An Adaptive Study Design to Evaluate for the Onset, Progression, and Reversibility of Lenticular Changes in Wistar Han IGS rats

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ABSTRACT

During a three-month general toxicology study in Wistar Han IGS rats, test article (TA)-related lenticular changes were identified during clinical observation and confirmed as cataracts by slit-lamp biomicroscopy. The lenticular changes were unexpected, given the target biology/pharmacology and lack of ocular findings in previous six- and nine-month studies in Wistar Han rats and Beagle dogs, respectively. To evaluate the onset, progression, and potential reversibility of the lenticular change, rats were orally administered vehicle or TA (n=20/sex/group) and once weekly ophthalmoscopic examinations were conducted by a board-certified veterinary ophthalmologist. Based on ophthalmoscopic findings, animals were assigned to one of three phases (onset, progression, or reversibility) with an equal proportion of animals in each phase. Onset of lenticular changes occurred by Week 4 of dosing. Progression of lenticular changes included 1) swelling/splitting of the posterior cortical suture lines; 2) radially oriented anterior and posterior lenticular opacities; 3) triangular-shaped opacification of the posterior cortex in the region of the suture lines; 4) opacification of anterior and posterior cortical fibers to the point of obscuring fundus examination; and/or 5) prominence of the lenticular nuclear/cortical junction. Histopathology findings consisted of minimal to moderate swelling or swelling/degeneration of lens fibers. A majority of recovery phase animals developed a prominence of the lenticular nuclear/cortical junction, with mild to moderate lens fiber degeneration. In conclusion, assigning animals to study phase (onset, progression, or recovery) based on weekly ophthalmoscopic findings afforded an adaptive study design to characterize the time course of TA-related lenticular changes in rats.

METHODS: STUDY DESIGN

Study Design: Two groups: vehicle and test article (n=20/sex/group). Control animals were paired with test article animals by the suffix of animal identification numbers, so there was a matching number of control animals for each necropsy throughout the study.

Dose Administration: Onset: Animals (n=7/sex/group) were administered test article for a range of 25 to 39 days, with necropsy the day after the last dose. Progression: Animals (n=5-6/sex/group) were administered test article up to 71 days, with necropsy the day after the last dose. Recovery: Animals (n=7-8/sex/group) were placed on recovery (test article free period) for up to 91 days following the last dose administration (between Days 25 and 39).

METHODS: STUDY STUDY ENDPOINTS

Ophthalmoscopic examinations: Once weekly, consisting of indirect ophthalmoscopy and slit-lamp bimicroscopy.

Histopathology: At necropsy, the right eye was collected, preserved, and processed to slide for microscopic evaluation.

Bioanalysis: Parent and metabolite were evaluated in plasma (Days 1 and last dose at 4 and 24 hours post-dose) and lens (left eye only), collected at necropsy.

DISCLOSURES

The design, analyses, and financial support of these studies was provided by AbbVie. AbbVie and MPI Research participated in the interpretation of data, writing, review, and approval of the content. All co-authors are employees of AbbVie, Inc. or MPI Research.

STUDY WEEKS

1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17

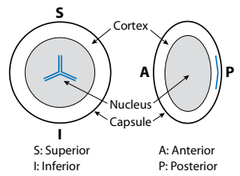
Dosing Period

ONSET PHASE

(n=7 males; 7 females)

- Observed in females approximately one week earlier than males.
- Weeks 4 to 6: Splitting of lens suture lines (Fig. 1).

Fig. 1: Splitting of Lens Suture Lines



PROGRESSION PHASE

(n=6 males; 5 females)

- Weeks 6–9: Radially oriented cortical opacities (Fig. 2).
- Week 8: Triangular-shaped opacity at suture lines (Fig. 3).
- Weeks 10–13: Unable to visualize fundus (Fig. 4).

