CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	215092
Priority or Standard	Standard
Submit Date(s)	November 19, 2020
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PDUFA Goal Date	September 19, 2021
Division/Office	Ophthalmology
Reviewer Name(s)	Martin P Nevitt, M.D., M.P.H
Review Completion Date	See DARRTS Stamp Date
Established/Proper Name	Omidenepag isopropyl ophthalmic solution, 0.002%
(Proposed) Trade Name	(b) (4)
Applicant	Santen, Inc.
Dosage Form(s)	Topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye(s) once daily in the evening
Applicant Proposed Indication(s)/Population(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

(b) (4) (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.

(b) (4) 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. (b) (4) 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.

Established Name:	Omidenepag isopropyl ophthalmic solution, 0.002%
Proposed Trade Name:	(b) (4)
Chemical Class:	new molecular entity
Pharmacological Class:	relatively selective agonist of EP2 receptor, a prostaglandin E2 (PGE2) receptor, subtype 2
Proposed Indication:	reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Dosing Regimen:	one drop in the affected eye(s) once daily in the evening
Age Groups:	patients 18 years or older

1.2. Conclusions on the Substantial Evidence of Effectiveness

NDA 215092 is recommended for approval with the labeling revisions found in this review.

The application supports the safety and effectiveness of omidenepag isopropyl ophthalmic solution, 0.002% for the treatment of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

1.3. Benefit-Risk Assessment

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 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 IOP lowering products.

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 is currently the accepted standard for establishing the efficacy of ocular hypotensive 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	This product would add another prostaglandin analogue to the approved U.S. products.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(miotic) agents, carbonic anhydrase inhibitors, and prostaglandin analogues.	
Benefit	• Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive medications. The primary efficacy endpoint was mean IOP measured at multiple time points for studies 01171505 and 011710IN. Studies 01171505 and 011710IN demonstrated that omidenepag isopropyl ophthalmic solution, 0.002% was non-inferior to timolol maleate 0.5% and to latanoprost, 0.005% at all time points measured. The safety database was adequate.	This product, if approved, would add to the choice of prostaglandin analogues/ selective EP2 receptor agonists which reduce elevated IOP. 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	• 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.	Routine monitoring and reporting of all adverse events are adequate.

1.4. 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		[e.g., Sec 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Sec 6.1
		□	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.			

2. Therapeutic Context

2.1. 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. The various types of glaucoma are distinguished by the causative physiological defect. It affects one person in 200 over the age of 40. It is a leading cause of irreversible blindness in the United States. One of the primary risk factors is elevated intraocular pressure (IOP). The reduction and control of elevated IOP in open-angle glaucoma and ocular hypertension is usually managed by chronic, long-term topical ocular therapy.

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.

2.2. Analysis of 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 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

Pharmacologic Class/ Applicant	Trade Name	Established Name
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
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

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Omidenepag isopropyl ophthalmic solution, 0.002% is being reviewed as a new molecular entity. It is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

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.

3.3. Foreign Regulatory Actions and Marketing History

DE-117 ophthalmic solution is approved for glaucoma and ocular hypertension in Japan under the trade name of (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.

A post-marketing observational study (PMS) was initiated on 27 November 2018 and is currently ongoing in Japan to evaluate the safety and efficacy in long-term use of DE-117 in real-world clinical practice and to review the safety of long-term co-administration of DE-117 with other glaucoma drugs. One serious SAR of increased IOP has been reported in the study. No new significant safety information or signal has been identified.

In summary, based on the data collected to date from PMS and post-marketing spontaneous reports there has been no change to the overall safety profile of DE-117. There are no ongoing signals under investigation.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No issues were identified in the review of the clinical portion of the NDA to suggest a problem with data integrity. Routine clinical inspections were requested from OSI. The final consult report is pending. See CDTL review for complete findings.

4.2. Product Quality

Table 2: Qualitative and Quantitative Composition of Omidenepag isopropyl ophthalmic solution, 0.002%

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)			USP
Citric acid monohydrate				USP
Polyoxyl 35 castor oil				NF
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)

The final Product Quality review is pending. See CDTL review for complete findings.

4.3. Clinical Microbiology

Not applicable. The drug product is not an antimicrobial.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. Clinical Pharmacology

After topical ocular administration, omidenepag isopropyl is metabolized in the eye to omidenepag (active moiety) by carboxylesterase-1. This principal metabolic pathway of omidenepag isopropyl s, which was tested in vitro, is the hydrolysis to the pharmacologically active form, omidenepag, which is further metabolized by oxidation, *N*-dealkylation, glucuronidation, sulfate conjugation or taurine conjugation. CYP3A4 is involved in the metabolism of omidenepag.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The table below lists the three clinical studies that were reviewed to evaluate safety and efficacy of omidenepag isopropyl ophthalmic solution, 0.002%.

Table 3: Table of Clinical Studies

	Pivotal Studies	
	Study 01171505	**Studies 011710IN and 011709IN** [a]
Region	Asia (India, Taiwan, Korea, Singapore)	US
Duration of comparative treatment period	3 months	
Basic design of comparative treatment period	Randomized, masked, parallel comparison of DE-117 0.002% QD and active control regimen	
Active control	latanoprost 0.005% QD	timolol 0.5% BID
Diagnosis	OAG and OHT	OAG, OHT, and pediatric glaucoma [b]
Follow-up visits during comparative treatment period	Week 1, Week 6, Month 3	
Scheduled timepoints of IOP assessments	09:00, 13:00, and 17:00	08:00, 10:00, and 16:00

Abbreviations: BID = twice per day; OAG = open-angle glaucoma; OHT = ocular hypertension; QD = once per day;
a The 3-month comparative treatment periods of the US studies were run under identical protocols.
b In total, 13 pediatric subjects were enrolled, all in study 011709IN.

5.2. Review Strategy

The submitted clinical study reports and protocols identified in section 5.1 were reviewed and formed the primary basis of safety and efficacy for this application.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study Design

Study 01171505

Overview and Objective

Primary objective:
To determine if the mean diurnal IOP reduction with DE-117 ophthalmic solution, 0.002% was noninferior to latanoprost ophthalmic solution, 0.005% at Month 3 in subjects with OAG or OHT.

Safety objective:
To determine the safety of DE-117 ophthalmic solution 0.002% as compared to latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT.

Trial Design

This 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 OAG or OHT. Subjects participated in a screening phase and a washout period of up to 4 weeks. Once the subjects were qualified for the study per inclusion and exclusion criteria, the subjects were randomized using a stratified randomization (based on baseline IOP [< 25, ≥ 25 mmHg] and primary diagnosis of OAG or OHT) and received study medication for 3 months. Either DE-117 0.002% or latanoprost 0.005% ophthalmic solutions were instilled into both eyes once-daily (QD).

A total of 360 subjects (180 in each arm) were planned to be enrolled in Asian countries including Singapore, India, Taiwan, and Korea. In total 370 subjects were randomized and included in the intent to treat population, with 185 subjects randomized to the DE-117 arm and 185 subjects randomized to the latanoprost arm.

Table 4: Study 01171505 Schedule of Events and Procedures

	Screening Phase		Treatment Phase				
	Visit 1 Screening	Mid-washout Period (optional Visit 1a)	Visit 2 Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7, Exit)	ET[a]
Informed consent(s)[b]	X						
Inclusion/Exclusion criteria	X		X				
Demographics and medical History	X						
Medications/therapies	X	X	X	X	X	X	X
Dosing compliance				X	X	X	X
Adverse events		X	X	X	X	X	X
Pregnancy test[c]	X		X			X	X
Biomicroscopy[d]	X	X	X (09:00)	X (09:00)	X (09:00)	X (09:00)	X (09:00)
IOP[e]	X	X	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00
Central corneal thickness[f]	X		X (09:00)	X (09:00)	X (09:00)	X (09:00)	X (09:00)
Corrected visual acuity	X	X	X	X	X	X	X
Iris, Eyelash, Eyelid			X (Photo)	X	X	X	X
Ophthalmoscopy[g]	X		X			X	X
Gonioscopy[h]	X						
Visual field[i]	X					X[i]	X[i]

	Screening Phase		Treatment Phase				
	Visit 1 Screening	Mid-washout Period (optional Visit 1a)	Visit 2 Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7, Exit)	ET[a]
Randomization via IWRS			X				
Dispense study medication[j]			X		X		
Collect study medication[k]					X	X	X
Saliva sampling for pharmacogenetics[l]	X						

Abbreviations: ET = early termination; IOP = intraocular pressure; IWRS = Interactive Web Response System.
a The specified examinations and observations were performed as much as possible if a subject was terminated early.
b Informed consent and authorization, as appropriate for local privacy regulations, was signed and dated before study procedures were performed. Informed consent for the optional pharmacogenetic laboratory research study was obtained at any visit prior to study exit.
c Urine pregnancy test was conducted for all female subjects of childbearing potential.
d Biomicroscopy examination was completed immediately before the 09:00 IOP measurement at all visits except Visit 1/1a (screening or mid-washout visit). For Visit 1/1a, the biomicroscopy examination was performed before the single IOP assessment.
e IOP measurements were taken at 09:00 ± 60 min, 13:00 ± 60 min, and 17:00 ± 60 min at all visits except Visit 1/1a (screening or mid-washout visit). A single assessment was performed at Visit 1/1a.
f Central corneal thickness measurements were performed immediately after the 09:00 IOP measurement at all visits except Visit 1/1a (screening or mid-washout visit). For Visit 1, central corneal thickness measurement was performed after the single IOP assessment.
g Ophthalmoscopy (fundus) examination was performed without pupil dilation.
h Gonioscopy was performed if not done within the prior 3 months of Visit 1.
i Visual field measurement was performed, if not done within the prior 3 months of Visit 1, for all sites except those in India.
The India amendment, issued on 20 January 2017, specified that visual field measurement was to be performed at Visit 1 (screening) and Visit 5 (Month 3)/ET.
j One kit containing 4 eye drop bottles of study medication was dispensed at Visit 2 and Visit 4. To maintain masking of the Principal Investigators and examiner during this study, authorized study staff, other than the Investigator or examiner dispensed and collected study medications.
k One kit containing 4 eye drop bottles of study medication was collected at Visit 4 and Visit 5 Study Exit/ET, respectively. When collecting the study medications, the kit containing the used and unused 4 eye drop bottles were sealed.
l A saliva sample for the pharmacogenetic laboratory research study was to be collected at any visit after obtaining optional informed consent for pharmacogenetics.

