

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215092Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader, Division Director, and Office Director Review of NDA 215092

Review Completion Date	See DARRTS Stamp Date
From	William M. Boyd, M.D., Wiley Chambers, M.D., Charles Ganley, M.D.
Subject	Cross-Discipline Team Leader, Division Director, and Office Director Review
NDA #	215092
Applicant	Santen, Inc.
Date of Submission	May 6, 2022
PDUFA Goal Date	November 6, 2022
Proprietary Name	Omlonti
Established	Omidenepag isopropyl ophthalmic solution, 0.002%
Dosage Form	Ophthalmic solution
Dosing Regimen	One drop in the affected eye(s) once daily in the evening
Regulatory Action	Approval
Indication	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager	Jacqueline Smith
Medical Officer Review	Martin Nevitt
Statistical Review	Abel Eshete
Pharmacology Toxicology Review	Andrew McDougal
OPQ Review	Chunchun Zhang, Eric Adeeku
Clinical Pharmacology Review	Suneet Shukla
OPDP	Carrie Newcomer, David Foss
DMPP	Maria Nguyen
OSI	Ling Yang
CDTL Review	William M. Boyd
Division Director	Wiley A. Chambers
OSE/DMEPA	Nasim Roosta

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 DMPP= Division of Medical Policy Programs
 OSI=Office of Scientific Investigations
 CDTL=Cross-Discipline Team Leader
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

1. Summary

Omidenepag isopropyl ophthalmic solution 0.002% is a prodrug of omidenepag, a prostaglandin analog, indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Throughout this application, omidenepag isopropyl ophthalmic solution may also be referred to as DE-117.

Omidenepag isopropyl ophthalmic solution 0.002% was evaluated in three randomized and controlled clinical trials in subjects with open-angle glaucoma or ocular hypertension with average baseline IOP of 24-26 mmHg. The treatment duration was 3 months in all 3 studies. Omlonti 0.002% once daily in the evening demonstrates a consistent IOP-lowering effect of 5.4 to 7.4 mmHg, which was similar to latanoprost 0.005% dosed once daily or timolol 0.5% dosed twice daily. The safety and effectiveness in pediatric patients have not been established.

The risk for using this drug is consistent with other currently marketed IOP prostaglandin analog lowering products. The most common ocular adverse events were conjunctival hyperemia (9%) and photophobia (5%). Similar to other prostaglandin analog trials, class events such as increases in iris pigment would not have been expected to be observed in the clinical trials of 3-month duration and/or in the absence of a contralateral eye comparison.

In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the “device” definition. FDA will be regulating these products, including this product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including this product.

The compliance status of the drug product manufacturing facility, (b) (4) Woodstock Sterile Solutions (FEI 1419377) and testing facility (b) (4) were determined unacceptable in the original review cycle based on the most recent inspections. Therefore, the Office of Pharmaceutical Manufacturing Assessment (OPMA) issued an overall recommendation of “Withhold” on August 3, 2021, reconfirmed October 26, 2021. Based on this sole deficiency, the regulatory action for this application was a Complete Response with a letter date of November 9, 2021.

In this second cycle of review, the overall manufacturing inspection recommendation is for approval. The applicant proposed a new testing facility (b) (4) for the commercial batch testing functions (release and stability testing) replacing (b) (4). On August 3, 2022, the firm confirmed that (b) (4)

(b) (4) would not perform commercial testing of the subject product. OPMA issued an overall approval recommendation of on August 10, 2022. NDA 215092, Omlonti (omidenepag isopropyl ophthalmic solution) 0.002% will be approved with the labeling found in the appendix of this review.

2. Benefit-Risk Assessment

NDA 215092 Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of omidenepag isopropyl ophthalmic solution, 0.002% dosed once daily in the evening for the treatment of elevated IOP in patients with open-angle glaucoma or ocular hypertension. Studies 01171505 and 011710IN demonstrated the IOP lowering ability of omidenepag isopropyl ophthalmic solution, 0.002%. Omidenepag isopropyl ophthalmic solution, 0.002% was not clinically inferior to timolol maleate ophthalmic solution 0.5% or to latanoprost, 0.005%.

The safety profile of omidenepag isopropyl ophthalmic solution, 0.002% is similar to other currently marketed topical prostaglandin analog IOP lowering products. The most common ocular adverse events are conjunctival hyperemia (9%) and photophobia (5%).

The benefit of omidenepag isopropyl ophthalmic solution, 0.002% for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension has been demonstrated in this NDA application. The risk of using this drug is consistent with other currently marketed topical prostaglandin analog IOP lowering products.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	<ul style="list-style-type: none"> Glaucoma is a life-long progressive disease that is characterized by irreversible damage to the optic nerve and corresponding loss of visual field. One of the primary risk factors is elevated intraocular pressure (IOP). 	<p>Intraocular pressure reduction is currently the accepted standard for establishing the efficacy of ocular hypertensive medications.</p>
<u>Current Treatment Options</u>	<ul style="list-style-type: none"> There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasymphomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues. Patients often need more than one class of IOP lowering products concurrently. 	<p>This product would add another prostaglandin analogue to the approved U.S. products.</p>
<u>Benefit</u>	<ul style="list-style-type: none"> Intraocular pressure (IOP) lowering is currently the accepted standard for establishing the efficacy of ocular hypertensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points, including peak and trough time points for studies 01171505 and 011710IN. 	<p>Studies 01171505 and 011710IN demonstrated that omidenepag isopropyl ophthalmic solution, 0.002% was non-inferior to the active controls, timolol maleate ophthalmic solution, 0.5% and latanoprost, 0.005%, respectively.</p>
<u>Risk and Risk Management</u>	<ul style="list-style-type: none"> There is a 25-year history of topical ophthalmic prostaglandin analog use. Topical prostaglandin analogs have a well-defined risk profile which include risks of conjunctival hyperemia, macular edema, worsening of inflammation, if inflammation is already present and increased melanosomes within melanocytes. 	<p>The observed safety profile was consistent with other prostaglandin analog products. Product will be labeled to include monitoring consistent with all approved prostaglandin analogs. No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Post-marketing Requirements or Phase 4 Commitments.</p>

3. Background

Treatment of elevated intraocular pressure consists of both medical and surgical interventions. The treatments are designed to decrease the intraocular pressure by decreasing aqueous secretion or increasing aqueous outflow. Omidenepag isopropyl ophthalmic solution, 0.002% is a relatively selective agonist of EP2 receptor, a prostaglandin E2 (PGE2) receptor, subtype 2, believed to reduce IOP largely due to increased uveoscleral outflow of aqueous humor. The exact mechanism of action is unknown at this time. Omidenepag isopropyl ophthalmic solution, 0.002% is being reviewed as a new molecular entity.

DE-117 ophthalmic solution is approved for glaucoma and ocular hypertension in Japan ^{(b) (4)} as of 21 September 2018. As of 20 March 2020, based on the number of bottles sold and considering that 1 month of dosing equals a single bottle, the estimated total cumulative patient exposure in post-marketing use is about ^{(b) (4)} patient years. DE-117 was approved in Korea on December 3, 2019, in Thailand on August 11, 2020, and in Taiwan on July 17, 2020, but no patients have been exposed to DE-117 in Korea, Thailand, or Taiwan as the product is not yet launched in these countries.

There are many ophthalmic drug products approved for lowering intraocular pressure in patients with open-angle glaucoma and ocular hypertension. These treatments include beta-adrenergic antagonists (beta-blockers), alpha-adrenergic agonists, parasympathomimetic (miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogs.

Table 1: Drug Products with Approved NDAs

Pharmacologic Class/ Applicant	Trade Name	Established Name
Alpha-2 agonists		
Allergan, Inc.	Alphagan/Alphagan P	brimonidine tartrate
Beta-adrenergic antagonists		
Alcon	Betoptic/Betoptic S	betaxolol hydrochloride
Novartis	Ocupress	carteolol hydrochloride
Allergan	Betagan	levobutanol hydrochloride
Bausch & Lomb	Optipranolol	Metipranolol
Vistakon	Betimol	timolol hemihydrate
Aton Pharma	Timoptic	timolol maleate
Ista	Istalol	timolol maleate
Aton Pharma	Timoptic XE	timolol maleate gel forming solution
Systemic Carbonic Anhydrase Inhibitors		
Duramed Pharmaceuticals	Diamox	acetazolamide
Sandoz, Inc.	N/A	methazolamide
Topical Carbonic Anhydrase Inhibitors		
Alcon	Azopt	brinzolamide
Merck	Trusopt	dorzolamide hydrochloride
Cholinergic agonist		
Alcon	Pilopine HS	pilocarpine hydrochloride gel
Alcon	Isopto Carpine	pilocarpine hydrochloride

Pharmacologic Class/ Applicant	Trade Name	Established Name
Prostaglandin Analogues		
Allergan	Lumigan	bimatoprost
Pharmacia	Xalatan	latanoprost
Alcon	Travatan	travoprost
Alcon	Travatan Z	travoprost
Merck	Zioptan	tafluprost
Alcon	Izba	travoprost
Sun Pharma Global	Xelpros	latanoprost
Bausch & Lomb	Vyzulta	latanoprostene bunod
Allergan	Durysta	bimatoprost
Sympathomimetics		
Allergan	Propine	dipivefrin hydrochloride
Combination Products		
Merck	Cosopt	dorzolamide hydrochloride/timolol maleate
Merck	Cosopt PF	dorzolamide hydrochloride/timolol maleate
Allergan	Combigan	brimonidine tartrate/timolol maleate
Alcon	BetopticPilo	betaxolol hydrochloride/pilocarpine HCl
Alcon	Simbrinza	carbonic anhydrase inhibitor/brinzolamide
Other		
Sucampo Pharma Americas, Inc.	Rescula	unoprostone isopropyl

Santen sought scientific and regulatory advice from the Food and Drug Administration (FDA), Division of Ophthalmology on the clinical development program for DE-117, and the relevant meeting information is outlined below.

