#5073

Sustained Delivery of Prostaglandin from Drug-Containing Depots Using Ocular Rings in Beagles

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Commercial Relationships: KSC:C, JYE:I, P, JR:F, SJ:F, FL:F, EJE:I, P, CDL:I, P

Purpose

To evaluate the efficacy of sustained-release latanoprost from depots in a topical ophthalmic drug delivery device (TODDD™). The TODDD™ is designed and intended to continually deliver drug while worn on the superior sclera 24/7 for several months at a time. The human TODDD™ design has been demonstrated to be safe and retained comfortably in human volunteers (Poster #1078, ARVO 2013). To facilitate the use of the depots in beagle dogs, a ring device to carry the depots was configured.

Methods

The right eyes of 8 ocular normotensive adult beagle dogs were fitted with ocular ring devices, each containing 2 latanoprost-drug depots (cylindrical cores, 600 µg latanoprost). The depots were matched in volume and surface release area to those of the human-configured device. A device with blank depots containing no latanoprost was placed on the right eye of 1 additional animal. All left eyes remained untreated. Clinical slit-lamp exams were performed pre-placement on Day 1 and post-placement on Days 1, 8 and 17. Daily observations were performed to assess the presence of the device (retention) and any ocular abnormalities. Intraocular pressure (IOP, TonoVet rebound tonometer) and pupil diameter were measured pre- and post- placement on Day 1, and on Days 4, 8, and 16. Plasma samples were collected on Day 1 prior to, and approximately 4 hours after device insertion, and on Day 8. Tear samples were collected on Day 16 by Schirmer strip in the lower cul-de-sac. Tear and plasma samples were analyzed by LC/MS/MS for latanoprost and latanoprost acid. The lower limit of quantitation was 0.5 ng/mL.
The *in vivo* portion of the study was conducted by Toxikon Corporation, Bedford, MA. The bioanalytical work was performed by Agilux Laboratories, Worcester, MA.

Results

IOP reduction in the treated eye compared to the control eye was approximately 3 mmHg on Day 4 (n=6) and Day 8 (n=4), and 7 mmHg on Day 16 (n=3) in the dogs that had retained the latanoprost-loaded devices, representing a 31-42% reduction in normotensive IOP from baseline. This response is consistent in magnitude to what has been achieved with latanoprost eyedrops in this species. There was no effect on IOP in the animal wearing the placebo device. The IOP returned to baseline levels in all eyes after removal of the devices. A range of 25 - 215 ng/mL latanoprost was recovered from the tears of animals wearing the drug devices. No latanoprost was detected in any plasma samples, or in the tear samples from untreated eyes.

TODDD™ - Topical Ophthalmic Drug Delivery Device for continuous (24/7) drug delivery for up to 90+ days

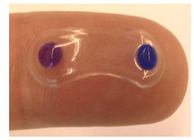
Device design – Utilizes modified contact lens design features to provide sustained comfort, retention, stability and capacity.
- •Central curvature
- •Peripheral curves
- •Edge apex contours
- •Edge lift

Inserted and completely concealed under the eyelid
- •No intrusion into the visual field
- •No inter-blink surface drying or deposits

Material formulation – (Matrix TODDD – non-erodible)
- •Proprietary platform technology with customized formulation for each drug
- •Comfort and biocompatibility emphasized in polymer selection
- •Drug is mixed with polymers prior to molding polymerization
- •Drug molecule unaffected by polymerization process

Drug Depot TODDD
- •Material with drug is placed in distinct pockets or chambers
- •TODDD acts as the depot carrier

