Study Protocol Cover Page

Official Study Title:	ANGEL-2: A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension.
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DE-126 PROTOCOL
STUDY 012604IN

TITLE: ANGEL-2: **A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension**

PROTOCOL NUMBER: 012604IN

COMPOUND NUMBER: DE-126

STUDY PHASE: Phase IIb

SPONSOR: SANTEN INCORPORATED

LEGAL REGISTERED ADDRESS: 6401 Hollis Street, Suite 125, Emeryville, CA 94608

REGULATORY AGENCY IDENTIFIER NUMBER(S): IND Number: 112026

PROTOCOL VERSION/DATE: ORIGINAL 16OCT2020

AMENDMENT 1: 18FEB2021

I have read the 012604IN protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form (eCRF) indicates that the data therein has been reviewed and accepted by me as the Investigator.

INVESTIGATOR:

Date: _____

Signature: _____

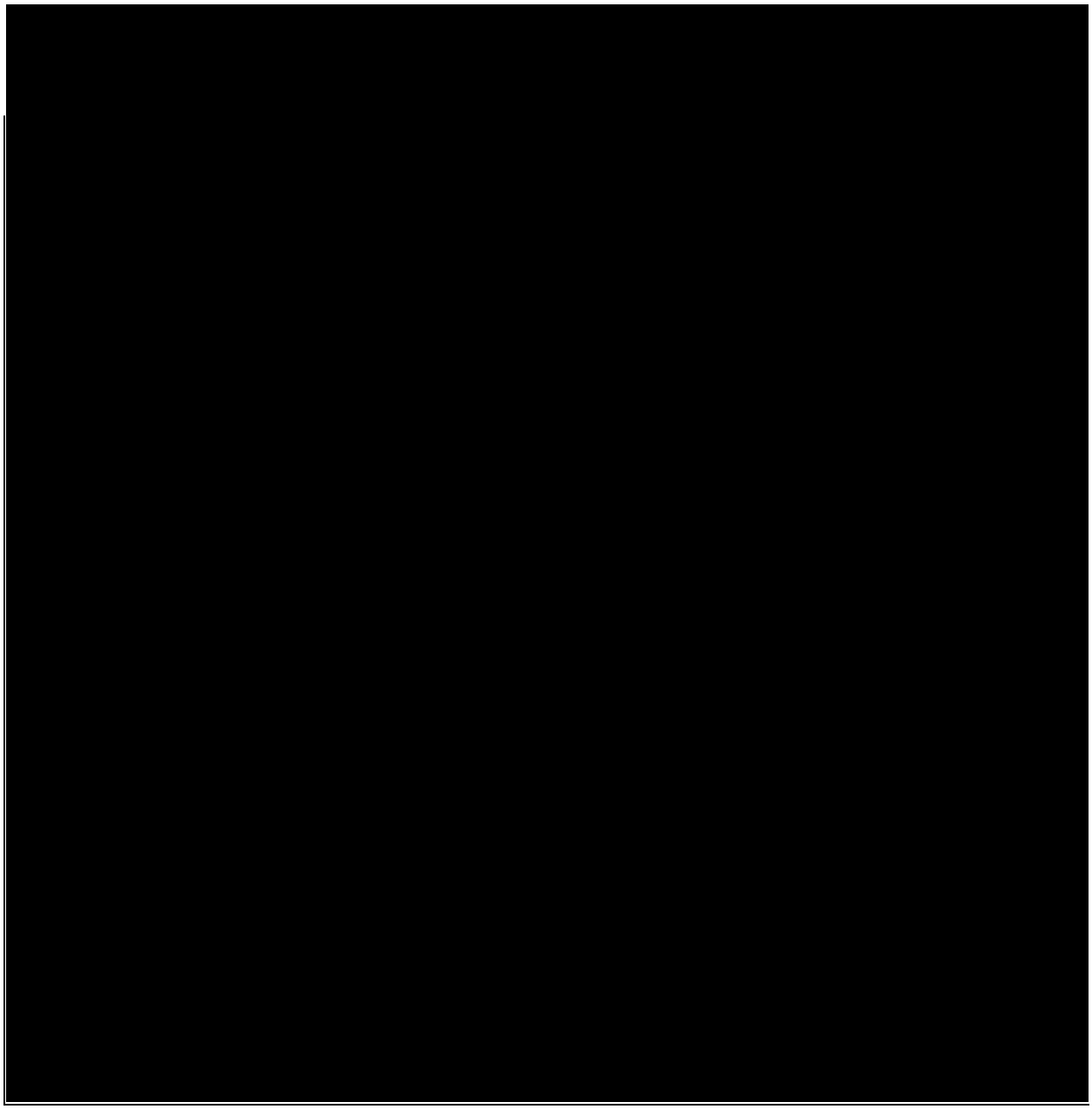
Name: _____

Address: _____

_____

Phone: _____

This study will be conducted in accordance with applicable Good Clinical Practices (GCP), United States Code of Federal Regulations, International Conference on Harmonization (ICH) guidelines, and the Declaration of Helsinki.



1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company:

Santen Inc.
6401 Hollis Street, Suite 125
Emeryville, CA 94608, USA

Name of Investigational Product: DE-126 Ophthalmic Solution

Name of Active Ingredient:

Propan-2-yl 4-{(3S,5aR,6R,7R,8aS)-6- [(1E,3R)-4-(2,5-difluorophenoxy)-3- hydroxybut-1-en-1-yl]-7-hydroxyoctahydro- 2H-cyclopenta[b]oxepin-3-yl}butanoate

Title of Study: ANGEL-2: A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension

Protocol Number: 012604IN

Number of Subjects (planned): Approximately 294 adult subjects (147 in each treatment arm) with Primary Open-Angle Glaucoma (POAG) or Ocular Hypertension (OHT) will be randomized in this study

Number of Sites (planned): Approximately 45 sites in the United States

Study Period: Approximately 19 weeks	**Phase of Development**: Phase IIb

Study objectives and endpoints:

Study Objectives	**Corresponding Study Endpoints**
Primary Efficacy Objective To investigate whether the IOP lowering efficacy of DE-126 ophthalmic solution 0.002% dosed once daily (QD, in the evening at 20:00) is non-inferior to that of Timolol maleate 0.5% dosed twice daily (BID, 8:00 and 20:00) in subjects with POAG or OHT after treatment for 3 months. If non-inferiority is met, superiority will be tested.	**Primary Efficacy Endpoint** The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00, and 16:00 at Week 2 (Visit 3), Week 6 (Visit 4), and Month 3 (Visit 5).