Pre-IND: Santen conducted a Pre-IND meeting in 12JUN2011 to get initial advice on the development of DE-117.

End of Phase 2: 16OCT2017 – Santen discussed the development of the phase 3 studies of DE-117.

Pediatric Study Plan (PSP): Santen submitted the initial PSP on 14DEC2017. After comments were provided by FDA and clarifications were made; Santen submitted the *Agreed Initial PSP* on 05JUN2018, with the agreement that the 2 US pivotal studies would each allow for the enrollment of pediatric subjects.

SAP Meeting: 21MAY2019 – Santen requested advice on the proposed statistical analysis plan for 011710IN and after receiving FDA preliminary comments, decided to proceed with the originally proposed primary endpoint to be consistent with FDA recommendations.

Pre-NDA: 12JUL2019 – Santen discussed with the Agency the content and format of the NDA package and its adequacy to support the DE-117 application.

Pre-NDA: 10JUN2020 – Santen discussed the outcome of the clinical studies that were determined to be adequate and well-controlled and would comprise the phase 3 package of the NDA, specifically, 01171505, 011710IN, and 011709IN. Santen indicated that while studies 01171505 and 011710IN met the FDA-specified non-inferiority criteria, study 011709IN failed to do so; nevertheless, the efficacy profile of DE-117 from the 011709IN study was consistent with that seen in study 011710IN. The Agency agreed that the studies intended to support the NDA

appeared to be adequate and well-controlled and that the data package would most likely be fileable.

4. Product Quality

OPQ completed their integrated review of the original application on 08/28/2021, and an addendum on 10/8/2021. OPQ completed their review of the Class 2 resubmission on 8/10/2022.

4.1. Drug Substance

The active pharmaceutical ingredient or drug substance of DE-117 ophthalmic solution, omidenepag isopropyl (USAN), is manufactured by (b) (4)

Specifications for Omidenepag Isopropyl Drug Substance

Test Item	Test Method / Method	Specification
1. Description	Visual	White to light brown crystals or crystalline powder
2. Identification	IR ^a USP <197>	Spectrum exhibits similar intensities of absorptions at the same wave numbers as that of the reference spectrum.
3. Related substance (RS)	HPLC	Each single RS: NMT ^b (b) (4)% Total: NMT (b) (4)%
4. Water	USP <921> Karl Fischer	NMT (b) (4)%
5. Residue on ignition	USP <281>	NMT (b) (4)%
6. Assay (anhydrous and residual solvent-free basis)	HPLC	(b) (4)%
7. Microbial Enumeration Tests	USP < 61> Membrane Filtration Method	TAMC ^c : NMT (b) (4) CFU/g TYMC ^d : NMT (b) (4) CFU/g

^a: IR: infrared absorption

^b: NMT: not more than

^c: TAMC: Total Aerobic Microbial Count

^d: TYMC: Total Combined Yeasts and Molds Count

Source: Module 3.2.S.4.1

4.2. Drug Product

The drug product, 0.002% DE-117 ophthalmic solution, is a sterile aqueous preparation that contains the pharmaceutical ingredient omidenepeg isopropyl. In addition, the formulation contains excipients required to produce a stable ophthalmic solution dosage form. The solution is preserved with 0.005% benzalkonium chloride (BAK).

Composition of Drug Product

Qualitative and Quantitative Composition of 0.002% DE-117 Ophthalmic Solution

Ingredient	Function	Quantity (mg/mL)	Quantity per unit (2.5 mL)	Reference to Standards
Omidenepeg isopropyl	Active ingredient	0.02	0.05	In-house ^a
Sodium citrate ^b	(b) (4)			USP
Citric acid monohydrate				USP
Polyoxyl 35 castor oil				NF
Benzalkonium chloride				Preservative
Edetate disodium	(b) (4)			USP
Glycerin				USP
Sodium hydroxide / hydrochloric acid	pH adjuster	Adjust pH to (b) (4)	Adjust pH to (b) (4)	NF
Water for injection	(b) (4)			USP
Total volume		1 mL	2.5 mL	

^a: Refer to Module 3.2.S.4.1-Santen Drug Substance specifications

^b: (b) (4)

Source: Module 3.2.P.1

4.3. Drug Product Specification

The specifications for 0.002% DE-117 ophthalmic solution are shown below.

Specifications for 0.002% DE-117 Ophthalmic Solution

Test Item	Test Method / Method # ^a	Specification	
Description/Appearance	Visual Inspection PDR-ATM-MAG-0003	Clear, colorless solution, free from visible particulate matter.	
Identification	HPLC/PDA ^b PDR-ATM-SEO-0001	(b) (4)	
Omidenepeg isopropyl assay	HPLC PDR-ATM-SEO-0001		
Related substances of Omidenepeg Isopropyl	HPLC PDR-ATM-SEO-0001		
Benzalkonium chloride assay	HPLC PDR-ATM-SEO-0003		
Edetate disodium assay	HPLC PDR-ATM-SEO-0002		
Osmolality	USP <785>		
pH	USP <791>		
Particulate matter	USP <789>		
Sterility	USP <71>		Sterile

^a Test method # at (b) (4)

^b PDA- photodiode array

^c NMT - Not more than

Source: Module 3.2.P.5

4.4. Drug Product Container Closure

Sterile DE-117 ophthalmic solution is (b) (4)

[Redacted content]

(b) (4)



4.5. Microbiology

The applicant has provided adequate sterility assurance.

(b) (4)



4.6. Establishment Information

Woodstock Sterile Solutions (b) (4) / **1419377**

During the first cycle: Woodstock Sterile Solutions had low process experience, quality oversight, data concerns, and other potential contributing risks. A DFR was requested of ORA, and an acceptable based on previous history was recommended. This facility was inspected on (b) (4) according to (b) (4), Pre-Approval Inspections, for a (b) (4). The inspection resulted in a (b) (4) FDA-483 with deficiencies (b) (4).

(b) (4), OPMA/DBM determined that the response was inadequate, and recommended a withhold (b) (4).

Additional information can be found in (b) (4). The primary manufacturing reviewer evaluated the (b) (4) FDA-483, EIR, firm's response, and OPMA/DBM PAL. It was confirmed that the (b) (4) systems used (b) (4) is the same as for the proposed commercial manufacturing process as this NDA. The primary manufacturing reviewer recommended a facility withhold, and that this facility be re-evaluated during the next review cycle to assess the risk for the proposed commercial manufacturing process.

During this cycle (current cycle): A pre-approval inspection of this manufacturing facility at Woodstock Sterile Solutions, Inc., was conducted between (b) (4) for BLA (b) (4). The inspection focused on (b) (4).

The final outcome of the inspection is VAI.

Given that the previous withhold decision of this facility was based on (b) (4) and during the current PAI no deficiencies were identified with regards to the facility's CAPAs to address (b) (4), the facility has sufficiently addressed the concerns. The facility is considered acceptable.

(b) (4)

During the first cycle: (b) (4) was inspected on (b) (4) and was initially classified pOAI. It was a for-cause inspection of the drug and combination (drug/medical device) contract manufacturer. Documentation reviewed during the inspection included but was not limited to manufacturing batch records, complaints, deviations, investigations, change controls and validation records. At the conclusion of the inspection, a Form FDA 483, Inspectional Observations was issued for the following deficiencies in current good manufacturing practices observed during the inspection: (b) (4)

(b) (4) PHRRM2-GRP3 and CDER reviewed the inspection result and firm’s response, and both recommended the firm be classified OAI. A regulatory meeting was held with the firm on 5/19/2021, and CDER/OMQ determined that the facility will remain OAI until a follow-up for-cause inspection can be performed when the facility has completed implementing all promised CAPAs.

During this cycle (present cycle): Santen once again listed this facility as pending on the Form FDA 356h, with responsibilities including “Drug substance release testing, Drug product release and stability testing (for commercial product)”. In addition, Santen Inc. proposed a new testing facility (b) (4) for the commercial batch testing functions (release and stability testing). On 8/3/2022, Santen, Inc. confirmed that (b) (4) would not perform commercial testing of the subject product. OPMA has issued an overall approval recommendation of on August 10, 2022.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Woodstock Sterile Solutions (b) (4) 2210 Lake Shore Drive, Woodstock, IL, USA, 60098	1419377	Drug Product manufacturing, (b) (4) (b) (4) SLQ	Approve - Based on Previous History for (b) (4) No Evaluation at this time
(b) (4)			No Evaluation Necessary because facility was withdrawn Approve – Based on Previous History No Evaluation Necessary

(b) (4)		Sterilization of tips and caps	No Evaluation Necessary
		Drug product release SLQ	No Evaluation Necessary
SANTEN PHARMACEUTICAL CO., LTD., Nara Research & Development Center 8916-16 Takayama-cho, Ikoma, Nara, Japan, 630-0101	3004595895	Drug product stability studies (registration) LCP	No Evaluation Necessary
(b) (4)		Coordination of drug substance production at (b) (4) Drug substance stability testing, and MF holder LCP	Approve - Based on Previous History
		Drug substance manufacturing, Drug substance release testing, Drug substance packaging and labeling, and Drug substance stability testing CSN	Approve - Based on Previous History

Office of Product Quality Recommendation

From the OPQ integrated review of the Class 2 resubmission completed on 8/10/2022:

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects, and each discipline upholds the approval recommendations in the resubmission after reviewing analytical methods transfer and the drug product stability update.

