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CASE STUDY

Ophthalmic Preclinical Case Study, Safety Assessment of Intravitreal Implants in Dutch Belted Rabbits

STUDY OVERVIEW

In support of their IND, Altasciences' client commissioned a chronic toxicology study to evaluate the ocular safety of a cylindrical intravitreal implant, which was loaded with an API intended for the treatment of age-related macular degeneration. Dutch belted (DB) rabbits were chosen based on (1) the historical use of this breed for ocular safety assessment, (2) the need for an animal model with pigmented eyes to evaluate the potential for ocular melanin binding, and (3) the availability of animals in sufficient quantity for an IND-enabling study.

As is often the case for nonclinical safety studies, the doses given to the rabbits needed to be several-fold higher than the human dose, which required that up to six implants be delivered to each eye. The large number of implants presented both technical and scientific challenges. Rabbits have a much smaller vitreous space (~1.5 mL total vitreous volume in rabbits versus ~5 mL in humans) and larger lenses (~8 mm in rabbits versus ~4 mm in humans). These factors present an increased risk of the implants coming into contact with the soft tissues in the posterior segment of the eye during injection, and potentially post-injection. Special consideration was needed when designing the study to ensure that any lesions resulting from the dosing procedure could be identified, monitored throughout the study, and ultimately differentiated from API-related effects.

STUDY DETAILS

Class of Drug or Device:	Cylindrical intravitreal implant
Indication:	Age-related macular degeneration
Animal Model:	DB rabbits
# of Animals:	7M/7F per cohort
Dose Route:	Intravitreal implantation
Dose Regimen:	Single intravitreal delivery to both eyes on Day 1
Study Design:	General observations: clinical signs, body weights, food consumption. Ocular measurements/observations: ophthalmic examination, intraocular pressure, electroretinogram, fundus photography, ocular histopathology

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STUDY PURPOSE

The objective of the study was to assess the toxicity and toxicokinetics of the client's intravitreal implants for a period of up to 1.5 years following a placement of the implants in the vitreous space of both eyes in DB rabbits.

METHODS

Animals were dosed by intravitreal injection using proprietary injectors provided by the client. All eyes were dosed once at the start of the study according to the table below.

GROUP	TREATMENT	# OF IMPLANTS PER EYE
Control	Placebo implant	2
Test article low-dose	Test implant	2
Test article mid-dose	Test implant	3
Test article mid-dose	Test implant	4
Test article high-dose	Test implant	6

All test implants contained the same mg amount of API. Implants were delivered with a single injection (control and low-dose) or two successive injections (mid- and high-dose).

Standard safety observations and measurements were performed over the course of the study, including detailed clinical observations, body weights, food consumption, and clinical pathology.

Ocular assessments were done prior to injection, once during the week following injection, approximately once a month during the first year, and then approximately once every two months during the final six months of the study.

Ocular assessments included fundus imaging (RetCam Shuttle), intraocular pressure (Reichert TonoPen), ophthalmology examination, and electroretinography. Ophthalmology examinations were performed by a board-certified veterinary ophthalmologist, and included examination of the anterior segment with the aid of a slit lamp and examination of the fundus using an indirect ophthalmoscope and an aspheric condensing lens.

Blood samples were collected periodically over the course of 18 months to assess systemic exposure.

Animals were euthanized at approximately six months and 18 months following placement of the implants. Complete necropsies were conducted, and standard organ weights were recorded. The eyes were collected and preserved en bloc for histopathology evaluation. The eyes were then sectioned at three levels, processed to slide, and stained with hematoxylin and eosin. Slides were read by a board-certified veterinary pathologist.

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RESULTS

Although minimal systemic exposure to the API was detected in test group animals, there was no evidence of systemic effects.

Non-adverse findings were noted for the eyes during the in-life phase.

The pathologist noted microscopic findings in the vitreous, lens, and retina of control, and test eyes. All vitreous findings were deemed non-adverse due to limited severity. Microscopic observations noted for the lens were considered injection procedure-related and adverse. Microscopic findings in the retina were considered to be injection procedure-related, some adverse and some not.

Electroretinography revealed waveform abnormalities in some eyes that received six implants, including reduced b-wave positivity in the dark-adapted response reduced light-adapted response.

The general appearance of the implants was observed by indirect ophthalmoscopy and fundus imaging. The implants remained intact over the course of the study. A gradual decrease in coloration of the API-containing implants was observed and attributed to depletion of the test drug.

CONCLUSION

The technical and scientific challenges associated with the placement of multiple implants in the relatively small vitreous space of DB rabbits required specialized instruments and qualified experts in the fields of veterinary ophthalmology, veterinary pathology, and electroretinography. The combined expertise of our team, familiarity with the test species, and commitment to making the review and interpretation of the data a collaborative effort, allowed for us to differentiate between effects associated with the injection procedure, the API, and/or the implant itself. These distinctions can be critical to acceptance of the study results by regulatory agencies.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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