

Santen Announces Initiation of Phase 3 Clinical Development Program (SPECTRUM) in the United States Evaluating Omidenepag Isopropyl (DE-117) for the Treatment of Glaucoma or Ocular Hypertension

Emeryville, CA., October 22, 2018 – Santen Inc., a U.S. subsidiary of Santen Pharmaceutical Co., Ltd., a global company focused exclusively on ophthalmology, today announced the initiation of the pivotal Phase 3 development program (SPECTRUM) in the United States, evaluating the investigational use of omidenepag isopropyl (DE-117), a selective agonist for the prostanoid receptor EP2, for the treatment of glaucoma or ocular hypertension (OHT).

The SPECTRUM program includes two pivotal, Phase 3, randomized, double-masked, active-controlled, parallel-group, multicenter trials assessing the efficacy and safety of omidenepag isopropyl 0.002% ophthalmic solution compared with timolol maleate 0.5% ophthalmic solution in patients with glaucoma or OHT.

SPECTRUM 3 ([NCT03691649](#)) and SPECTRUM 4 ([NCT03691662](#)) will each enroll approximately 400 adult patients and up to 30 pediatric patients diagnosed with glaucoma or OHT across 70 clinical sites in the United States. Patients who meet eligibility criteria are randomized in a 1:1 ratio to receive either omidenepag isopropyl once-daily or timolol twice-daily. SPECTRUM 3 is a twelve months trial, consisting of a three-month double-masked treatment period and a nine-month open-label period, while SPECTRUM 4 spans over a total of three months. The primary objective of both studies is to demonstrate whether once-daily omidenepag isopropyl is non-inferior to twice-daily timolol in reducing intraocular pressure (IOP) after three months.

“Santen’s deep commitment to glaucoma drives us to advance therapeutic innovation in areas of unmet needs,” said Naveed Shams, MD, PhD, Chief Scientific Officer and Head of Global Research and Development at Santen. “Currently when glaucoma treatments fail, patients urgently need therapeutic options with differentiated mechanisms of action to effectively reduce intraocular pressure. By increasing the aqueous humor outflow through both uveoscleral and trabecular pathways,¹ omidenepag isopropyl has the potential to provide physicians with a novel option to treat elevated pressure in glaucoma.”

The initiation of the U.S. Phase 3 SPECTRUM program follows positive Phase 1/2, 2 and 2b dosing studies demonstrating that omidenepag isopropyl 0.002% is the most appropriate dose and performed similarly to latanoprost in IOP reduction. Omidenepag isopropyl was generally safe and well tolerated. Common side effects of FP agonists – such as iris and eyelid pigmentation, abnormal eyelash changes and deepening of upper eyelid sulcus – were not observed during long-term (12 months) use in a study conducted in Japan.²

In September 2018, Santen announced receipt of manufacturing and marketing approval for glaucoma and ocular hypertension treatment omidenepag isopropyl (DE-117) 0.002% ophthalmic solution in Japan under the name EYBELIS.³ DE-117 is in global development and is also currently in a Phase 3 trial in Asia (beyond Japan).

About Glaucoma

Glaucoma is characterized by optic neuropathy frequently associated with elevated intraocular pressure (IOP) which, when left untreated, can lead to retinal ganglion cell death and optic nerve damage, resulting in progressive and irreversible visual loss.⁴ A leading cause of blindness,⁵ glaucoma affects more than three million Americans and 60.5 million individuals worldwide.⁶ In “open-angle” glaucoma, the most common form, the most significant yet modifiable risk factor for glaucoma is elevated IOP, caused by a buildup of eye fluid, aqueous humor. Normally, after the eye produces this fluid to nourish tissues, it exits the eye through two main routes: the trabecular meshwork and uveoscleral pathway. In glaucoma, one or both routes do not allow adequate drainage of the fluid, increasing IOP which can damage the optic nerve.⁷ Treatments include a variety of medications and specialized surgical techniques and generally lower IOP by decreasing production and/or increasing outflow of intraocular fluid.⁸

About Omidenepag Isopropyl (DE-117)

Omidenepag isopropyl, or DE-117, is a topical ophthalmic solution in clinical development for the treatment of elevated intraocular pressure in patients with glaucoma or ocular hypertension. The active metabolite of the medication, omidenepag, has a different, novel mechanism of action compared to other currently available medications. It is a selective agonist for the prostanoid receptor, EP2,⁹ in contrast to the prostaglandin analogs (PGAs), a commonly prescribed class of medications that acts on a FP receptor. Omidenepag isopropyl increases the pathway of aqueous humor drainage through the conventional (or trabecular) and uveoscleral outflow pathways, while PGAs are thought to increase the uveoscleral outflow pathway only.^{10,11,12} Omidenepag isopropyl was licensed by Santen from Ube Industries, Ltd. and co-developed as a treatment for glaucoma or ocular hypertension by the two companies. Under the agreement, Ube is responsible for manufacturing and the supply of omidenepag isopropyl active product ingredient.

