Preclinical and clinical development of SYL040012 eye drops for the treatment of increased intraocular pressure associated to glaucoma

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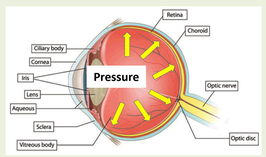
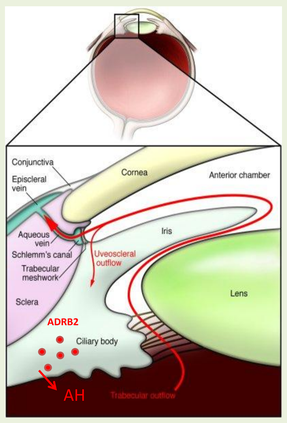
INTRODUCTION

GLAUCOMA



Glaucoma is a progressive ocular syndrome characterized by degeneration of the optic nerve and irreversible visual field loss. Main risk factor is increased IOP.



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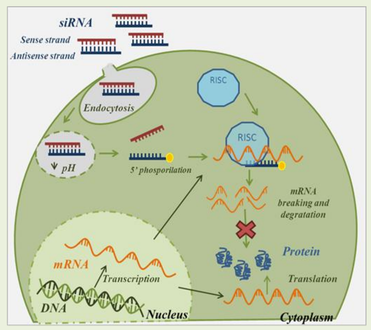


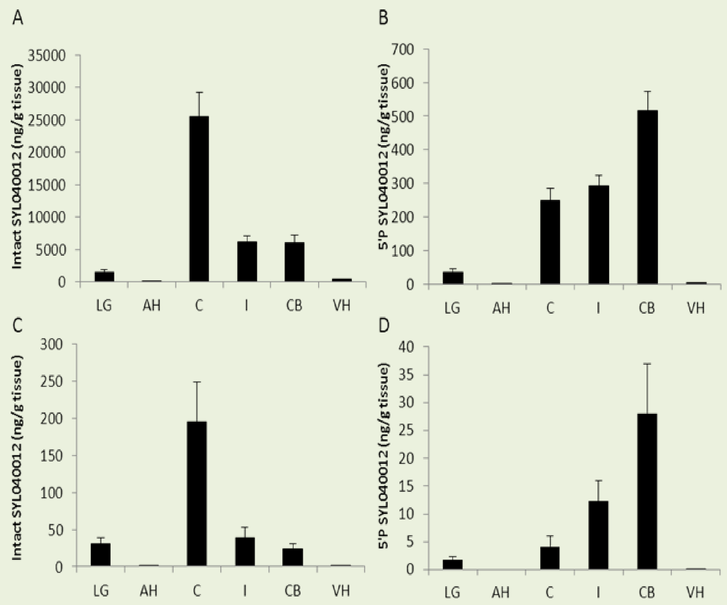
5'Phosphorilation of AS stand as a marker of intracellular delivery.

SYL040012

Sense	3'- dT dT GACCUAGUGUACGUGUUAC- 5'
Antisense	5'- CUGGAUCACAUGCACAAUG dT dT- 3'

- Targets ADRB2 ⟶ Reduction on the synthesis and release of aqueous Humor ⟶ Reduction of IOP
- Formulated in PBS
- Applied in eye drops

FIGURE 1: EYE BIODISTRIBUTION



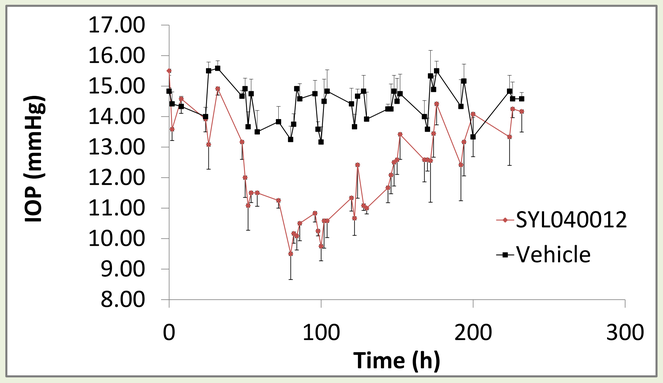
Quantification of intact SYL040012 (A and C) and 5'-P-SYL040012 (B and D) in ocular structures. Animals were administered with a single dose of 60 nmol/eye SYL040012 and sacrificed 5 (A and B) and 30 (C and D) minutes after administration. Data represent means ± SEM of three animals per group. LG: lachrymal gland; AH: aqueous humor; C: cornea; I: iris; CB: ciliary body and VH: vitreous humor.