Secondary Efficacy Objectives • To compare the mean diurnal IOP between DE-126 ophthalmic solution 0.002% and Timolol maleate ophthalmic solution 0.5% after 3 months of treatment. If non- inferiority is met, superiority will be tested. • To evaluate the changes and percent changes in IOP from baseline at all post-baseline visits. • To evaluate proportions of subjects achieving target pressure reductions expressed as either in percent reductions of ≥ 20%, ≥ 25%, or ≥ 30% or in achieving a target IOP value of IOP ≤ 18 mmHg.	**Secondary Efficacy Endpoints** Key Secondary Efficacy Endpoint • Mean diurnal IOP in the study eye at Month 3 (Visit 5) Other Secondary Efficacy Endpoints • Mean diurnal IOP in the study eye at Week 2 (Visit 3) and Week 6 (Visit 4) • Change and percent change from Baseline (Visit 2, Day 1) in IOP in the study eye at each timepoint of each post-baseline visit • Change and percent change from Baseline (Visit 2, Day 1) in mean diurnal IOP in the study eye at each post-baseline visit • Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2, Day 1) in the study eye at each post-baseline visit • Having a mean diurnal IOP ≤ 18mmHg in the study eye at each post-baseline visit
Safety Objectives To evaluate the safety of DE-126 ophthalmic solution 0.002% as compared to Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.	**Safety Endpoints** • Adverse Events (AEs) and serious AEs (SAEs), including both ocular and non-ocular AEs • Visual acuity: measured by best corrected visual acuity (BCVA) • Slit-lamp biomicroscopy • Ophthalmoscopy • Vital signs (blood pressure and pulse rate)

Exploratory Objectives	Exploratory Endpoints
To explore Quality of Life in subjects with POAG or OHT when given DE-126 or Timolol for 3 months.	• Glaucoma Quality of Life-15 (GQL-15) questionnaire at Baseline (Visit 2, Day 1) and Month 3 (Visit 5).

Duration of Treatment: 3 months

Methodology:

This is a Phase IIb, randomized, double-masked, active-controlled, parallel-group and multicenter study assessing the efficacy and safety of DE-126 ophthalmic solution 0.002% compared with Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.

Subjects diagnosed with POAG or OHT who meet eligibility criteria at Visit 1 (Screening) will washout of their current topical IOP-lowering medication(s), if any. After completing the required washout period, subjects will return for Visit 2 (Baseline, Day 1). Subjects who meet all eligibility criteria at baseline will be randomized to receive treatment for 3 months.

Approximately 294 adult subjects with POAG or OHT who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either:

- DE-126 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- Timolol Maleate Ophthalmic Solution 0.5% BID (20:00 and 08:00)

Study Design: **Please see** Figure 1.

This study will consist of a Screening Period of up to 35 days including a washout period of up to 28 days (+ 7 days window) and a 3-month Double-Masked Treatment Period.

At the Screening visit (Visit 1), subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications, if any, during a washout period as follows (up to +7 days as a window is allowed):

- Miotics: 7 days
- Oral/topical Carbonic Anhydrase Inhibitors (CAIs): 7 days
- Alpha agonists: 14 days
- Alpha/beta agonists: 14 days
- Alpha antagonists (α1 blocker): 28 days
- Beta antagonists (β blocker, including αβ blockers): 28 days
- Prostaglandin Analogs (PGA): 28 days
- Rho kinase inhibitor: 28 days
- Combination drugs: The longest washout period of the individual component will be used.

Please note: Subjects are only allowed to be treated with a maximum of two active ingredients for IOP reduction prior to screening.

During the required washout period, subjects who discontinue their current treatment may, if the Investigator deems it necessary, be treated with a short-acting IOP lowering agent, topical CAI, e.g., brinzolamide or dorzolamide eye drops, one drop twice daily. Topical CAI treatment must be stopped 1 week before the randomization at Visit 2 (Baseline, Day 1). An interim safety visit during the washout period (mid-washout visit; Optional Visit 1a) may be performed during the washout period if, in the Investigator's opinion, a subject's IOP may be of concern during the washout period. If subjects are treated with a topical CAI during the washout period, mid-washout visit (Optional Visit 1a) is recommended to be performed.

Final eligibility for randomization will be determined at Visit 2 (Baseline, Day 1) after all necessary washout from prior IOP-lowering medications have been completed.

At Visit 2 (Baseline, Day 1), baseline IOP will be measured for both eyes at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 (Baseline, Day 1) will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study, even if only one eye is eligible per IOP inclusion criteria.

Please note: Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) may be combined into one visit for treatment-naïve subjects as long as the additional requirements of Visit 2 (Eligibility/Baseline, Day 1) are fulfilled on the day of this combined visit; in particular, full diurnal IOP measurements (at 08:00, 10:00, 16:00) must be taken.

Double-Masked Treatment Period (3 months):

Approximately 294 eligible adult subjects will be randomized to receive either DE-126 ophthalmic solution 0.002% QD in the evening and vehicle QD in the morning or Timolol maleate ophthalmic solution 0.5% BID in a 1:1 ratio. Subjects will be treated for 3 months with scheduled visits at Visit 2 (Baseline, Day 1), 3 (Week 2), 4 (Week 6), and 5 (Month 3). Subjects will be contacted approximately 2 weeks post last study drug administration by a phone call to confirm AE.