Study Endpoints

The original primary efficacy endpoint was the mean diurnal IOP (average of IOP at 3 time points: 09:00, 13:00, 17:00) in the study eye at Month 3. The Division of Ophthalmology (DO) does not consider this an acceptable endpoint and reviewed the results of each independent timepoint.

Statistical Analysis Plan

The primary analysis on the primary endpoint was performed using mixed-effects model for repeated measures (MMRM), with treatment, visit, diagnosis, country, treatment-by-visit interaction, and baseline mean diurnal IOP as covariates on the FAS. Least squares (LS) means of the treatment response within each arm and treatment differences between the DE-117 arm and the latanoprost arm were reported along with 95% confidence intervals (CIs). Non-inferiority was to be established if the upper limit of the 95% CIs for the difference between DE-117 and latanoprost in the mean diurnal IOP at Month 3 was within 1.5 mmHg.

Studies: 01109IN and 011710IN

Phase III, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Glaucoma or Ocular Hypertension

NOTE: Studies 01109IN and 011710IN were of identical design/methods in all aspects, including inclusion/exclusion criteria, study endpoints, analysis methods, and non-inferiority criteria; except study 01109IN after the 3-month double-masked treatment period (DMTP) was followed by a 9-month open-label treatment period (OLTP). Both of the studies were conducted in the US with no noted differences in the geographic distribution of sites. Study 01109IN was also referred to as Spectrum 3 and Study 011710IN as Spectrum 4.

Trial Design

These 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 in subjects with glaucoma or OHT. The active control was Timolol Maleate Ophthalmic Solution 0.5% BID. The study consisted of a washout period of up to four weeks followed by a three-month double-masked treatment period.

Planned enrollment: Both studies planned to enroll approximately 400 adult subjects and up to 30 pediatric subjects.

Table 5: Studies: 01109IN and 011710IN Schedule of Events and Procedures

	Washout Period		Double-Masked Treatment Period				Open-Label Treatment Period		
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/ Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7)	Visit 6 Month 6 (Day 181±10)	Visit 7 Month 9 (Day 271±10)	Visit 8 Month 12 (Day 361±10) Exit or Early Termination[a]
Informed consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study[b]	X								
Inclusion/exclusion criteria	X		X						
Demographics and medical history, including prior PGA[c]	X								
Concomitant medications/ therapies	X	X	X	X	X	X	X	X	X
Dosing compliance				X	X	X	X	X	X
AEs		X	X	X	X	X	X	X	X
Pregnancy test[d]	X		X			X	X	X	X
Vital signs (blood pressure/pulse rate)[e]	X		X (08:00)			X (08:00)			X (08:00)
Refraction[f]	X								
BCVA[f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy[g]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)

	Washout Period		Double-Masked Treatment Period				Open-Label Treatment Period		
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/ Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7)	Visit 6 Month 6 (Day 181±10)	Visit 7 Month 9 (Day 271±10)	Visit 8 Month 12 (Day 361±10) Exit or Early Termination[a]
IOP[h]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00
Pachymetry[i]	X								
Instill study medication after IOP measurement				X (08:00)	X (08:00)	X (08:00)			
Iris color, eyelash, eyelid[j]			X (photo)			X (photo)	X	X	X (photo)
Gonioscopy[k]	X								
Visual field[l]	X								
Ophthalmoscopy[m]	X (pupil dilation)		X (16:00)			X (16:00)			X (16:00, pupil dilation)
Blood sampling for pharmacogenomics/genomics[n]							X		
Dispense study medication			X		X	X	X	X	
Collect study medication					X	X	X	X	X

	Washout Period		Double-Masked Treatment Period				Open-Label Treatment Period		
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/ Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7)	Visit 6 Month 6 (Day 181±10)	Visit 7 Month 9 (Day 271±10)	Visit 8 Month 12 (Day 361±10) Exit or Early Termination[a]
Phone call to remind subject to take evening dose on the day before each visit				X	X	X	X	X	X

a Optional at unscheduled visit; required for subjects who were terminated early from the study.
b Informed consent form had to be signed and dated before study procedures were performed. Informed consent for the optional pharmacogenomics/genomics laboratory research study could be obtained at any visit prior to study exit.
c Prostaglandin-naive subjects were defined as subjects who were not known to have used prostaglandin as their glaucoma treatment. The previous use of prostaglandin was to be confirmed by subject's medical records or history.
d A urine pregnancy test was conducted for all female subjects of childbearing potential.
e Vital signs (resting blood pressure and pulse rate) were collected with the subject in a sitting position at any time during Visit 1 (Screening), at approximately 08:00 for Visit 2 (Baseline), and at Visit 5 before the morning dose. Vital signs were also collected at Visit 8 at approximately 08:00.
f Refraction was performed at the Screening Visit. If more than 10 letters in BCVA were lost compared with the Screening Visit, refraction was to be performed again. BCVA examination was completed before IOP measurement at 08:00.
g Biomicroscopy examination was to be completed before the IOP measurement at 08:00. Aqueous flare and cell evaluation were performed before fluorescein instillation.
h The IOP measurements were performed at 08:00, 10:00, and 16:00 (± 60 min) at all visits, except for Visit 1 and the optional Visit 1a (Screening and midwashout visits, respectively).
i Pachymetry was performed after the IOP measurement at Visit 1 (Screening).
j Eye photographs were taken at Visits 2 (Baseline), 5 (Month 3), and 8 (Month 12).
k If gonioscopy was performed within 3 months (90 days) prior to Screening Visit and was documented in the subject's records, no additional Screening gonioscopy examination was necessary. Gonioscopy was performed after the IOP measurement at Visit 1 (Screening).
l If a visual field test was performed within 3 months (90 days) prior to the Screening Visit and was documented in the subject's records, no additional Screening visual field test was necessary.
m Ophthalmoscopy was performed at Visits 1, 2, 5, and 8 (i.e., Screening, Baseline, Month 3, and Month 12) after the 16:00 IOP measurements. Ophthalmoscopy was performed with pupil dilation at the Screening Visit and Visit 8/Exit or Early Termination. Dilation of the pupil was performed after the 16:00 IOP measurement.
n Blood sampling for the pharmacogenomics/genomics laboratory research study was performed at any visit after pharmacogenomics/genomics informed consent was obtained, the subject was randomized, and study drug dosing had begun.

NOTE: Only Study 011709IN continued as an Open-Label Treatment Period through Month 12.

Study Endpoints

The primary efficacy endpoint was IOP in the study eye at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 1 (Visit 3), Week 6 (Visit 4), and Month 3 (Visit 5) (referred to subsequently as 9 timepoints).

Statistical Analysis Plan

The primary analysis of the primary endpoint was performed using a mixed-effects model for repeated measures (MMRM) of IOP based on the Full Analysis Set. For each scheduled timepoint (08:00, 10:00, and 16:00), the MMRM included treatment, visit (Week 1, Week 6, or Month 3), and treatment-by-visit interaction as fixed effects, and Baseline IOP at the scheduled timepoint as a covariate. Correlations of IOP measurements within-subject were modeled using an unstructured covariance matrix. Least squares (LS) mean IOP values for each treatment arm

and differences between LS treatment arm means were reported along with 95% confidence intervals. A fixed sequence hypothesis testing procedure was used to control the overall Type I error rate across the hypothesis tests involving the primary and key secondary efficacy endpoints at the 0.05 level (two-sided). A hypothesis test in the sequence could only be performed if the testing for each of the tests prior to it in the sequence had resulted in rejection of the null hypothesis.

The criteria for determining non-inferiority of DE-117 to timolol for the primary efficacy endpoint were as follows: upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (DE-117 minus timolol) ≤ 1.5 mmHg at all 9 timepoints and ≤ 1.0 mmHg at a majority (5 or more) of the 9 timepoints.

Table 6: List of Study Sites and Principal Investigators (PIs): Study 01171505

Site Number	Principal Investigator(s)	Site Name and Address	Number of Randomized Subjects
1001	Chan Yun Kim	Severance Hospital 50-1 Yonsei-ro, Seodaemun-gu Seoul, South Korea	3
1003	Chan Kee Park	The Catholic University of Korea, Seoul St. Mary's Hospital 222 Banpo-daero, Seocho-gu Seoul, South Korea	6
1004	KiHo Park	Seoul National University Hospital 101 Daehak-ro, Jongno-gu Seoul, South Korea	4
1005	MoonSuk Kook	Asan Medical Center 88 Olympic-ro 43-gil, Songpa-gu Seoul, South Korea	3
1006	Chang Won Kee	Samsung Medical Center 81 Irwon-ro, Gangnam-gu Seoul, South Korea	3
1007	Joon Mo Kim	Kangbuk Samsung Hospital 29, Saemunan-ro, Jongno-gu Seoul, South Korea	5
1008	Ji Woong Lee	Pusan National University Hospital 179, Gudeok-ro, Seo-gu Seoul, South Korea	8
1010	Jongjin Jung	Kim's Eye Hospital 136 Yeongshin-ro Seoul, South Korea	6
1012	Kyoung Nam Kim	Chungnam National University Hospital 282 Munhwa-ro, Jung-gu Daejeon, South Korea	3
2001	Da-Wen Lu	Tri-Service General Hospital-Neihu Main Facility No. 325, Section 2, Cheng-Kung Road, Neihu Taipei, Taiwan	13

