CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

CROSS DISCIPLINE TEAM LEADER 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	November 19, 2020
PDUFA Goal Date	November 19, 2021
Proprietary Name	Omlonti
Established or Proper Name	Omidenepag isopropyl ophthalmic solution, 0.002%
Dosage Form(s)	Ophthalmic solution
Dosing Regimen(s)	One drop in the affected eye(s) once daily in the evening
Regulatory Action	Complete Response
Indication(s)/Population(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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 based on the most recent inspections. Therefore, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall recommendation of "Withhold" on August 3, 2021, reconfirmed October 26, 2021. There are additional OPQ deficiencies. The regulatory action for this application will be **Complete Response.**

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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 for using this drug is consistent with other currently marketed topical prostaglandin analog IOP lowering products.

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Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• 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).	Intraocular pressure reduction is currently the accepted standard for establishing the efficacy of ocular hypertensive medications.
Current Treatment Options	• 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	This product would add another prostaglandin analogue to the approved U.S. products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	analogues. Patients often need more than one class of IOP lowering products concurrently.	
Benefit	• 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.	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.
Risk and Risk Management	• 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.	The observed safety profile was consistent with other prostaglandin analog products. Routine monitoring and reporting of all adverse events has been adequate for other 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.

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 Pharamaceuticals	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.

4.1. Drug Substance

The active pharmaceutical ingredient or drug substance of DE-117 ophthalmic solution, omidenepag isopropyl (USAN), is manufactured by [redacted (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] [redacted (b) (4)]% Total: NMT [redacted (b) (4)]%
4. Water	USP <921> Karl Fischer	NMT [redacted (b) (4)]%
5. Residue on ignition	USP <281>	NMT [redacted]%
6. Assay (anhydrous and residual solvent-free basis)	HPLC	[redacted (b) (4)]%
7. Microbial Enumeration Tests	USP < 61> Membrane Filtration Method	TAMC[c]: NMT [redacted (b) (4)] CFU/g TYMC[d]: NMT [redacted] 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 omidenepag 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 (mg)	Reference to Standards
Omidenepag isopropyl	Active ingredient	0.02	0.05	In-house[a]
Sodium citrate[b]	(b) (4)			
Citric acid monohydrate				
Polyoxyl 35 castor oil				
Benzalkonium chloride	Preservative	0.05	0.125	NF
Edetate disodium	(b) (4)			USP
Glycerin				USP
Sodium hydroxide / hydrochloric acid	pH adjuster	q.s. Adjust pH to (b) (4)	q.s. 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)
Omidenepag isopropyl assay	HPLC PDR-ATM-SEO-0001	
Related substances of Omidenepag 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)

(b) (4)

4.5. Microbiology

The applicant has provided adequate sterility assurance. (b) (4)

4.6. Establishment Information

The compliance status of the drug product manufacturing facility, (b) (4) Woodstock Sterile Solutions (FEI 1419377) and testing facility (b) (4) , were determined unacceptable based on the most recent inspections. Therefore, OPMA issued an overall recommendation of "Withhold" on Aug 3, 2021.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)	1419377	Drug Product manufacturing, packaging, sterility testing || 356h Status: Pending	Withhold - Based on CGMP
	1000110912	Drug substance release testing, Drug product release and stability testing || 356h Status: Pending LCP	Withhold - Based on CGMP
Santen Incorporated 6401 Hollis Street Suite 125, Emeryville, CA, USA, 94608	1000606419	Drug product release || 356h Status: Pending 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) || 356h Status: Pending LCP	No Evaluation Necessary
(b) (4)		Coordination of drug substance production at (b) (4) ., Drug substance stability testing, and MF holder || 356h Status: Pending	Approve - Based on Previous History
		Drug substance manufacturing, Drug substance release testing, Drug substance packaging and labeling, and Drug substance stability testing || 356h Status: Pending	Approve - Based on Previous History

Office of Product Quality Recommendation

From the OPQ integrated review 08/28/2021, recommended language for action letter:

> "During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.
>
> Following an evaluation of an inspection performed at the (b) (4) Woodstock Sterile Solutions (FEI 1419377) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the

> representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.
>
> We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency- preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders."

