinal detachment	3	(1.6%)	5	2	(0.4%)	2	3	(1.2%)	5	4	(0.5%)	6
Eye inflammation	0		0	1	(0.2%)	1	0		0	1	(0.1%)	1
Hyphaema	0		0	1	(0.2%)	1	1	(0.4%)	1	1	(0.1%)	1
Posterior capsule opacification	0		0	1	(0.2%)	1	0		0	2	(0.3%)	2
Vitreous haemorrhage	0		0	1	(0.2%)	1	1	(0.4%)	1	1	(0.1%)	1
Macular oedema	1	(0.5%)	1	0		0	1	(0.4%)	1	1	(0.1%)	1
Cataract	0		0	0		0	0		0	3	(0.4%)	3
Optic disc vascular disorder	0		0	0		0	0		0	1	(0.1%)	1
Retinal artery occlusion	0		0	0		0	0		0	1	(0.1%)	1
Retinal vein occlusion	0		0	0		0	0		0	1	(0.1%)	1
Intraocular pressure increased	0		0	0		0	0		0	1	(0.1%)	1
Anterior chamber inflammation	0		0	0		0	0		0	1	(0.1%)	1
Choroidal detachment	0		0	0		0	0		0	1	(0.1%)	1
Macular degeneration	0		0	0		0	0		0	1	(0.1%)	1
Retinal tear	0		0	0		0	0		0	1	(0.1%)	1
Cataract traumatic	0		0	0		0	0		0	1	(0.1%)	1
Choroidal haemorrhage	0		0	0		0	1	(0.4%)	1	0		0

[a] Patients allocated to placebo, sham injection or no treatment.

In ongoing studies there have been four reports of visual acuity reduced, two reports of retinal detachment, one report of lens subluxation and one report each of acute cholecystitis, metastatic prostate cancer, urinary tract infection, femur fracture, cystitis, angina pectoris and infected ventriculoperitoneal shunt.

After i.v. administration of ocriplasmin in a Phase 1 healthy volunteer study (TG-M-001) of doses several orders of magnitude higher than the intended IVT dose, no adverse effects on vital sign assessments were observed. No specific evaluation of vital signs was made in the studies that evaluated ocriplasmin following IVT injection; however, no vital sign findings reported as AEs were considered suspected ADRs.

Ocular adverse events of special interest

AEs of special interest were selected based on their potential or actual clinical relevance, and include:

- visual function changes (vision alteration, colour vision alteration, ERG changes),
- structural retinal findings (retinal oedema (MedDRA preferred term for subretinal fluid) and macular oedema, macular hole, retinal pigment epithelium changes),
- retinal breaks (retinal tears / detachments),
- cataracts,
- events known to be associated with the intravitreal injection procedure,
- subluxation of the lens,
- immunogenicity potential

- Functional and structural retinal findings

During the clinical development program of ocriplasmin 6 patients (5 from company-sponsored studies and 1 additional patient from an investigator-initiated study) had 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 motion, and was associated with transient visual field constriction in 3 of the 6 patients.

In total, 16 events of mild and 1 of severe dyschromatopsia have been reported; of these 9 subjects had ERG changes. Of these, 12 resolved at end of study or during follow up. Of the 5 remaining patients, 1 patient has died, 1 was lost to follow up and 2 reported resolution in post-study contact, 11 and 28 months after injection. The remaining patient is reported from Study TG-MV-014, an ongoing study. This patient had also ERG changes and as well as other SAEs. Chromatopsia is reported as a common AE in section 4.8 of the SmPC and is identified as a risk in the RMP. Initially, there was a concern that the event could be associated with retinal toxicity and further evaluation was needed..

In the Applicant's Day 120 responses, data on events of ERG abnormalities were provided for the total number of subjects given ocriplasmin as per May 2012 (976 patients). The number of patients who had a post-injection ERG is estimated to be 141, and a total of 11 subjects (7.8%) have been reported with ERG-changes. Of the 11 cases, 9 also had dyschromatopsia. Also in older studies a number of ERG-changes difficult to interpret were reported, and the incidence may thus be higher. Overall, the chronology is compatible with an effect of ocriplasmin and the majority of events were detected one week after injection.

Recovery was indicated in 6 cases with 2 ongoing events (including the subject in the ongoing TG-MV-014) and no follow up is available for 3 subjects. The time to recovery was reported as 3-6 months, while one subject still has an abnormal ERG after 28 months. The latter patient had however confounding disease (vitelliform dystrophy) which is a probable cause for the persistent ERG-changes.

The most recently reported event of ERG-changes from study TG-MV-014 (follow-up ongoing) was reported as serious and the patient was diagnosed with serious photoreceptor toxicity, worsening of the MH, vasculitis (at day of vitrectomy= day 19) and relative afferent pupillary defect (1 day post vitrectomy). ERG was reported as extremely reduced and visual field evaluation indicated a decreased retinal sensitivity day 7. While some events are resolved, ERG abnormalities and colour vision changes are ongoing but improved. The last report on VA was within 2 letters of the pre-injection baseline BCVA. Presently, there are two patients with ongoing ERG changes.

The analysis of function of the different cell-types in the retina indicated that the primary abnormalities were on the photoreceptor levels (a-wave reduction followed by a secondary b-wave decrease). Also the isoelectric changes (flat ERG) were believed to be produced by a primary effect upon photoreceptors.

Results of TG-MV-012 were submitted with the Day 180 responses. This study included 24 patients taken from the two highest enrolling sites of the pivotal studies. ERGs were performed at the single visit in TG-MV-012, but no baseline ERGs were available. This makes it difficult to evaluate the ERG changes observed during the study. Furthermore, the time between treatment in the pivotal studies and the ERG in TG-MV-012 varied among patients, extending up to nearly 3 years in some patients. Confounding factors were present for patients with abnormal ERGs, and similar ERG abnormalities were observed in both study and non-study eyes, including in placebo patients, suggesting that ERG has low specificity in detecting retinal abnormalities. None of the patients with a severe ERG abnormality had clinically significant deterioration in visual acuity. The ERG results emphasise the need to perform the prospective study TG-MV-014 in order to characterize the relevance of ERG abnormalities on visual function.

Review of these cases shows that all subjects with significant, early vision loss, and the majority of subjects with dychromatopsia and/or ERG changes also experienced resolution of their vitreomacular adhesion. This suggests a mechanical aetiology, ie, that rapid resolution of vitreomacular traction secondary to ocriplasmin's mechanism of action that may temporarily disturb the photoreceptor layer, causing decreased vision, and changes to colour vision. A detrimental biochemical effect of the product on the RPE or photoreceptors cannot, however, be ruled out, though this is unlikely. There are also no reports of changes in placebo-treated patients of which a proportion also had resolution of the VMT. As pointed out in the expert review commissioned by the applicant, patients with large areas of 'bare RPE' (ie, separation of the inner retinal layers from the RPE at the macula), or severe retinal degenerative changes are at the highest risk of developing these changes.

