The Pharmacodynamic Effect of LatanoSol Eye Drops on IOP of Normotensive Dogs

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Introduction

LatanoSol is a novel water- and preservative free formulation based on Novaliq`s proprietary EyeSol-Technology containing the prostaglandin analogue latanoprost as active ingredient. LatanoSol is expected to lower the intraocular pressure (IOP) by increasing the aqueous humor outflow, primarily through the uveoscleral pathway[1].
The EyeSol-Technology is based on semifluorinated alkanes (SFAs), a physically and chemically inert substance class, possessing low surface tension with the property of high spreading. While forming a transparent, colorless and laser stable solution with the same refractive index as water it is amphilic[2,3] and therefore able to formulate poorly soluble drugs.
LatanoSol has a considerably smaller droplet size and excellent spreading properties on the ocular surface compared to a marketed aqueous latanoprost formulation. Ocular tolerability and the effect on lowering IOP of LatanoSol compared to vehicle or to the marketed product Xalatan were investigated.

Methods

Tolerability and pharmacodynamic effect on IOP was assessed in conscious normotensive dogs in a blinded, randomized study. Animals (n = 8) received a topical ocular dose with LatanoSol or Vehicle (11 µL/drop) or Xalatan (30 µL/drop) once daily for seven days to each eye, followed by a washout period (Table 1). IOP measurements and ocular irritation scoring were performed multiple times during each phase.

Topical Ocular Dose Regime		Target Dose (µg/eye/day)	
OD	OS	OD	OS
0.00125% LatanoSol	Vehicle	0.14	0
Vehicle	0.0025% LatanoSol	0	0.28
Vehicle	0.005% LatanoSol	0	0.55
0.01% LatanoSol	Vehicle	1.1	0
Vehicle	0.015% LatanoSol	0	1.7
0.01% LatanoSol	Xalatan	1.1	1.5

Table 1: Study design, dosing for 7 days

Figure 1: Measuring the IOP of the dog using the TONOVET tonometer
Reference http://beyondvetstore.com

All procedures adhered to the guidelines on the use of animals by the Association for Research in Vision and Ophthalmology (ARVO) and had the approval of Covance's institutional animal care and use committee.

Statistical Analysis

Changes in IOP including maximal effect (E_{max}) and area under the effect curve (AUC_E) were calculated from the differences in percentage change from baseline between the two eyes of each animal (% change IOP $LatanoSol_{tx}$ - % change IOP $LatanoSol_{t0}$) – (% change IOP $Xalatan_{tx}$ - % change IOP $Xalatan_{t0}$). Data are expressed as mean of IOP ± SEM (Figure 3) and mean of IOP change ± SEM (Figure 2). The IOP change in Figure 2 was calculated as follows (LatanoSol IOP_{tx} – LatanoSol IOP_{t0}). IOP_{tx} is the IOP at time of interest and IOP_{t0} is the IOP before the first dose.

	LatanoSol	Xalatan
Targeted dose (µg/eye)	1.1	1.5
mean E_{max} (%)	-35.3 ± 4.48	-39.7 ± 3.76
mean AUC_E (% x hour)	-2360 ± 360	-2860 ± 498

Table 2: Change (E_{max}, AUC_E) in IOP for LatanoSol and Xalatan

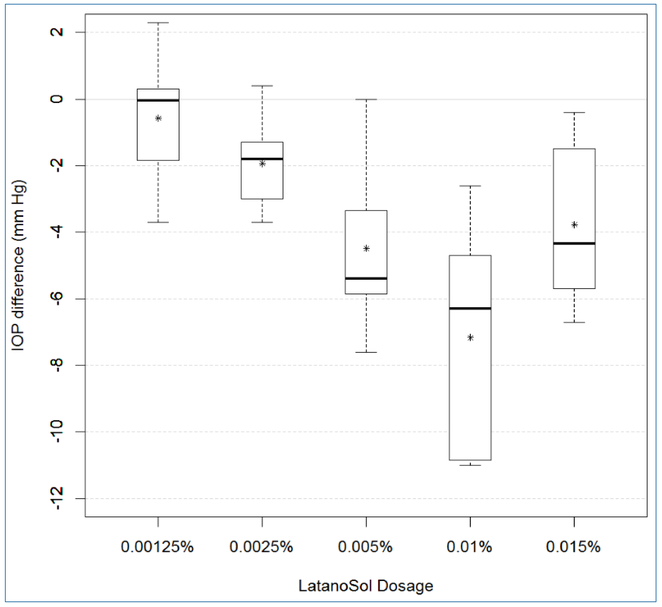

Figure 2: Comparison of IOP change for different LatanoSol concentrations on day 7, 6 hours postdose

The differences are presented using boxplots. Within the box 50% of the data are covered. The so-called whiskers describe the minimum and maximum of the data.