From the OPQ integrated review addendum dated 10/8/2021:

> NDA 215092 (Omidenepag Isopropyl Ophthalmic Solution, 0.002 %) was recommended for Complete Response from product quality perspective. Refer to IQA #1 on Aug 18, 2021. The drug product has been switched to a drug device combination product because of the Genus decision. However, the device component is a low-density polyethylene (LDPE) multi-dose eyedrop bottle and one drop is instilled in the affected eye(s) once daily. A CDRH consult review is not necessary as it is considered as a low risk for a Class 2 combination product based on MAPP 5017.7. Dr. Ashley Boam confirmed that a CDRH QS review/facility consult is not needed on Sep 23, 2021. It is also in agreement with Dr. Wiley Chambers' assessment that no additional review is necessary in the email communication dated Sep 20, 2021. OPPQ recommended to ask the applicant to update 356h form with the device constituent part facilities on Sep 29, 2021. Therefore, NDA 215092 upholds CR recommendation from product quality perspective with the additional IR and comments:

The following Information Request was sent**:**
"Your proposed product is a drug-device combination product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

General Comments:
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 your product.

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity."

5. Nonclinical Pharmacology/Toxicology

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

Omidenepag isopropyl is a small molecule pro-drug; its main metabolite, omidenepag, 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). Omidenepag 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.

From the draft internal labeling from the product:

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 spermatic cord 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
Spermatic cord 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 MHROD based on plasma Cmax).

Nasal cavity respiratory epithelium metaplasia was observed in cynomolgus monkeys receiving unilateral topical ocular instillations of omidenepag 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. In addition, the review refers to a P/T information request which was sent to the applicant on May 27, 2021. The applicant provided a response to these items on June 10, 2021.

6. Clinical Pharmacology

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

The drug product contains omidenepag isopropyl (OMDI), a prodrug of the pharmacologically active metabolite, omidenepag. Omidenepag is a prostaglandin E2 (EP2) receptor agonist and has a non-prostaglandin structure.

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. Three 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 omidenepag 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 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 omidenepag concentration on Days 1, 3, and 7 reached maximum concentration (Cmax) 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 ($AUC_{0\text{-}8h}$) 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 ^{14}C-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.

7. 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 limits 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

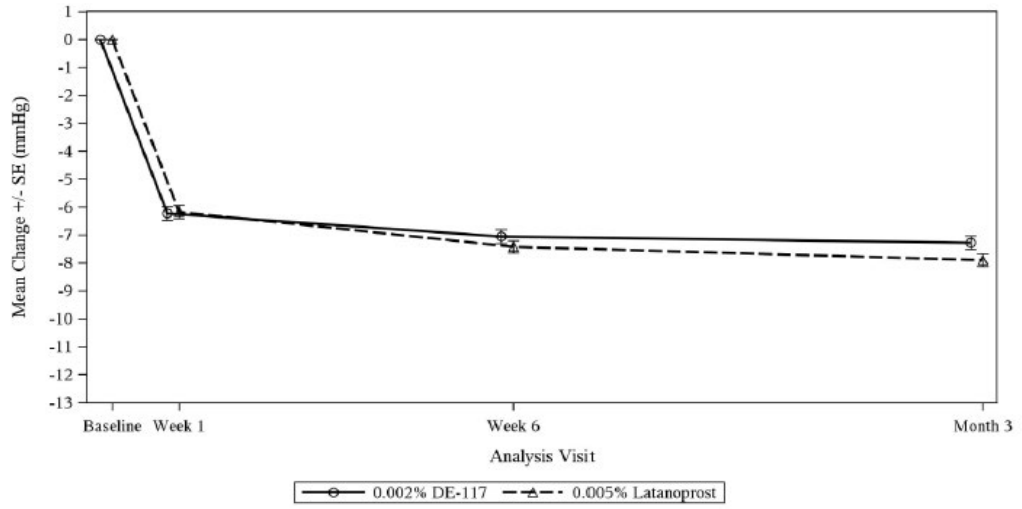
Study 01171505, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Latanoprost) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	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.

