TG-MV-008	An open-label, single centre trial of ocriplasmin (generic name of the molecule microplasmin) intravitreal injection for non-surgical treatment of focal vitreomacular adhesion	

Summary of study results

Sponsor ThromboGenics Ltd.
Investigational drug Microplasmin
Title of study An open-label, single centre trial of ocriplasmin (generic name of the molecule microplasmin) intravitreal injection for non-surgical treatment of focal vitreomacular adhesion
Participating Countries Belgium
Publication Hahn P, Chung MM, Flynn HW Jr, Huang SS, Kim JE, Mahmoud TH, Sadda SR, Dugel PU. Safety profile of ocriplasmin for symptomatic vitreomacular adhesion. A Comprehensive analysis of premarketing and postmarketing experiences. *Retina*. 2015 Jun;35(6):1128-34.
Studied period Date first subject enrolled: 28-Jan-2010 Date last subject completed: 07-Apr-2011
Phase of development Phase II
Objectives To evaluate the safety and efficacy of 125µg intravitreal ocriplasmin injection in subjects with focal vitreomacular adhesion.
Methodology All eligible subjects received the study drug. The study drug was administered in the mid-vitreous by injection. After injection, the study eye was examined to exclude retinal non-perfusion or other complications. If after 4 weeks from time of study drug injection, the underlying condition had not improved (i.e., the traction had not been relieved), the investigator could proceed to vitrectomy at his/her discretion. Additionally, if before this time, the best corrected visual acuity (BCVA) in the study eye worsened by ≥ 2 lines or the underlying condition worsened (e.g., progression of macular hole), the investigator could proceed to vitrectomy at his/her discretion..
Number of patients *Planned:* 30 patients *Treated:* 17 patients

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Diagnosis and main criteria for inclusion

Subjects who met all the following inclusion criteria were eligible to be included in the study:

- Male or female subjects aged ≥ 18 years.
- Presence of focal vitreomacular adhesion (VMA) (i.e. central vitreal adhesion within 6mm optical coherence tomography (OCT) field surrounded by elevation of the posterior vitreous cortex.
- BCVA of 20/32 or worse in the study eye.
- BCVA of 20/400 or better in the contralateral eye.
- Written informed consent obtained from the patient prior to inclusion in the study

Test product, dose and mode of administration

Ocriplasmin administered as a single intravitreal injection of study drug (125µg ocriplasmin) into the mid-vitreous of the study eye

Duration of treatment

Single dose administration

Reference therapy, dose and mode of administration

Not applicable

Endpoints for evaluation

Safety

The safety profile was assessed based on:
Post-injection complications (including worsening visual acuity, change in vision, worsening macular oedema, vitreous haemorrhage, retinal tear or detachments, inflammation [presence, severity, location], intraocular pressure (IOP) alteration.

Efficacy

Primary efficacy endpoint:

- Proportion of subjects with non-surgical resolution of focal vitreomacular adhesion at the 28 day visit.

Secondary efficacy endpoints:

- Proportion of subjects with non-surgical resolution of focal VMA evaluation at study visits other than the Day 28 post-injection visit.
- Proportion of subjects with total PVD induction.
- Proportion of subjects requiring additional treatment (vitrectomy).
- Macular oedema resolution (change from baseline in macular thickness in the central subfield).
- Change in best corrected visual acuity (BCVA).
- Achievement of ≥ 2 and ≥ 3 lines improvement in BCVA without need for alternative therapy (i.e. intravitreal drug injection, laser photocoagulation, or vitrectomy) and time to ≥ 2 and ≥ 3 lines improvement in BCVA without need for vitrectomy.
- 25-Item Visual Function Questionnaire (VFQ-25).

Statistical methods

The Safety Set was the primary population for the safety analysis and consisted of all subjects who received at least one dose of the study medication.
The Full Analysis Set (FAS) included all subjects, according to the intent to treat principle, who were administered the study medication and for whom data for at least one post-baseline efficacy assessment was present.
Summary statistics including number of observations (n), mean, standard deviation (SD), median, minimum and maximum were presented for continuous variables. Frequencies and percentages were presented for categories of categorical variables. Percentages were calculated using the total subjects

or number of subjects with non-missing data, as appropriate. Data listings were prepared for all data. Data listings were prepared for all data. Selected data were also graphically presented.

Summary of results

Efficacy results:

Following a single intravitreal injection of ocriplasmin 125 µg a total of 8/17 (47.1%) of subjects showed resolution of focal VMA at Day 28 without the need for surgery and were therefore successful on the primary endpoint.

In the Full Analysis Set (FAS), the proportion of subjects who achieved non-surgical resolution of focal VMA determined at Day 7 and Day 14 post-injection visits was the same as the Day 28 post-injection visit (47.1%). At the Month 3 and 6 post-injection visits 52.9% of subjects achieved non-surgical resolution of focal VMA.

There were no subjects with total PVD induction, by success on the primary endpoint, at Day 7 post-injection. At Day 14 and Day 28, 1 subject had total PVD induction, at Month 3, 2 subjects had total PVD induction, and at Month 6, 3 subjects had total PVD induction.

