B0038

Presented at:
Association for Research in Vision and Ophthalmology
April 23–27, 2023 • New Orleans, LA

Melanocortin Receptor Agonist PL9588 Reduces Intraocular Pressure in Normotensive Rabbits

Paul S. Kayne, PhD; Alison Obr, PhD; John H. Dodd, PhD; Carl Spana, PhD
Palatin Technologies, Inc., Cranbury, NJ

Introduction

- Glaucoma comprises a group of eye conditions that damages the optic nerve. The optic nerve sends visual information from your eye to your brain and is vital for good vision. Damage to the optic nerve is often related to high pressure in the eye. However, glaucoma can happen even with normal eye pressure[1,2]
- Glaucoma can occur at any age but is more common in older adults. It is one of the leading causes of blindness for people older than 60 years[3]
- Melanocortins are a family of neuropeptide hormone agonists that includes several melanocyte-stimulating hormones (MSH) and adrenocorticotropin hormone (ACTH)[4-6]
- Melanocortin receptors (MCRs) are present in numerous body tissues including the eye[4,6,7]
- The melanocortin pathway plays an important role in resolving inflammatory tissue healing processes throughout the body and maintaining immunological homeostasis[4]
- MCR agonists have been shown to have an important role in maintaining ocular immunity and reducing ocular inflammation in animal models of disease[8-11]
- The melanocortin pathway is therefore a potentially attractive target for new therapies to control inflammatory diseases[5,12,13]
- In a study of normotensive rabbits, topically administered α-MSH has been shown to reduce intraocular pressure (IOP) in a dose-related manner with no side effects[14]
- PL9588 is a peptide with MC1R and MC5R agonist activity that is being investigated as a potential treatment for glaucoma

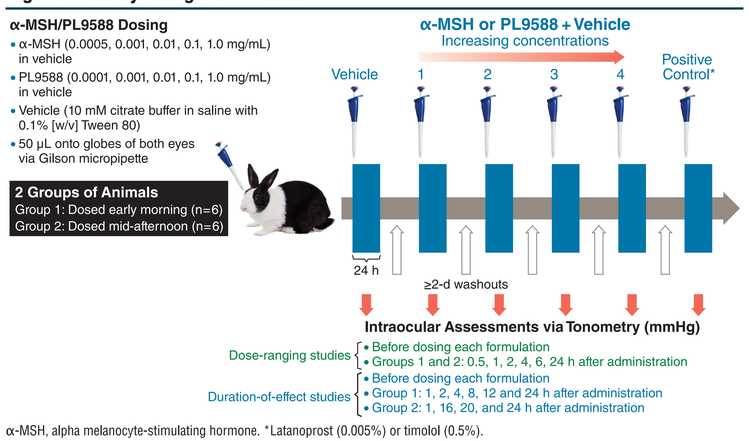
Objective

- PL9588 was investigated in a series of dose-ranging and duration-of-effect studies to establish its effects on IOP after administration in healthy, normotensive rabbits

Methods

- In different studies, male, experimentally naive, normotensive Dutch belted rabbits (age 3–4 mo) were treated topically with different concentrations of α-MSH (0.0005–1.0 mg/mL), and PL9588 (0.0001–1.0 mg/mL) in a vehicle of citrate buffer in saline with 0.1% (w/v) Tween 80 (**Figure 1**)

Figure 1. Study Design for PL9588



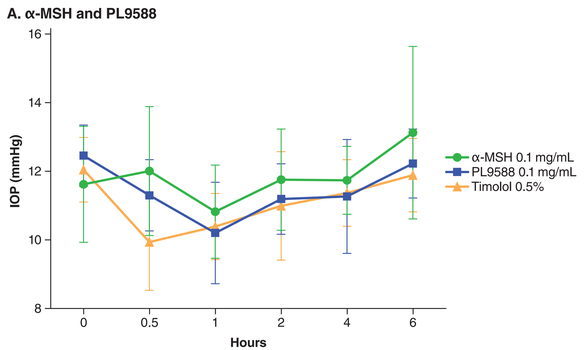
α-MSH, alpha melanocyte-stimulating hormone. *Latanoprost (0.005%) or timolol (0.5%).

- Latanoprost (0.005%) and timolol (0.5%) were positive controls
- The first dose was vehicle, followed by increasing α-MSH or PL9588 concentrations and finishing with the positive control (maximum 7 doses per animal)
- Each dose was separated by a ≥2-day washout
- For extended time courses, 2 groups of animals were dosed: group 1 (n=6) in the early morning and group 2 (n=6) in mid-afternoon
- IOP measurements (mmHg) were taken by tonometry before dosing each formulation and at times shown on the graphs after topical administration

Results

- In an initial test, α-MSH was compared to PL9588, and the 24-hour dose-response curves after a single administration of α-MSH were determined (**Figure 2**)

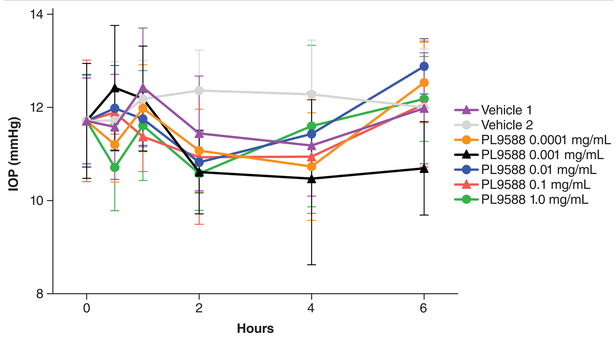
Figure 2. Initial Test of α-MSH and PL9588



α-MSH, alpha melanocyte-stimulating hormone; IOP, intraocular pressure.