Site Number	Principal Investigator(s)	Site Name and Address	Number of Randomized Subjects
2002	Mei-Ju Chen	Taipei Veterans General Hospital 201 Shih-Pai Road, Section 2 Taipei, Taiwan	10
2003	Shin-Lin Chiu	Changhua Christian Hospital 135 Nan-Hsiao Street Changhua, Taiwan	9
2004	Pei-Yao Chang	Far Eastern Memorial Hospital No.21, Section 2, Nanya South Road, Banciao District New Taipei City, Taiwan	9
2005	Kwou-Yeung Wu	Kaohsiung Medical University Chung-Ho Memorial Hospital No. 100, Tzyou 1st Road Kaohsiung, Taiwan	3
2006	Peng-Tai Tien	China Medical University Hospital 2, Yude Road Taichung, Taiwan	5
2007	Ying-Ying Chen	Kaohsiung Veterans General Hospital 386 Ta-Chung 1st Road Kaohsiung, Taiwan	21
2008	Yi-Chun Chen	Cathay General Hospital No.280, Sec.4, Ren Ai Road Taipei, Taiwan	2
2009	Tsing-Hong Wang	National Taiwan University Hospital No. 7, Chung-Shan South Road Taipei, Taiwan	29
3001	Aung Tin	Singapore National Eye Centre 20 College Road Discovery Tower Level 6 Singapore	17
3002	Seng Chee Loon	National University Hospital (S) Pte Ltd. 5 Lower Kent Ridge Road Singapore	5
3003	Wei Leon Yip	Tan Tock Seng Hospital 11 Jalan Tan Tock Seng Singapore	1
3004	Jocelyn Chua	Ng Teng Fong General Hospital	2

Site Number	Principal Investigator(s)	Site Name and Address	Number of Randomized Subjects
		KMT Workshop Kolhapur, India	
4010	Nishit Dhoka	S. R. Kalla Memorial Gastro & General Hospital 78-79 Dhuleshwar Garden, Sardar Patel Marg Jaipur, Rajastan, India	30
4011	Susan Philip	Regional Institute of Ophthalmology Thiruvananthapuram, Kerala India	32
4012	Ronnie George	Sankara Nethralaya (a unit of Medical Research Foundation) New No.41/Old18, College Road,Nungambakkam Chennai, Tamil Nadu India	12
4013	Prakash D N	K.R. Hospital Irwin Road, Department of Ophthalmology, K R Hospital, Mysore Medical College and Research Institute Mysuru, Karnataka India	15
4014	Lional Raj	Dr. Agarwal's Eye Hospital 10 South Bypass Road Vannarpetti, Tirunelveli, Tamil Nadu India	23

Site Number	Principal Investigator(s)	Site Name and Address	Number of Randomized Subjects
		1 Jurong E St 21 Singapore	
3005	Kelvin Lee	Eagle Eye Centre 820 Thomson Road Singapore	1
4001	Ganesh Venkataraman	Aravind Eye Hospital – Coimbatore 87/22A, Avinashi Road, Civil Aerodrome Post, Peelamedu Coimbatore, Tamil Nadu India	6
4002	Rajesh Parekh	Bhagwan Mahaveer Jain Hospital 17 Millers Road Bengaluru, Karnataka India	22
4003	Sirisha Senthil	L V Prasad Eye Institute L V Prasad Marg Hyderabad, Telangana India	6
4004	Chandrima Paul	B B Eye Foundation 2/5 Sarat Bose Road Kolkata, West Bengal India	9
4005	Julie Pegu	Dr. Shroff's Charity Eye Hospital 5027 Kedarnath Road New Delhi, Delhi India	6
4006	Pramod Kumar	Chhtrapati Shahuji Maharaj, Medical University Chowk Lucknow, Uttar Pradesh India	16
4008	Mariam Mansuri	M & J Institute of Ophthalmology Civil Hospital Ahmedabad, Gujarat India	5
4009	Sujata Navare	Aster Aadhar Hospital (Prerana Hospital Ltd.) R S No 628, B Ward, Near Shastri Nagar,	20

Table 7: List of Study Sites and Principal Investigators (PIs): Study 0117109IN

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400019 Arizona Glaucoma Specialists 20940 N Tatum Blvd., Suite 250 Phoenix, AZ 85050	Max Kim, M.D.	Kaylee Rosenbusch Erin Fox Melanie Maline Heather Yoshimura Gerald Walman, M.D. Crystal Brown Steven Shively Lindsey Arcuri	7
8400021 Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803-2493	William L. Haynes, M.D.	Brian Edward Smith, M.D. James Crandall, M.D. Rebecca Michelle Keener	2
8400023 DCT- Shah Research LLC dba Discovery Clinical Trials 1506 E. Griffin Pkwy Mission, TX 78572-2425	Pankajkumar Shah, M.D.	Charles Randall Norman, M.D. Jonathan Leroy Gandy, O.D. Salvador Alcantar, O.D. Liana L. Del Barro, L.V.N., S.C.	5
8400025 Dixophthal PC dba Dixon Eye Care 806 N Jefferson Street Albany, GA 31701	El-Roy Dixon, M.D.	Rajesh Rangaraj, M.D. Shawn Wynn Jennifer Hunter	30
8400030 Carolina Eyecare Physicians 721 Long Point Rd., Suite 407 Mt Pleasant, SC 29464	Elizabeth Sharpe, M.D.	Terri Pruitt Jill Bloser Lauren Read Leah Kammerdiener, M.D. Rhonda Dugan	9
8400033 Heart of America Eye Care P.A. 8800 W 75th St., Suite 140/141 Shawnee Mission, KS 66204	Bradley Kwapiszeski, M.D.	Jodianne Carter, M.D. Caroline Chang, M.D. Brandy Sage, C.O.A. Carrie Lister, C.O.A. Nicole King	20

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400034 Hernando Eye Institute 14543 Cortez Blvd. Brooksville, FL 34613	Leonard Cacioppo, M.D.	James Richard Jachimowiez, M.D. Carol B. Smith	13
8400035 Office of Mark Weiss M.D. 1717 S Utica Ave., Suite 107 Tulsa, OK 74104	Mark Weiss, M.D.	Todd Brockman, M.D. Cheena Culp LeeAnn Howard Sally Catron	13
8400038 R and R Eye Research LLC 5430 Fredericksburg Rd., Suite 100 San Antonio, TX 78229-3539	William Flynn, M.D.	Edward R. Rashid, M.D. Charles D. Reilly, M.D. Robert A. Rice, M.D. Gregory Brunin, M.D. Catherine Hazen Griselda Rodrigues Michelle Jackson	11
8400044 Total Eye Care P.A. 6060 Primacy Pkwy., Suite 200 Memphis, TN, 38119-5770	Eugene McLaurin, M.D.	David G. Evans, O.D. Roxanne Barnett Don W. Gayso, O.D. Ariel McNatt Brandon Rushing, O.D. Seyi Adeleye Stefan Ramos Daniel J Ashe Kim Smith Kaitlyn McCalmon	Site did not screen
8400045 University Eye Specialist 622 Smithview Drive Maryville, TN 37803	Kenneth Olander, M.D., Ph.D.	J. Matthew Rouse, M.D. Kim Rivera	16
8400210 Specialty Eye Care Centre 1920 116th Ave. NE Bellevue, WA 98004	Howard Barnebey, M.D.	Ernesto Golez III, M.D. Renee Cook	0

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400325 Keystone Research, Ltd. 5717 Balcones Dr. Austin, TX 78731-4203	Thomas Walters, M.D.	Robert E. Marquis, M.D. Yen D. Nieman, M.D. Blythe E. Monheit, M.D. Robert Stapper Sarah Benedict Jamie Johnson Tracey Knox Elaine Marcin Jody Redden Carol Stapper Scott Vandigriff Jess Lieblich Jennifer Cooper	21
8400509 Black Hills Regional Eye Institute 2800 3rd Street Rapid City, SD 57701	Adam Jorgensen, M.D.	Terrence Spencer, M.D. Stephen Khachikian, M.D. Kayla Riley	5
8400511 Eye Associates of Fort Myers 4225 Evans Ave Fort Myers, FL 33901-9311	Stephan Smith, M.D.	Angela R. Kaplan, O.D. Nancy O. Gribosky Debra Zaeringer	13
8400512 Northern New Jersey Eye Institute 71 2nd St. South Orange, NJ 07079-1855	Charles Crane, M.D.	Christine Szeweczyk-Fitzpatrick, O.D. Shirley Vitale, L.P.N., O.S.C. Mary Crupa, C.O.A., O.S.C.	10
8400513 South Shore Eye Care LLP 2185 Wantagh Ave. Wantagh, NY 11793	Todd Flicker, M.D.	Howard Adam Lane, M.D. Michelle Go Mijares, O.D. Cara Fidnarick Mary Modica Janet Bulit	4
8400514 Scott & Christie and Associates PC 105 Brandt Drive, Suite 201 Cranberry Twp, PA 16066	William Christie, M.D.	Daniel V. Zimmer, M.D. George J. Grisnik, O.D. Derek W. O'Donnell, O.D.	12

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400212 Cornerstone Eye Care 1400 E Hartley Dr. High Point, NC 27262	Michael Tepedino, M.D.	Robert J. DaVanzo, M.D. J. Zachary Forsey, M.D. Michael Evans, M.D. Chelsea Allred, C.O.A. Miranda Whittle Amy Riddle	7
8400217 Coastal Research Associates, LLC 11205 Alpharetta Highway, Suite J3 Roswell, GA 30076	Douglas Day, M.D.	John L. Schuhr Debbie Y. Locke	23
8400219 Shettle Eye Research 13113 66th Street N Argo, FL 33773	Phillip Shettle, D.O.	Debbie Shettle	18
8400295 North Bay Eye Associates Inc 104 Lynch Creek Way, Suite 15 Petaluma, CA 94954-2387	Jason Bacharach, M.D.	Michael Saidel, M.D. Lisa Teel, O.D. Roger Weeks, M.D. Angela Reynolds Megan Crane Maria Suarez	3
8400296 North Valley Eye Medical Group 11550 Indian Hills Rd., Suite 341 Mission Hills, CA 91345	Robert Smyth-Medina, M.D.	Steven Howard Rauchman, M.D. Joanne Perry Rocio Rodriguez Cecilia Casas Sandra Mejia Marie Contreras Christie Delgadillo	31