In the evening of Visit 2 (Baseline, Day 1), subjects will receive their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (±60 min). The next day, subjects will subsequently dose with their assigned study medication at 08:00 (±60 min), and 20:00 (±60 min). For the DE-126/Vehicle arm, the 08:00 (±60 min) instillation will be DE-126 vehicle and the 20:00 (±60 min) instillation will be DE-126 ophthalmic solution 0.002%. At each scheduled follow-up visit, subjects will receive their morning dose of study medication/eye drops following the 08:00 (±60 min) IOP measurement at the investigative site (the doctor's office).

IOP will be measured at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min) at Visit 3 (Week 2), Visit 4 (Week 6), and Visit 5 (Month 3). At these scheduled visits, BCVA and slit-lamp biomicroscopy will be performed just prior to the 08:00 (±60 min) IOP measurement. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and 5 (Month 3). After the 16:00 (±60 min) IOP measurement at Visit 5 (Month 3), ophthalmoscopy with the pupil

dilated will be performed. Subjects will be contacted approximately 2 weeks post last study drug administration by a phone call to confirm AE.

Pharmacogenomics/Genomics:

Subjects who consent to the optional pharmacogenomics/genomics (PGx) laboratory study will provide a blood sample for future testing. The earliest this sample is to be collected at Visit 3 (Week 2), but it may also be collected at any later time during the study after Visit 2 (Eligibility/Baseline) or at a separate post-study visit, if necessary. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

Masking:

This is a double-masked study. The subjects, Investigators, Examiners, and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member at the investigator site who is not the Investigator or Examiner will dispense and collect study medication(s) and will query about dosing compliance.

Subjects will be instructed not to show the eye drop bottles or discuss the eye drops to either the Investigator or the Examiner or other study subjects. The active control treatment (Timolol Maleate) bottles will be over-labeled and packaged in the same secondary package (e.g., cardboard carton) as the investigational treatment (DE-126). Subjects in DE-126/Vehicle arm will receive a kit containing 2 bottles labeled "morning" for the morning dose and 2 bottles labeled "evening" for the evening dose. Subjects on Timolol arm will receive a kit containing 2 bottles labeled morning/evening for the BID dosing.

Each eligible subject will receive a numbered study medication kit assigned by Central randomization via Interactive Response Technology (Medidata Rave RTSM) at Visit 2 (Baseline, Day 1) and at Visit 4 (Week 6).

Inclusion Criteria: Please see Section 5.1 Subject Inclusion Criteria

Exclusion Criteria: Please see Section 5.2 Subject Exclusion Criteria

Investigational product, dosage, and mode of administration:

Subjects will be randomly assigned in a 1:1 ratio to the DE-126/Vehicle arm and Timolol Maleate arms to receive either DE-126/Vehicle or Timolol Maleate, as described below:

Investigational Product:

DE-126 Ophthalmic Solution contains 0.002% DE-126. Other ingredients include [redacted]

Vehicle:

The vehicle is identical to the investigational product but does not contain the active ingredient DE-126.

Active Control:

Timolol maleate ophthalmic solution 0.5% contains the active ingredient, Timolol 5 mg/ml, and the preservative BAK 0.01%. Other ingredients include monobasic and dibasic sodium phosphate and purified water. The pH is adjusted to 6.5 to 7.5 with sodium hydroxide.

Each subject will be instructed to instill one drop of study medication in each eye at 20:00 and at 08:00 starting the evening of Visit 2 (Baseline, Day 1) through the morning of Visit 5 (Month 3).
Route of Administration of Investigational Product: Topical ocular
Duration of the Study: The study duration includes up to a 5- weeks Screening Period, a 3-month Double-Masked Treatment Period, and up to a 2- weeks Follow-up Period.
Statistical Methods: The sample size calculation is based on a two-sided Type I error rate of 5% and a non-inferiority margin of 1.5 mmHg. Assuming a between-treatment difference of 0 mmHg, a standard deviation (SD) of 4.0 mmHg, and a correlation coefficient of 0.6 among repeated measures, approximately 280 adult subjects in total (140 subjects per treatment arm) will provide 70% power to demonstrate non-inferiority of DE-126 0.002% to Timolol 0.5%. Assuming a drop-out rate of 5%, the final needed sample size will be 294 in total, i.e. 147 subjects/arm. For the primary efficacy endpoint, a mixed-effects model for repeated measures (MMRM) will be fitted and 95% confidence interval for least square mean difference in IOP in the study eye between the DE-126/Vehicle arm and the Timolol Maleate arm at each scheduled time point of each post-baseline visit up to Month 3 will be estimated. Non-inferiority is achieved if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (DE-126 0.002% - Timolol Maleate 0.5%) is ≤ 1.5 mmHg at all nine time points and ≤ 1.0 mmHg in majority (5 or more) of the 9 time points. If non-inferiority is achieved for the primary endpoint, superiority will be tested. For the key secondary efficacy endpoint, a MMRM will be fitted on observed cases up to Month 3 on the mean diurnal IOP in the study eye. The least square mean diurnal IOP of each treatment arm and 95% confidence interval for the difference between DE-126/Vehicle and Timolol at Month 3 will be estimated. If non-inferiority in the primary endpoint is achieved, then the key secondary endpoint will be tested at the 0.05 significance level (2-sided). Non-inferiority is achieved if the upper limit of the two-sided 95% confidence interval for the difference in the mean diurnal IOP (0.002% DE-126 - Timolol Maleate) at Month 3 is ≤ 1.5 mmHg. If non-inferiority is achieved for the key secondary endpoint, superiority will be tested. All safety outcome measures will be summarized descriptively. Incidences of AEs will be tabulated by the system organ classes and preferred terms specified in the Medical Dictionary for Regulatory Activities (MedDRA). Separate summaries will be provided for ocular and non-ocular AEs.