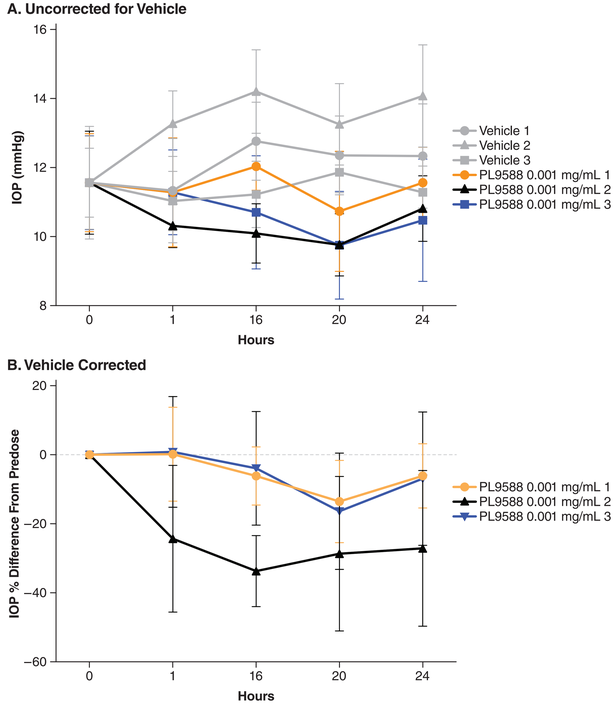
- 0.1 mg/mL PL9588 reduced IOP by a greater amount than 0.1 mg/mL α-MSH after 1 hour postdose, and its duration of effect lasted ~4 hours. PL9588 had a similar impact on IOP as timolol
- The most efficacious α-MSH dose was 0.001 mg/mL, which showed the greatest decrease in IOP at 4 hours postdose, a decrease comparable to that seen with latanoprost
- The dose curves for PL9588 are shown in **Figure 3**

Figure 3. PL9588 Dose Curves



IOP, intraocular pressure.

Figure 4. PL9588 Extended Time Course



IOP, intraocular pressure.

- The most efficacious PL9588 dose was 0.001 mg/mL, which produced a 12%–18% reduction in IOP beginning at approximately 1 hour postdose, which persisted through the end of the experiment at 6 hours postdose (**Figure 3**)
- Latanoprost (0.005%) reduced ocular pressure similar to results in **Figure 2B** (data not shown)
- The optimized PL9588 dose was evaluated at longer times after administration. In 3 replicate experiments, PL9588 at 0.001 mg/ml consistently lowered IOP at 16–24 hours post-dose (**Figure 4A**).
- To correct for diurnal variations in IOP, % IOP change from vehicle was calculated for each replicate experiment. Reductions in IOP from 5–30% are evident at 16–24 hours postdose (**Figure 4B**)
- Latanoprost (0.005%) reduced ocular pressure at 1 hour but showed no reduction at later measured timepoints (data not shown)

Conclusions

- 0.001 mg/mL PL9588 showed reductions in IOP with magnitudes similar or greater to the positive controls latanoprost and timolol when administered into the eyes of rabbits
- The effect of this single low dose persisted for 24 hours
- There are currently no glaucoma medications that modulate the melanocortin pathway
- A therapeutic melanocortin agonist could provide new options for treatment, both as a single agent or in combination with a complementary medicine
- Given that melanocortins have been shown to provide neuroprotection in neuroinflammatory disorders,[15] they may provide long-term benefit to patients with glaucoma in addition to reducing IOP
- Our data provide support for continued development of PL9588 with the aim of providing a novel, once-daily treatment for glaucoma

Support Palatin Technologies, Inc.

Acknowledgments Writing and editorial assistance was provided by Robin Smith, PhD, of The Curry Rockefeller Group, LLC (Tarrytown, NY, USA), which was funded by Palatin Technologies, Inc.

Disclosures **Paul S. Kayne**, **Alison Obr**, **John H. Dodd**, and **Carl Spana** are employees of Palatin Technologies, Inc.

References

1. Weinreb RN, et al. *JAMA*. 2014;311(18):1901-1911. **2.** Kang JM and Tanna AP. *Med Clin North Am*. 2021;105(3):493-510. **3.** Schuster AK, et al. *Dtsch Arztebl Int*. 2020;117(13):225-234. **4.** Ahmed TJ, et al. *Int J Inflam*. 2013;2013:985815. **5.** Perretti M, et al. *Trends Pharmacol Sci*. 2015;36(11):737-755. **6.** Wang W, et al. *Front Endocrinol (Lausanne)*. 2019;10:683. **7.** Catania A, et al. *Sci World J*. 2010;10:1840-1853. **8.** Cai S, et al. *Cell Physiol Biochem*. 2018;45(2):505-522. **9.** Rossi S, et al. *Mediators Inflamm*. 2016;2016:7368389. **10.** Taylor AW, et al. *Cell Mol Biol (Noisy-le-Grand)*. 2006;52(2):53-59. **11.** Taylor AW and Lee D. *Adv Exp Med Biol*. 2010;681:143-149. **12.** Montero-Melendez T, et al. *Semin Immunol*. 2022;59:101603. **13.** Spana C, et al. *Front Pharmacol*. 2018;9:1535. **14.** Naveh N, et al. *Br J Ophthalmol*. 2000;84(12):1411-1414. **15.** Mykicki N, et al. *Sci Transl Med*. 2016;8(362):362ra146.