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400515 Kozlovsky Delay Winter Eye Consuktants LLC 2929 Mossrock, Suite 104 Shawnee Mission, TX 78260-5141	John Kozlovsky, M.D.	Richard L. Delay, O.D. Jeannine E. Camacho, O.D. Patricia Martinez, B.A. Bruce L. Winter, M.D.	2
8400516 Samsum Clinic 4151 Foothill Rd., Building B Santa Barbra, CA 93440	Douglas Katsev, M.D.	Tori Meyers, M.D. Kaylee Rosenbusch	4
8400517 Tauber Eye Center 4400 Broadway St., Suite 202 Kansas City, MO 64111	Joseph Tauber, M.D.	Crystal Remington, O.D., F.A.A.O. Megan Hefter	5
8400518 Havana Research Institute 2211 W Magnolia Blvd., Suite 290 Burbank, CA 91506	Armin Vishteh, M.D.	John De Beixedon, M.D.	4
8400519 Indiana University - Glick Eye Institute 1160 W Michigan Street Indianapolis, IN 46202	Elizabeth Martin, M.D.	Jennifer Eikenberry, M.D. Yasemin Sozeri, M.D. Linda Morgan, C.O.A. Michele Spriggs, C.O.A.	4
8400520 Bowden Eye & Associates 7205 Bonneval Road Jacksonville, FL 32256	Frank Bowden, M.D., F.A.C.S.	Jerry Robben, O.D. Amanda Kovacs, O.D. Natasha Kryanowski, O.D. Jessica Montgomery, C.O.A.	5
8400522 Emerson Clinical Research Institute 410 S. Washington Street Falls Church, VA 22046	Gustavo Corrales, M.D.	Khurram J. Malik, M.D.	7

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400541 AdvanceMed Clinical Research 8565 S. Eastern Avenue, Suite 102 Las Vegas, NV 89123	Matthew J. Swanic, M.D.	Gregory Hsu, D.O. Lindsey Szeto Katie Kowal	4
8400543 MCB Clinical Research Centers LLC 2770 North Union Blvd., Suite 240 Colorado Springs, CO 80909	Scott Smetana, M.D.	Robert Foerster, M.D. Rhonda Guthrie Kristin Scalva Jackie Belcher	7
8400544 Ophthalmology Associates 1201 Summit Avenue Fort Worth, TX 76102	Brian Flowers, M.D.	Kelly Starr Unni K. Nair, M.D.	3
8400545 Wellish Vision Institute 2110 East Flamingo Road, Suite 210 Las Vegas, NV 89119	Kent Wellish, M.D.	Mazeyar Saboori, M.D. Jay Kenneth Mattheis, M.D., M.S.P.H., F.A.C.S. Isaac J Ortez, O.D.	2
8400546 Charlotte Eye Ear Nose and Throat Associates P.A. 6035 Fairview Road Charlotte, NC 28210	Robert Saltzmann, M.D.	Donald H. Stewart III, M.D. N. Ron Melton, O.D. Robert A. Flores, M.D. Walter G. Atlas, M.D. Pedro Cervantes Fanning, M.D. Sarah A. Ennis Sherry L. Fredenberg Angie S. Karow Kayla A. Bratcher Angela K. Price	5
8400547 Walman Eye Center 10615 W Thunderbird Blvd., Suite D-180 Sun City, AZ 84351-3019	Gerald Walman, M.D.	Kaylee Rosenbusch Nicole Adams Gloria Alvarado Gricelda Orquiz Connie Ronquillo Max Kim, M.D.	14

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400523 Macy Eye Center 8635 W 3rd St., Suite 360W Los Angeles, CA 940048-6149	Jonathan Macy, M.D.	Scott A. Kaesemeyer Andrea Veneziano	1
8400530 Clayton Eye Clinical Research, LLC 1000 Corporate Center Drive, Suite 120 Morrow, GA, 30260	Jennifer Kim, M.D.	Joon Y. Kim, M.D. Brenton Smith, O.D. Yvonne Nguyen Ronald Webber, M.D. Daniel Strait, O.D. Jean Jouffroy Peter Chen, P.D., Ph.D. Trung Bui Thuy "Tia" Ngo Carey Phlong, O.D. Heather Ambrosia, O.D. Helen DuBiner, PharmD	5
8400531 San Antonio Eye Center 511 Dallas Street San Antonio, TX 78215-1936	Jake Trinidad, M.D.	Kundandeep Nagi, M.D. Maria Stephanie Jardeleza, M.D. Gawain Dyer, M.D. Marvin Martinez Shelby Lambrecht Chris Castillo Renee Bononcini	5
8400535 Stacy R. Smith M.D. P.C. 1548 East 4500 South, Suite 105, Salt Lake City, Utah 84117	Stacy R. Smith, M.D.	Adam M. Bowman, M.D. Sheri Faircloth, C.O.T.	8
8400538 VRF Eye Specialty Group 825 Ridge Lake Blvd, 3rd Floor, Memphis, TN 38120	John Elfervig, M.D.	Henry McQuirter, O.D. Tawnee Stephens Michael Sanford	7

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400549 Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	Joseph Martel, M.D.	James Martel, M.D., M.P.H. Liliya Golas, M.D. Nataliya Karpach Unsa Anwar Susana Galvez-Miranda Liliya Shuprudko	7
8400557 Advanced Vision Research 4306 Harding Pike, Suite 206-B Nashville, TN 37205	Gary Jerkins, M.D.	Megan Medlin Brandi Wilson Kasey Hughes	Site did not screen
8400620 The Cataract and Glaucoma Center 4171 N. Mesa Street, Building D, Suite 100 El Paso, TX 79902	Louis Alpern, M.D.	Lawrence Tafoya, M.D. Terri Cintron, C.O.A.	12
8400626 Ohio Eye Surgeons 262 Neil Avenue, Suite 430 Columbus, OH 43215	Norman Baker, M.D.	David Lehmann, M.D. Megan Chambers, M.D.	1
8400643 Apex Eye Clinical Research, LLC 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242	Robert Benza, M.D.	Radhika L. Kumar, M.D. Candace D. Hayes	6
8400644 Levenson Eye Associates 751 Oak Street, Suite 200 Jacksonville, FL 32204	Jeffery Levenson, M.D.	Frank McDonald, M.D. Vontrece Williams Shavon Nelson	7
8400645 East West Eye Institute 420 E. 3rd Street, Suite 603 Los Angeles, CA 90013	Michelle Sato, M.D.	Nicholas Marsico, M.D. James Masunaga Anthony Vazquez Natalie Ly Ilanie Shiell	4

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400549 Martel Eye Medical Group 11216 Trinity River Drive Rancho Cordova, CA 95670	Joseph Martel, M.D.	James Martel, M.D., M.P.H. Liliya Golas, M.D. Nataliya Karpach Unsa Anwar Susana Galvez-Miranda Liliya Shuprudko	7
8400557 Advanced Vision Research 4306 Harding Pike, Suite 206-B Nashville, TN 37205	Gary Jerkins, M.D.	Megan Medlin Brandi Wilson Kasey Hughes	Site did not screen
8400620 The Cataract and Glaucoma Center 4171 N. Mesa Street, Building D, Suite 100 El Paso, TX 79902	Louis Alpern, M.D.	Lawrence Tafoya, M.D. Terri Cintron, C.O.A.	12
8400626 Ohio Eye Surgeons 262 Neil Avenue, Suite 430 Columbus, OH 43215	Norman Baker, M.D.	David Lehmann, M.D. Megan Chambers, M.D.	1
8400643 Apex Eye Clinical Research, LLC 10615 Montgomery Road, Suite 202 Cincinnati, OH 45242	Robert Benza, M.D.	Radhika L. Kumar, M.D. Candace D. Hayes	6
8400644 Levenson Eye Associates 751 Oak Street, Suite 200 Jacksonville, FL 32204	Jeffery Levenson, M.D.	Frank McDonald, M.D. Vontrece Williams Shavon Nelson	7
8400645 East West Eye Institute 420 E. 3rd Street, Suite 603 Los Angeles, CA 90013	Michelle Sato, M.D.	Nicholas Marsico, M.D. James Masunaga Anthony Vazquez Natalie Ly Ilanie Shiell	4

There were 5 additional sites that were Selected but not Activated for this study.

Table 8: List of Study Sites and Principal Investigators (PIs): Study 011710IN

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400018 Arizona Eye Center 1500 W Ray Road Chandler, AZ 85224	Michael Depenbusch, M.D.	Frank Caserta, M.D. Kaylee Rosenbusch, MS Crystal Brown Guadaulpe Robles Melanie Maline Lindsey Arcuri David Tatelbaum Erin Fox Ashley Martin Heather Yoshimura Christine Kraus	19
8400021 Asheville Eye Associates 8 Medical Park Drive Asheville, NC 28803-2493	William L. Haynes, M.D.	James Crandall, M.D. Vrian Smith, M.D. Jennifer Gilberga Lea Raymer Ashely Donecho Denise Ammons Andrea Menzel Monica Hamrick Rebecca Michelle Keener	9
8400022 Comprehensive Eye Care Ltd. 901 E 3rd Street, Washington, MO 63090-3010	Michael S. Korenfeld, M.D.	Matthew R. Lazarus, OD Michelle M. Mueller Brooke M. Wideman	6
8400024 Discover Vision Centers 4741 S Cochise Drive Independence, MO 64055-6974	Ajay Singh, M.D.	Derek Horkey, M.D. Doug O. Dehning, M.D. Judy Rosenthal Patti Williams	6

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400026 Medical Center Ophthalmology Associates 9157 Huebner Road San Antonio, TX 78240-1502	Richard M. Evans, M.D.	Jason, D. Burns, M.D. Daniel P. Nolan, DO Michael A. Orozco, OD Brian Matthews Catherine Alderete	13
8400027 East Florida Eye Institute 509 SE Riverside Drive, Suite 302 Stuart, FL 34994	Ronald Frenkel, M.D.	Joseph Fenton Faust, M.D. Kathleen Gold, RN Laura Punckowski Brandy Millett Larry Malott Carol Garthwaite M. Leanne Houle Anelkis Vieira Emma McKiernan Allison Kiss Kendralynn Ruth	11
8400028 Florida Ophthalmic Institute 7106 NW 11th Place, Suite B Gainesville, FL 32605-3192	Norman S. Levy, M.D.	Trudy K. Ramjattan, M.D. Kelsey V. Kolasa Tim Silber	8
8400029 Glaucoma Associates of Texas 10740 N Central Expwy Suite 300 Dallas, TX 75231-2168	Michelle Butler, M.D.	Jennifer Rinn Kandace Robertson Davinder S. Grover, M.D., MPH	2
8400031 Global Research Management 1510 S Central Ave, Suite 300 Glendale, CA 91204-2569, USA	Sherif El-Harazi, M.D., MPH	Lilit Minasyan, M.D. Lucy Bataneant Norman Maldonado Karin Saran Jaime Zapeda	33