NDA 215092 is recommended approval from Product Quality perspective.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 5/28/2021:

Omidenepeg isopropyl is a small molecule pro-drug; its main metabolite, omidenepeg, exhibits intended pharmacology (lowering of intraocular pressure (IOP) in animal models). The prostaglandin E receptor family has four known members: EP1, EP2, EP3, and EP4. EP2 is a G protein-coupled transmembrane protein with wide tissue expression, including the eye (corneal epithelium, corneal choriocapillaris, conjunctiva, trabecular meshwork and Schlemm's canal, iris and ciliary body, retina), gastrointestinal (GI) tract, lung, heart, liver, kidneys, and bone. EP2 has high affinity for endogenous prostaglandin E2 (PGE2, dinoprostone). Omidenepeg isopropyl has moderate binding affinity for EP2 (IC50 = 52.06 ng/mL).

Omidenepag is a high-potency agonist of EP2 (IC50 and EC50 values ranging from 4.79 to 3.45 ng/mL), and weak affinity for other prostaglandin receptors (EP4 and DP1).

Nonclinical exposure margins for labeling were based on the NDA reporting of a clinical AUC of 27.0 pg*h/mL for omidenepag, following bilateral once daily topical ocular dosing of omidenepag isopropyl 0.0025% eye drops. The general toxicology study package spans two species: two topical ocular monkey studies, and a series of subcutaneous-route studies in the Sprague Dawley rat.

Lifetime rodent studies have not been performed to evaluate the carcinogenic potential of omidenepag isopropyl or omidenepag. The applicant justified this by citing ICH S1A, “*Pharmaceuticals administered by the ocular route may not need carcinogenicity studies unless there is cause for concern or unless there is significant systemic exposure.*” Omidenepag isopropyl showed evidence of tumorigenicity in rats dosed by subcutaneous injection daily for 26 weeks. Nephroblastoma and a spermatid tumor were found at 0.003 mg/kg/day (22.2 times the RHOD based on AUC). Mammary adenocarcinoma and pituitary pars distalis adenomas were observed at 0.03 mg/kg/day (212.6-fold the RHOD based on AUC).

Table 2: tumorigenicity summary for the GLP 26-week rat subcutaneous toxicity study (report # B7774)

Lesion	Both sexes combined			
	0	0.003 mg/kg/day	0.01 mg/kg/day	0.03 mg/kg/day
Pancreas acinar cell carcinoma	1/30	0/0	0/0	0/30
Nephroblastoma	0/30	1/1	0/0	0/30
Spermatid nodule (males only)	0/15	1/1	0/0	0/15
Pituitary pars distalis adenoma	0/30	0/30	0/30	2/30
Mammary adenocarcinoma (females only)	0/15	0/15	0/15	1/15

Omidenepag was not mutagenic in the bacterial reverse mutation (Ames) test. Omidenepag isopropyl was positive (mutagenic and clastogenic) without metabolic activation in the *in vitro* mouse lymphoma forward mutation assay. In a rat fertility and early embryonic development study, daily subcutaneous doses of omidenepag isopropyl did not affect male or female fertility at doses up to 1 mg/kg/day (66.2 times the MRHOD based on plasma C_{max}).

The rabbit embryofetal development study administered omidenepag isopropyl to pregnant rabbits beginning on gestation day 6, covering the period of implantation [see Pregnancy (8.1)]. Preimplantation losses were observed at 0.8 mg/kg/day (2,935 times the MRHOD based on plasma C_{max}). The NOAEL for rabbit preimplantation loss was 0.08 mg/kg/day (204 times the MRHOD based on plasma C_{max}).

Nasal cavity respiratory epithelium metaplasia was observed in cynomolgus monkeys receiving unilateral topical ocular instillations of omidenepeg isopropyl at 0.003% (0.9 mcg/eye) [1.07 fold the MRHOD, based on ocular dose comparison]. In the 13-week monkey study, the 0.9 mcg/eye dose was associated with nasal cavity respiratory epithelial metaplasia, and increased nasal cavity goblet cell respiratory epithelium mucosa. In the 39-week monkey study, the 0.9 mcg/eye dose was associated with increased incidence and severity of nasal cavity respiratory epithelium metaplasia.

Pharmacology/Toxicology (P/T) review concludes that there is no objection to approval, presuming concurrence is reached for labeling.

Clinical Pharmacology

From the original Clinical Pharmacology review dated 8/18/2021:

The drug product contains omidenepeg isopropyl (OMDI), a prodrug of the pharmacologically active metabolite, omidenepeg. The clinical pharmacology program for the proposed product included a Phase 1 plasma PK and safety study (01171502). In addition, the submission contained seven *in vitro* studies characterizing metabolism, protein binding, partitioning in blood cells and *in vitro* metabolic/transporter-based drug interactions. Dose-finding studies (33-001, 33-002, 33-003, and 01171503 Stage 1) and one dose regimen-finding study (011712IN) were conducted to optimize the dosing, but PK parameters were not assessed in these studies.

PK of OMDI ophthalmic solution 0.0025% was evaluated in healthy subjects (Study 01171502). The study was a single-arm open-label study where OMDI ophthalmic solution 0.0025% was administered into both eyes of 7 Japanese and 7 Caucasian subjects for 7 consecutive days. Plasma concentrations of omidenepeg were measured before instillation and at 5, 15, 30, 60, 120, 240, and 480 minutes after instillation on Days 1, 3, and 7. It should be noted that the dosing strength of OMDI 0.0025% used to assess PK is different from OMDI 0.002% which was evaluated in Phase 3 studies and is being proposed as final regimen.

Absorption

Following instillation of one drop of OMDI ophthalmic solution 0.0025% in both eyes once daily in healthy subjects for 7 days, plasma omidenepeg concentration on Days 1, 3, and 7 reached maximum concentration (C_{max}) of 34.36 to 35.51 pg/mL at times within the range of 0.17 to 0.25 h after instillation. The area under the concentration curve at time 0 to 8 hours (AUC_{0-8h}) and area under the concentration curve at infinity (AUC_{inf}) were 20.72 to 22.41 pg·h/mL and 21.43 to 22.42 pg·h/mL, respectively.

Distribution

No distribution data is available for OMDI. The plasma protein binding ratios at plasma omidenepag concentrations of 2.5 and 20 ng/mL were both 97.8%, indicating no concentration dependent changes in the plasma protein binding ratios.

Metabolism

After topical ocular administration, OMDI is rapidly metabolized in the eye to omidenepag (active moiety) by carboxylesterase-1. Omidenepag, the pharmacologically active form, is further metabolized by liver through oxidation, *N*-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation. CYP3A4 is involved in the metabolism of omidenepag.

Excretion

The terminal plasma elimination half-life of omidenepag following once-daily dosing in both eyes for seven days was in the range of 0.449 to 0.507 h. Following ocular instillation or subcutaneous injection of ¹⁴C-OMDI to rats, most of the administered radioactive dose was excreted through bile into feces.

The Office of Clinical Pharmacology/Division of Immune and Inflammation Pharmacology (OCP/DIIP) finds the application acceptable to support approval from a clinical pharmacology perspective. No dose adjustment is recommended for patients based on intrinsic and extrinsic factors.

6. Clinical Efficacy

From the original Medical Officer Review dated 10/13/2021:

Study 01171505 was a randomized, observer-masked, active-controlled, parallel-group, multinational, multicenter study assessing the safety and efficacy of DE-117 ophthalmic solution 0.002% compared with latanoprost ophthalmic solution 0.005% in subjects with open angle glaucoma or ocular hypertension.

Studies: 01109IN and 011710IN were phase 3, randomized, double-masked, active-controlled, parallel-group, multicenter studies assessing the efficacy and safety of DE-117 Ophthalmic Solution 0.002% QD compared with timolol maleate ophthalmic solution 0.5% BID in subjects with open angle glaucoma or ocular hypertension.

For the FDA's review of all of the phase 3 studies, the non-inferiority limits applied in the analysis of IOP at 9 timepoints consisted of two criteria with both being required to be satisfied to demonstrate non-inferiority. Non-inferiority criteria for IOP at 9 timepoints – the upper limit of the two-sided 95% CIs for the difference (DE-117 minus control) between the least squares (LS) treatment means for IOP were required to be (criterion #1:) within 1.5 mmHg at all 9 timepoints and (criterion #2:) within 1.0 mmHg at a majority (5 or more) of the 9 timepoints.

Study 01171505 Efficacy Results – Primary Endpoint

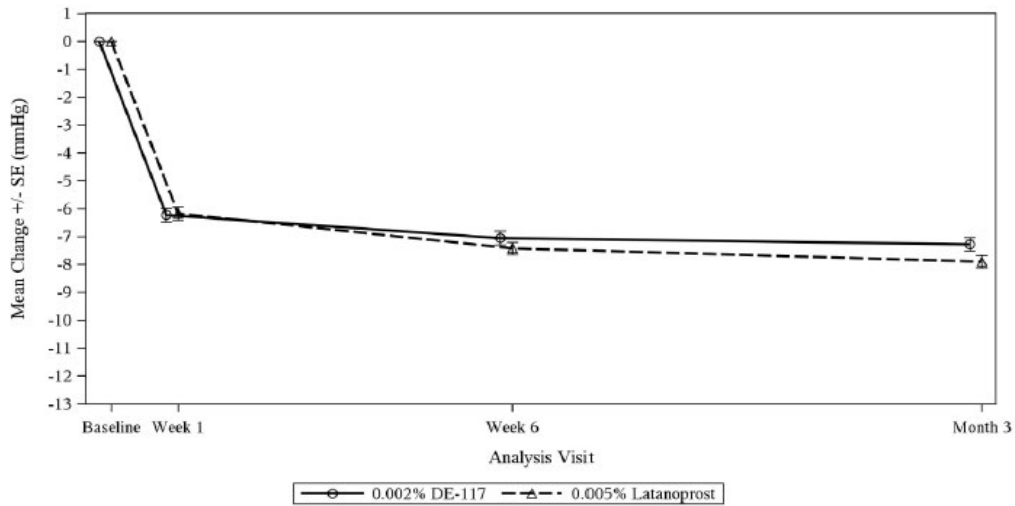
Study 01171505, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Latanoprost) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	Week 1			Week 6			Month 3		
	09:00	13:00	17:00	09:00	13:00	17:00	09:00	13:00	17:00
Plotted Values (mmHg):									
Upper CI	0.9	0.7	0.5	1.0	1.0	1.0	1.5	1.2	1.1
Mean Diff.	0.2	0.0	-0.2	0.4	0.4	0.4	0.9	0.6	0.5
Lower CI	-0.5	-0.7	-0.9	-0.3	-0.3	-0.3	0.2	-0.0	-0.2

LS means and p-values were obtained by fitting a MMRM to the IOP values from each visit at each timepoint (09:00, 13:00, 17:00) separately. Each model included treatment, visit, diagnosis, country, and treatment-by-visit interaction as fixed effects, and baseline IOP at the given timepoint as a covariate. Within-subject errors were modeled using an unstructured covariance matrix.