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List of Abbreviations and Definition of Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Definition
ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AGIS	Advanced Glaucoma Intervention Study
ARB	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
BAK	Benzalkonium Chloride
BCVA	Best-Corrected Visual Acuity
BID	Twice a Day
CAI	Carbonic Anhydrase inhibitor
CV	Curriculum Vitae
D	Diopter
dB	Decibel
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMGT	Early Manifest Glaucoma Trial
ESI	Events of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GQL	Glaucoma Quality of Life
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IOP	Intraocular Pressure
IRB	Institutional Review Board

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
IUDs	Intrauterine Devices
LASIK	Laser-Assisted-in-Situ Keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
Medidata Rave RTSM	Medidata Rave Randomization & Trial Supply Management
µg	Microgram
µm	Micrometer
mg	Milligram
MIGS	Minimally Invasive Glaucoma Surgery
min	Minute
mL	Milliliter
mmHg	Millimeters of Mercury
MMRM	Mixed-effects Model for Repeated Measures
N	Number of subjects
OAG	Open-Angle Glaucoma
OCT	Optical Coherence Tomography
OD	Right Eye
OHT	Ocular Hypertension
OHTS	Ocular Hypertension Treatment Study
OS	Left Eye
OU	Both Eyes
PCR	Polymerase Chain Reaction
PGx	Pharmacogenomic/genomics
PGA	Prostaglandin Analogue
PMM	Pattern Mixture Model
POAG	Primary Open-Angle Glaucoma
PPS	Per-Protocol Set
PRK	Refractive Keratectomy
PT	Preferred Term
QD	Once a day

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
RK	Radial Keratotomy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SUN	Standardization of Uveitis Nomenclature
WHO-DDE	World Health Organization Drug Dictionary Enhanced

2. INTRODUCTION

2.1. Study Rationale

This Phase IIb study (012604IN) will assess the safety and efficacy of DE-126 ophthalmic solution 0.002% QD against Timolol maleate ophthalmic solution 0.5% BID in subjects with POAG or OHT after 12 weeks of treatment. The efficacy and safety profiles for DE-126 have been explored in early clinical studies. Four clinical studies were conducted in the U.S. and Japan with DE-126 in healthy adult subjects, or subjects with POAG or OHT to evaluate the safety and efficacy of DE-126. As a result, DE-126 ophthalmic solution in concentration of 0.002% appeared to be tolerated and effective. This data, along with the novel mechanism of action of DE-126, support the initiation of the clinical study presented in this protocol.

2.2. Background

Glaucoma is a group of diseases of the optic nerve, often associated with elevated IOP. When left untreated, glaucoma can lead to retinal ganglion cell death and optic nerve damage that result in progressive and irreversible loss of vision. Glaucoma is the leading cause of irreversible blindness in the world (King et al., 2013). While people of all ages can be diagnosed with glaucoma, it primarily affects adults who are 40 years of age or greater, and the prevalence increases substantially with increasing age group. In 2013, the global prevalence of glaucoma for the population 40 to 80 years of age was 3.54%, or 64.3 million, and the prevalence was estimated to increase to 76.0 million by 2020 and 111.8 million by 2040 (Tham et al., 2014).

Although currently there is no cure for open-angle glaucoma, results from multiple studies, including the Advanced Glaucoma Intervention Study (AGIS) (AGIS_Investigators, 2000), the Ocular Hypertension Treatment Study (OHTS) (Kass et al., 2002), and the Early Manifest Glaucoma Trial (EMGT) (Leske et al., 2003), have demonstrated that treating elevated IOP with topical ocular hypotensive agents is effective in delaying or preventing disease progression. The lowering of IOP is currently the only method for reducing the risk of glaucomatous visual field loss and remains the primary goal of therapy.

Topical hypotensive agents are typically the first-line treatment option for patients with OAG or OHT; there are several classes and they are differentiated by their mechanisms of action (MOAs) at the cellular/molecular level:

1. Prostanoid FP receptor agonists (FP agonists) (all FP agonists approved for the reduction of elevated IOP in patients with Open-Angle Glaucoma (OAG) or OHT are PGAs or prostamides)
2. Beta-adrenergic antagonists (beta blockers)
3. CAIs
4. Alpha-adrenergic agonists
5. Rho kinase (ROCK) inhibitors
6. Parasympathomimetics

Some classes of ocular hypotensive medications lower IOP primarily by reducing aqueous humor production (beta blockers, CAIs, and alpha-adrenergic agonists), and some lower IOP

mainly by increasing aqueous humor outflow (FP agonists, ROCK inhibitors, and parasympathomimetics). Of those medications that primarily increase aqueous humor outflow, ROCK inhibitors, and parasympathomimetics mainly increase trabecular outflow and FP agonists primarily increase uveoscleral outflow. Additional distinctions exist among the MOAs, and thus the pharmacodynamic effects of these medications can differ substantially.

Of the available topical hypotensive agents, FP agonists are the most frequently prescribed first-line topical therapies (Cheema et al., 2016; European_Glaucoma_Society, 2017), as they lower IOP in most patients and have minimal systemic side effects.

First line treatment with PGAs or β-blockers is very effective in IOP reduction; however, mono-therapy is often insufficient to achieve target IOP. Therefore, adjunctive therapy or combination therapy with a drug of other classes is often chosen as an alternative. Limited treatment options for non- or low-responders are also an issue. To address these issues, a first line treatment with more potent IOP reduction than existing PGAs or β-blockers, or an ocular hypotensive agent with a novel mechanism of action is still needed.

To address these needs, Santen is developing an ophthalmic topical formulation of sepetaprost (code number: DE-126) for the reduction of elevated IOP in patients with OHT or OAG.

The ocular hypotensive effects of PGAs have been fully investigated in many animal models. Although current PGAs, such as latanoprost, are thought to lower IOP mainly via the prostanoid FP receptor, a novel mechanism of action via EP3 receptor has been reported recently (Ota et al., 2006). The prostanoid EP3 and FP receptors have distinct cellular distributions in the tissues involved in the uveoscleral and conventional pathways which regulate IOP (Schlotzer-Schrehardt et al., 2002). Based on these reports, it was hypothesized that compounds which stimulate both prostanoid FP and EP3 receptors simultaneously can achieve more profound IOP reduction than PGAs alone, and it was demonstrated compounds targeted both FP/EP3 receptor exhibit more potent IOP reduction than latanoprost (Data on file). Among such dual FP and EP3 receptor agonists tested, DE-126 was chosen for its high agonistic activities for both FP and EP3 receptors.