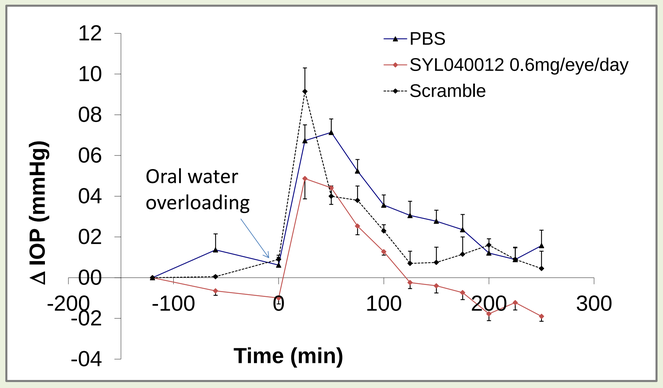
FIGURE 2: SYSTEMIC BIODISTRIBUTION

Intact duplex (ng/g tissue)	5'
Plasma	1.10 ± 0.49
Kidney Medulla	0.96 ± 0.45
Kidney Cortex	0.58 ± 0.26
Liver	0.35 ± 0.23
Lung	0.23 ± 0.11

Systemic and plasma bioavailability of SYL040012 in rabbit following administration of 60 nmol/eye SYL040012 eye drops. Five minutes after administration blood samples were collected and processed to obtain plasma. Immediately thereafter systemic tissues were isolated and processed for analysis of SYL040012 and 5'P-SYL040012 (LOD: 0,25ng/g or mL). No 5'P-SYL040012 was detected in any systemic tissue.

FIGURE 3: EFFICACY



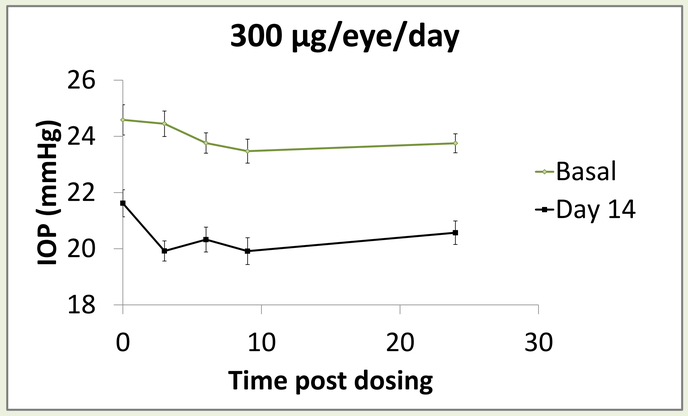


A. NZW rabbits were administered either 20nmol/eye/day SYL040012 or vehicle for a period of 4 days and IOP was assessed every 2h after the last administration. B. Rabbits were administered either 40 nmol/eye day SYL040012, a scrambled sequence or vehicle for 4 days and IOP was assessed every 20 min following induction of ocular hypertension.

FIGURE 4: CLINICAL DEVELOPMENT

Clinical Trial	Country/Sites	Dose Regime	Dose (µg/eye/day)	Number of partic.	Frequency of administration	Outcomes
Phase 1A	Spain Clinica Universitaria de Navarra	Single Dose	600	6 healthy volunteers	1	Main Outcome: Ocular surface tolerance Secondary Outcomes: Local tolerance after each dose and systemic tolerance. Repercussion on the ocular fundus and visual acuity Pharmacokinetics Effect on IOP
		Repeated dose	600	12 healthy volunteers	1/day for 7 days	
		Repeated dose	900	12 healthy volunteers		
Phase 1B	Spain Clinica Universitaria de Navarra Hospital Ramón y Cajal	Repeated dose	600	30 ocular hypertens. patients (non-glaucoma)	1/day for 7 days	
Phase 2A	Spain, Germany, Estonia, 12 sites	Repeated dose	Placebo	80 ocular hypertens. patients glaucoma patients	1/day for 14 days	Main Outcome: Ocular surface tolerance 24h after the last administration and effect on IOP. Secondary outcomes: Ocular surface tolerance after each dose Changes in ocular fundus or visual acuity and systemic tolerability.
			80			
			300			
			900			

- Very well tolerated locally and systemically in healthy subjects and individuals with increased IOP.
- Not detected in blood following a single or seven repeated administrations (LOD: 44,2 ng/mL).
- No side-effects observed.



SYL040012 Phase 2A. The dose of 300 µg/eye/day significantly reduced IOP compared to basal values and to placebo.
SYL040012 was well tolerated both locally and systemically. No compound related side events were observed.

Martínez et al., 2013. Mol Ther, in press; Moreno-Montañés et al., 2013. Mol. Ther, in press.