However, the events should be put into perspective as they seem to reverse, and importantly, on average, patients improved their VA with an average 9 letters and none of the subjects with ERG-changes lost > 5 letters in the long term.

VMA resolution was strongly associated with a higher incidence of vision alteration. Consistent with this, the other subgroups with higher incidence of vision alteration were generally those that achieved higher rates of VMA resolution. Vision alteration AEs were reported more frequently in younger (< 65 years) patients treated with ocriplasmin than older (≥ 65 years) patients treated with ocriplasmin or placebo patients of each age group. Phakic patients who received ocriplasmin were more likely to report vision alteration AEs than pseudophakic patients. Vision alteration AEs were reported more frequently in patients with FTMH at baseline in both placebo and ocriplasmin groups. Ocriplasmin-treated patients without ERM at baseline were more likely to report vision alteration AEs compared with placebo. Patients from the USA generally reported more vision alteration AEs than European patients.

Overall, there was a higher incidence of AEs retinal/macular oedema and RPE changes after vitrectomy. However, there are too few events to conclude on whether ocriplasmin followed by vitrectomy may increase the risk for retinal/macular oedema and RPE changes, or if these events mainly reflected complications after vitrectomy as such. Out of 19 reports of macular oedema in ocriplasmin-treated patients, 8 events were reported following vitrectomy (8/82, 9.8%). In ocriplasmin-treated patients who did not have vitrectomy, 11/465 (2.4%) reported macular oedema. Similarly, out of 7 reports of retinal pigment epitheliopathy, 4 events were reported in ocriplasmin-treated patients following vitrectomy (4/82, 4.9%) compared to 3/465 (0.6%) in patients who did not have vitrectomy. Similar findings were observed for retinal degeneration and macular degeneration.

The percentage of patients without a FTMH at baseline who developed a FTMH post-injection was low and comparable between treatments at Day 7, Day 28 and the EOS visit. In the approximately 60% of FTMHs in the ocriplasmin group and the approximately 90% of FTMHs in the placebo group that did not achieve non-surgical FTMH closure by Day 28, the MH diameter (the maximum - minimum width and the maximum width at RPE) increased at post-treatment visits. This increase was larger in the ocriplasmin group compared with the placebo group, particularly for the diameter as measured at the RPE level. In the ocriplasmin group of pivotal studies, the MH diameter increased from 283 (SD 127) at baseline to 574 (SD 226) µm at month 6. Corresponding data for placebo treated group was 247 (SD 102) and 416 (SD 159) µm, respectively.

In 1/11 (9%) ocriplasmin treated subjects losing ≥20 letters ETDRS there was no AE which potentially might reduce visual acuity reported. Among subjects losing ≥15 - <20 letters ETDRS

there was no AE potentially affecting VA reported in 2/9 (22%). Corresponding figure for subjects losing ≥10 - <15 letters ETDRS was 13/24 (54%).

. Analysis of patients with acute change in BCBA of ≥10 letters ETDRS decrease from completed and ongoing studies

	Total no			AEs reported which potentially might reduce VA				
Change in visual acuity		Placebo	Ocriplasmin	Retinal detach-ment	Subretinal fluid, macular oedema	Floaters	Macular hole	Total
Loss ≥20 letters ETDRS	12	1	11	2	2	4	2	10
Loss ≥ 15 - <20 letters ETDRS	9	0	9	0	4	3	0	7
Loss ≥ 10 - <15 letters ETDRS	26	2	24	0	4	6	1	11
	47	3	44	2	10	13	3	28

BCVA returned to within 1 line (5 letters ETDRS) of baseline values during the study except in 6/820 (0.7%) ocriplasmin patients and 1/269 (0.4%) placebo patients. In 2 subjects losing >15 letters ETDRS the event was ongoing. One subject reported recovery of visual function with sequelae.

Analysis by outcome. Patients with acute change in BCBA of ≥10 letters ETDRS decrease from completed and ongoing studies

	Total no			AE	Outcome ocriplasmintreated subjects			
Change in visual acuity		Placebo	Ocriplasmin	Reduced vision reported	Recovered	Recovered with sequelae	Ongoing	No information with regards to VA
Loss ≥20 letters ETDRS	12	1	11	8	6	1	1	0
Loss ≥ 15 - <20 letters ETDRS	9	0	9	3	1	0	1	1
Loss ≥ 10 - <15 letters ETDRS	26	2	24	5	5	0	0	0
	47	3	44	16	12	1	2	1

Ocriplasmin was favoured in both subjects with and without a history of macular dystrophies in terms of gain of VA. However, 7.9 and 5.4% of subjects with macular dystrophies in the ocriplasmin-treatment groups had lost ≥2 and 3 lines of VA, respectively, compared to 3.9 and 1.6% in the placebo-group at month 6. Further information is required on the characteristics (including vitrectomy) of these patients to evaluate whether disease progression is the underlying factor of VA loss in this subgroup of patients.

Taken together, alterations in visual function included rapid decrease in visual acuity. The visual impairment was most often transient and correlated with rapid resolution of VMA. However, there were a number of patients, more in the ocriplasmin-treatment groups, whose visual acuity is significantly reduced at 6 months compared to baseline. Plausible reasons for the persistent loss of visual acuity were enlargement or development of new macular holes (more frequently in ocriplasmin-treated subjects) interpreted as being due to increased tractions, secondary to ocriplasmin's enzymatic action. In addition, in a number of these cases, the end of study visual acuity was evaluated shortly after vitrectomy (8/13 were evaluated within 3 months).

- Retinal breaks

This category included the preferred terms retinal tears and retinal detachments. In the pivotal placebo-controlled studies, the incidence of retinal tears was lower for the ocriplasmin 125µg group than for the placebo group. Most of the AEs occurred during the time interval of Day 8 to EOS and all but 1 event in each treatment group were of mild or moderate intensity.

- Cataracts

This category included the preferred terms cataract, cataract cortical, cataract nuclear, lenticular opacities, posterior capsule opacification and cataract subcapsular. The incidence of cataract (any event) in phakic patients in the pivotal placebo studies was 8.2% in the ocriplasmin group compared with 11.9% in the placebo group. The overall benefit in the ocriplasmin group in terms of decreased incidence of cataract is consistent with the lower rate of vitrectomy in the ocriplasmin group, since vitrectomy is known to be a significant risk factor in the development of cataract.

- Events known to be associated with the intravitreal injection procedure

Increased IOP, intraocular inflammation, intraocular haemorrhage and intraocular infection are risks known to be associated with the intravitreal injection procedure. No clinically meaningful differences between treatments were observed for the incidence of AEs in the intraocular haemorrhage or increased IOP categories. There was one report (Study TG-MV-005) of vision loss due to acute increase in intraocular pressure. Vitreous haemorrhage was reported as an SAE (verbatim: vitreous bleeding immediately after injection) for an additional patient (Study TG-MV-007). There was no report of endophthalmitis in any patient treated with ocriplasmin.