DE-126 is unique with a significantly different agonistic profile compared to selective FP agonists. DE-126 is rapidly hydrolyzed by ocular esterases to the active free acid ONO-AG-367, a highly selective and potent agonist for not only the prostanoid FP receptor, but also the prostanoid EP3 receptor. In efficacy studies with monkeys and dogs, DE-126 showed more potent and longer-lasting reduction of IOP than approved PGAs or the fixed combination of PGA and β-adrenergic blocker. In toxicology studies, DE-126 was well tolerated both systemically and locally in rodent and non-rodent species for up to 13 weeks.

Prior to the licensing agreement with Santen, three clinical studies (ONO-9054IOU001, ONO-9054IOU002, ONO-9054IOU003) were conducted by ONO in the U.S. with DE-126 in healthy adult subjects, or subjects with POAG or OHT to evaluate the safety and efficacy of DE-126. As a result, DE-126 ophthalmic solution in concentrations of up to 0.003% appeared to be tolerated and effective.

After the licensing agreement, a Phase IIb Study 012601IN (Refer to 012601IN CSR), also known as a dose-finding study, was conducted in the US and Japan to assess the safety and efficacy of four concentrations of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002%, and 0.003%) when compared to placebo and latanoprost 0.005% in subjects with POAG or OHT.

Based on the primary and other efficacy endpoints at Month 3, DE-126 0.002% was the optimal dose from among the four concentrations assessed with respect to IOP lowering, and the magnitude of the effect for this concentration was similar to that observed for latanoprost 0.005%. All four DE-126 concentrations were well-tolerated. Most AEs were mild in severity. The most frequently observed AE was conjunctival hyperemia. No DE-126 dose-related trend was observed with related to conjunctival hyperemia incidence. AE incidence was lower with DE-126 concentration 0.0005%, 0.001% and 0.002% compared with latanoprost 0.005% and DE-126 0.003%. No safety issues were identified by ocular safety assessments. One serious AE (SAE) was reported (left hand weakness) while the patient was receiving placebo. Three patients experienced AEs that led to discontinuation. For further information, refer to the current investigator's brochure for DE-126.

DE-126 with a novel mechanism of action could be a new hypotensive agent for patients with OHT or OAG.

2.3. Benefit/Risk Assessment

Topical PGAs, such as latanoprost, are increasingly chosen over topical beta blockers and other medications as first-line therapy for patients with POAG or OHT (AAO-PPP et al., 2015). While PGAs typically reduce IOP via the FP receptor, DE-126 (Sepetaprost), a novel prodrug that is rapidly hydrolyzed by esterases to its active metabolite, targets both the FP and EP3 receptors simultaneously; preliminary data suggest that this mechanism can enhance IOP reduction. In Phase I and II studies, DE-126 demonstrated good tolerability and was efficacious in patients with POAG and OHT (Berlin et al., 2015; Miller Ellis et al., 2017; Suto et al., 2015). The effects of DE-126 in IOP lowering appear to persist longer than those of latanoprost (Miller Ellis et al., 2017).

In 012601IN study, in both Japan- and US-based patients, DE-126 0.002% was identified as the optimal dose among the four concentrations assessed with respect to IOP lowering and safety profile. The magnitude of IOP reduction was similar to that observed for latanoprost 0.005% at Month 3 and significantly greater than that of placebo at Week 6. Most AEs were mild in severity; AE incidence was lower with DE-126 concentrations 0.0005%, 0.001%, and 0.002% compared with latanoprost 0.005% or DE-126 0.003%.

The most common adverse reaction from the previous Phase IIb 012601IN study was conjunctival hyperemia. Since DE-126 is a potent dual agonist for both Prostaglandin F2α receptor and EP3 receptor, we have observed some similar side effects of Prostaglandin F2α analog (i.e., latanoprost). It has been reported that latanoprost cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, and growth of eyelashes.

DE-126 should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. DE-126 should be used with caution in patients who do not have an intact posterior capsule or who have known risk factors for macular edema.

In summary, DE-126 is anticipated to provide clinically meaningful decrease in IOP in patients with open angle glaucoma or ocular hypertension. The adverse reactions observed in patients receiving DE-126 were generally well-tolerated. No serious suspected adverse reaction has been reported. The severity and the frequency of the reported ocular AEs were not unexpected for a topical ophthalmic medication. Consequently, benefit-risk balance continued to be favorable after taking into consideration the safety data from nonclinical assessment and clinical trials. Santen will continue to actively characterize the benefit: risk profile of DE-126.

More detailed information about the known and expected benefits and risks and reasonably expected AE of DE-126 may be found in the Investigator's Brochure.

3. STUDY OBJECTIVES AND PURPOSE

3.1. Primary Objective

To investigate whether the IOP lowering efficacy of DE-126 ophthalmic solution 0.002% dosed once daily (QD, in the evening at 20:00) is non-inferior to that of Timolol maleate ophthalmic solution 0.5% dosed twice daily (08:00 and 20:00) in subjects with POAG or OHT after treatment for 3 months. If non-inferiority is met, superiority will be tested.

3.2. Secondary Objectives

To compare the mean diurnal IOP between DE-126 ophthalmic solution 0.002% and Timolol maleate ophthalmic solution 0.5% after 3 months of treatment. If non- inferiority is met, superiority will be tested.

To evaluate the changes and percent changes in IOP from baseline at all post-baseline visits.

To evaluate proportions of subjects achieving target pressure reductions expressed as either in percent reductions of ≥ 20%, ≥ 25%, or ≥ 30% or in achieving a target IOP value of IOP ≤ 18 mmHg.

3.3. Safety Objective

To evaluate the safety of DE-126 ophthalmic solution 0.002% as compared to Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.

3.4. Exploratory Objective

To explore Quality of Life in subjects with POAG or OHT (using the Glaucoma Quality of Life (GQL)–15 Questionnaire) when given DE-126 or Timolol for 3 months.

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase IIb, randomized, double-masked, active-controlled, parallel-group, and multicenter study assessing the efficacy and safety of DE-126 ophthalmic solution 0.002% compared with Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.