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400032 Great Lakes Eye Care 2848 Niles Road Saint Joseph, MI 49085	David L. Cooke, M.D.	Ronald L. McKey, M.D. David N. Brown, M.D. Stanley W. Plether M.D. Duane A. Tolsma, DO Jennifer L. Adams Leslie Wild Jennifer R. Zech James R. Duryee Elizabeth A. Halcombe Kathryn Webber Shirl DiGregorio Megan Everett	13
8400040 Silverstein Eye Centers 4240 Blue Ridge Blvd, Suite 1000 Kansas City, MO 64133	Steven M. Silverstein, M.D., FACS	Timothey M. Stout, M.D. Jeff L. Lookhart, OD Cindy Bentley	Site did not screen
8400041 The Eye Clinic of Texas 1100 Gulf Fwy S, Suite 114 League City, TX 77573-5148	Da-Thuy Van	Bernard A Milstein, M.D. Chance Caddell Angie Carter	7
8400042 The Eye Research Foundation 520 Superior Ave, Suite 235 Newport Beach, CA 92663-3642	David L. Wirta, M.D.	David Salvay, M.D., MS, Ph.D. Linda Wirta Heather Tyner Haley Noel Yvetter Abbascia Kimberly Abbascia Jenny Ryan Madison Haly Melinda Fischer William Kiely Chelsea Vesely Mai Giang Tina Johns	28

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400043 Tidewater Clinical Research 2540 Unbridled Lane Virginia Beach, VA 23456	John A. Foley, Jr. M.D.	April Rusch	7
8400044 Total Eye Care PA 6060 Primacy Pkwy, Suite 200 Memphis, TN, 38119-5770	Eugene B. McLaurin, M.D. FACS	David G Evans, OD Don W. Gayso, OD Brandon Rushing, OD Rozanne Barnett Stafan Ramos Ariel McNatt Daniel J Ashe Kim Smith Kaitlyn McCalmon	42
8400267 Houston Eye Associates 2855 Gramercy Street Houston, TX 77025-1756	Fiaz Zaman, M.D.	Elaine G. Thung, M.D. Norma A DelBosque Chance Caddell	7
8400270 Rochester Ophthalmological Group, P.C. 2100 S. Clinton Avenue Rochester, NY 14618	Paul James Hartman, M.D.	Alan H. Gruber, M.D. Gerard Cairns OD, PhD Mindy Van Voorhis Melissa Hart Michelle Hurley Rachel Rivera Michelle Dunn	48
8400295 North Bay Eye Associates Inc 104 Lynch Creek Way, Suite 12 Petaluma, CA 94954-2387	Jason Bacharach, M.D.	Michael Saidel, M.D. Lisa Teel, OD Roger Weeks, M.D. Angela Reynolds Megan Crane Maria Suarez	9

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400525 United Medical Research Institute 431-433 N Prairie Ave. Inglewood, CA 90301	James H. Peace, M.D.	Carmelina Marin Evelyn alvarez Daisy Hernandez Lori Birndorf, DO Xyryl De Leon Valerie Hernandez	18
8400530 Clayton Eye Clinical Research, LLC 1000 Corporate Center Drive, Ste 120 Morrow, GA 30260	Harvey Dubiner, M.D.	Ronald Webber, M.D. Jennifer Kim, M.D. Brenton Smith, OD Carey Phlong, OD Heather Ambrosia, OD Daniel Strait, OD Helen DuBiner Ethan Seville Courtney Parsons Thuy "Tia" Ngo Hannah Davis Melissa Byrd Yvonne Nguyen Jean Jouffroy Abel Nguyn	23
8400533 Sacramento Eye Consultants 1515 River Park Drive, Suite 100 Sacramento, CA 95815-4605	Jacob Brubaker, M.D.	Richard Lewis, M.D. Monica Robinson, OD Alice Mahoney	5
8400534 Michael K. Tran, M.D., Inc. 15355 Brookhurst Street, Suite 104 Westminster, CA 92683-7071	Michael Khanh Le Tran, M.D., FACS	Uyen Tran Thanh Ngoe Mai Tuyetnhung Tran	4

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400535 Stacy R. Smith M.D. P.C. 1548 East 4500 South, Suite 105 Salt Lake City, UT 84117	Stacy R. Smith, M.D.	Adam M. Bowman, M.D. Sheri Faircloth, COT	5
8400536 Seidenberg Protzko Eye Associates 2023 Pulaski Highway Havre de Grace, MD 21078	Eugene E. Protzko, M.D.	Jonathan A. Seidenberg, M.D. Scott M. Smearman, M.D. David Reed Daniel C. Byron Carol Seidenberg Anthony Franco Gonzales Alexander Waverly Van Dyck Jessica Young Won Hahm Lizanette Paulino	13
8400537 International Eye Associates PA 1545 Hand Ave, Suite B3 Ormond Beach, FL 32174	Mark S. Rubin, M.D.	Michael J. Mequio, M.D. Jennifer Wilson Michelle Marie Wholly, COA Patrizia Rubin	6
8400538 VRF Eye Specialty Group 825 Ridgelake Blvd, 3rd Floor Memphis, TN 38120	John Elfervig	Henry McQuirter Adria Dodson Tawnee Stephens Michael Sanford	23
8400541 AdvanceMed Clinical Research 9555 S. Eastern Avenue, Suite 260 Las Vegas, NV 89123	Matthew J. Swanic, M.D.	Gregory Hsu, DO Lindsey Szeto Katie Kowal	12

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400542 AdvanceMed Clinical Research 3655 Nobel Drive, Suite 130 San Diego, CA 92122	Mihir Parikh, M.D.	Steven G. Peterson, OD Lindsey Szeto Katie Kowal	4
8400550 Haas Vision Center 6385 Corporate Drive, Suite 307 Colorado Springs, CO 80919-5913	Michael Haas, M.D.	David Davis, M.D. Timothy Reese, OD Erin Fox, MS Kaylee Rosenbusch, MS Tonya Rylant, MLS, COA Sarah Roberts Zachary Soroka	6
8400552 St. Michaels Eye Laser Institute 1030 West Bay Drive Largo, FL 33770-3225	John Luis Michaelos, M.D.	James Rowsey, M.D. Gregory Michaelos	11
8400553 M & M Eye Institute 3192 Willow Creek Road Prescott, AZ 86301-6610	Scott Markham, DO	Steven Mortenson, M.D. Byron Tabbut, M.D. James Arthus, M.D. Kaylee Rosenbusch Rachel Wells, OD Brett Christensen, OD Nicole Adams Erin Fox Melanie Maline Heather Yoshimura Sheri Compson Crystal Brown	9
8400554 Vistar Eye Center 707 S Jefferson Street Roanoke, VA 24016-5100	Frank Cotter, M.D.	Tad Schoedel, M.D. Patrese Pyle Amanda Lee	2

Site No.	Investigator Name	Sub-Investigator(s) Name	Total Randomized
8400558 Tekwani Vision Center 9911 Kennerly Road, Suite A St. Louis, MO 63128	Navin Tekwani, M.D.	Jessica Jones Brooke Reynolds Lisa Dinsmore Ally Prunty Lisa Schepp	1
8400622 Abrams Eye Center 2322 E. 22nd Street, Suite 102 Cleveland, OH 44115	Marc Abrams, M.D.	Margaret Smith, RN Scott Tompkins, L.D.O.	7
8400625 Baylor College of Medicine Alkek Eye Center 1977 Butler Blvd, 3rd Floor Houston, TX 77030	Lauren Blieden, M.D.	Peter Chang, M.D. Annika Joshi, CCRC	0

There were two additional sites that were selected but not activated for this study.

Reviewer's comments:

No site enrolled a majority of the subjects that would have had significantly influenced data.

6.2 Study Results

Compliance with Good Clinical Practices

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

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.* See Section 13.2 of this review.

There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the applicant.

Patient Disposition

Table 9: Subject Disposition for the 3-Month Comparative Treatment Period of Phase 3 Studies 01171505, 011710IN, and 011709IN

	01171505		011710IN		011709IN	
	DE-117 0.002%	Latanoprost 0.005%	DE-117 0.002%	Timolol 0.5%	DE-117 0.002%	Timolol 0.5%
Safety Population	185	185	204	205	211	215
Full Analysis Set	184	185	204	205	212	213
Disposition (Safety Population):						
Completed Study Drug Dosing of 3-Month Treatment Period	170 (91.9%)	177 (95.7%)	187 (91.7%)	196 (95.6%)	189 (89.6%)	204 (94.9%)
Discontinued Study Drug During 3-Month Treatment Period	15 (8.1%)	8 (4.3%)	17 (8.3%)	9 (4.4%)	22 (10.4%)	11 (5.1%)
Adverse Event	4 (2.2%)	2 (1.1%)	13 (6.4%)	3 (1.5%)	10 (4.7%)	3 (1.4%)
Withdrawal by Subject	8 (4.3%)	5 (2.7%)	N/A	N/A	N/A	N/A
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (2.4%)	2 (0.9%)
Protocol Deviation	2 (1.1%)	0 (0.0%)	N/A	N/A	N/A	N/A
Death	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Other	1 (0.5%)	1 (0.5%)	3 (1.5%)	6 (2.9%)	7 (3.3%)	5 (2.3%)

N/A = Not applicable–Distinct recording and summary of study drug discontinuations for *Withdrawal by Subject* and *Protocol Deviation* was only done for study 01171505. In studies 011710IN and 011709IN, study drug discontinuation for a reason other than *Adverse Event*, *Lack of Efficacy*, or *Death* was recorded and summarized under *Other*, and a text field was used to record a description of the specific reason.