In the pivotal placebo-controlled studies, the overall incidence of AEs in the intraocular inflammation category was higher in the ocriplasmin group than in the placebo group (7.1% vs. 3.7%). Of the 90 cases that occurred in the development program, the majority could be classified as mild anterior uveitis. Half occurred in the first week after treatment. There were only 15 cases of vitritis or vitreous cells. There were no cases of intraocular infections including endophthalmitis reported in any patient treated with ocriplasmin.

- Subluxation of the lens

Lens subluxation was observed in 3 species of animals: rabbits, Cynomolgus monkeys and Göttingen mini-pigs, at ocriplasmin concentrations at or above 41µg/mL vitreous volume, a concentration above the intended clinical concentration of 29µg/mL. Furthermore subluxation was observed in all Cynomolgus monkeys receiving a repeat dose at Day 28.

In clinical studies, subluxation of the lens or lens instability was reported in 3 patients. One occurred in a 4-month old premature male infant (Study TG-MV-009) who received a single dose of 175 µg ocriplasmin IVT one hour before vitrectomy. During the vitrectomy, it appeared to the investigator as if the lens was slightly displaced nasally and loss of zonules was suspected.

The other two cases, in adults, are less-clearly related to the product. One patient from Study TG-MV-010 received ocriplasmin and had a combined procedure (phacoemulsification / intraocular lens [IOL] implant and vitrectomy) 3 hours after injection. One day later the patient had an AE of “lens luxation” (MedDRA PT: Lens dislocation) that was non-serious, mild in intensity, considered unrelated to ocriplasmin and resolved upon IOL repositioning. Subsequently, an AE of “superior lens dislocation” (MedDRA PT: Lens dislocation) was reported. The SAE of lens instability (Study TG-MV-007) occurred during vitrectomy 323 days after the patient was treated with ocriplasmin, with no clinical signs noted prior to the vitrectomy; however, there is at least a reasonable possibility of this being related to treatment.

The reported cases include phakic patients only. Based on the proteolytic activity of ocriplasmin, and non-clinical and clinical findings, the potential for subluxation of the lens or phacodonesis cannot be ruled out.

- Immunogenicity potential

See below.

Laboratory findings

Clinical laboratory tests were only performed in one clinical study with intravitreal ocriplasmin, the Phase II study TG-MV-001. Samples were obtained at baseline and at Day 28 from the 30 subjects who received ocriplasmin prior to vitrectomy. The amount of clinical laboratory data available for intravitreal ocriplasmin is therefore extremely limited. However, given the negligible amounts reaching the systemic circulation, and the availability of results from the IV dosing studies (summarised below) this is considered acceptable.

Safety in special populations

Subgroup analyses were conducted on the following intrinsic variables: gender, age (<65 years vs. ≥65 years; <75 years vs. ≥75 years); BMI (<25 kg/m2 vs. ≥25 kg/m2); lens status at baseline; baseline DR status; baseline FTMH status; baseline ERM status; and whether the primary efficacy endpoint was achieved. Race was analysed as Caucasian and non-Caucasian because the number of patients in each of the other racial categories was too few to compare to Caucasians. Several minor differences were observed between the subgroups, but no particular pattern of clinical relevance is clear.

VMT is a condition prevalent in the elderly and the overall adverse events profile where a relation to drug/injection procedure is suspected is presented by age in the below table. While the proportion of the very elderly is low and consequently impairs the precision of the detection of AEs, the overall data indicate no increased risks in the elderly population within the above predefined categories. This would also not be expected due to the local mode of action of ocriplasmin.

Summary of Drug Related Adverse Events by Age Group: All Studies Combined:

	< 65 years (N = 190) n (%)	**65-74 years (N = 304) n (%)**	**75-84 years (N = 219) n (%)**	**⩾ 85 years (N = 28) n (%)**
Total	73 (38.4%)	118 (38.8%)	68 (31.1%)	4 (14.3%)
Fatal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious	9 (4.7%)	4 (1.3%)	3 (1.4%)	0 (0.0%)
Withdrawal	0 (0.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
CNS	1 (0.5%)	4 (1.3%)	0 (0.0%)	0 (0.0%)
AEs related to falling	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CV events	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebrovascular events	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Infections	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Regarding extrinsic factors, geographic region and expected need for vitrectomy were analysed. A higher reporting rate of AEs in the US compared to Europe is suggested by the Company to be due to cultural differences concerning reporting. The outcome in the reporting of AEs mirrors to some extent the differences in effect observed between regions, i.e. an overall higher proportion of subjects achieved resolution of the anatomical defects in the US compared to the EU region, supporting that the reported events may be associated with a release of a VMA.

Immunological events

The finished ocriplasmin drug product contains 3 substances that may be of potential immunogenic concern: the ocriplasmin protein itself, and the process-related impurities: *Pichia pastoris*-derived host cell protein (HCP.

Ocriplasmin is known to share the exact amino acid sequence of its truncated human homologue and is considered to be highly similar at the level of the secondary and tertiary structure. The absence of post-translational modifications such as glycosylation decreases the immunogenic potential of ocriplasmin.

Ocriplasmin is not known to share immunogenic motifs with other proteins. Antibodies against plasminogen and plasmin have been described in patients suffering from auto-immune disorders.

During the vascular clinical program, 4 subjects treated with high vascular doses of ocriplasmin developed pseudo-allergic reactions during infusion. There is a suggestion that high i.v. doses of ocriplasmin drug product can cause a rise in staphylokinase antibodies. The clinical significance of this finding for the single intravitreal administration of ocriplasmin doses that are 1,000-fold lower is not clear. Furthermore, the antibody responses seen after the administration of high systemic doses of ocriplasmin was not different from that seen on placebo.

No systemic antibody assays were done during the ophthalmic development of ocriplasmin. This was justified in view of the single localised administration of relatively low amounts of ocriplasmin and the low immunogenic potential of ocriplasmin as evidenced by the relatively low incidence / magnitude of treatment emergent anti-ocriplasmin antibodies detected. There were no differences among ocriplasmin-treated subjects and controls for systemic or ocular allergy-type reactions.

Cases of anterior uveitis were reported, at a higher frequency than in placebo-treated subjects, though these were generally mild and short-lived. Few subjects have been exposed to repeat injections, but in those who have, there does not appear to be an increased incidence of immunogenicity.

Safety related to drug-drug interactions and other interactions

No local or systemic drug interaction studies were considered relevant to support the intravitreal indication, and no intraocular pharmacodynamic drug interactions using co-administration with ocriplasmin were investigated. A published study has been referred to, involving injection of ocriplasmin in rabbit eyes followed by bevacizumab 11 days after (Goldenberg 2011). No adverse effects or increased initial retinal penetration of bevacizumab were observed.

The potential for drug interactions is low, given the rapid inactivation of intravitreal ocriplasmin, and the single use of the product.