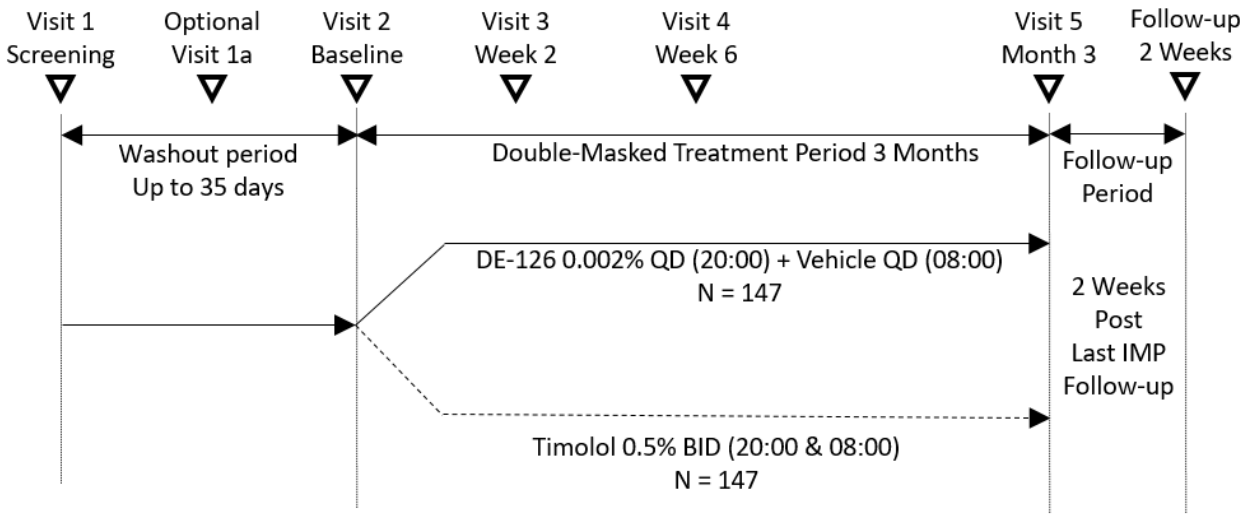
Subjects diagnosed with POAG or OHT who meet eligibility criteria at Visit 1 (Screening) will washout of their current topical IOP-lowering medication(s) if any. After completing the required washout period, subjects will return for Visit 2 (Baseline, Day 1). Subjects who meet all eligibility criteria at baseline will be randomized to receive treatment for 3 months.

Approximately 294 adult subjects with POAG or OHT who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either:

- DE-126 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- Timolol Maleate Ophthalmic Solution 0.5% BID (20:00 and 08:00)

In the Double-Masked Treatment Period, Timolol maleate ophthalmic solution 0.5% will be used as active control.

Figure 1: Study Design



See the study design diagram in Figure 1. This study will consist of a Screening Period of up to 35 days including a washout period of up to 28 days (+ 7 days window) and a 3-month Double-Masked Treatment Period.

At the Screening visit (Visit 1), subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications, if any, during a washout period as follows (up to +7 days as a window is allowed):

- Miotics: 7 days
- CAIs: 7 days
- Alpha agonists: 14 days
- Alpha/beta agonists: 14 days
- Alpha antagonists (α1 blocker): 28 days
- Beta antagonists (β blocker, including αβ blockers): 28 days
- PGA: 28 days
- Rho kinase inhibitor: 28 days
- Combination drugs: The longest washout period of the individual component will be used.

Please note: Subjects are only allowed to be treated with a maximum of two active ingredients for IOP reduction prior to screening.

During the required washout period, subjects who discontinue their current treatment may, if the Investigator deems it necessary, be treated with a short-acting IOP lowering agent, topical CAI, e.g., brinzolamide or dorzolamide eye drops, one drop twice daily. Topical CAI treatment must be stopped 1 week before the randomization at Visit 2 (Baseline, Day 1). An interim safety visit during the washout period (mid-washout visit; Optional Visit 1a) may be performed during the washout period if, in the Investigator's opinion, a subject's IOP may be of concern during the washout period. If subjects are treated with a topical CAI during the washout period, mid-washout visit (Optional Visit 1a) is recommended to be performed.

Final eligibility for randomization will be determined at Visit 2 (Baseline, Day 1) after all necessary washout from prior IOP-lowering medications have been completed.

At Visit 2 (Baseline, Day 1), baseline IOP will be measured for both eyes at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 (Baseline, Day 1) will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study, even if only one eye is eligible per IOP inclusion criteria.

Please note: Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) may be combined into one visit for treatment-naïve subjects as long as the additional requirements of Visit 2 (Eligibility/Baseline, Day 1) are fulfilled on the day of this combined visit; in particular, full diurnal IOP measurements (at 08:00, 10:00, 16:00) must be taken.

Double-Masked Treatment Period (3 months):

Approximately 294 eligible adult subjects will be randomized to receive either DE-126 ophthalmic solution 0.002% QD in the evening and vehicle QD in the morning or Timolol maleate ophthalmic solution 0.5% BID in a 1:1 ratio. Subjects will be treated for 3 months with scheduled visits at Visit 2 (Baseline, Day 1), 3 (Week 2), 4 (Week 6), and 5 (Month 3). Subjects

will be contacted approximately 2 weeks post last study drug administration by a phone call to confirm AE.

In the evening of Visit 2 (Baseline, Day 1), subjects will receive their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (±60 min). The next day, subjects will subsequently dose with their assigned study medication at 08:00 (±60 min), and 20:00 (±60 min). For the DE-126/Vehicle arm, the 08:00 (±60 min) instillation will be DE-126 vehicle and the 20:00 (±60 min) instillation will be DE-126 ophthalmic solution 0.002%. At each scheduled follow-up visit, subjects will receive their morning dose of study medication/eye drops following the 08:00 (±60 min) IOP measurement at the investigative site (the doctor's office).

IOP will be measured at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min) at Visit 3 (Week 2), Visit 4 (Week 6), and Visit 5 (Month 3). At these scheduled visits, BCVA and slit-lamp biomicroscopy will be performed just prior to the 08:00 (±60 min) IOP measurement. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and 5 (Month 3). After the 16:00 (±60 min) IOP measurement at Visit 5 (Month 3), ophthalmoscopy with the pupil dilated will be performed. Subjects will be contacted approximately 2 weeks post last study drug administration by a phone call to confirm AE.