Protocol Violations/Deviations

Refer to table in Subject Disposition where in Study 01171505 protocol deviations were low at approximately 1% in the drug group (DE – 117) and varied from 1.5% to 3.3% in Studies 011710IN and 011709IN.

Table of Demographic Characteristics

Table 10: Subject Demographics in Phase 3 Studies 01171505, 011710IN, and 011709IN (full Analysis Set)

	01171505		011710IN		011709IN	
	DE-117 0.002% (N=184)	Latanoprost 0.005% (N=185)	DE-117 0.002% (N=204)	Timolol 0.5% (N=205)	DE-117 0.002% (N=212)	Timolol 0.5% (N=213)
Age						
n	184	185	204	205	212	213
Mean (SD)	54.6 (12.87)	52.6 (13.08)	64.0 (11.43)	64.8 (11.56)	64.7 (14.91)	63.5 (14.48)
Median	55.0	53.0	65.5	66.0	68.0	65.0
Min, Max	19, 82	19, 82	21, 82	23, 91	12, 93	13, 90
Age Group (year)						
n	184	185	204	205	212	213
< 18	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (2.8%)	7 (3.3%)
>= 18 and <65	137 (74.5%)	143 (77.3%)	89 (43.6%)	87 (42.4%)	83 (39.2%)	91 (42.7%)
>=65	47 (25.5%)	42 (22.7%)	115 (56.4%)	118 (57.6%)	123 (58.0%)	115 (54.0%)
Sex						
n	184	185	204	205	212	213
Male	106 (57.6%)	88 (47.6%)	83 (40.7%)	96 (46.8%)	89 (42.0%)	78 (36.6%)
Female	78 (42.4%)	97 (52.4%)	121 (59.3%)	109 (53.2%)	123 (58.0%)	135 (63.4%)
Race						
n	184	185	204	205	212	213
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.5%)
Asian	184 (100.0%)	185 (100.0%)	8 (3.9%)	8 (3.9%)	0 (0.0%)	2 (0.9%)
Black or African American	0 (0.0%)	0 (0.0%)	72 (35.3%)	54 (26.3%)	48 (22.6%)	52 (24.4%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	2 (0.9%)	0 (0.0%)
White	0 (0.0%)	0 (0.0%)	122 (59.8%)	140 (68.3%)	160 (75.5%)	155 (72.8%)
Multiple	0 (0.0%)	0 (0.0%)	2 (1.0%)	1 (0.5%)	2 (0.9%)	3 (1.4%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 11: Baseline Iris Color Characteristics in Phase 3 Studies 01171505, 011710IN, and 011709IN (study Eye, Full Analysis Set)

	01171505		011710IN		011709IN	
Iris Color						
n	184	185	204	205	212	213
Brown	181 (98.4%)	183 (98.9%)	125 (61.3%)	124 (60.5%)	123 (58.0%)	133 (62.4%)
Yellow-brown	0 (0.0%)	1 (0.5%)	9 (4.4%)	3 (1.5%)	2 (0.9%)	3 (1.4%)
Green-brown	0 (0.0%)	0 (0.0%)	8 (3.9%)	8 (3.9%)	10 (4.7%)	7 (3.3%)
Green with slightly brown	0 (0.0%)	0 (0.0%)	6 (2.9%)	10 (4.9%)	11 (5.2%)	14 (6.6%)
Green	0 (0.0%)	0 (0.0%)	1 (0.5%)	6 (2.9%)	3 (1.4%)	4 (1.9%)
Blue/gray-brown	0 (0.0%)	1 (0.5%)	5 (2.5%)	5 (2.4%)	5 (2.4%)	3 (1.4%)
Blue/gray with slightly brown	0 (0.0%)	0 (0.0%)	15 (7.4%)	17 (8.3%)	16 (7.5%)	19 (8.9%)
Blue/gray	3 (1.6%)	0 (0.0%)	35 (17.2%)	32 (15.6%)	42 (19.8%)	30 (14.1%)

	01171505		**011710IN**		**011709IN**	
	DE-117 0.002% (N=184)	**Latanoprost 0.005% (N=185)**	**DE-117 0.002% (N=204)**	**Timolol 0.5% (N=205)**	**DE-117 0.002% (N=212)**	**Timolol 0.5% (N=213)**

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

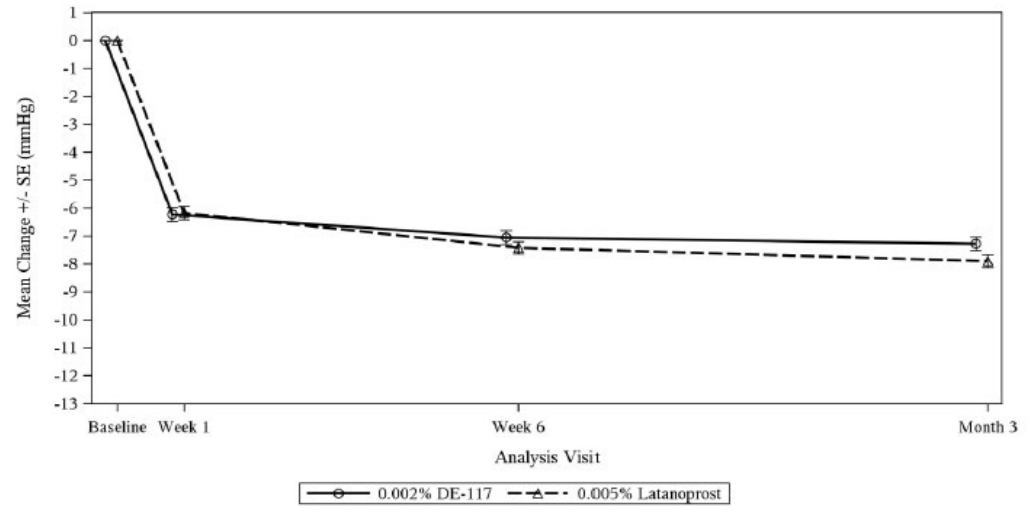
Refer to table in Subject Disposition section where approximately 90% to 92% of subjects completed the study drug dosing of the 3 month treatment period compared to approximately 95% in the active control groups.

Efficacy Results – Primary Endpoint

For the FDA's review, of all 3 of the phase 3 studies, the non-inferiority criteria applied in the analysis of IOP at 9 timepoints consisted of 2 criteria and both were 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.

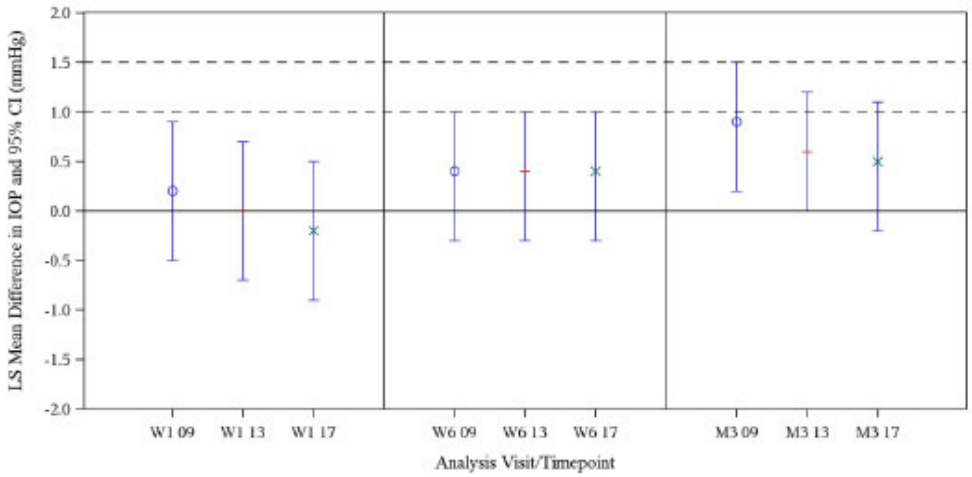
Study 01171505

Table 12: 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.

Table 13: 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.

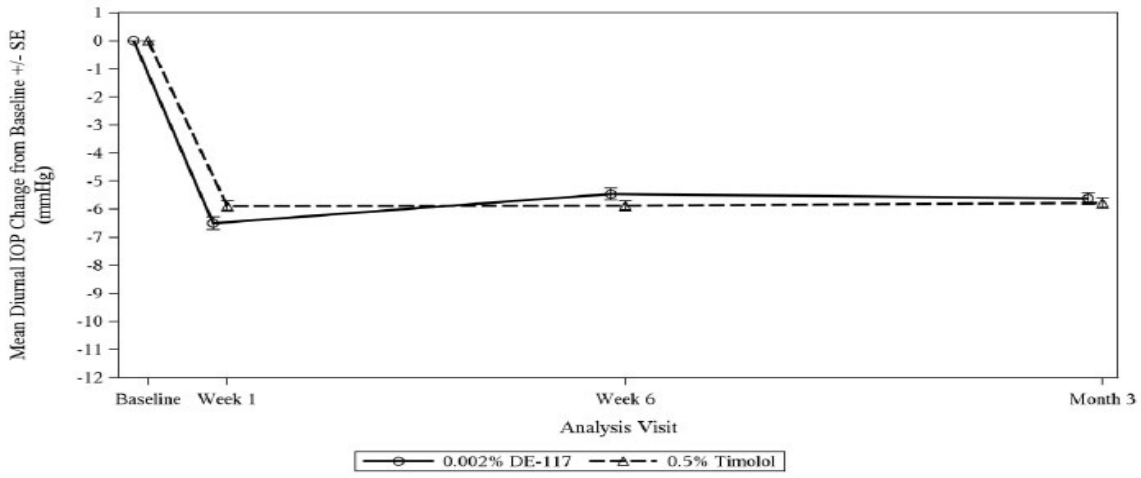
Table 14: Study 01171505, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Latanoprost) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	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

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.
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.