Discontinuation due to AES

The incidence of AEs leading to withdrawal from the pivotal placebo-controlled studies was comparable between the ocriplasmin (0.9%) and placebo (1.1%) groups.

Discussion on clinical safety

The safety database for ocriplasmin comes from 7 completed clinical studies (most of which are of 6 months duration) together with preliminary data from several ongoing studies. From these completed studies, 738 subjects have been exposed to intravitreal ocriplasmin (582 to the proposed 125µg dose). In one study 38 subjects were exposed to ocriplasmin for up to 12 months. The pivotal studies compared ocriplasmin with a placebo injection, in a 2:1 or a 3:1 ratio. A further 116 subjects have been exposed to intravenous ocriplasmin, at doses ranging from 50 to 2000 times higher than that proposed for intravitreal use.

Several signals were highlighted in the non-clinical development program: inflammatory response and transient ERG changes in two species, lens subluxation in all species, and intraocular haemorrhage in two species.

In the pivotal studies the most frequently reported ocular TEAEs were vitreous floaters, conjunctival haemorrhage, eye pain, photopsia (sensation of flashing lights) and blurred vision. All of these were more frequently reported in ocriplasmin-treated subjects than those receiving placebo. Vitreous floaters, photopsia, and blurred vision are a (temporary) consequence of PVD and so may be expected from successful treatment. Other TEAEs of note that occurred more frequently in ocriplasmin-treated subjects included retinal/macular oedema, anterior chamber cells/iritis, and photophobia. It is not unlikely that injury by mechanical traction on the retina produced during the intended posterior vitreous detachment could cause functional visual symptoms as well as a temporary disruption of the blood-retina barrier causing retinal/macular oedema and subretinal fluid. It might also be that the proteolytic activity of ocriplasmin can affect not only the vitreoretinal interface but also the function of the Müller cells, which are the retinal cells in closest apposition of the vitreoretinal interface and which span the entire retina.

Rates of non-ocular TEAEs were similar in subjects treated with ocriplasmin and placebo, and do not raise any specific concerns.

Whilst ocriplasmin may cause an acute, and in most cases transient, reduction of VA, there are reports of persistent reduction of VA and there are a number of patients whose VA was significantly reduced at 6 months compared to baseline. At end of study (6 months), 25/465 (5.4%) patients in the ocriplasmin group and 6/187 (3.2%) placebo patients had ≥ 3-line loss in BCVA. In the majority of these subjects, VMA was not resolved on Day 28. The Applicant has demonstrated that among subjects with the ≥3 lines VA loss at end of study, there were some baseline differences between treatment arms. At baseline, 5/6 placebo-treated and 7/25 ocriplasmin-treated subjects had FTMHs while all placebo-treated and 9 ocriplasmin-treated subjects had ERM. However, the size of the MH does not appear to have influenced this outcome since despite the proportion with large (≥1000µm) MHs was higher in the ocriplasmin-group, at EOS, none of these subjects had either 2- or 3-line loss in BCVA. Although there were too few subjects to draw any firm conclusion, the larger MHs at baseline did not appear to increase the risk for long-term adverse effects on VA.

Overall, important and plausible reasons for the VA loss were enlargement or development of new MHs. This happened more frequently in ocriplasmin-treated subjects. In approximately 60% of the FTMHs in the ocriplasmin group and approximately 90% of the FTMHs in the placebo group that did not achieve non-surgical FTMH closure by Day 28, the macular hole diameter (the maximum - minimum width and the maximum width at RPE) increased at post-treatment visits. This increase was larger in the ocriplasmin group compared with the placebo group, particularly for the diameter as measured at the RPE level. It possible that there may be an increased risk

for an incomplete enzymatic cleavage of the adhesion between the posterior vitreous cortex and the internal limiting membrane following treatment, which may result in additional traction. This may lead to enlargement or development of new macular holes, which is of concern. However, the Applicant put these figures into a clinical perspective since with active treatment, significantly more ocriplasmin-treated subjects achieved macular hole closure without vitrectomy by day 28 (40 vs. 10%).

It is also possible that in a number of these cases, end of study VA was evaluated too shortly after vitrectomy (8/13 were evaluated within 3 months) and that more patients in the ocriplasmin group that underwent vitrectomy showed a ≥3 line improvement in VA compared to placebo. Of the events where causality cannot be excluded, 2 ocriplasmin-treated subjects had vitrectomy 2 and 3 months before end of study. Overall, there seems to be no evidence that ocriplasmin treatment followed by vitrectomy increased the risk for a persistent loss of visual function. However, all events of a significant long-term loss of VA are not fully clarified, and the risk of development of new macular holes should be addressed in the SmPC, section 4.4, as well as in the RMP as an identified risk.

Additionally, there were reports of ongoing alteration in colour vision as well as reports of abnormal ERG up to 1 year after ocriplasmin administration. Review of these cases shows that all subjects with significant, early vision loss, and the majority of subjects with dychromatopsia and/or ERG changes also experienced resolution of their vitreomacular adhesion. This suggests a mechanical aetiology, ie, that rapid resolution of vitreomacular traction may temporarily disturb the photoreceptor layer, causing decreased vision, and changes to colour vision. A detrimental biochemical effect of the product on the RPE or photoreceptors cannot, however, be ruled out, though this is unlikely. A limited number of ERGs were available from the extension study TG-MV-012, but confounding factors were present for patients with abnormal ERGs, and similar ERG abnormalities were observed in both study and non-study eyes, including in placebo patients, suggesting that ERG has low specificity in detecting retinal abnormalities. The expert review commissioned by the applicant mentions that patients with large areas of ‘bare RPE’ (ie, separation of the inner retinal layers from the RPE at the macula), or severe retinal degenerative changes are at the highest risk of developing these changes.

However, the events should be put into perspective as they seem to reverse, and importantly, on average, patients improved their VA with an average 9 letters and none of the subjects lost > 5 letters in the long term.

Still, the concerns that ocriplasmin could induce retinal/photoreceptor toxicity, resulting in ERG-changes and dyschromatopsia, remain and are. included in the Protocol of the ongoing Study TG-MV-014. Similar to previous studies, ffERG is chosen to evaluate the whole retinal surface instead of mfERG which focuses on the topographical resolution of ERG-changes in the central retina. The OCT-measurements will give further information on anatomical disruptions at the photoreceptor level. Even though the concern regarding retinal toxicity has been alleviated, this study is considered to have the potential to give further reassurance and to gain further understanding of the consequences of the ERG-changes. For Study TG-MV-014 last patient estimated completion is November 2014 and the report is expected to be submitted Q3 2015.

The risks of retinal tears or detachments, cataracts, intraocular haemorrhage, and raised intraocular pressure do not appear to be any higher with ocriplasmin as compared with placebo injections. There were no cases of endophthalmitis reported in the clinical studies. However, this is a known risk associated with intravitreal injections that occurs in approximately 1 per 1000 injections. The size of the safety database is sufficient only to detect events with an incidence of

at least 0.4%. It is therefore not clear whether endophthalmitis occurs at an equivalent rate to other intravitreally administered drugs.