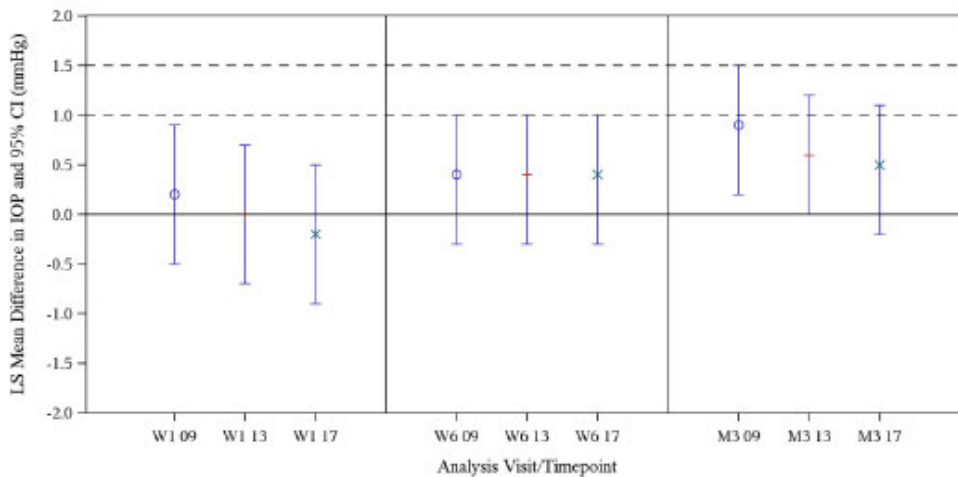
Abbreviations: CI = confidence interval; diff. = difference; IOP = intraocular pressure; LS = least squares; mmHg = millimeters of mercury; MMRM = mixed-effects model for repeated measures; Upper/Lower CI = upper/lower two-sided 95% confidence interval limit. Difference was calculated as DE-117 - latanoprost.

Study 01171505: Mean Change from Baseline in Mean Diurnal IOP (\pm SE) by Visit (Study Eye, Full Analysis Set)



Abbreviations: IOP = intraocular pressure; mmHg = millimeters of mercury; SE = standard error.

Study 01171505, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Latanoprost) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

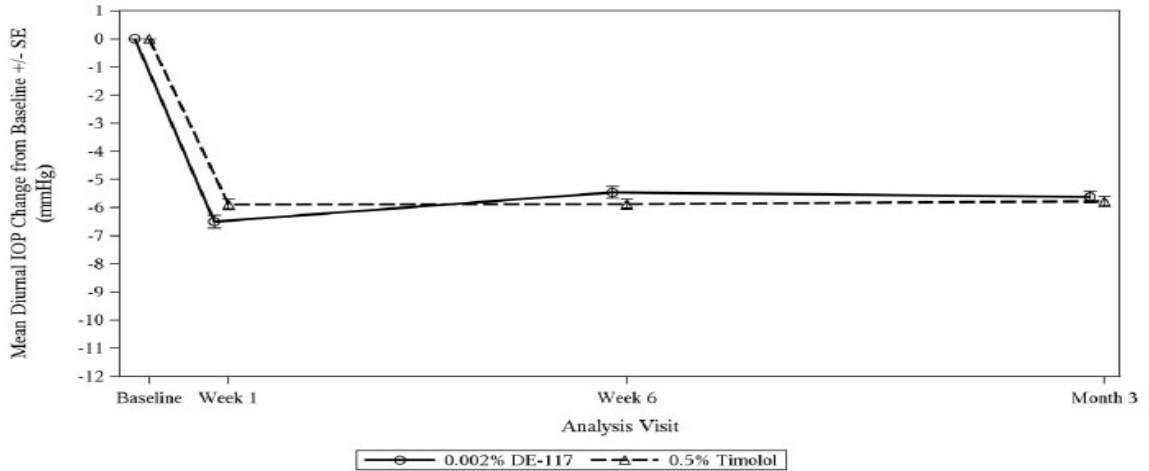


Analysis Visit/Timepoint: 09 = 09:00; 13 = 13:00; 17 = 17:00; W1 = Week 1; W6 = Week 6; M3 = Month 3.

Study 01171505 satisfied the primary endpoint of the means for IOP being within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority (5 or more) of the 9 timepoints.

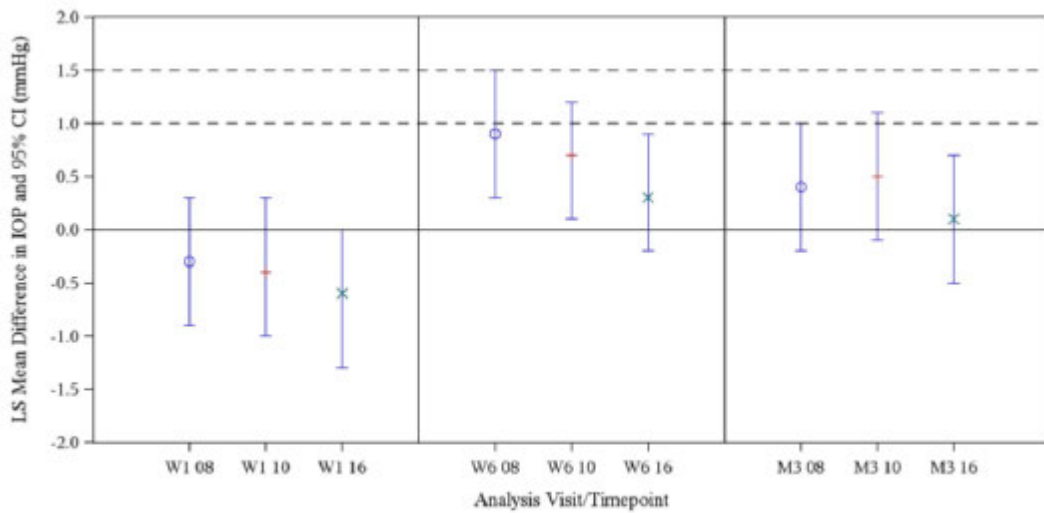
Study 011710IN Efficacy Results – Primary Endpoint

Study 011710IN: Mean Change from Baseline in Mean Diurnal IOP (\pm SE) by Visit (Study Eye, Full Analysis Set)



Abbreviations: IOP = intraocular pressure; mmHg = millimeters of mercury; SE = standard error.

Study 011710IN, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Timolol) and 95% Confidence Intervals (Study Eye, Full Analysis Set)



Analysis Visit/Timepoint: 08 = 08:00; 10 = 10:00; 16 = 16:00; W1 = Week 1; W6 = Week 6; M3 = Month 3.

Study 011710IN, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Timolol) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	Week 1			Week 6			Month 3		
	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00
Plotted Values (mmHg):									
Upper CI	0.3	0.3	-0.0	1.5	1.2	0.9	1.0	1.1	0.7
Mean Diff.	-0.3	-0.4	-0.6	0.9	0.7	0.3	0.4	0.5	0.1
Lower CI	-0.9	-1.0	-1.3	0.3	0.1	-0.2	-0.2	-0.1	-0.5

Abbreviations: CI = confidence interval; diff. = difference; IOP = intraocular pressure; LS = least squares; mmHg = millimeters of mercury; MMRM = mixed-effects model for repeated measures; Upper/Lower CI = upper/lower two-sided 95% confidence interval limit.

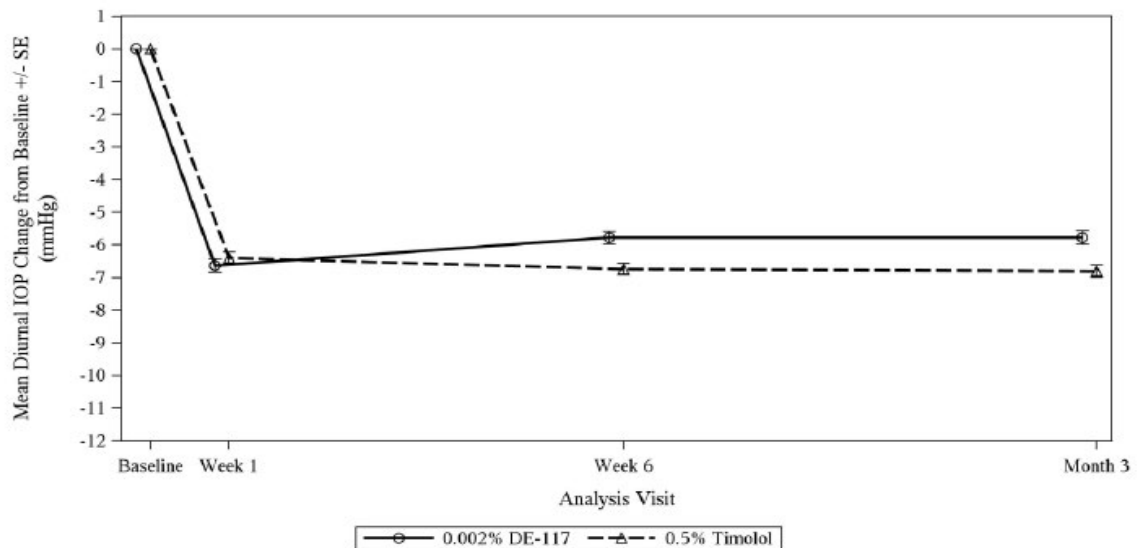
Difference was calculated as DE-117 - timolol.