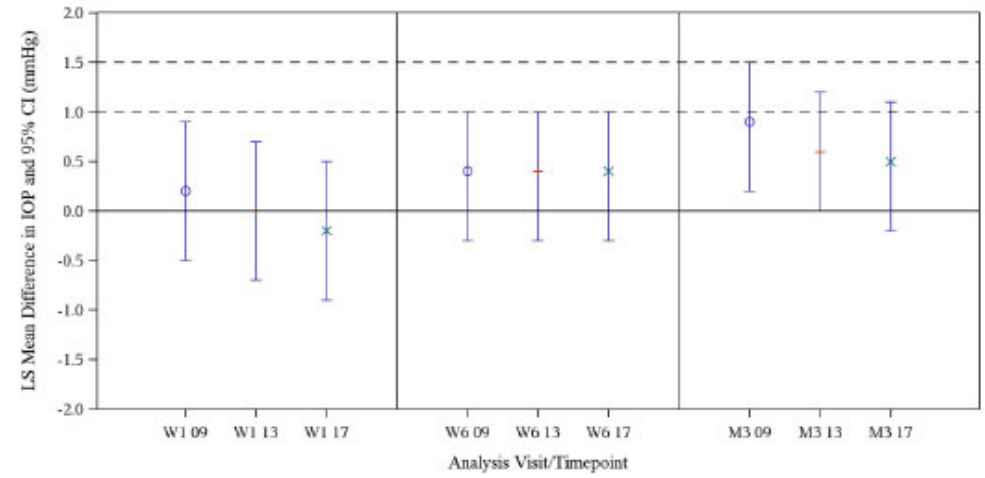
Abbreviations: CI = confidence interval; diff. = difference; IOP = intraocular pressure; LS = least squares; mmHg = millimeters of mercury; MMRM = mixed-effects model for repeated measures; Upper/Lower CI = upper/lower two-sided 95% confidence interval limit. Difference was calculated as DE-117 - latanoprost.

Study 01171505: Mean Change from Baseline in Mean Diurnal IOP (±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)

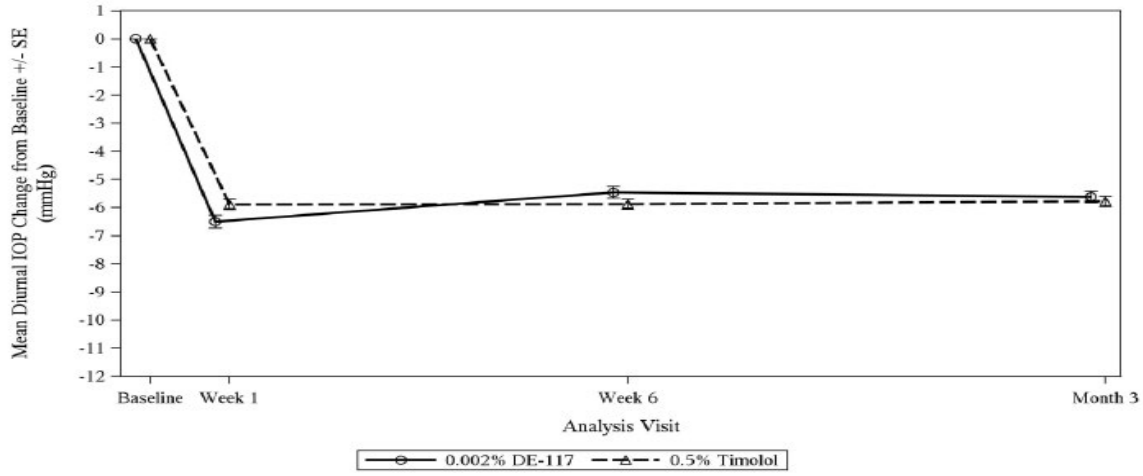


Analysis Visit/Timepoint: 09 = 09:00; 13 = 13:00; 17 = 17:00; W1 = Week 1; W6 = Week 6; M3 = Month 3.

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.

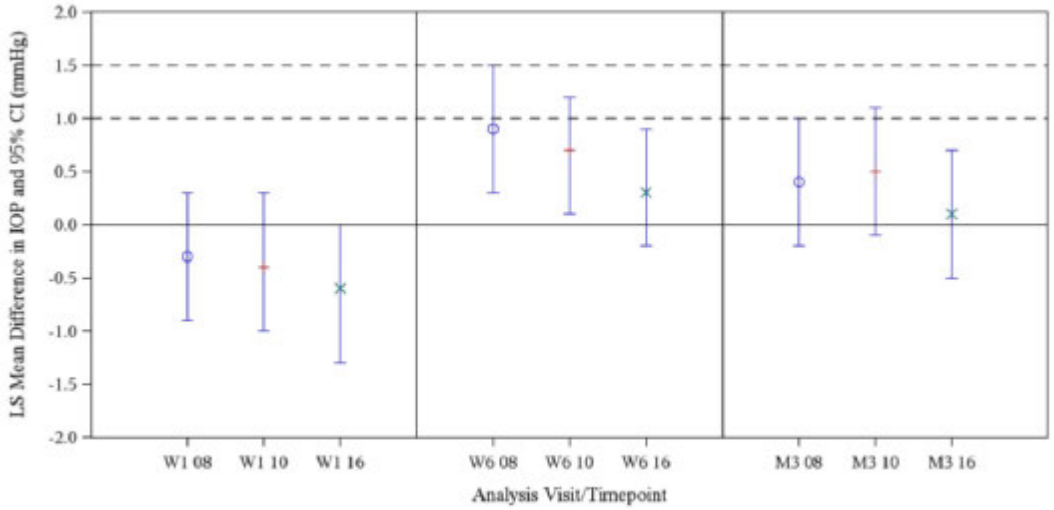
Study 011710IN Efficacy Results – Primary Endpoint