Results

Ocular irritation scoring revealed no test article-related findings for the preservative free LatanoSol formulations at all tested dose levels and they were well tolerated.
A dose-dependent reduction in IOP was observed with increasing latanoprost concentrations in the EyeSol vehicle at a dose range from 0.00125% to 0.01%.
No gain in efficacy was observed with a further increase in dose (Figure 2).
Comparable IOP lowering effect for LatanoSol (1.1 µg/eye/day) and Xalatan (1.5 µg/eye/day) was observed following daily topical ocular administration for seven days to dogs (Table 2 and Figure 3).

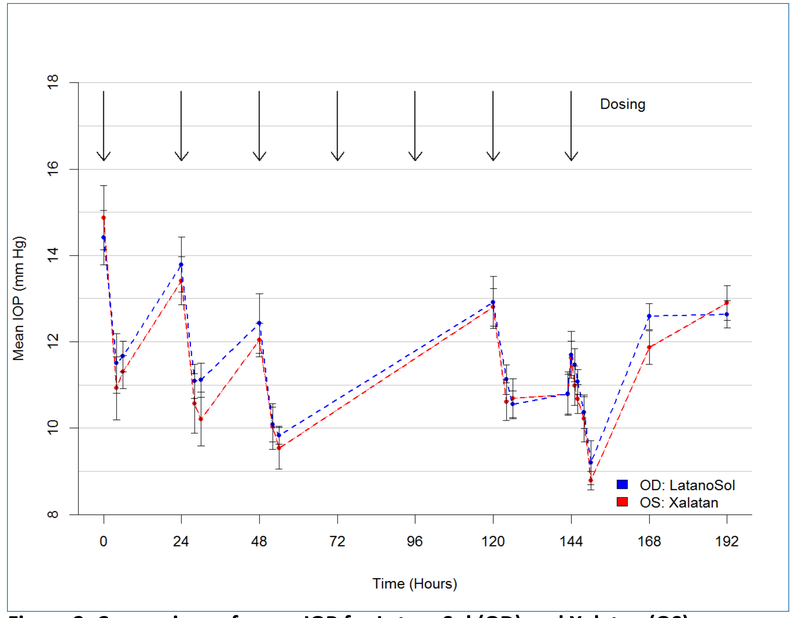

Figure 3: Comparison of mean IOP for LatanoSol (OD) and Xalatan (OS)
During the weekend no IOP measurements were obtained (54 - 120 hours).

Conclusion

LatanoSol had a comparable effect to Xalatan which was reached even with a smaller droplet size and a lower targeted dose. Repeated dosing with LatanoSol eye drops was well tolerated and resulted in a considerable IOP-lowering effect in normotensive dogs.

References:

1. Weinreb R.N. et al. The Pathophysiology and Treatment of Glaucoma, A Review, JAMA. 2014, 311(18), 1901-11
2. Krafft M.P., Riess J.G. Chemistry, Physical Chemistry, and Uses of Molecular Fluorocarbon-Hydrocarbon Diblocks, Triblocks, and Related Compounds. Chem.Rev. 2009, 109, 1714-1792.
3. Kim Y.K. et al. A new, heavier-than-water silicone oil. Eur J Ophthalmol. 2005, 15(5), 627-37.

Commercial Relationships Disclosure: K. Eickhoff, keickhoff@novaliq.com, Novaliq GmbH (E) | J. Prusakiewicz, Covance Laboratories Inc. (E)| L. Uhlmann, University Heidelberg (E)| C. Struble, Covance Laboratories Inc. (E) | F. Löscher, Novaliq GmbH (E) | S. Krösser, Novaliq GmbH (E)