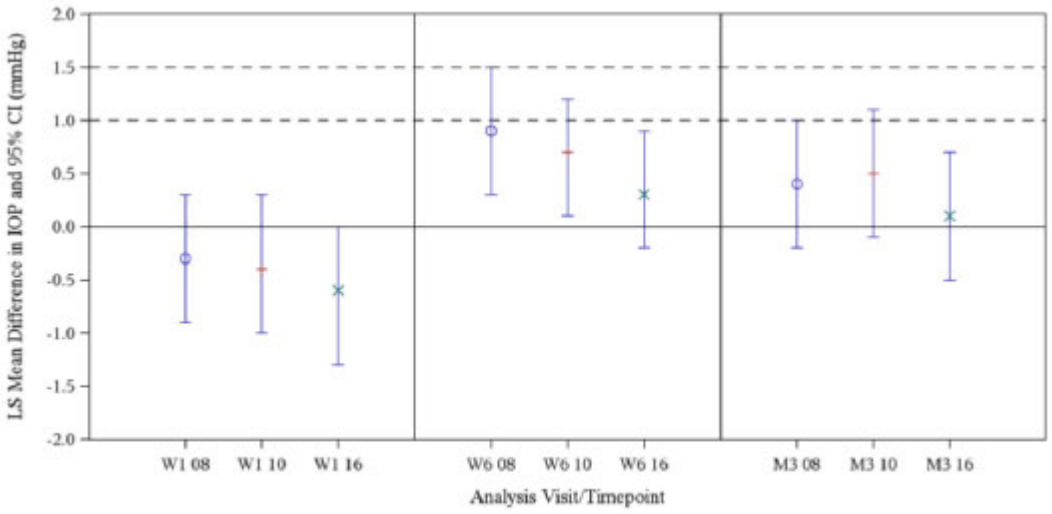
Study 011710IN

Table 15: 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.

Table 16: 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.

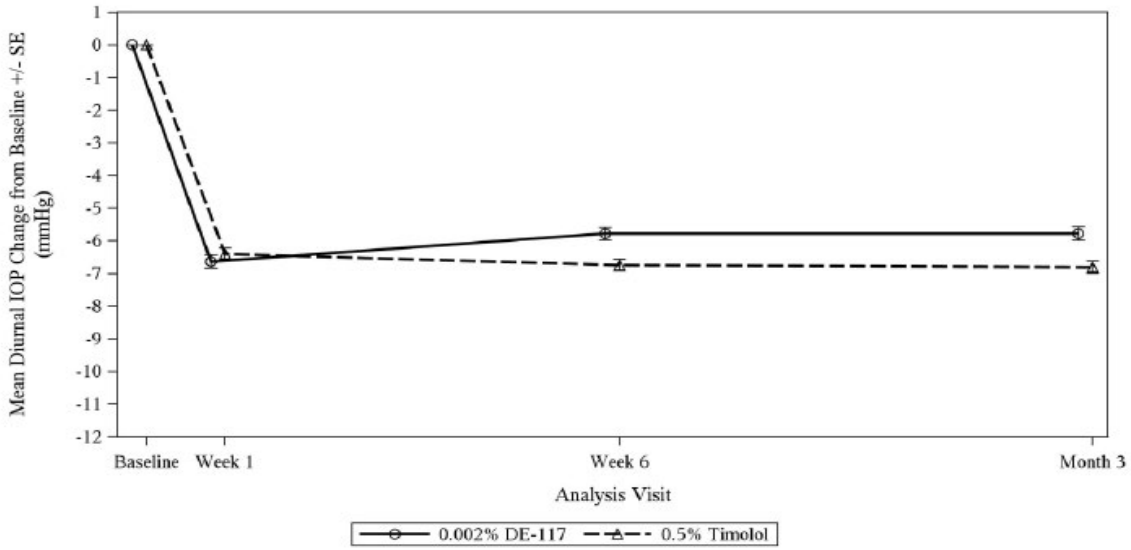
Table 17: Study 011710IN, IOP at 3 Timepoints at Each of 3 Visits: Treatment Arm LS Mean Differences (DE-117 Minus Timolol) and 95% Confidence Intervals (Study Eye, Full Analysis Set)

	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.

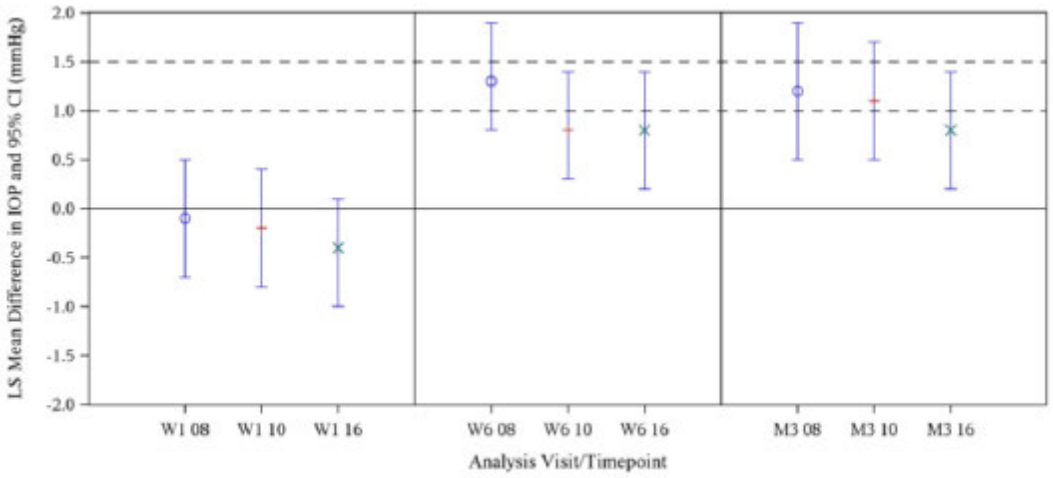
Study 011709IN

Table 18: 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.

Table 19: 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.

Table 20: 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.

Reviewer's comments:
Studies 01171505 and 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 did not satisfy both of these criteria but trended in the right direction adding supportive data to the recommended approval of this NDA.

Data Quality and Integrity

This submission is of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

Efficacy Results – Secondary and other relevant endpoints

The key endpoint to evaluate reduction of intraocular pressure is mean IOP. This was performed in the primary efficacy endpoint analyses. The secondary endpoint analyses are exploratory.

Dose/Dose Response

A dose ranging study, Study 33-002 was performed prior to initiation of the Phase 3 trials.

Table 21: Study 33-002: Numbers of Subjects Dosed/Completed and Mean Duration of Exposure

Treatment Groups	Number of Subjects Dosed/Completed	Mean Duration of Exposure, Days
DE-117 Overall	61/61	28.0
DE-117 0.0003% QD	17/17	28.2
DE-117 0.001% QD	15/15	28.0
DE-117 0.002% QD	14/14	27.9
DE-117 0.003% QD	15/15	28.1
Latanoprost 0.005% QD	15/15	28.1
Placebo	15/15	28.2
Overall Total	91/91	nc

Abbreviations: nc = not computed; QD = once daily.

Efficacy: A positive dose-response relationship for IOP-lowering was observed among the 3 lower DE-117 concentrations (0.0003%, 0.001%, and 0.002%) and the IOP reduction of 0.002% was similar to that of latanoprost. The IOP reduction in the 0.003% group was consistently numerically lower than that in the 0.002% group.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Intraocular pressure (IOP) is currently the accepted standard for establishing the efficacy of ocular hypotensive 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). Studies 01171505 and 011710IN demonstrated that omidenepag isopropyl ophthalmic solution, 0.002% was non-inferior to Latanoprost ophthalmic solution 0.005% (Study 01171505) or timolol maleate ophthalmic solution, 0.5% (Study 011710IN). Study 011709IN though not satisfying the primary endpoint criteria was trending in the right direction in the comparison of omidenepag isopropyl ophthalmic solution, 0.002% to timolol maleate ophthalmic solution, 0.5%.

7.1.2. Secondary and Other Endpoints

The secondary endpoint analyses are exploratory.

7.1.3. Subpopulations

The amount of reduction in IOP was consistent across all relevant subpopulations including age, sex, race/ethnicity, and geographic region.

7.1.4. Dose and Dose-Response

Study 303-02 (Refer to Table in Section 6.1.2) demonstrated a positive dose-response relationship for IOP-lowering observed among the 3 lower DE-117 concentrations (0.0003%, 0.001%, and 0.002%).

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Intraocular pressure was measured at three time points at Baseline, Week 1, Week 6, and Month 3 in studies 01171505 and 011710IN. The mean IOP reduction for each of the 3 time points over the three-month evaluation period were similar.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

No potential efficacy issues in the post-market setting have been identified.

7.2.2. Other Relevant Benefits

There are no other relevant benefits for this drug product.

7.3. Integrated Assessment of Effectiveness

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% (Study 01171505) 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.

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 efficacy of this drug is consistent with other currently marketed IOP lowering drugs.

8. Review of Safety

8.1. Safety Review Approach

The analysis of integrated safety in this report is based on 3-month data collected for DE-117 0.002%, dosed once a day (optimal concentration and dosing regimen) during masked periods of the 3 pivotal studies in the US (011709IN and 011710IN) and Asia (01171505) and an additional 9-month follow-up in Study 011709IN.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The Table presents the summary of study drug exposure for the pooled studies. 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).

Table 22: 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".

8.2.2. Relevant characteristics of the safety population:

The safety population is representative of the population that the drug product is intended to treat. The safety population included primarily subjects with open-angle glaucoma or ocular hypertension.

8.2.3. Adequacy of the safety database:

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. Categorization of Adverse Events

Adverse events were coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). All calculations were performed using the preferred term (PT) by system organ class (SOC). The most recent version of MedDRA (MedDRA version 21.1) was used to generate all the AE tables for the ISS.

8.3.3. Routine Clinical Tests

The routine clinical testing to evaluate safety concerns for omidenepag isopropyl ophthalmic solution, 0.002% was adequately addressed in the design and conduct of the clinical trials.

8.4. Safety Results

8.4.1. 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.