LS means and p-values were obtained by fitting a MMRM to the IOP values from each visit at each timepoint (08:00, 10:00, 16:00) separately. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline IOP at the given timepoint as a covariate. Within-subject errors were modeled using an unstructured covariance matrix.

Study 011710IN satisfied the primary endpoint of the means for IOP being within 1.5 mmHg at all 9 timepoints and within 1.0 mmHg at a majority (5 or more) of the 9 timepoints.

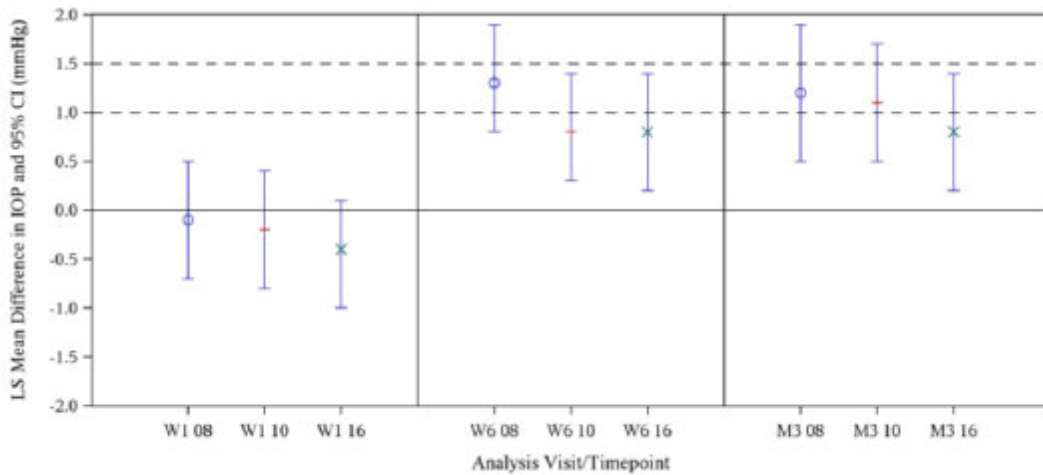
Study 011709IN Efficacy Results – Primary Endpoint

Study 011709IN: Mean Change from Baseline in Mean Diurnal IOP (\pm SE) by Visit (Study Eye, Full Analysis Set)



Abbreviations: IOP = intraocular pressure; mmHg = millimeters of mercury; SE = standard error.

Study 011709IN, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 minus Timolol) and 95% Confidence Intervals (Study Eye, Full Analysis Set)



Analysis Visit/Timepoint: 08 = 08:00; 10 = 10:00; 16 = 16:00; W1 = Week 1; W6 = Week 6; M3 = Month 3.

Study 011709IN, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 minus Timolol) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	Week 1			Week 6			Month 3		
	08:00	10:00	16:00	08:00	10:00	16:00	08:00	10:00	16:00
Plotted Values (mmHg):									
Upper CI	0.5	0.4	0.1	1.9	1.4	1.4	1.9	1.7	1.4
Mean Diff.	-0.1	-0.2	-0.4	1.3	0.8	0.8	1.2	1.1	0.8
Lower CI	-0.7	-0.8	-1.0	0.8	0.3	0.2	0.5	0.5	0.2

Abbreviations: CI = confidence interval; diff. = difference; IOP = intraocular pressure; LS = least squares; mmHg = millimeters of mercury; MMRM = mixed-effects model for repeated measures; Upper/Lower CI = upper/lower two-sided 95% confidence interval limit.

Difference was calculated as DE-117 - timolol.

LS means and p-values were obtained by fitting a MMRM to the IOP values from each visit at each timepoint (08:00, 10:00, 16:00) separately. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline IOP at the given timepoint as a covariate. Within-subject errors were modeled using an unstructured covariance matrix.

Study 011709IN did not satisfy both of these criteria but trended in the right direction adding supportive data to the recommended approval of this NDA.

Efficacy Summary Statement

Intraocular pressure (IOP) reduction is currently the accepted standard for establishing the efficacy of ocular hypertensive medications. The primary efficacy endpoint for studies 01171505, 011710IN and 011709IN were nearly the same. The primary endpoint was mean IOP measured at multiple time points that are intended to capture the peak and trough of latanoprost ophthalmic solution 0.005% dosed once daily (QD) in the evening, timolol maleate 0.5% dosed twice-daily (BID).

The data contained in this submission establishes the efficacy of omidenepeg isopropyl ophthalmic solution, 0.002% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension. Studies 01171505 and 011710IN demonstrate that the IOP lowering ability of omidenepeg isopropyl ophthalmic solution, 0.002% does not differ from latanoprost ophthalmic solution, 0.005% or timolol maleate ophthalmic solution 0.5% by a clinically significant amount. Omidenepeg isopropyl ophthalmic solution, 0.002% lowers IOP by a clinically significant amount.

7. Safety

From the original Medical Officer Review dated 10/13/2021:

7.1. Safety Database

During the masked period of the pooled studies (011709IN, 011710IN and 01171505), 600 subjects were exposed to once daily dosing of DE-117 0.002% for a maximum of 121 days (median 91 days); the majority were treated > 90 days (for 1 subject the duration of exposure was unknown).

Exposure to Study Medication (Pooled Studies) - Analysis Population: Safety - Analysis Period: Masked

Duration of Exposure to Treatment (days)	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%+ DE-117 (N=415)	0.002%+ DE-117 (N=600)	0.5% Timolol (N=420)
N	211	215	204	205	184	185	415	599	420
Mean (SD)	85.5 (19.8)	89.3 (14.7)	85.6 (17.0)	88.0 (15.8)	85.2 (17.9)	87.3 (13.6)	85.6 (18.5)	85.4 (18.3)	88.7 (15.2)
Median	92.0	92.0	91.0	92.0	90.0	91.0	91.0	91.0	92.0
Min, Max	3, 121	8, 134	3, 101	2, 124	7, 112	3, 103	3, 121	3, 121	2, 134
1 – 30 days	10 (4.7%)	5 (2.3%)	6 (2.9%)	6 (2.9%)	10 (5.4%)	5 (2.7%)	16 (3.9%)	26 (4.3%)	11 (2.6%)
31 – 60 days	7 (3.3%)	4 (1.9%)	7 (3.4%)	3 (1.5%)	3 (1.6%)	3 (1.6%)	14 (3.4%)	17 (2.8%)	7 (1.7%)
61 – 90 days	58 (27.5%)	49 (22.8%)	73 (35.8%)	59 (28.8%)	84 (45.4%)	81 (43.8%)	131 (31.6%)	215 (35.8%)	108 (25.7%)
> 90 days	136 (64.5%)	157 (73.0%)	118 (57.8%)	137 (66.8%)	87 (47.0%)	96 (51.9%)	254 (61.2%)	341 (56.8%)	294 (70.0%)
Unknown***	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)

Abbreviations: SD = standard deviation; QD = once daily.

* Pooled studies are 011709IN and 011710IN

** Pooled studies are 011709IN, 011710IN and 01171505

***If treatment end date is missing or not inputted for a subject, the exposure of the subject is classified as "Unknown".

7.2. Deaths

Three subject deaths have been reported during the double-masked and open-label periods of studies 011709IN and 011710IN. During the masked period in study 011709IN, an 82-year-old Caucasian female treated with timolol died due to a stroke. In study 11710IN, a 67-year-old Caucasian male treated with DE-117 0.002% experienced a fatal myocardial infarction. In the open-label period of study 011709IN, a 76-year-old male subject (received DE-117 during both the masked and open-label periods) due to a cardiac event.

7.3. Serious Adverse Events

Adverse Events: Summary of Serious Adverse Events by System Organ Class and Preferred Term – Analysis Population: Safety - Analysis Period: Double-Masked

System organ class Preferred term	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%+ DE-117 (N=415)	0.002%+ DE-117 (N=600)	0.5% Timolol (N=420)
Subjects with Any SAE(s)	4 (1.9%)	4 (1.9%)	7 (3.4%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	11 (2.7%)	13 (2.2%)	5 (1.2%)
Eye disorders	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.5%)	0 (0.0%)
Cystoid macular oedema	1 (0.5%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.7%)	3 (0.5%)	0 (0.0%)
Nervous system disorders	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)	2 (0.3%)	1 (0.2%)
Dizziness	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Generalised tonic-clonic seizure	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Cerebrovascular accident	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Cardiac disorders	0 (0.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	2 (0.5%)
Myocardial infarction	0 (0.0%)	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Atrial fibrillation	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Ear and labyrinth disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Tinnitus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Hepatobiliary disorders	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Cholecystitis	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)

System organ class Preferred term	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%+ DE-117 (N=415)	0.002%+ DE-117 (N=600)	0.5% Timolol (N=420)
Infections and infestations	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Pneumonia	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Metabolism and nutrition disorders	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Hyperglycaemia	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (0.5%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
Osteoarthritis	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Arthralgia	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Renal and urinary disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Urinary retention	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)
Respiratory, thoracic, and mediastinal disorders	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Pleuritic pain	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Vascular disorders	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)
Hypertension	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	1 (0.2%)	0 (0.0%)

System organ class Preferred term	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%* DE-117 (N=415)	0.002%** DE-117 (N=600)	0.5% Timolol (N=420)
Gastrointestinal disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Food poisoning	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigations	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Influenza A virus test positive	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Intraductal proliferative breast lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary of Regulatory Activities; SAE = serious adverse event.

Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term.

Subjects were classified by actual treatment received.

AEs were coded using MedDRA Version 21.1.

