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Financial disclaimer: JF; BJ: employees of ThromboGenics NV; KT: employee of Charles River Laboratories

Repeated injections of ocriplasmin in the Göttingen mini-pig

#4043

Purpose

The purpose of this study was to determine the safety of up to six consecutive intravitreal (IVT) injections of ocriplasmin in the mini–pig.

Methods

- Two (2), 3 and 6 ocriplasmin injections 4 weeks apart, were administered by IVT to Göttingen mini-pigs. Each group consisted of 3 males and 3 females. The experimental eye received ocriplasmin at a dose of 63µg/eye
- The vehicle was given to the contralateral eye which acted as a control. Fifty (50) microliters were injected mid vitreous with a 29G ½" needle.
- Animals were subjected to ophthalmic toxicology screening consisting of funduscopic and biomicroscopic (slit lamp) examination (mydriatic and non-mydriatic) and tonometry. In addition a monthly full-field ERG was performed. Enucleated eyes were processed for detailed histopathological analysis at the Charles River Laboratories in Montreal.

Table 1: Experimental Design

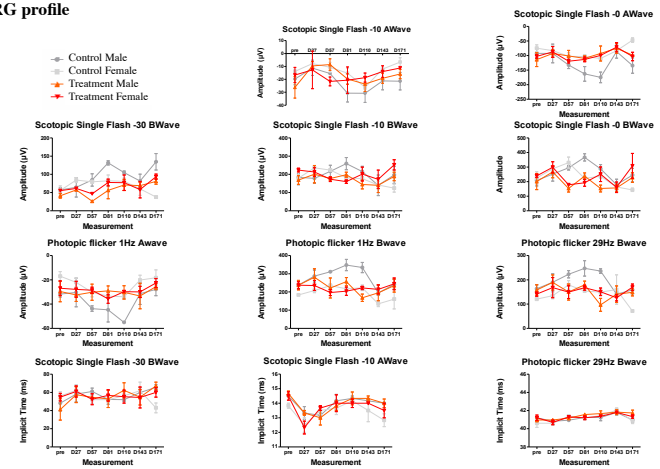
Group No.	Test Material	Dose Level[a] (µg/eye/dose)	Dose Volume (µL)	No. of Animals		Dosing Days	Scheduled Euthanasia Day
				Males	Females		
1	Ocriplasmin	63	50	3	3	1, 28	58
2	Ocriplasmin	63	50	3	3	1, 28, 56	86
3	Ocriplasmin	63	50	3	3	1, 28, 56, 84, 117, 147	177

[a] Dose administered to the left eye; the right eye received reference item.

Table 2: Noteworthy ophthalmic findings

Finding	Timepoint	Incidence	Description
Lens subluxation	5th injection	4/6	Recorded as a very slight aphakic crescent in the superotemporal aspect of the lens
Anterior uveitis	6th injection	1/6	Moderate and transient anterior uveitis consisting of anterior chamber cells and flare, keratic precipitates, corneal vascularization, iris hyperemia and incomplete pupil dilation. These changed had resolved prior to necropsy.

ERG profile



Averaged ERG profiles for Group 3 animals (N=3). Amplitude profiles for the different measured stimuli and a selection of representative latency times are shown. No remarkable changes in response amplitude or latency was revealed after 6 administrations. DXX indicates day post first administration.

Findings considered not related to ocriplasmin administration:

- One animal had grayish vitreal opacities beginning prior to the last dose, which were suspected to be related to previous minor vitreal hemorrhage that occurred at time of dosing, and therefore, were secondary to the experimental procedures.
- Minor and transient conjunctival hyperemia in both eyes and a bulbar conjunctival mass in No. 3502 were secondary to the ERG procedures (ocular manipulation and suture placement).

Results

- An apparent reduction in b-wave amplitude was observed on Day 53, following the second dose. No changes were observed in the a-wave. Although the reason for this reduction is unknown, it was considered to be unrelated to test item administration for the following reasons:
  - Responses remained normal in several other ocriplasmin-treated eyes at this occasion,
  - No effect on b-wave amplitude was observed at subsequent occasions following additional doses, and
  - There were no correlating ophthalmology or microscopic findings.
- One (1) animal developed a moderate and transient anterior uveitis in the treated eye following the last (6th) ocriplasmin injection consisting of anterior chamber cells and flare, keratic precipitates, corneal vascularization, iris hyperemia and incomplete pupil dilation; these changes had resolved prior to necropsy.
- In the group receiving up to 6 injections, lens subluxation, recorded as a very small aphakic crescent in the superotemporal lens quadrant, was noted in four out of six eyes following the 5th injection. Damage to the lens zonules was noted supero temporally. After 6 administrations, microscopic findings of minimal mononuclear cell infiltration (vitreous, 4/6 eyes; injection site, 2/6 eyes; iris/ciliary body, 2/6 eyes) were noted. No signs of inflammation or lens subluxation were observed in the control eyes.

Conclusions

Administration of ocriplasmin at 4-week intervals for up to 3 months was well tolerated in Göttingen mini-pigs at 63 µg/eye/injection and did not result in any adverse events.