Lens subluxation and retinal break/retinal detachment were infrequently reported. Lens subluxation was also observed in pre-clinical toxicology studies. Lens subluxation and retinal break/retinal detachment might be caused by the pharmacological action of vitreolysis. These adverse events are manageable but treatment requires additional surgery. The surgical procedure to treat subluxation is more complicated than conventional cataract surgery.

There also appears to be a small risk of intraocular inflammation associated with intravitreal use of ocriplasmin. Of the 90 cases that occurred in the development program, the majority could be classified as mild anterior uveitis. Half occurred in the first week after treatment. There were only 15 cases of vitritis or vitreous cells. Several of the later cases of intraocular inflammation were attributable to vitrectomy.

The immunogenicity potential of single dose intravitreal ocriplasmin appears to be low. Several cases of anterior uveitis were reported, at a higher frequency than in placebo-treated subjects, though these were generally mild and short-lived. Few subjects have been exposed to repeat injections, but in those who have, there does not appear to be an increased risk of immunogenicity.

2.5.1. Conclusions on the clinical safety

In summary, the majority of the adverse events seen following administration of intravitreal ocriplasmin appear to be attributable to either the injection procedure, or to successful resolution of vitreomacular traction. However, reports of severe and persistent reduction in visual function were received. These may be related to release of the mechanical traction of the underlying condition, but there is some evidence that successfully treated subjects are at risk of incomplete enzymatic cleavage of the vitreous base, resulting in additional traction that may predispose to enlargement of macular hole or development of new macular holes.

There were also a number of cases of ongoing alteration in colour vision as well as reports of abnormal ERG up to 1 year after ocriplasmin administration. Again the risk of such events leading to sequelae appears small, and in most cases the abnormalities resolved on follow-up. The currently available data indicate that these events were related to the secondary traction induced by ocriplasmin or even influenced by the underlying condition, but are too scarce to exclude an involvement of the pharmacological effect of ocriplasmin. These issues should be further investigated in the post-marketing setting.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan.

Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
Visual impairment	**Routine Pharmacovigilance** ***Risk characterisation*** • Intensive follow-up of cases of severe acute visual acuity reduction, dyschromatopsia or ERG abnormalities as events of special interest both from clinical trials and non-clinical trial sources. • Further characterisation of all the retinal risks in ongoing and future clinical trials. • Communication in DSURs and PSURs until otherwise agreed with Rapporteur. • Communication in the IB, SmPC and RMP as new relevant information becomes available.	**Routine** ***Risk communication by SmPC*** • Section 4.2 recommends a 7-day delay between injections in case treatment of the fellow eye is needed, to monitor the post-injection course including the potential for decreased vision in the injected eye • Section 4.4 'Special warnings and precautions for use' includes the risk for a significant, but transient loss of visual acuity during the first week after the injection, and recommends post-injection monitoring • Section 4.7 'Effects on ability to drive and use machines' includes wording warning of possible temporary vision alterations and recommendation not to drive or use machines until the vision impairment resolves • Section 4.8 'Undesirable effects' lists visual impairment and related terms as adverse reactions seen in clinical trials and provides additional information on observed cases of acute transient decreases in visual acuity • Patient Leaflet to instruct patients to report visual or ocular symptoms without delay

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
	Additional Pharmacovigilance ***Risk characterisation*** • Clinical trial TG-MV-014 • Targeted follow-up questionnaires for cases of acute loss of visual acuity, dyschromatopsia or ERG abnormalities for a duration of 2 to 3 years after the first launch in a EU country. • Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Additional** Patient education materials 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
Dyschromatopsia	**Routine Pharmacovigilance** ***Risk characterisation*** • Intensive follow-up of cases of severe acute visual acuity reduction, dyschromatopsia or ERG abnormalities as events of special interest both from clinical trials and non-clinical trial sources • Further characterisation of all the retinal risks in ongoing and future clinical trials • Communication in DSURs and PSURs until otherwise agreed with Rapporteur • Communication in the IB, SmPC and RMP as new relevant information becomes available **Additional Pharmacovigilance** ***Risk characterisation*** • Clinical trial TG-MV-014 • Targeted follow-up questionnaires for cases of acute loss of visual acuity, dyschromatopsia or ERG abnormalities for a duration of 2 to 3 years after the first launch in a EU country	**Routine** ***Risk communication by SmPC*** • Section 4.7 'Effects on ability to drive and use machines' includes wording warning of possible temporary vision alterations and recommendation not to drive or use machines until the alterations resolve • Section 4.8 'Undesirable effects' lists chromatopsia as an adverse reaction seen in clinical trials and provides additional information on observed cases • Package Leaflet to instruct patients to report visual or ocular symptoms without delay
ERG abnormalities	**Routine Pharmacovigilance** ***Risk characterisation*** • Intensive follow-up of cases	**Routine** ***Risk communication by SmPC*** • Section 4.7 'Effects on ability

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
	of severe acute visual acuity reduction, dyschromatopsia or ERG abnormalities as events of special interest both from clinical trials and non-clinical trial sources • Further characterisation of all the retinal risks in ongoing and future clinical trials • Communication in DSURs and PSURs until otherwise agreed with Rapporteur • Communication in the IB, SmPC and RMP as new relevant information becomes available **Additional Pharmacovigilance** ***Risk characterisation*** • Clinical trial TG-MV-014 • Targeted follow-up questionnaires for cases of acute loss of visual acuity, dyschromatopsia or ERG abnormalities for a duration of 2 to 3 years after the first launch in a EU country	to drive and use machines' to include wording warning of possible temporary vision alterations and recommendation not to drive or use machines until the alterations resolve • Section 4.8 'Undesirable effects'lists ERG abnormalities (MedDRA PT 'retinogram abnormal' as an adverse reaction seen in clinical trials and provides additional information on observed cases • Package Leaflet to instruct patients to report visual or ocular symptoms without delay
Retinal Detachment	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 4.8 lists retinal detachment as an adverse reaction seen in clinical trials and provides additional information on observed cases • Section 4.4 'Special warnings and precautions for use' to include text on post-injection monitoring and for ophthalmologists to instruct patients to report any visual or ocular symptoms without delay • Package Leaflet to instruct patients to report visual or ocular symptoms without delay

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
	Additional Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Additional** Patient education materials 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
Intraocular pressure increased	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 4.4 'Special warnings and precautions for use' recommends post-injection monitoring with particular emphasis on increases in intraocular pressure • Section 4.2 'Posology and method of administration' recommends availability of sterile paracentesis, if required
Intraocular haemorrhage	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 4.2 'Posology and method of administration' to include wording on pre-treatment precautions, relevant aseptic techniques and injection location (mid vitreous) • Section 4.4 'Special warnings and precautions for use' to include text on post-injection monitoring and for ophthalmologists to instruct patients to report any visual or ocular or symptoms without delay