* Pooled studies are 011709IN and 011710IN

** Pooled studies are 011709IN, 011710IN and 01171505

7.4. Treatment Emergent Adverse Events and Adverse Reactions

Adverse Events: Summary of Suspected Adverse Reactions by System Organ Class and Preferred Term occurring at a rate of $\geq 1\%$ in the DE-117 pooled population - Analysis Population: Safety - Analysis Period: Double-Masked

System organ class* Preferred term	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%* DE-117 (N=415)	0.002%** DE-117 (N=600)	0.5% Timolol (N=420)
Subjects with Any SAR(s)	51 (24.2%)	32 (14.9%)	47 (23.0%)	27 (13.2%)	43 (23.2%)	22 (11.9%)	98 (23.6%)	141 (23.5%)	59 (14.0%)
Eye disorders	42 (19.9%)	22 (10.2%)	37 (18.1%)	14 (6.8%)	42 (22.7%)	22 (11.9%)	79 (19.0%)	121 (20.2%)	36 (8.6%)
Conjunctival hyperaemia	10 (4.7%)	7 (3.3%)	14 (6.9%)	4 (2.0%)	18 (9.7%)	7 (3.8%)	24 (5.8%)	42 (7.0%)	11 (2.6%)
Photophobia	9 (4.3%)	1 (0.5%)	8 (3.9%)	0 (0.0%)	6 (3.2%)	1 (0.5%)	17 (4.1%)	23 (3.8%)	1 (0.2%)
Ocular hyperaemia	5 (2.4%)	3 (1.4%)	3 (1.5%)	2 (1.0%)	3 (1.6%)	2 (1.1%)	8 (1.9%)	11 (1.8%)	5 (1.2%)
Vision blurred	5 (2.4%)	3 (1.4%)	4 (2.0%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	9 (2.2%)	11 (1.8%)	4 (1.0%)
Eye pain	4 (1.9%)	1 (0.5%)	2 (1.0%)	2 (1.0%)	3 (1.6%)	4 (2.2%)	6 (1.4%)	9 (1.5%)	3 (0.7%)
Corneal thickening	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	7 (3.8%)	1 (0.5%)	0 (0.0%)	7 (1.2%)	0 (0.0%)
Dry eye	4 (1.9%)	1 (0.5%)	1 (0.5%)	2 (1.0%)	2 (1.1%)	2 (1.1%)	5 (1.2%)	7 (1.2%)	3 (0.7%)
Growth of eyelashes	2 (0.9%)	3 (1.4%)	2 (1.0%)	5 (2.4%)	0 (0.0%)	1 (0.5%)	4 (1.0%)	4 (0.7%)	8 (1.9%)
General disorders and administration site conditions	6 (2.8%)	12 (5.6%)	11 (5.4%)	13 (6.3%)	0 (0.0%)	0 (0.0%)	17 (4.1%)	17 (2.8%)	25 (6.0%)
Instillation site pain	5 (2.4%)	12 (5.6%)	11 (5.4%)	13 (6.3%)	0 (0.0%)	0 (0.0%)	16 (3.9%)	16 (2.7%)	25 (6.0%)

System organ class* Preferred term	011709IN		011710IN		01171505		Integrated Summary		
	0.002% DE-117 (N=211)	0.5% Timolol (N=215)	0.002% DE-117 (N=204)	0.5% Timolol (N=205)	0.002% DE-117 (N=185)	0.005% LAT (N=185)	0.002%+ DE-117 (N=415)	0.002%++ DE-117 (N=600)	0.5% Timolol (N=420)
Investigations	2 (0.9%)	1 (0.5%)	5 (2.5%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	7 (1.7%)	9 (1.5%)	1 (0.2%)
Vital dye staining cornea present	2 (0.9%)	1 (0.5%)	2 (1.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	4 (1.0%)	5 (0.8%)	1 (0.2%)
Nervous system disorders	2 (0.9%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	4 (1.0%)	6 (1.0%)	0 (0.0%)
Headache	2 (0.9%)	0 (0.0%)	2 (1.0%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	4 (1.0%)	6 (1.0%)	0 (0.0%)

Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities; SAR = suspected adverse drug reactions.

Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term. Subjects were classified by actual treatment received.

AEs were coded using MedDRA Version 21.1.

* Pooled studies are 011709IN and 011710IN

** Pooled studies are 011709IN, 011710IN and 01171505

^a n and % each SOC is cumulative for all PTs, including those occurring at a rate < 1% that are not represented in this table

Eye disorders were the majority of Suspected Adverse Events (SARs) in the pooled population. Conjunctival hyperemia was the most common SAR across all treatments, occurring at a higher rate for DE-117 0.002% (7.0%) than timolol (2.6%) and latanoprost (3.8%). Photophobia followed occurring at a rate of 3.8% for DE-117 0.002%, compared with 0.2% for timolol and 0.5% for latanoprost.

7.5. Corneal Endothelium

Central corneal endothelial cell density was evaluated by specular microscopy in a one long-term study in Japan (Study 01171504, 52-week follow up). This was an open-label study of DE-117 ophthalmic solution, alone and in combination with timolol ophthalmic solution, in subjects with open angle glaucoma or ocular hypertension.

Group 1 received DE-117 ophthalmic solution 0.002% monotherapy instilled once daily in both eyes after a 4-week washout period. Group 2, with no previous treatments, also received DE-117 ophthalmic solution 0.002% monotherapy instilled once daily in both eyes. Group 3, with no previous treatments, received both DE-117 ophthalmic solution 0.002% instilled once daily in both eyes plus timolol ophthalmic solution instilled twice daily in both eyes.

Although the study report states that there were no clinically significant changes in corneal endothelial cell density reported, there is significant endothelial cell loss in both omdenepeg isopropyl ophthalmic solution monotherapy arms seen in the following tables.

Table 14.3.7.1.1 Corneal Endothelial Cell Density: Score by Analysis Visit (Study Eye) Study Population: Safety

Analysis Visit	Corneal Endothelial Cell Density (cells/mm ²)	Group 1 (N=48)	Group 2 (N=37)	Group 1 + 2 (N=85)	Group 3 (N=40)	Overall (N=125)
Screening	N	48	37	85	40	125
	Mean (SD)	2602.4 (323.8)	2559.1 (289.6)	2583.5 (308.4)	2620.9 (326.7)	2595.5 (313.5)
	Median	2625.0	2577.0	2597.0	2660.0	2625.0
	Min, Max	2000, 3273	2000, 3134	2000, 3273	1801, 3210	1801, 3273
Baseline	N	48	37	85	40	125
	Mean (SD)	2606.7 (360.5)	2570.6 (281.2)	2591.0 (327.0)	2602.7 (308.9)	2594.7 (320.1)
	Median	2638.5	2610.0	2624.0	2577.0	2614.0
	Min, Max	1824, 3322	2000, 3095	1824, 3322	1891, 3105	1824, 3322
Week 2	N	48	37	85	40	125
	Mean (SD)	2583.9 (370.4)	2502.1 (294.5)	2548.3 (340.0)	2633.8 (290.1)	2575.7 (326.1)
	Median	2570.0	2500.0	2556.0	2635.5	2577.0
	Min, Max	1623, 3472	1843, 3000	1623, 3472	2000, 3215	1623, 3472
Week 4	N	48	37	85	36	121
	Mean (SD)	2627.9 (332.2)	2502.2 (254.8)	2573.2 (305.8)	2598.1 (278.1)	2580.6 (296.9)
	Median	2566.0	2481.0	2551.0	2534.5	2548.0
	Min, Max	1838, 3267	2000, 3000	1838, 3267	2000, 3000	1838, 3267
Week 8	N	48	37	85	34	119
	Mean (SD)	2585.9 (329.3)	2506.9 (290.1)	2551.5 (313.5)	2538.6 (282.1)	2547.8 (303.7)
	Median	2558.5	2525.0	2555.0	2484.5	2545.0
	Min, Max	1694, 3236	1945, 3000	1694, 3236	2000, 3093	1694, 3236

Cross-Discipline Team Leader, Division Director, Office Director Review
 NDA 215092 Omlonti (omidenepeg isopropyl ophthalmic solution) 0.002%

Analysis Visit	Corneal Endothelial Cell Density (cells/mm ²)	Group 1 (N=48)	Group 2 (N=37)	Group 1 + 2 (N=85)	Group 3 (N=40)	Overall (N=125)
Week 12	N	45	34	79	33	112
	Mean (SD)	2593.0 (336.6)	2526.6 (298.1)	2564.5 (320.3)	2563.0 (281.3)	2564.0 (308.1)
	Median	2618.0	2561.0	2604.0	2518.0	2586.5
	Min, Max	1834, 3258	2000, 3086	1834, 3258	2000, 3030	1834, 3258
Week 26	N	44	33	77	30	107
	Mean (SD)	2519.7 (445.2)	2479.8 (256.1)	2502.6 (374.4)	2550.5 (328.1)	2516.0 (361.1)
	Median	2596.0	2439.0	2525.0	2551.0	2525.0
	Min, Max	1413, 3155	2000, 3000	1413, 3155	1611, 3125	1413, 3155
Week 40	N	38	32	70	27	97
	Mean (SD)	2631.5 (351.8)	2516.5 (261.9)	2579.0 (317.0)	2591.7 (265.2)	2582.5 (302.2)
	Median	2695.5	2525.0	2624.5	2551.0	2568.0
	Min, Max	1912, 3341	2000, 3000	1912, 3341	2000, 3067	1912, 3341
Week 52	N	37	31	68	27	95
	Mean (SD)	2605.5 (395.8)	2545.8 (270.0)	2578.3 (343.1)	2551.7 (324.6)	2570.8 (336.5)
	Median	2703.0	2562.0	2593.5	2522.0	2590.0
	Min, Max	1620, 3341	2000, 3000	1620, 3341	1784, 3114	1620, 3341