Study 011710IN: Mean Change from Baseline in Mean Diurnal IOP (±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)

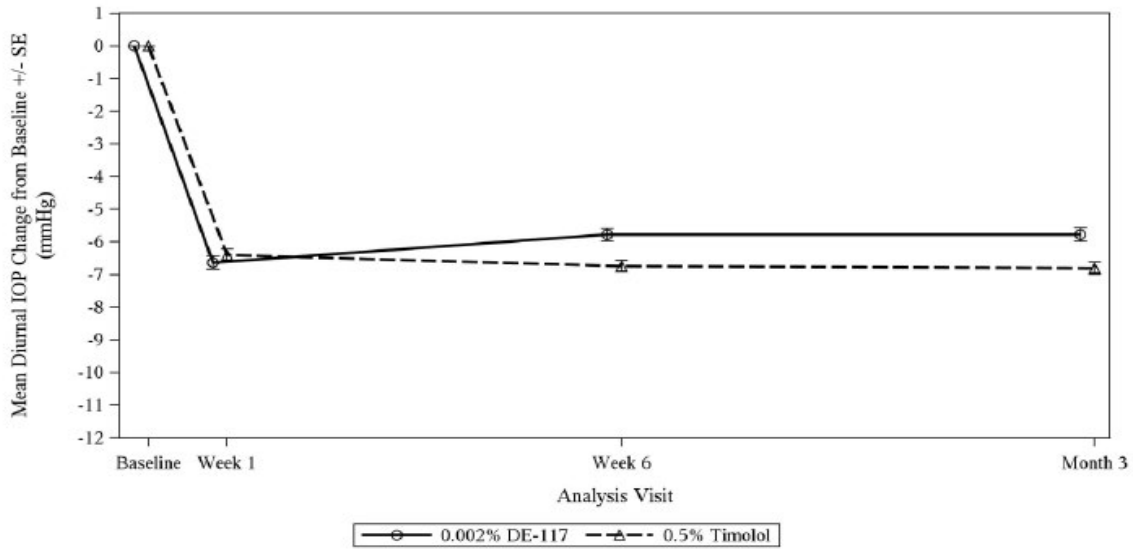
	Week 1			Week 6			Month 3		
	08:00	**10:00**	**16:00**	**08:00**	**10:00**	**16:00**	**08:00**	**10:00**	**16:00**
Plotted Values (mmHg):									
Upper CI	0.3	0.3	-0.0	1.5	1.2	0.9	1.0	1.1	0.7
Mean Diff.	-0.3	-0.4	-0.6	0.9	0.7	0.3	0.4	0.5	0.1
Lower CI	-0.9	-1.0	-1.3	0.3	0.1	-0.2	-0.2	-0.1	-0.5

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.

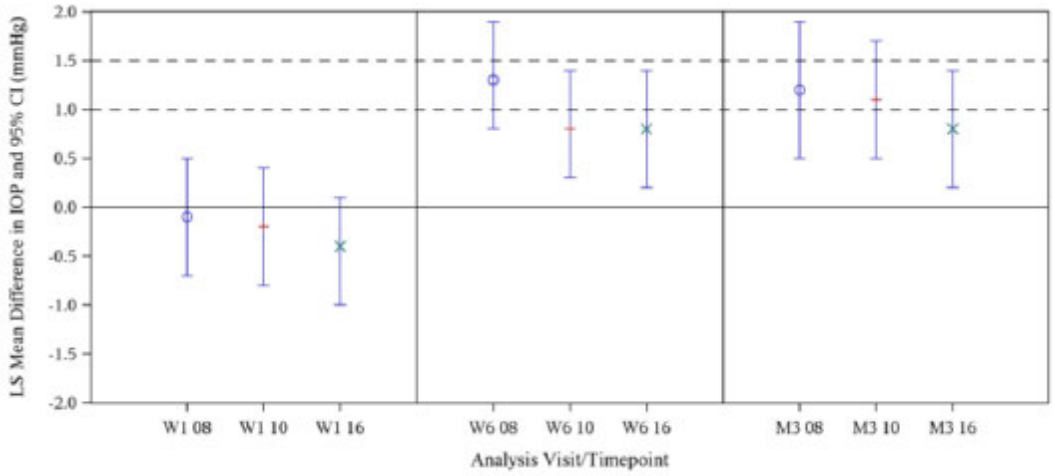
Study 011709IN **Efficacy Results – Primary Endpoint**