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
	Additional Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Additional** Patient education materials 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
Intraocular inflammation	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 4.2 'Posology and method of administration' to include wording on pre-treatment precautions, relevant aseptic techniques and injection location (mid vitreous) • Section 4.3 'Contraindications': to include contraindications in active or suspected ocular or periocular infections • Section 4.4 'Special warnings and precautions for use' to include text on post-injection monitoring and for ophthalmologists to instruct patients to report any visual or ocular or symptoms without delay
Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
Increased vitreomacular traction	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional Pharmacovigilance**	**Routine** ***Risk communication by SmPC*** • Section 4.8 'Undesirable effects' lists 'vitreous adhesions' (MedDRA term for 'vitreomacular traction') as an adverse reaction seen in clinical trials and provides additional information on observed cases **Additional** Patient education materials

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
	• Clinical trial TG-MV-014 • Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	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
Development of new macular holes or progression of macular hole size	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional Pharmacovigilance** • Clinical trial TG-MV-014 • Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Routine** ***Risk communication by SmPC*** • Section 4.4 'Special warnings and precautions for use' mentions the risk for occurrence of new or enlarged macular holes as a result of increase in tractional forces • Section 4.8 'Undesirable effects' lists macular hole as an adverse reaction seen in clinical trials and provides additional information on observed cases **Additional** Patient education materials 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

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
Retinal / macular oedema	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 4.8 'Undesirable effects' lists retinal and macular oedema as adverse reactions seen in clinical trials
Lens Subluxation	**Routine Pharmacovigilance** Intensive follow-up will be performed for any case reports received. ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional** • Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Routine** ***Risk communication by SmPC*** • Section 4.4 'Special warnings and precautions for use' warns about a potential for lens subluxation or phacodonesis and recommends avoiding treatment of patients with lens zonule instability • Section 4.8 'Undesirable effects' lists lens subluxation as an adverse reaction seen in clinical trials and provides additional information on observed cases **Additional** Patient education materials 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

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Identified Risk		
Endophthalmitis	**Routine Pharmacovigilance** Intensive follow-up will be performed for any relevant case reports received. ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional** • Drug Utilisation Study will include a survey to evaluate the success of the patient educational materials.	**Routine** ***Risk communication by SmPC*** • Section 4.2 'Posology and method of administration' recommends pre-operative administration of antibiotic drops at the discretion of the treating ophthalmologist and recommends aseptic conditions for the intravitreal injection procedure. • Section 4.3 'Contraindications': includes contraindications in active or suspected ocular or periocular infections • Section 4.4 'Special warnings and precautions for use' includes text on aseptic injection technique and post-injection monitoring and for ophthalmologists to instruct patients to report any visual or ocular or symptoms without delay **Additional** Patient education materials 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

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Potential Risks		
Immunogenicity (including hypersensitivity / allergic reactions)	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** • Section 2 'Qualitative and Quantitative Composition' indicates the proteinic nature of ocriplasmin • Section 4.2 'Posology and method of administration' indicates single use of ocriplasmin • Section 4.3 'Contraindications' list hypersensitivity to the active substance or to any of the excipients as contraindications • There is insufficient evidence to include more specific wording on this risk in the SmPC at present
Off-label use **Off-label Use Including Paediatric Use**	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional** • Drug Utilisation Study	**Routine** ***Risk communication by SmPC*** • Section 4.1 'Therapeutic indications' specifies the indication limiting its use in adults • Section 4.2 'Posology and method of administration' subsection 'Paediatric population'. The safety and efficacy of JETREA in the paediatric population have not been established. No data are available

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimisation Activities
Important Potential Risks		
Interactions with other intraocular medications	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	**Routine** ***Risk communication by SmPC*** Section 4.5 'Interactions with other medicinal products and other forms of interaction' includes the following statements: • 'No formal interaction studies have been performed' • 'JETREA is a proteolytic enzyme with serine protease activity which could be present in the eye for several days after intravitreal injection (see section 5.2 'Pharmacokinetic properties')' • 'Co-administration with other medicinal products in the same eye may affect the activity of both medicinal products and is therefore not recommended'
Medication errors	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed **Additional** • Drug Utilisation Study	**Routine** ***Risk communication by SmPC*** The SmPC provides instructions for correct storage, handling and use in section 6.2 'Incompatibilities', section 6.3 'Shelf life', section 6.4 'Special precautions for storage' and section 6.6 'Special precautions for disposal and other handling'.
Traumatic cataract	**Routine Pharmacovigilance** ***Risk communication*** • Communication in IB, DSUR and PSURs • Update of RMP and SmPC as needed	None. Traumatic cataract is a known complication of intravitreal injections. The risk is mitigated by the product's exclusive use by specialized ophthalmologists familiar with the injection technique.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Drug Utilisation Study - TG-MV-017 (planned)	Protocol submission by end March 2013 • First patient in (FPI) approximately 6 to 12 months after launch in first country • Last patient in (LPI): approximately 36 months after FPI; Final Study report submission: 12 months after last patient out (LPO).
TG-MV-014 (on-going)	evaluate inter-relationship of VMA resolution and BCVA with microperimetry and full field ERG (ffERG) Clinical Study Report: Q3 2015
Targeted follow-up questionnaire.	Collect data on cases of ERG abnormalities, for a period of two to three years after EU launch. Findings will be presented at least annually in PSURs. Questionnaire submitted for review by April 17 2013

The following additional risk minimisation activities were required:

- A patient information pack should be provided in printed and in audio format, and contain 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

2.7. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Data from two Phase III studies with ocriplasmin in patients with symptomatic focal vitreomacular adhesion show a statistically significant improvement in the proportion of subjects achieving resolution of vitreomacular adhesion by Day 28 after a single injection of ocriplasmin. In the two studies 28 and 25% of patients achieved success in this endpoint, compared with 13 and 6% of patients who had received a placebo injection. Although success may in part be due to the injection procedure itself, a clear effect of the medicinal product has been shown.

A range of both anatomical and functional secondary endpoints were also examined. The proportion of subjects achieving total posterior vitreous detachment at Day 28 was approximately 10 % higher following treatment with ocriplasmin as opposed to placebo. In both studies the proportion of subjects who required a vitrectomy during the study was lower in the ocriplasmin group than in the placebo group. However in neither study was this difference statistically significant, and the difference itself was small at 8 %.

The proportion of subjects achieving non-surgical closure of their full thickness macular hole by Month 6 was 35 to 45% in the two studies. This compares to closure rates of around 90% after vitrectomy with inner limiting membrane peeling. A difference of 30 percentage points was observed in both studies between ocriplasmin and placebo in the proportion of subjects achieving closure by Day 28. This difference becomes less impressive at Month 6 in study TG-MV-007, mainly due to an increase in the placebo response rate, and smaller group sizes.