Table 14.3.7.2.1 Corneal Endothelial Cell Density: Change from Baseline by Analysis Visit (Study Eye) Study Population: Safety

Analysis Visit	Change from Baseline (cells/mm ²)	Group 1 (N=48)	Group 2 (N=37)	Group 1 + 2 (N=85)	Group 3 (N=40)	Overall (N=125)
Week 2	N	48	37	85	40	125
	Mean (SD)	-22.8 (217.3)	-68.6 (188.7)	-42.7 (205.5)	31.1 (186.7)	-19.1 (201.9)
	Median	-44.0	-21.0	-42.0	1.5	-7.0
	Min, Max	-497, 656	-505, 238	-505, 656	-389, 518	-505, 656
Week 4	N	48	37	85	36	121
	Mean (SD)	21.2 (253.7)	-68.5 (232.1)	-17.8 (247.2)	17.8 (194.1)	-7.2 (232.4)
	Median	0.0	-21.0	0.0	3.0	0.0
	Min, Max	-549, 1085	-878, 392	-878, 1085	-374, 653	-878, 1085
Week 8	N	48	37	85	34	119
	Mean (SD)	-20.8 (229.3)	-63.8 (225.3)	-39.5 (227.2)	-46.3 (192.6)	-41.4 (217.1)
	Median	0.0	-15.0	-8.0	-16.5	-8.0
	Min, Max	-731, 410	-1095, 303	-1095, 410	-665, 328	-1095, 410
Week 12	N	45	34	79	33	112
	Mean (SD)	-10.2 (164.2)	-50.1 (248.0)	-27.4 (204.0)	-26.9 (190.6)	-27.2 (199.3)
	Median	-7.0	10.0	0.0	-11.0	0.0
	Min, Max	-457, 425	-1025, 204	-1025, 425	-346, 393	-1025, 425
Week 26	N	44	33	77	30	107
	Mean (SD)	-93.1 (374.4)	-111.9 (238.1)	-101.1 (321.4)	-47.1 (257.1)	-86.0 (304.5)
	Median	-32.0	-72.0	-49.0	0.0	-25.0
	Min, Max	-1373, 514	-967, 243	-1373, 514	-738, 443	-1373, 514

Cross-Discipline Team Leader, Division Director, Office Director Review
 NDA 215092 Omlonti (omidenedpag isopropyl ophthalmic solution) 0.002%

Analysis Visit	Change from Baseline (cells/mm ²)	Group 1 (N=48)	Group 2 (N=37)	Group 1 + 2 (N=85)	Group 3 (N=40)	Overall (N=125)
Week 40	N	38	32	70	27	97
	Mean (SD)	-8.7 (244.0)	-81.3 (182.8)	-41.8 (219.7)	8.8 (215.4)	-27.8 (218.6)
	Median	-25.5	-43.0	-26.0	0.0	-15.0
	Min, Max	-449, 581	-557, 313	-557, 581	-446, 508	-557, 581
Week 52	N	37	31	68	27	95
	Mean (SD)	-51.9 (327.8)	-57.4 (226.1)	-54.4 (283.9)	-31.2 (249.8)	-47.8 (273.6)
	Median	0.0	-13.0	-3.5	0.0	0.0
	Min, Max	-1258, 581	-753, 299	-1258, 581	-910, 429	-1258, 581

Study 1171504 demonstrated significant endothelial cell loss in both omidenepeg isopropyl ophthalmic solution monotherapy arms particularly between Weeks 12 and 26. In the absence of a control arm without omidenepeg isopropyl treatment, the trial is suggestive of potential harm to the corneal endothelial cells. The lack of corneal edema seen in any of the clinical trials suggests that if there is an issue with corneal endothelial cells, it is a slow process. A concurrently controlled, randomized, 12-month clinical study in which omidenepeg isopropyl ophthalmic solution is dosed as monotherapy and corneal endothelial cell counts are compared to a concurrent control without omidenepeg isopropyl should be conducted and submitted. A post-marketing requirement (PMR) for this study will be included with the approval of this application.

Safety Summary Statement

With the exception of concerns regarding corneal endothelial cell loss (see Section 8.5), the safety database contained in this submission establishes the safety of omidenepeg isopropyl ophthalmic solution, 0.002% dosed once daily in the evening for the treatment of elevated IOP in open-angle glaucoma or ocular hypertension.

The risk for using this drug is consistent with other currently marketed prostaglandin analog IOP lowering products. The most common ocular adverse events were conjunctival hyperemia (9%) and photophobia (5%). Similar to other prostaglandin analog trials, class events such as increases in iris pigment would not have been expected to be observed in the clinical trials of 3-month duration and/or in the absence of a contralateral eye comparison.

Per the resubmission cover letter:

As requested in the CR letter and subsequently discussed with the review division, Santen is prepared to conduct a controlled, randomized, 12-month clinical postmarketing study with omidenepeg isopropyl ophthalmic solution dosed as monotherapy and a concurrent control without omidenepeg isopropyl to further elucidate the impact of DE-117 on corneal endothelial cell counts. We shall conduct this postmarketing study according to the following schedule:

Draft Protocol Submission: 10/2022

Final Protocol Submission: 03/2023

Study Completion: 09/2026

Final Report Submission 12/2026

The submissions listed above shall be made to the IND 111518 with a cross-reference letter to this NDA.

This is acceptable.

8. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the NDA.

9. Pediatrics

The applicant has requested a full product specific waiver for all pediatric age groups (i.e., birth to < 18 years) on the grounds that studies would be impossible or highly impractical due to the very limited number of pediatric patients. Despite efforts to recruit and enroll pediatric subjects, Santen was not able to enroll pediatric subjects in 011710IN. In study 011709IN, they were only able to enroll 13 subjects, of which 6 of them were for DE-117 and 7 for timolol.

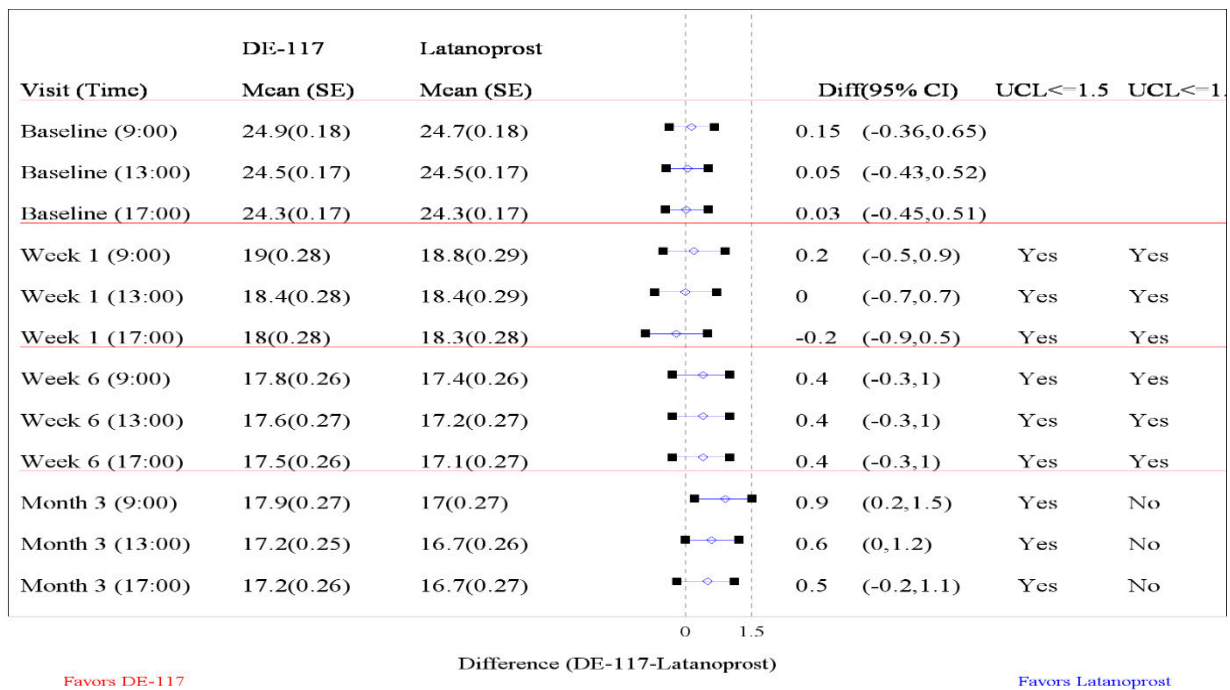
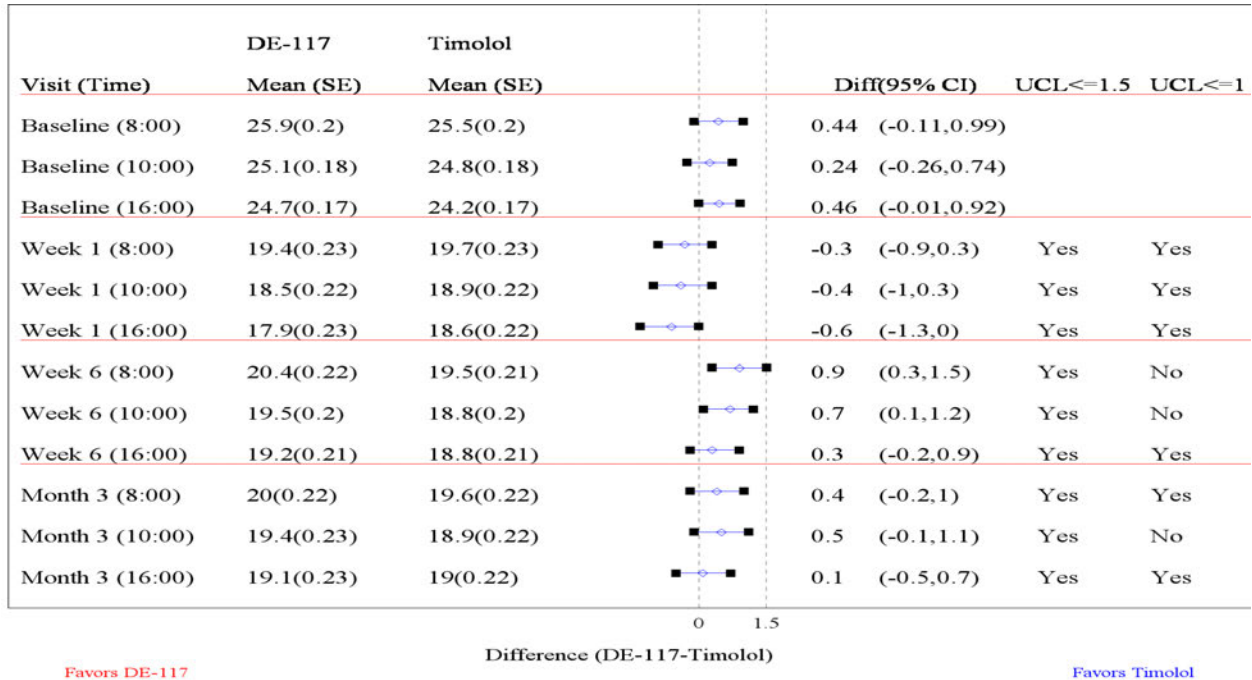
The product triggers PREA as a new molecular entity and was presented at the Pediatric Review Committee (PeRC) on August 24, 2021. The PeRC agreed with granting full waiver for intraocular pressure reduction.