Study 011709IN: Mean Change from Baseline in Mean Diurnal IOP (±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 but did not capture the peak for the active-control, timolol maleate 0.5% dosed twice-daily (BID).

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 open-angle glaucoma or ocular hypertension. Studies 01171505 and 011710IN demonstrate that the IOP lowering ability of omidenepag 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. Omidenepag isopropyl ophthalmic solution, 0.002% lowers IOP by a clinically significant amount.

8. Safety

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

8.1. 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

	011709IN		011710IN		01171505		Integrated Summary		
Duration of Exposure to Treatment (days)	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".

8.2. 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 assessed.

8.3. 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

8.4. 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 ≥ 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%)

	011709IN		011710IN		01171505		Integrated Summary		
System organ class[a] Preferred term	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.

8.5. 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 omidenepag 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

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

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 omidenepag isopropyl ophthalmic solution monotherapy arms particularly between Weeks 12 and 26. In the absence of a control arm without omidenepag 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 omidenepag isopropyl ophthalmic solution is dosed as monotherapy and corneal endothelial cell counts are compared to a concurrent control without omidenepag isopropyl should be conducted and submitted.

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 omidenepag 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 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.

9. 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.

10. 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.

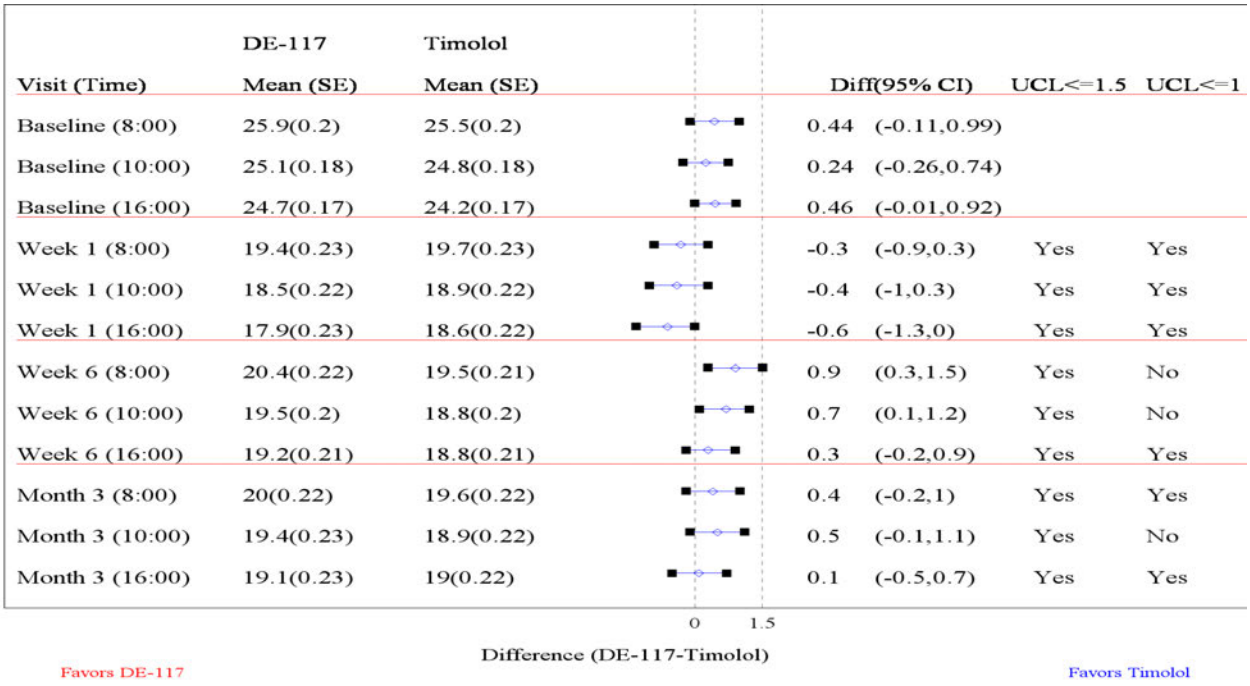
11. BIOSTATISTICS

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

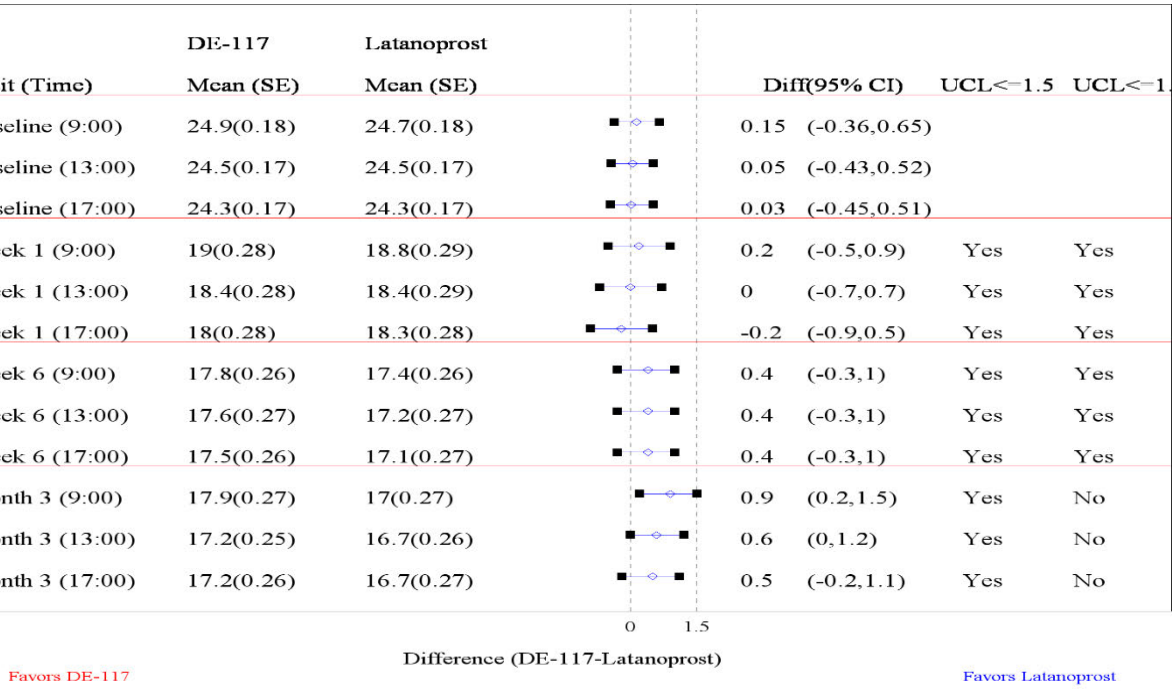
The three studies were all randomized, double-masked, active-controlled studies. The active control in Study 01171505 was latanoprost 0.005% QD. The two US based studies (011709IN and 011710IN) used timolol 0.5% BID as the active control. All three studies had a 3-month comparative treatment period. 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.

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff	(95% CI)	UCL<=1.5	UCL<=1
Baseline (8:00)	25.9(0.2)	25.5(0.2)	0.44	(-0.11,0.99)		
Baseline (10:00)	25.1(0.18)	24.8(0.18)	0.24	(-0.26,0.74)		
Baseline (16:00)	24.7(0.17)	24.2(0.17)	0.46	(-0.01,0.92)		
Week 1 (8:00)	19.4(0.23)	19.7(0.23)	-0.3	(-0.9,0.3)	Yes	Yes
Week 1 (10:00)	18.5(0.22)	18.9(0.22)	-0.4	(-1,0.3)	Yes	Yes
Week 1 (16:00)	17.9(0.23)	18.6(0.22)	-0.6	(-1.3,0)	Yes	Yes
Week 6 (8:00)	20.4(0.22)	19.5(0.21)	0.9	(0.3,1.5)	Yes	No
Week 6 (10:00)	19.5(0.2)	18.8(0.2)	0.7	(0.1,1.2)	Yes	No
Week 6 (16:00)	19.2(0.21)	18.8(0.21)	0.3	(-0.2,0.9)	Yes	Yes
Month 3 (8:00)	20(0.22)	19.6(0.22)	0.4	(-0.2,1)	Yes	Yes
Month 3 (10:00)	19.4(0.23)	18.9(0.22)	0.5	(-0.1,1.1)	Yes	No
Month 3 (16:00)	19.1(0.23)	19(0.22)	0.1	(-0.5,0.7)	Yes	Yes