Pharmacogenomics/genomics:

Subjects who consent to the optional PGx laboratory study will provide a blood sample for future testing. The earliest this sample is to be collected at Visit 3 (Week 2) but it may also be collected at any later time during the study after Visit 2 (Eligibility/Baseline) or at a separate post-study visit, if necessary. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

4.2. Number of Subjects

Approximately 294 subjects from approximately 45 sites in the U.S. are planned to be enrolled in this study.

4.3. Treatment Assignment

Subjects are randomized to one of two following treatment arms in a 1:1 ratio during the Double-Masked Treatment Period:

- DE-126 ophthalmic solution 0.002% QD (20:00) and Vehicle QD (08:00)
- Timolol maleate ophthalmic solution 0.5% BID (20:00 and 08:00)

4.4. Schedule of Events and Procedures

The schedule of events and procedures is provided in Table 3.

Table 3: Schedule of Events and Procedures

	Washout Period		Double-Masked Treatment Period				Follow-up Period
	Visit 1 Screening *	**Optional Visit 1a**	**Visit 2 Eligibility/Baseline ***	**Visit 3 Week 2**	**Visit 4 Week 6**	**Visit 5 Month 3 Exit or Early Termination [a]**	**2 weeks of post-Last Study Drug Administration**
Study day	**D-28**		**D1**	**D14**	**D42**	**D90**	**Study Exit + D14**
Visit window in days	**+7**		**NA**	**±3**	**±3**	**±7**	**+7**
Signed and dated informed consent [b]	X						
Inclusion/Exclusion Criteria [b]	X		X				
Demographics and Medical History, including prior PGA [c]	X						
Other prior or Concomitant Medications/ and Therapies/Procedures	X	X	X	X	X	X	
Dosing Compliance Check				X	X	X	
AEs [d]	X	X	X	X	X	X	X
Pregnancy Test [e]	X		X		X	X	
Vital Signs (blood pressure/pulse rate) [f]	X		X (08:00)			X (08:00)	
Refraction [g]	X						
BCVA [g]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	
Slit-lamp Biomicroscopy [h]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	
IOP [i]	X	X	08:00	08:00	08:00	08:00	
			10:00	10:00	10:00	10:00	
			16:00	16:00	16:00	16:00	
Pachymetry [j]	X						
Instill study medication after IOP measurement at site by unmasked site staff and record dosing				X (08:00)	X (08:00)	X (08:00)	
Gonioscopy [k]	X						
Visual Field [l]	X						

Table 3: Schedule of Events and Procedures (Continued)

	Washout Period		Double-Masked Treatment Period				Follow-up Period
	Visit 1 Screening	Optional Visit 1a	Visit 2 Eligibility/Baseline	Visit 3 Week 2	Visit 4 Week 6	Visit 5 Month 3 Exit or Early Termination [a]	2 weeks of post-Last Study Drug Administration
Study day	**D-28**		**D1**	**D14**	**D42**	**D90**	**Study Exit + D14**
Visit window in days	**+7**		**NA**	**±3**	**±3**	**±7**	**+7**
Ophthalmoscopy [m]	X		X (16:00)			X (16:00)	
Blood Sampling for PGx [n]				X			
Dispense Study Medication & Diary			X		X		
Collect Study Medication & Diary					X	X	
Phone call [o]				X	X	X	X
GQL-15 questionnaire [p]			X			X	

** Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) may be combined into one visit for treatment-naïve subjects as long as the additional requirements of Visit 2 (Eligibility/Baseline, Day 1) are fulfilled on the day of this combined visit; in particular, full diurnal IOP measurements (at 08:00, 10:00, 16:00) must be taken.*

[a] Optional at unscheduled visit, required for early terminated subjects.
[b] Informed Consent Form must be signed and dated before study procedures are performed. Informed consent for the optional PGx laboratory research study may be obtained at any visit prior to the study exit.
[c] Prostaglandin naive subjects are defined as subjects who are not known to have used prostaglandin as their glaucoma treatment. The previous use of prostaglandin should be confirmed by either subject's medical records or subject history.
[d] AE will be recorded starting after the signing of the informed consent form until 2 weeks post Last Study Drug Administration. Regardless of the source of the reported occurrence of an AE in a subject, the masked investigator will assess the causality of the AE.
[e] A urine pregnancy test will be conducted for all female subjects of childbearing potential.
[f] Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately at 08:00 for Visit 2 (Baseline, Day 1), and Visit 5 (Month 3)/exit or early termination before the morning dose.
[g] Refraction will be performed at the screening visit anytime. If more than 10 letters in BCVA are lost compared to the screening visit, then refraction should be performed again. BCVA examination will be completed before IOP measurement at 08:00.
[h] Slit-lamp Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before fluorescein instillation.
[i] IOP measurements using Goldmann applanation tonometer will be performed at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min) at all visits except for Visit 1 (Screening), and Optional Visit 1a (mid-washout).
[j] Pachymetry will be performed after IOP measurement at Visit 1 (Screening).
[k] If gonioscopy was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary. If needed, Gonioscopy will be performed after IOP measurement at Visit 1 (Screening).
[l] If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.

[m] Ophthalmoscopy with pupil dilated will be performed at Visit 1 (Screening) anytime, Visit 2 (Baseline), and Visit 5 (Month 3)/exit or early termination at the 16:00 (±60 min) after IOP measurements.
[n] Blood sampling for the PGx laboratory research study may be performed at any visit after PGx informed consent obtained, subject randomized, and study drug dosing has begun. The earliest this sample is to be collected at Visit 3 (Week 2) but it may also be collected at any later time during the study after Visit 2 (Eligibility/Baseline) or at a separate post-study visit, if necessary.
[o] At Visit 3, 4, and 5, subject will be reminded to take evening dose on the day before each visit. At Follow-up Period, subject will be contacted by a phone call to confirm AE after 2 weeks post last study drug administration.
[p] GQL-15 questionnaire will be administered by subject.