Regarding the effect of ocriplasmin on vision, in general higher proportions of subjects treated with ocriplasmin gained vision during the studies than those treated with placebo. At Month 6 a higher proportion of ocriplasmin-treated subjects had gained vision (≥1, 2, or 3 lines) than those receiving placebo. Those with poorer baseline vision (<20/50, or <65 letters) appeared to respond better to treatment with ocriplasmin, with a quarter gaining at least 3 lines of vision. The average change in visual acuity for subjects treated with ocriplasmin, however, was not particularly impressive with subjects in both studies gaining only 2 to 3 letters after treatment, and no difference observed between active treatment and placebo. This may not be a particularly sensitive endpoint however, since subjects generally had only a mild loss of vision at baseline. However, in those subjects who achieved resolution of their focal vitreomacular adhesion, the average improvement in vision was between 7 and 9 letters, suggesting that success in the primary endpoint is associated with an improvement in vision, if not in other symptoms of vitreomacular adhesion.

Finally, ocriplasmin-treated subjects in both studies generally achieved numerically larger changes from baseline in subscale and composite scores of the visual function questionnaire.

Subgroup analyses suggest that patients who are likely to require a vitrectomy (but not for an ERM), who have a smaller diameter focal VMA, a FTMH, and poorer baseline vision may benefit the most from ocriplasmin.

Uncertainty in the knowledge about the beneficial effects

The principal uncertainty with the efficacy data is whether the results observed in the clinical studies are representative of what might be seen in the general population within the EU, given apparent differences in efficacy between EU and US subjects, both between and within trials. These differences, however, appear largely due to variations in prognostic baseline characteristics between subjects recruited in different regions.

Results for the secondary endpoints of induction of PVD, and avoidance of vitrectomy are not fully convincing. However, in the context of a treatment that is administered only once, and that would be unlikely to significantly delay alternative treatment (ie, observation, followed by vitrectomy), this level of efficacy can be regarded as acceptable.

The primary endpoint (resolution of focal VMA) represents a surrogate for prevention of the deterioration of vision which may occur with untreated and progressive vitreomacular traction. There is little experience of the reliability of this as a surrogate endpoint, and there was no assessment of whether the initial symptoms had resolved after resolution of the VMA. However, success in this endpoint has been demonstrated to confer an average improvement in visual acuity, and may avoid surgery.

There is only partial support for the primary endpoint from the secondary endpoints. The proportion achieving total PVD was only 10 percentage points higher after ocriplasmin than placebo. Likewise, the proportion requiring vitrectomy was only 8 points lower, and the acual vitrectomy rate was lower than expected from the inclusion criteria. The closure rate for full thickness macular holes was between 35 and 45% in ocriplasmin-treated subjects. This represents a 30 point difference to placebo at 1 and 6 months in study TG-MV-006. However in study TG-MV-007 the result at Month 1 was of uncertain statistical significance, by Month 6 this difference in the closure rate between active and placebo-treated subjects had halved, and the relatively few subjects had a macular hole at baseline.

Subgroup analyses show that in subjects with an ERM or a diameter of VMA ≥1500 µm, ocriplasmin showed little advantage over placebo in several endpoints. It is accepted that the group sizes were small, and that limited conclusions can be made on the statistical significance of these results.

However, there was a trend towards VMA resolution in subjects with ERM treated with ocriplasmin. Given that the alternative for these patients is vitrectomy, which is also more complicated in these subgroups, that the risks of treating such patients with ocriplasmin do not appear greater than in the overall population, and that a single injection of ocriplasmin need not delay a subsequent vitrectomy if required, restricting use to patients without an ERM or with only small diameter adhesions does not appear warranted.

Risks

Unfavourable effects

The most commonly occurring adverse reactions include vitreous floaters (13%), conjunctival haemorrhage (15%), eye pain (11%), photopsia (sensation of flashing lights; 10%) and blurred vision (7%). These are not of specific concern since they appear to be a consequence either of the injection procedure itself, or of successful resolution of the VMA, and are generally manageable and/or transient. Other less frequently occurring adverse events of note include

retinal/macular oedema (4%), and photophobia (3%), both of which are also probably related to resolution of the VMA.

Important ocular adverse events included vision alterations, structural findings of the retina and lens subluxations. In the pooled pivotal studies, vision alterations (e.g. vision blurred, reduced VA, visual impairment, metamorphopsia, scotoma, visual field defect, loss of contrast sensitivity, visual field loss, colour vision alterations, ERG abnormalities), the majority mild in severity, were observed in 20.2 and 7.5% of ocriplasmin and placebo-treated patients, respectively. More than half of the vision alteration AEs (any event) reported for patients in the ocriplasmin 125µg group from the pivotal placebo-controlled studies occurred during the first 7 days after injection. VMA resolution was strongly associated with a higher incidence of vision alterations. Vision alteration AEs that occurred pre-vitrectomy or in patients with no vitrectomy were more frequent after ocriplasmin than placebo. In the pivotal placebo-controlled studies, the majority of vision alteration AEs resolved in both treatment groups, i.e. in 61 of 94 (64.9%) ocriplasmin patients and in 9 of 14 (64.3%) placebo patients. In all, there were 6 cases judged as severe by the Applicant, 5 ocriplasmin cases and 1 placebo case.

Whilst ocriplasmin may cause an acute, and in most cases transient, reduction of VA, there are reports of persistent reduction of VA and there are a number of patients whose VA was significantly reduced at 6 months compared to baseline. At end of study (6 months), 25/465 (5.4%) patients in the ocriplasmin group and 6/187 (3.2%) placebo patients had ≥ 3-line loss in BCVA. In the majority of these subjects, VMA was not resolved on Day 28. Overall, important and plausible reasons for the VA loss were enlargement or development of new MHs.. It is possible that there may be an increased risk for an incomplete enzymatic cleavage of the adhesion between the posterior vitreous cortex and the internal limiting membrane following treatment, which may result in additional traction. This may lead to enlargement or development of new macular holes. However, the Applicant put these figures into a clinical perspective since with active treatment, significantly more ocriplasmin-treated subjects achieved macular hole closure without vitrectomy by day 28 (40 vs. 10%).

In total, 16 events of mild and 1 of severe dyschromatopsia have been reported; of these 9 subjects had ERG changes. Of these, 12 resolved at end of study or during follow up. Of the 5 remaining patients, 1 patient has died, 1 was lost to follow up and 2 reported resolution in post-study contact, 11 and 28 months after injection. The remaining patient is reported from Study TG-MV-014, an ongoing study. This patient had also ERG changes and as well as other SAEs.

A total of 11 subjects (7.8%) have been reported with ERG-changes. Of the 11 cases, 9 also had dyschromatopsia. Also in older studies a number of ERG-changes difficult to interpret were reported, and the incidence may thus be higher. Overall, the chronology is compatible with an effect of ocriplasmin and the majority of events were detected one week after injection. Recovery is indicated in 6 cases with 2 ongoing events (including the subject in the ongoing TG-MV-014) and no follow up is available for 3 subjects. The time to recovery was reported as 3-6 months, while one subject still has an abnormal ERG after 28 months. The latter patient had however confounding disease (vitelliform dystrophy) which is a probable cause for the persistent ERG-changes.