Fig 2: Radially Oriented Cortical Opacities

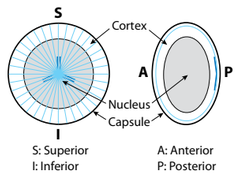
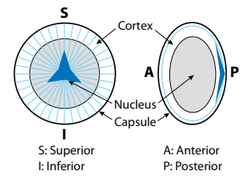


Fig. 3: Triangular-shaped Opacity



Non-dosing Period

REVERSIBILITY PHASE

(n=7 males; 8 females)

- Lenticular opacification progressed at a slower rate than the progression phase.
- A majority of animals developed a prominence of the lenticular nuclear/cortical junction, with mild to moderate lens fiber degeneration (Fig. 5).

Fig. 4: Obscuring of Fundic Exam

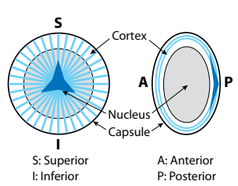
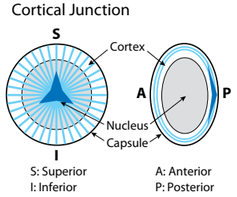


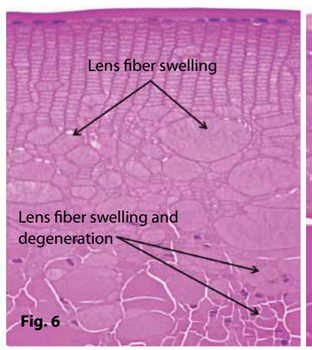
Fig. 5: Prominent Nuclear/ Cortical Junction

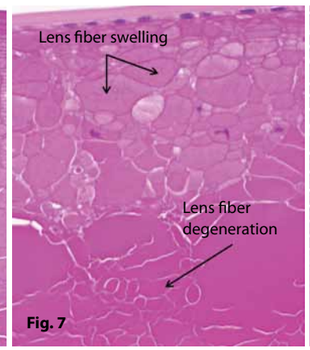


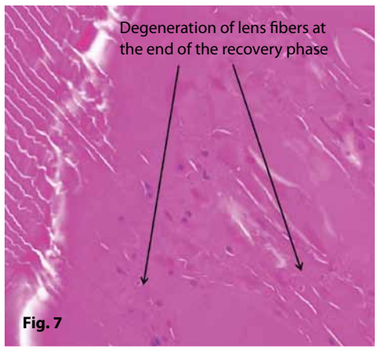
Plasma and Lens Pharmacokinetics

In general, there were higher concentrations of both parent and metabolite in lens vs. plasma.

	Last Dose – Plasma			Lens		
Onset						
	Parent (P) (µg/mL)	Metabolite (M) (µg/mL)	P:M Ratio	Parent (µg/g)	Metabolite (µg/g)	P:M Ratio
Males	2.9	1.7	1.8	16.2	8.4	1.9
Females	20.8	6.0	3.5	27.1	11.3	2.4
Progression						
	Last Dose – Plasma			Lens		
	Parent (µg/mL)	Metabolite (µg/mL)	P:M Ratio	Parent (µg/g)	Metabolite (µg/g)	P:M Ratio
Males	3.6	1.6	2.2	12.4	5.2	2.4
Females	7.1	3.0	2.4	26.6	8.1	3.3







Figures 6–8, Ocular lens of rats (40X): During the progression phase, histopathology findings consisted of minimal to moderate swelling or swelling/degeneration of lens fibers. Although a progression of changes was evident by ophthalmoscopic examination, the nature and severity of the microscopic findings were similar at the various time points.

Lens fiber swelling was characterized by enlarged, rounded fibers with loss of fiber detail (Fig. 6 and 7). Lens fiber degeneration was characterized by loss of lens fiber integrity with areas of globular eosinophilic material containing cellular and nuclear debris (Fig. 7). At the end of the recovery phase, lens fiber degeneration was the primary finding and often occurred in a paracentral ring around the middle of the lens with loss of lens fiber integrity (Fig. 8).