8.4.2. Serious Adverse Events

Table 23: Adverse Events: Summary of Serious Adverse Events by System Organ Class and Preferred Term – Analysis Population: Safety - Analysis Period: Double-Masked

	011709IN		011710IN		01171505		Integrated Summary		
System organ class 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)
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

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Table 24: Study 01171505: Dropouts and/or Discontinuations Due to Adverse Effects

Adverse Event	Treatment	Subject Number (b) (6)
Photophobia	DE-117	
Foreign body	DE-117	
Uveitis	DE-117	
Iritis	DE-117	
Headache	Latanoprost, 0.005%	
Blurred vision / Eye pain	Latanoprost, 0.005%	

Table 25: Study 011710IN: Dropouts and/or Discontinuations Due to Adverse Effects

Adverse Event	Treatment	Subject Number (b) (6)
Photophobia	DE-117	
Ocular discomfort/ hyperemia/ Visual Impairment	DE-117	
IOP increased	DE-117	
IOP increased	DE-117	
Eye pain / Vision blurred	DE-117	
Photophobia	DE-117	
Eye pain	DE-117	
Allergic conjunctivitis	DE-117	
Iritis / IOP increased	DE-117	
Cystoid macular edema	DE-117	
Cystoid macular edema	DE-117	
Conjunctivitis	DE-117	
Transient ischemic attack	DE-117	
Bradycardia	Timolol, 0.5%	
Dry eye / Visual impairment	Timolol, 0.5%	
Dry eye / Gingival swelling / Nasal dryness / Swelling face	Timolol, 0.5%	

Table 26: Study 011709IN: Dropouts and/or Discontinuations Due to Adverse Effects

Adverse Event	Treatment	Subject Number (b) (6)
Vision blurred	DE-117	
Visual impairment	DE-117	
Headache / Photophobia	DE-117	
Vision blurred	DE-117	
Allergic conjunctivitis	DE-117	
Photophobia / Instillation site pain / Vision blurred / Headache	DE-117	
Cystoid macular edema	DE-117	
Eye pain / Photophobia	DE-117	
Macular edema	DE-117	
Skin hypopigmentation	DE-117	

			(b) (6)
Macular edema	DE-117		
Hypermetropia	DE-117		
Eye irritation	DE-117		
Chemical eye injury	Timolol, 0.5%		
Alopecia	Timolol, 0.5%		
Instillation site pain	Timolol, 0.5%		
Influenza A	Timolol, 0.5%		
Eye irritation	Timolol, 0.5%		

8.4.4. Significant Adverse Events

Refer to Section 8.3.2

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 27: 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

	011709IN		011710IN		01171505		Integrated Summary		
System organ class* 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)
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.

8.4.6. Laboratory Findings

No clinically significant differences from baseline were observed in the data that was collected.

8.4.7. Vital Signs

Based on the review of measured vital signs, there was no indication that DE-117 had a systemic impact on heart rate or blood pressure.

8.4.8. Electrocardiograms (ECGs)

EKGs were not collected in any of the studies conducted in the clinical development program.

8.4.9. QT

QT studies were not performed.

8.4.10. Immunogenicity

There is no known potential to cause immunogenicity.

8.5. Analysis of Submission-Specific Safety Issues

Macular edema is a known risk of prostaglandin use and has been identified as a risk for aphakic or pseudophakic subjects treated with DE-117 based on previous data from studies with Japanese subjects.

8.5.1. Macular Edema in Pseudophakia Eyes

Of the 3 studies conducted in Japan, 2 (01171503 and 01171506) had a 28-day treatment period, with 1 case (4.5%) of macular edema (related to study drug) reported in both eyes for 1 subject (lens status unknown) in study 01171503 who received the 0.0025% concentration of DE-117. The third study (01171504), was a long-term study with a 52-week treatment period that largely contributed to the risk assessment of macular edema. Sixteen subjects were identified in study 01171504 who developed macular edema; 15 occurring in pseudophakic subjects, among which 14 were considered as related to study drug and 1 was non-related to study drug. Among all the pseudophakic subjects in this study, 51.7% (15/29) were reported as having developed macular edema.

Reviewer's comments:
Based on these results there was an association of macular edema in pseudophakic, and potentially aphakic, eyes.

8.6. Safety Analyses by Demographic Subgroups

The evaluation of intrinsic factors for AEs in the pooled population included age category (<65 years and ≥65 years), gender (male, female), race (White, Black or African American, and Asian), and lens status (Phakic, Pseudophakic). No meaningful difference was observed in the rates of reported AEs between males and females) or among age categories. There is no evidence among the studies conducted to date that race is an intrinsic risk factor for AEs.

There was no difference in the overall rates of AE's between phakic and pseudophakic eyes, but pseudophakia continues to be a risk factor for macular edema in subjects receiving DE-117, as subgroup analysis of lens status continued to indicate a higher rate of pseudophakic subjects with AEs for macular edema (including CME), which includes higher rates of SAEs and AEs leading to study drug discontinuation. No other intrinsic factors are considered to increase the risk of macular edema for subjects receiving DE-117.

8.7. Specific Safety Studies/Clinical Trials

Central corneal endothelial cell density was evaluated by specular microscopy in a one long-term study in Japan (study 01171504, 52-week follow up). No subjects in the study experienced medically significant changes in corneal endothelial cell density and no AEs related to changes in ECD were reported in the study. The mean change from baseline remained relatively stable for all treatment groups in the study and was < -57 cells/mm2 for study eyes and < -65 cells/mm2 for fellow eyes at Week 52.

8.8. Additional Safety Explorations

The 120-Day Safety Update was submitted 03/18/2021. The applicant has not received any safety information or detected any new safety signals that would significantly change the previously known risks of DE-117.

8.8.1. Human Carcinogenicity or Tumor Development

There is no data to suggest that omidenepag isopropyl ophthalmic solution, 0.002% has any tumorigenic potential.

8.8.2. Human Reproduction and Pregnancy

There have been no clinical studies in human reproduction or pregnancy performed. No clinical study or post-marketing data suggest an effect on human reproduction or pregnancy.

8.8.3. Pediatrics and Assessment of Effects on Growth

Effects on growth were not evaluated.

Pediatric Subjects enrolled in Study 011709IN

Thirteen pediatric subjects with bilateral juvenile angle glaucoma (mean age of 14.1 years) were enrolled in the double-masked period under study 011709IN, 6 of whom received DE-117 0.002%. One subject in the timolol arm was the only pediatric subject with a reported AE (chemical eye injury, related to study drug, and resolved) during the masked period in the study. Data from this study did not identify any safety concerns for the pediatric subjects, and DE-117 seemed well tolerated by the pediatric population in the study.

Table 28: Pediatric Subjects in 011709IN: Descriptive Statistics for Mean Diurnal IOP and Change from Baseline by Visit (Study Eye, Full Analysis Set)

		Mean Diurnal IOP (mmHg)		Change from Baseline in Mean Diurnal IOP (mmHg)	
Visit	Statistics	DE-117 0.002%	Timolol 0.5%	DE-117 0.002%	Timolol 0.5%
Baseline	n	6	7		
	Mean (SD)	22.6 (1.01)	22.9 (0.74)		
	SE	0.41	0.28		
	Median	22.6	22.8		
	Min, Max	21, 24	22, 24		
Week 1	n	6	7	6	7
	Mean (SD)	16.9 (1.76)	15.9 (1.34)	-5.8 (2.04)	-7.0 (1.02)
	SE	0.72	0.51	0.83	0.39
	Median	17.0	16.0	-5.0	-7.0
	Min, Max	15, 19	14, 18	-8, -4	-9, -6
Week 6	n	6	7	6	7
	Mean (SD)	16.1 (1.87)	16.8 (2.11)	-6.5 (1.79)	-6.0 (1.92)
	SE	0.76	0.80	0.73	0.72
	Median	16.2	16.3	-6.0	-6.3
	Min, Max	14, 19	14, 20	-9, -5	-8, -4
Month 3	n	6	6	6	6
	Mean (SD)	16.4 (2.09)	16.6 (1.75)	-6.3 (1.85)	-6.4 (1.38)
	SE	0.85	0.71	0.75	0.57
	Median	16.1	16.8	-6.1	-6.0
	Min, Max	15, 20	14, 19	-8, -3	-9, -5

Abbreviations: Max = maximum; Min = minimum; SD = standard deviation; SE = standard error.
In these descriptive summaries, mean diurnal IOP values were censored (i.e., treated as missing) after subjects took any rescue therapy.

Santen followed the agency's guidance to include the pediatric subjects in the US phase 3 clinical development program. The iPSP was agreed and finalized on 29 June 2018. Up to 30 pediatrics subjects (age of 1 to 18 years) were planned to enroll in the two US phase 3 studies (study protocol 011709IN and 011710IN). Efforts were made to enroll pediatric subjects. As a result, 13 pediatrics subjects were enrolled in one of the US phase 3 studies (011709IN). Per agency's agreement on 12 July 2019, Santen could proceed with the database lock once the adult subjects' enrollment had been completed, even though the total number of pediatric subjects enrolled had not reached 30 as planned in the protocol. In summary, Santen is

requesting a full waiver of pediatric studies for this application. See the CDTL review for additional information.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no evidence for the potential for overdose or potential abuse with omidenepag isopropyl ophthalmic solution, 0.002%.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Post-market Experience

A post-marketing observational study (PMS) was initiated on 27 November 2018, and is currently ongoing in Japan to evaluate the safety and efficacy in long-term use of DE-117 in real-world clinical practice and to review the safety of long-term co-administration of DE-117 with other IOP lowering drugs. One serious SAR of increased IOP has been reported in the study.
No new significant safety information or signal has been identified.

8.9.2. Expectations on Safety in the Post-market Setting

Information regarding these safety concerns is presented in the recommended labeling.

8.9.3. Additional Safety Issues From Other Disciplines

There are no specific safety concerns from other disciplines.

8.10. Integrated Assessment of Safety

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 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 and Other External Consultations

No Advisory Committee Meeting was required or convened for this NDA.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

NDA 215092 is recommended for approval with the draft labeling revisions found in this review once any outstanding OPQ or other deficiencies are resolved.

(b) (4)

8 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

10.2. Nonprescription Drug Labeling

Not applicable. This is a prescription NDA.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

Not applicable.

13. Appendices

13.1. References

An independent literature review was not conducted for this application.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 01171505

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 36		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 011710IN

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 35		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): 0117109IN

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: 55		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

MARTIN P NEVITT
10/13/2021 10:04:59 AM

WILLIAM M BOYD
10/13/2021 10:42:46 AM