The clinical package also highlights two other risks of treatment. Intravitreal administration of ocriplasmin is associated with a small risk of intraocular inflammation (7%), which generally occurs soon after treatment and is usually mild. There were also three reported cases of lens subluxation, at least one of which was clearly related to the drug.

There does not appear to be a significant risk of non-ocular events after intravitreal administration of ocriplasmin.

These risks should be considered in relation to the complications of vitrectomy, which include retinal tears (<5%), low intraocular pressure (0-25%), acute endophthalmitis (0.03-0.23%), progression of cataract (23-79%), retinal detachment (0-17%), recurrent macular oedema (10%), and recurrent vitreous haemorrhage (7-9%).General anaesthesia, if used, may add an additional risk, and the post-vitrectomy patient may also have to undergo a period of 4-6 weeks without being able to work, out of which 7-14 days may be in a “head-down” position to enhance the success rate of the surgical procedure.

Uncertainty in the knowledge about the unfavourable effects

The safety database is fairly small; 741 subjects were exposed to any dose of ocriplasmin, of whom 582 received the proposed dose of 125µg. Whilst the length of follow-up is acceptable, the size of the safety database limits the safety conclusions that can be drawn.

Concerns remain regarding the risk of persistent loss of vision following treatment with ocriplasmin. It seems plausible that in some patients at least, this may be caused by enlargement of macular hole or development of new macular holes due to increased traction following incomplete cleavage of the vitreous adhesion. In some patients who underwent vitrectomy, the end of study visual acuity may have been evaluated too shortly after surgery to allow for an accurate measurement. There seems to be no evidence that ocriplasmin treatment followed by vitrectomy increases the risk for a persistent loss of visual function. However, all events of a significant long-term loss of VA are not fully clarified, and the risk of development of new macular holes was addressed in the RMP as an identified risk.

The ongoing events of dyschromatopsia and ERG changes are likely to have been caused by a mechanical aetiology (rapid resolution of vitreomacular traction temporarily disturbing the photoreceptor layer). A detrimental biochemical effect of the product on the RPE or photoreceptors cannot, however, be ruled out, though this is unlikely.

There is also a shortage of information on the effects of repeat dosing, since only 12 patients received more than one dose of ocriplasmin in either eye. It is fairly likely that patients who have had one eye treated will require treatment in their second eye, but it is not known whether this poses an additional risk, for example of intraocular inflammation. It also cannot be excluded that patients could receive multiple treatments in a single eye is they fail to respond to initial treatment, even though this would not be within the terms of the licence. Again, the risks of this are unknown. Animal studies revealed an increased risk of lens subluxation with repeat doses of ocriplasmin.

Although no cases of endophthalmitis were reported, this is a known risk associated with intravitreal injections that occurs in approximately 1 per 1000 injections. The size of the safety database is sufficient only to detect events with an incidence of at least 0.4%. It is therefore not clear whether endophthalmitis occurs at an equivalent rate to other intravitreally administered drugs.

Balance

Importance of favourable and unfavourable effects

The primary endpoint in the pivotal clinical trials is a surrogate marker for prevention of the deterioration of vision which may occur with untreated and progressive vitreomacular traction. The two Phase III studies do provide evidence for an effect of ocriplasmin on resolution of vitreomacular adhesion, and show that this may be associated with an improvement in visual acuity. However, other symptoms of the visual disturbance that vitreomacular traction may cause were not assessed during follow-up.

Resolution of vitreomacular adhesion was achieved in 25 to 28% of treated patients, and posterior vitreous detachment in 11 to 16%. Between 35 and 45% of patients with a macular hole at the start of the study achieved closure without vitrectomy. This compares to a spontaneous closure rate for stage 2 holes of around 10%, and a surgical closure rate of around 90%. 26 to 30% of patients gained at least 2 lines of vision, and the average change in vision at Month 6 was around 3.5 letters. As discussed above, these results do not offer clear advantages over placebo treatment in all cases. However, treatment with ocriplasmin need not delay vitrectomy, and the outcome of vitrectomy does not appear to be negatively affected by prior treatment. Therefore, the effects of treatment, though modest, do offer a clear benefit to patients with vitreomacular traction, and may negate the need for surgery.

The more common adverse events that are associated with treatment are short-lived and manageable, and often occur as a response either to the injection procedure or to resolution of the disease condition. A small number of patients experienced more significant loss of vision after treatment, in some cases associated with disturbance of colour vision and electrophysiological changes. These cases appear to be related to resolution of vitreomacular traction, and are generally transient. However, there were a number of patients whose visual acuity remained significantly reduced at 6 months compared to baseline. This seems to be in part related to a small risk of incomplete cleavage of the vitreous adhesion by ocriplasmin, which can cause either an enlargement of an existing macular hole, or development of a new hole. The risk of this should, however, be viewed in the context of the number of subjects who achieved non-surgical resolution of their traction or macular hole.

Two further risks associated with the drug have emerged. The risk of intraocular inflammation appears to be small, and cases were generally mild. There is also a small risk of lens subluxation or phacodonesis, probably due to the effect of the drug on the lens zonules. The limited size of the safety database makes it difficult to accurately quantify the magnitude of these risks, or indeed to detect any other risks that have an incidence of less than 0.4% (such as endophthalmitis).

Benefit-risk balance

Cases of vitreomacular traction, including in association with macular hole, occasionally resolve spontaneously. However, following a period of observation, many patients require vitrectomy in order to prevent significant, progressive damage to the macula. Intravitreal ocriplasmin has been shown to have a modest effect, resulting in relief of vitreomacular traction in around a quarter of those treated, and resolution of macular hole in at least a third of cases. Successful treatment results in an improvement in visual acuity, and avoidance of surgery.

The commonest adverse events associated with ocriplasmin are not a serious concern, being usually transient and minor. The risks of more serious events, such as persistent loss of vision, other changes in retinal function, or damage to the supporting structures of the lens, appear to be small.

Discussion on the benefit-risk balance

The benefits of treatment, though modest, should be taken in context: ocriplasmin is administered as a one-off injection, which if successful will usually result in an improvement in vision and may remove the need for the patient to undergo an operation which itself carries a high complication rate. Should treatment fail to be successful, the option of surgery remains open.

Therefore, the CHMP concluded that the benefit-risk balance for ocriplasmin in the treatment of 'vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns' is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Jetrea in the treatment of adults with vitreomacular traction (VMT), including when associated with macular hole of diameter less than or equal to 400 microns is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in

the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted annually until renewal.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch in each Member State the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where JETREA is marketed, at launch and after launch, all healthcare professionals who are expected to use JETREA are provided with the following items:

- Summary of Product Characteristics (SmPC)
- Information packs for the patients

The patient information pack should be provided in printed and in audio format, and contain 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

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Ocriplasmin is qualified as a new active substance.