A total of 2/17 (11.8%) subjects required additional treatment by means of an intervention in the study eye (vitrectomy; SF6 intravitreal injection).

Macular oedema resolution: In terms of this assessment by success on the primary endpoint, the mean macular thickness generally decreased over the course of the study from Baseline with the greatest change being seen at Month 3 (mean 285.6 µm [n=8, SD: 79.32], a decrease of 34.6 µm [SD: 72.28]).

With respect to the change in BCVA (ETDRS score) in response to the primary endpoint, an overall improvement was seen from Baseline at all visits with the exception of the Day 7 visit, where the score was marginally lower than that of Baseline. By Month 6 the mean change in visual acuity for those subjects who responded positively to the primary endpoint (n=8) was 8.6 (SD: 8.72).

The percentage of subjects who showed at least a 2-line and a 3-line improvement in BCVA increased at each study visit. For those subjects who successfully achieved the primary endpoint of the study, 3/8 subjects (37.5%) showed a 2-line improvement by Day 28. By Month 3, 4/8 (50.0%) showed a 2-line improvement and 1/8 (12.5%) subjects showed a 3-line improvement in BCVA. At Month 6 a total of 5/8 subjects (62.5%) showed a 2-line improvement and 3/8 subjects (37.5%) showed a 3-line improvement in BCVA without the need for vitrectomy or other post-ocular intervention.

No subjects showed a worsening in BCVA (3-line or 6-line) by Month 6.

In the Full Analysis Set, mean improvements were seen for all VFQ-25 subscale and composite scores, with the exception of colour vision and dependency, by Month 6.

For those subjects who successfully achieved the primary endpoint, for all VFQ-25 subscale and composite scores, (with the exception of colour vision), a response (an increase in at least 5 points from baseline) was seen by Month 6, with the greatest response seen in distance activities, mental health subscales and composite score 5/8 subjects [62.5%]); followed by general health and general vision subscales 4/8 subjects [50.0%]). For all subscale and composite scores, (with the exception of colour vision), a response (an increase in at least 10 points from baseline) was seen by Month 6, with the greatest response seen in general health, general vision, distance activities, and mental health subscales (4/8 subjects [50%]).

Safety results:

Overall, all subjects (17/17) experienced at least one AE (55 AEs in total) during the study the majority of which were ocular AEs (39 AEs). All but one ocular AE occurred in the study eye. The majority of AEs were mild in intensity except one AE of reduced visual acuity which was classified as moderate in intensity, and there were no AEs classified as severe. A total of 13/17 subjects had at least one drug-related AE, the majority of which resolved without sequelae by the final study visit.

There were 2 treatment-emergent SAEs in 2/17 subjects (11.8%) during the study, of which one SAE was ocular and one non-ocular.

One subject experienced reduced visual acuity following the injection with ocriplasmin (same day). The SAE resolved without sequelae, was moderate in intensity and was considered by the Investigator to be ‘probably related’ to study medication.

One Subject experienced an episode of angina pectoris. The SAE resolved without sequelae, was mild in intensity and considered by the Investigator to be ‘unrelated’ to study medication.

A total of 7/17 subjects (41.2%) developed chromatopsia during the study. These events occurred after injection with ocriplasmin, were considered by the Investigator to be 'probably related' to study medication and were mild in intensity. By the final study visit 5 of the 7 subjects had recovered from the AE of chromatopsia without sequelae. Two of the 7 subjects had an AE of chromatopsia which was ongoing at the final study visit. These subjects were followed up at additional safety assessments (not detailed in the study protocol) until the events resolved. The AE of chromatopsia in one subject was reported by the site in a post-study communication as resolved after the patient had a vitrectomy.
Upon further investigation, the subjects with chromatopsia had no supporting evidence which would suggest an optic neuropathy. Additionally, the findings of reduced visual acuity and decreased ERG amplitudes with generally normal VEPs suggest the process is localized to the retina and not the optic nerve. It was concluded that the subject with the most significant ERG decrease should not have been entered into the study since they had a current condition of vitelliform macular degeneration, a condition known to be associated with ERG and colour vision abnormalities.
No subjects had a mean IOP value which was ≥ 25mmHg at any study visit.
Slit-lamp examinations and dilated retinal examinations did not identify any unanticipated safety concerns.
The most notable safety findings were those related to visual function changes (*i.e.* visual impairment, dyschromatopsia and / or ERG changes). Most of these findings were non-serious, of mild intensity and resolved. An independent, masked CRC reviewed the OCT scans and ERG examinations. No subjects showed a worsening in BCVA (3-line or 6-line) by the end of the study. There were no deaths during the study and no subjects were withdrawn due to an AE.

Conclusions

Overall, the results of this study demonstrate that a single intravitreal injection of ocriplasmin 125µg is effective in resolving focal VMA without the need for vitrectomy and achieving total PVD. In terms of the primary efficacy endpoint, the effect of the drug was rapid and consistently sustained throughout the 6-month study period