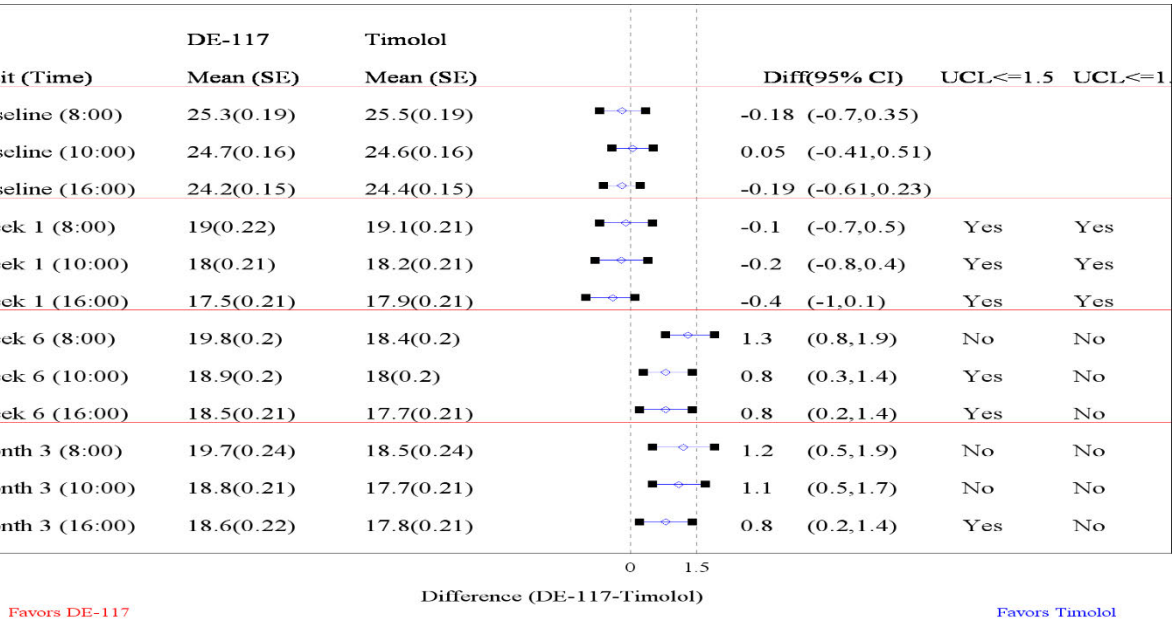


Visit (Time)	DE-117 Mean (SE)	Latanoprost Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1.
Baseline (9:00)	24.9(0.18)	24.7(0.18)	0.15 (-0.36,0.65)		
Baseline (13:00)	24.5(0.17)	24.5(0.17)	0.05 (-0.43,0.52)		
Baseline (17:00)	24.3(0.17)	24.3(0.17)	0.03 (-0.45,0.51)		
Week 1 (9:00)	19(0.28)	18.8(0.29)	0.2 (-0.5,0.9)	Yes	Yes
Week 1 (13:00)	18.4(0.28)	18.4(0.29)	0 (-0.7,0.7)	Yes	Yes
Week 1 (17:00)	18(0.28)	18.3(0.28)	-0.2 (-0.9,0.5)	Yes	Yes
Week 6 (9:00)	17.8(0.26)	17.4(0.26)	0.4 (-0.3,1)	Yes	Yes
Week 6 (13:00)	17.6(0.27)	17.2(0.27)	0.4 (-0.3,1)	Yes	Yes
Week 6 (17:00)	17.5(0.26)	17.1(0.27)	0.4 (-0.3,1)	Yes	Yes
Month 3 (9:00)	17.9(0.27)	17(0.27)	0.9 (0.2,1.5)	Yes	No
Month 3 (13:00)	17.2(0.25)	16.7(0.26)	0.6 (0,1.2)	Yes	No
Month 3 (17:00)	17.2(0.26)	16.7(0.27)	0.5 (-0.2,1.1)	Yes	No



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.