Santen Forward-looking Statements

Information provided in this news release contains so-called “Forward-looking Statements”. The realizations of these forecasts are subject to risk and uncertainty from various sources. Therefore, please note that the actual results may differ significantly from the forecasts. Business performance and financial condition are subject to the effects of changes in regulations made by the governments of Japan and other nations concerning medical insurance, drug pricing and other systems, and to fluctuations in market variables such as interest rates and foreign exchange rates.

About Santen

As a global specialized company dedicated to ophthalmology, Santen carries out research, development, marketing, and sales of pharmaceuticals, over-the-counter products, and medical devices. Santen is the market leader for prescription ophthalmic pharmaceuticals in Japan and its products now reach patients in over 60 countries. With scientific knowledge and organizational capabilities nurtured over a nearly 130-year history, Santen provides products and services to contribute to the well-being of patients, their loved ones and consequently to society. For more information, please visit Santen websites www.SantenUSA.com (United States) and www.santen.com (global).

U.S. Contact

Tanya Shnaydman
Director, Corporate Communications
Santen Inc.
E-mail: Tanya.Shnaydman@santen.com
Tel: +1-617-688-4858

¹ Fuwa M, Toris CB, Fan S, et al. Effects of a novel selective EP2 receptor agonist, omidenepag isopropyl, on aqueous humor dynamics in laser-induced ocular hypertensive monkeys. *J Ocul Pharmacol Ther.* 2018 Jul 10.

² Aihara M, et al. 12-month efficacy and safety study of a novel selective EP2 agonist omidenepag isopropyl in OAG and OHT: the RENGE study. Poster presented at the American Academy of Ophthalmology (AAO) congress 2018, October 27–30, Chicago, IL, USA (Abstract 30056242).

³ Santen Pharmaceutical Co., Ltd. EYBELIS ophthalmic solution 0.002% Package Insert.

⁴ Agarwal R1, Gupta SK, Agarwal P, Saxena R, Agrawal SS. Current concepts in the pathophysiology of glaucoma. *Indian J Ophthalmol.* 2009 Jul-Aug;57(4):257-66. doi: 10.4103/0301-4738.53049.

⁵ Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmology.* 2014 Nov;121(11):2081-90. doi: 10.1016/j.ophtha.2014.05.013. Epub 2014 Jun 26.

⁶ Bright Focus Foundation. Glaucoma: Facts & Figures. Available at: <https://www.brightfocus.org/glaucoma/article/glaucoma-facts-figures>. Accessed October 3, 2018.

⁷ American Academy of Ophthalmology. Aqueous outflow and glaucoma drug mechanisms of action. Available at: <https://www.aao.org/basic-skills/animation-of-aqueous-flow>. Accessed October 18, 2018.

⁸ National Institutes of Health / National Eye Institute. Facts about glaucoma. Available at: https://nei.nih.gov/health/glaucoma/glaucoma_facts. Accessed September 14, 2018.

⁹ Santen Pharmaceutical Co., Ltd. EYBELIS ophthalmic solution 0.002% Package Insert.

¹⁰ Cheema A, Chang RT, Shrivastava A, Singh K. [Update on the Medical Treatment of Primary Open-Angle Glaucoma.](#) *Asia Pac J Ophthalmol (Phila).* 2016 Jan-Feb;5(1):51-8. doi: 10.1097/APO.000000000000181.

¹¹ Doucette LP, Walter MA. Prostaglandins in the eye: Function, expression, and roles in glaucoma. *Ophthalmic Genet.* 2017 Mar-Apr;38(2):108-116. doi: 10.3109/13816810.2016.1164193. Epub 2016 Apr 12.

¹² Kirihaara T, Taniguchi T, Yamamura K, Iwamura R, Yoneda K, Odani-Kawabata N, Shimazaki A, Matsugi T, Shams N, Zhang JZ. Pharmacologic Characterization of Omidenepag Isopropyl, a Novel Selective EP2 Receptor Agonist, as an Ocular Hypotensive Agent. *Invest Ophthalmol Vis Sci.* 2018 Jan 1;59(1):145-153. doi: 10.1167/iops.17-22745.