Combination TODDD
- •A matrix TODDD with drug depots



Human TODDD™

Representation of Dog Ring, showing location of drug depots

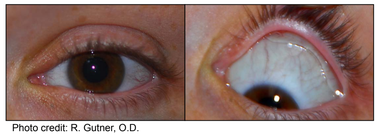
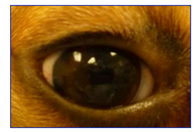
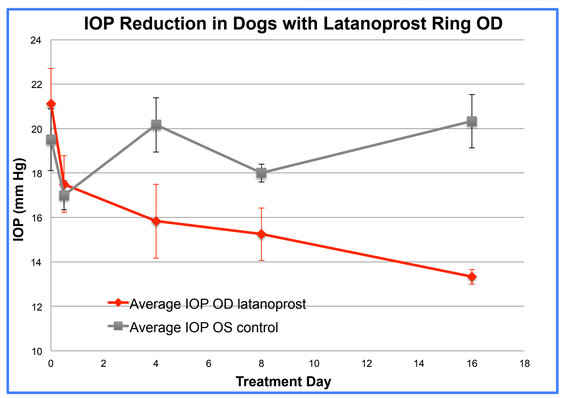
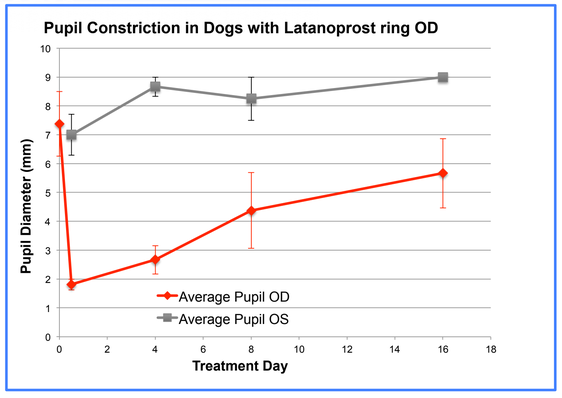


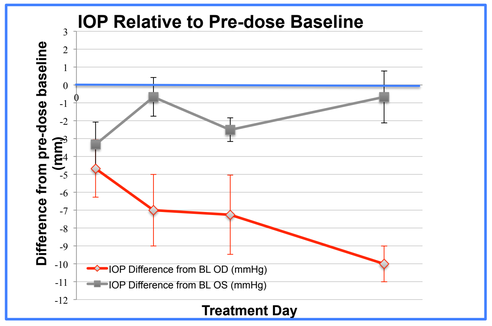
Photo credit: R. Gutner, O.D.



RESULTS







Latanoprost and Latanoprost Acid Concentration in Tears on Day 16

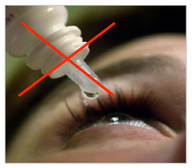
Animal #	Latanoprost (ng/mL) OD	Latanoprost Acid (ng/mL) OD	Latanoprost (ng/mL) OS	Latanoprost Acid (ng/mL) OS
2 – no ring in place	BQL	BQL	BQL	BQL
4 – latanoprost ring OD, no ring OS	21.33	BQL	BQL	BQL
7 – latanoprost ring OD, no ring OS	190.13	25.15	BQL	BQL
8 – latanoprost ring OD, no ring OS	85.80	BQL	BQL	BQL
9 – blank ring, ejected	BQL	BQL	BQL	BQL

BQL = Below Quantitation Limit (0.5 ng/mL)

* Plasma Samples were all BQL

Conclusions

This study demonstrates the therapeutic feasibility of these sustained-release depots. Although long-term retention of a ring device configuration of these particular dimensions in this species was not achieved, *in vitro* analysis of the worn devices and of the extended latanoprost release profile from new devices relative to tear levels measured at Day 16 indicates that sustained IOP-lowering would be achieved over a 2-3 month wear period. These results support the use of these depots in the TODDD design for human use.



Advantages of TODDD™ Platform:

- ✧ Eliminates prevalent poor eye drop insertion and dosing issues
- ✧ Adaptable to the drugs and combinations of drugs currently delivered by eye drops
- ✧ Fewer compliance issues. Continuous, 90+ day 24/7 release of drug independent of patient dosing regimen
- ✧ Preservative free
- ✧ Excellent retention and easy confirmation
- ✧ Simple replacement in less than a minute
- ✧ Fewer, perhaps elimination of, systemic side-effects resulting from eye drop excess drug delivery
- ✧ Can incorporate less soluble drugs not suitable for aqueous solution

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