Visit (Time)	DE-117 Mean (SE)	Timolol Mean (SE)	Diff(95% CI)	UCL<=1.5	UCL<=1.
Baseline (8:00)	25.3(0.19)	25.5(0.19)	-0.18 (-0.7,0.35)		
Baseline (10:00)	24.7(0.16)	24.6(0.16)	0.05 (-0.41,0.51)		
Baseline (16:00)	24.2(0.15)	24.4(0.15)	-0.19 (-0.61,0.23)		
Week 1 (8:00)	19(0.22)	19.1(0.21)	-0.1 (-0.7,0.5)	Yes	Yes
Week 1 (10:00)	18(0.21)	18.2(0.21)	-0.2 (-0.8,0.4)	Yes	Yes
Week 1 (16:00)	17.5(0.21)	17.9(0.21)	-0.4 (-1,0.1)	Yes	Yes
Week 6 (8:00)	19.8(0.2)	18.4(0.2)	1.3 (0.8,1.9)	No	No
Week 6 (10:00)	18.9(0.2)	18(0.2)	0.8 (0.3,1.4)	Yes	No
Week 6 (16:00)	18.5(0.21)	17.7(0.21)	0.8 (0.2,1.4)	Yes	No
Month 3 (8:00)	19.7(0.24)	18.5(0.24)	1.2 (0.5,1.9)	No	No
Month 3 (10:00)	18.8(0.21)	17.7(0.21)	1.1 (0.5,1.7)	No	No
Month 3 (16:00)	18.6(0.22)	17.8(0.21)	0.8 (0.2,1.4)	Yes	No



12. 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].

13. 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.

14. 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 originally submitted labeling on 4/21/2021.

Formal labeling review and negotiation is deferred until additional data is submitted to support the application.

15. OPDP

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

Formal labeling review and negotiation is deferred until additional data is submitted to support the application.

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.

Formal labeling review and negotiation is deferred until additional data is submitted to support the application.

16. Patient Experience Data

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

X □	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X □	Clinical outcome assessment (COA) data		Sec 7
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Sec 7
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

17. Labeling

The regulatory action for this application will be Complete Response. Formal labeling review and negotiation is deferred until additional data is submitted to support the application.

Draft labeling with edits from Clinical, Biostatistics, Pharmacology/Toxicology, Clinical Pharmacology is attached to this review as an appendix. This is draft labeling; it is not agreed upon labeling with the applicant.

18. Regulatory Action

NDA 215092 Omidenepag isopropyl ophthalmic solution 0.002% will receive a Complete Response letter because the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211, and the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability.

Complete Response Items for the Letter:

"We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

1. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product do not comply with the current good manufacturing practice regulations in parts 210 and 211, and the methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability, and bioavailability. During a recent inspection of the of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

   Following an evaluation of an inspection performed at the (b) (4) Woodstock Sterile Solutions (FEI 1419377) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.

   We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency- preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

2. The investigations required under section 505(b) of the Federal Food, Drug, and Cosmetic Act do not include adequate tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. Study 1171504 demonstrated significant endothelial

cell loss in both omidenepag isopropyl ophthalmic solution monotherapy arms particularly between Weeks 12 and 26. In the absence of a control arm without omidenepag isopropyl treatment, the trial is suggestive of potential harm to the corneal endothelial cells. A concurrently controlled, randomized, 12-month clinical study in which omidenepag isopropyl ophthalmic solution is dosed as monotherapy and corneal endothelial cell counts are compared to a concurrent control without omidenepag isopropyl should be conducted and submitted.

PRESCRIBING INFORMATION
We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources and Pregnancy and Lactation Labeling Final Rule websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

CARTON AND CONTAINER LABELING
We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME
Please refer to correspondence dated, October 21, 2021, which addresses the proposed proprietary name, Omlonti. This name was found conditionally acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE
When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

OTHER
Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

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 your 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 your product.

For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.

Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity."

19. Appendix

Draft labeling with edits from Clinical, Biostatistics, Pharmacology/Toxicology, Clinical Pharmacology, is attached to this review. This is draft labeling; it is not agreed upon labeling with the applicant.

12 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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
11/09/2021 03:24:14 PM

WILEY A CHAMBERS
11/09/2021 03:34:47 PM

CHARLES J GANLEY
11/09/2021 03:36:08 PM