10. BIOSTATISTICS

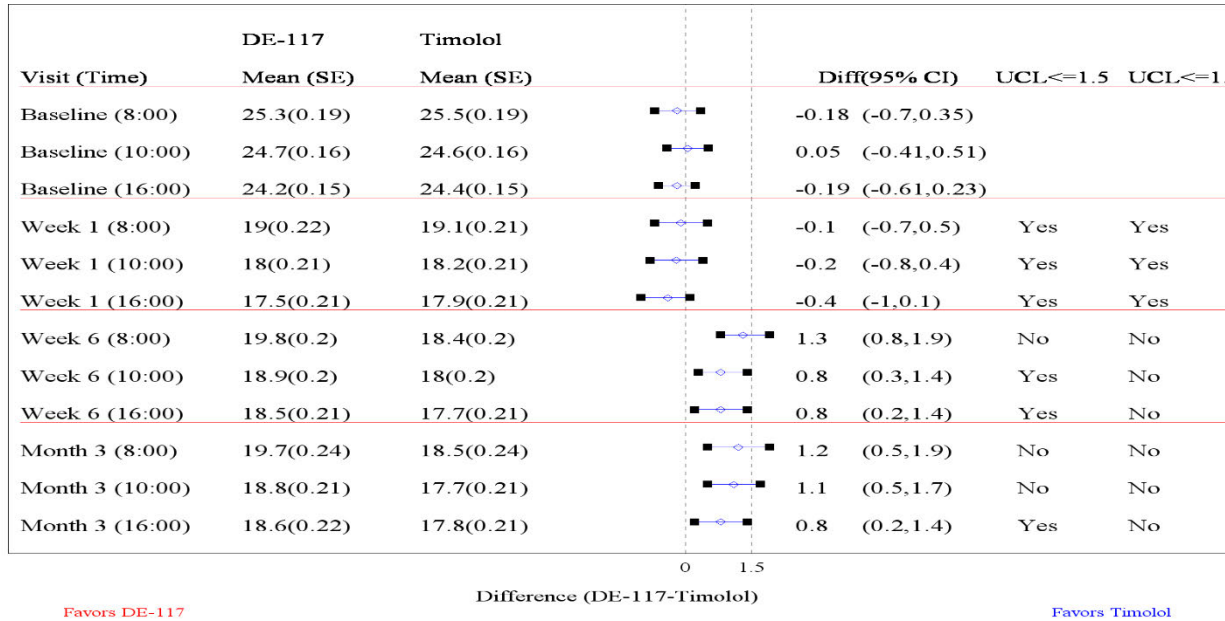
Per the original Biostatistics review dated 8/16/2021:

The three studies were all randomized, double-masked, active-controlled studies. The active control in Study 01171505 was latanoprost 0.005% QD. The two US based studies (011709IN and 011710IN) used timolol 0.5% BID as the active control. All three studies had a 3-month comparative treatment period. In addition, Study 011709IN included a 9-month open-label safety extension period, during which, all subjects received DE-117.

The protocol-defined primary efficacy analyses results are presented in the following figures. In Studies 011710IN and 01171505, the upper limits of the 95% confidence intervals (UCL) for the mean differences in IOP were less than the pre-specified non-inferiority margin of 1.5 mmHg for all measurement times (Statistical Criteria). Additionally, the UCLs did not exceed 1.0 mmHg at the majority of the nine post-baseline time points (Clinical Criteria). Therefore, the two studies met both the statistical and clinical criteria for non-inferiority.



However, because the UCLs are higher than 1.5 mm Hg for 3 of the 9 timepoints [Week 6 (08:00), Month 3 (08:00 & 10:00)], Study 011709IN did not demonstrate the non-inferiority of DE-117 over timolol.



11. Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. There were no investigators with disclosable financial interests/arrangements (Form FDA 3455). There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the Applicant for covered studies [i.e., 011709IN, 011710IN and 01171505].

12. Study Integrity

A routine Office of Scientific Investigations (OSI) audit was requested. Per the OSI review dated 6/10/2021:

Four clinical investigators (CIs): Drs. El-Roy Dixon (Site 8400025; Study 011709IN), Robert Smyth-Medina (Site 8400296; Study 011709IN), Eugene McLaurin (Site 8400044; Study 011710IN), and Paul James Hartman (Site 8400270; Study 011710IN) were selected for clinical inspections. The inspections verified that the applicant, Santen, Inc. (Santen), submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Studies 011709IN and 011710IN appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

Inspections for Protocol 01171505 were not requested because audit information from Studies 011709IN and 011710IN was adequate.

13. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, (b) (4) and found the proposed name unacceptable on 3/5/2021. DMEPA finalized a review of the proposed proprietary name, (b) (4), and found the proposed name unacceptable on 7/2/2021. The applicant submitted a new request for a proposed proprietary name review of an alternate proprietary name Omlonti, on 7/27/2021. DMEPA finalized a review of the proposed proprietary name, Omlonti, and found the proposed name conditionally acceptable on 10/21/2021.

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the 5/6/22 submitted labeling on 7/5/22. DO did not agree with two of DMEPA's carton/container comments because the comments are not supported by regulation:

As currently presented, the strength statement appears less prominently in size than the net quantity statement. Increase the prominence of the strength presentation.

As currently presented, the percentage sign in the strength statement appears to be smaller and offset compared to the strength. Ensure all parts of the strength statement (i.e., the numerical part and the percentage sign) are the same font size.

The established name should have a prominence commensurate with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. The following revised comment is supported by regulation and was send to the applicant:

The established name on all carton labels should be revised to a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

Clinical did not have any objections to the other DMEPA recommendations.

DMEPA finalized a review of the 9/9/22 submitted labeling on 9/16/22. DO transmitted DMEPA's recommendations to the applicant. Final labeling was submitted on 9/20/22. DMEPA had no additional recommendations.

OPDP

The Office of Prescription Drug Promotion (OPDP) completed a review of the product labeling dated 8/12/2021.

DMEPA and OPDP

The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) completed a joint review of the Applicant's proposed Instructions for Use (IFU) dated 8/19/2021.

14. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

<input checked="" type="checkbox"/>	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
<input checked="" type="checkbox"/>	Clinical outcome assessment (COA) data	Sec 6
<input type="checkbox"/>	<input type="checkbox"/> Patient reported outcome (PRO) <input type="checkbox"/> Observer reported outcome (ObsRO)	
<input checked="" type="checkbox"/>	Clinician reported outcome (ClinRO)	Sec 6
<input type="checkbox"/>	Performance outcome (PerFO)	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies (e.g., submitted studies or scientific publications)	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data that were not submitted in the application, but were considered in this review:	
<input type="checkbox"/>	Input informed from participation in meetings with patient stakeholders	
<input type="checkbox"/>	Patient-focused drug development or other stakeholder meeting summary reports	
<input type="checkbox"/>	Observational survey studies designed to capture patient experience data	
<input type="checkbox"/>	Other: (Please specify)	
<input type="checkbox"/>	Patient experience data was not submitted as part of this application.	

15. Labeling

The labeling that will be approved for NDA 215092 Omidenedepag isopropyl ophthalmic solution 0.002% for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension is attached to this review as an Appendix.

16. Regulatory Action

NDA 215092 Omidenepag isopropyl ophthalmic solution 0.002% will be approved for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. There are no recommended post-marketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of the drug product.

In a correspondence dated 9/16/22, Santen has committed to conduct a controlled, randomized, 12-month clinical post-marketing study (PMR) with omidenepag isopropyl ophthalmic solution dosed as monotherapy and a concurrent control without omidenepag isopropyl to further elucidate the impact of DE-117 on corneal endothelial cell counts.

4339-1: Conduct a randomized, controlled trial to evaluate the corneal endothelial health of eyes treated with omidenepag isopropyl ophthalmic solution by monitoring the number/density of corneal endothelial cells using specular microscopy at baseline and over a period of at least one year in at least 100 patients receiving omidenepag isopropyl ophthalmic solution.

Draft Protocol Submission: 10/2022

Final Protocol Submission: 3/2023

Trial Completion: 9/2026

Final Report Submission: 12/2026

17. Appendix – Package Insert, Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM M BOYD
09/21/2022 03:13:13 PM

WILEY A CHAMBERS
09/21/2022 03:55:46 PM

CHARLES J GANLEY
09/21/2022 03:58:44 PM