5. STUDY POPULATION

Subjects must meet all eligibility (inclusion and exclusion) criteria.

5.1. Subject Inclusion Criteria

At Visit 1 (Screening), the subjects must meet all of the following inclusion criteria:

1. Provide signed written informed consent on the IRB/EC approved ICF.
2. Be 18 years of age or older on the date of signing the ICF and be able and willing to comply with all treatment and follow-up study procedures.
3. If a subject is a female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of surgery]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
    - Abstinence
    - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
    - Placement of a copper-containing IUD
    - Condom with spermicidal foam/gel/film/cream/suppository
4. The male partner of the female subject of childbearing potential should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study ICF and beginning screening), or other contraception deemed adequate by the investigator during the study.
5. Male subjects, with a female partner of childbearing potential, should use or practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior to signing the study ICF), or other contraception deemed adequate by the investigator during the study.
6. Must have a diagnosis of POAG or OHT in both eyes, or one eye with OAG and the other with OHT.
7. BCVA of +0.60 logMAR (Snellen equivalent 20/80) or better in each eye.
8. Central corneal thickness ≥ 480 µm and ≤ 600 µm in each eye.
9. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition to continuing to meet inclusion criterion 7 (BCVA), the subject must meet the following criteria at Visit 2 (Baseline, Day 1):

10. Completed the required wait/washout period (if required per protocol).

11. At all-time points of IOP measurements (08:00, 10:00, and 16:00) at Visit 2 (Baseline, Day 1), have IOP of ≥ 22 mmHg in at least one eye (the same eye), and ≤ 34 mmHg in both eyes.

5.2. Subject Exclusion Criteria

At Visit 1 (Screening) and Visit 2 (Baseline, Day 1), subjects with any of the following ocular conditions in either eye or with any of the following non-ocular conditions or characteristics are not eligible to participate in the study:

General

1. Females who are pregnant, nursing, or planning a pregnancy.
2. Subjects with known or suspected drug or alcohol abuse.
3. Participation in other investigational drugs (oral or topical therapy) or device clinical trials within 28 days prior to Visit 2 (Baseline, Day 1) and/or participation in other investigational drugs (intravitreal injection therapy) within 3 months or 5 half-lives (whichever is longer) prior to Day 1 or planning to participate in other investigational drug or device clinical trials during a time which would overlap with the duration of the study. This includes both ocular and no-ocular clinical trials. Exposure to investigational biologics should be discussed with the medical monitor.

Medications / Therapies

4. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
5. Subjects who will be required to initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARBs]). Subjects using the above medications must be on a stable dose use for at least 28 days prior to Visit 2 (Baseline, Day 1) and the duration of the study.
6. Intended or current use of the following prohibited medications/therapies during the study duration:
    - All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications.
    - All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
    - Any ocular, periocular, inhaled, nasal, or systemic corticosteroids (excluding joint injections).
    - Lacrimal/punctual occlusion via plug (s) or cautery.
7. History of ocular surgery specifically intended to lower IOP (e.g., laser trabeculoplasty, filtering surgery, tube shunt, MIGS, or trabeculotomy) in either eye. Please note that laser iridotomy in history is allowed.

8. History of keratorefractive surgery (e.g., radial keratotomy [RK], photorefractive keratectomy [PRK], laser-assisted-in-situ keratomileusis [LASIK]) in either eye.
9. Use of contact lenses within 1-2 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye (1 week for soft contact lens wearers, and/or 2 weeks for rigid contact lens wearers).
10. Any ocular surgery within 180 days prior to Visit 2 (Baseline, Day 1) and throughout the study in either eye.

Diseases

11. Presence of advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
12. Presence of any corneal abnormality or other conditions interfering with or preventing reliable Goldmann applanation tonometry (e.g., Fuch's dystrophy or significant corneal surface abnormality) in either eye.
13. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
14. Presence of any lid structural abnormalities such as Ectropion or entropion at Visit 1 (Screening).
15. History of iritis and/or uveitis, corneal inflammatory conditions, and/or viral infection, such as herpes simplex virus (HSV), in either eye; history of adenovirus infection is not an exclusion criterion if no associated inflammation has been observed within 6 months prior to Visit 1 (Screening).
16. Aphakia, pseudophakia with a torn posterior lens capsule, history or presence of macular edema or known risk factors (e.g., retinal vein occlusion, diabetic retinopathy, uveitis, age-related macular degeneration) for macular edema in either eye.
17. History of severe ocular trauma in either eye.
18. Any condition that prevents clear visualization of the fundus in either eye.
19. History of retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may be progressive during the time course of the study in either eye.
20. Presence or history of any disease or condition that in the opinion of the study investigator may put the subject at significant risk may confound study results or may interfere significantly with the subject's participation in the study (e.g., recurrent corneal erosion syndrome, uncontrolled cardiovascular disease, etc.).
21. Subjects with a history or presence of contraindications to prostaglandins, beta-blockers, or any other components (e.g., Benzalkonium Chloride [BAK]) of the study medication or other study-related procedures /medication. Specifically, contraindications to beta-blockers include e.g.
    - chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema)
    - bronchial asthma

- second or third degree atrioventricular block
- uncontrolled congestive heart failure

22. Any decision by the Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.
23. Use of marijuana and/or marijuana derivatives within 28 days prior to Visit 2 (Baseline, Day 1); including, but not limited to, cannabidiol topical eye drops.

6. STUDY INTERVENTION

6.1. Study Medication

6.1.1. Investigational Product

DE-126 Ophthalmic Solution contains 0.002% DE-126. Each 5 mL bottle of DE-126 Ophthalmic Solution 0.002% contains 50 µg of DE-126. [redacted]

6.1.2. Vehicle

The vehicle is identical to the investigational product but does not contain the active ingredient in DE-126.

6.1.3. Active Control

The active control used in this clinical study, Timolol Maleate Ophthalmic Solution 0.5%, is supplied as a sterile, isotonic, buffered aqueous solution.

Timolol Maleate Ophthalmic Solution 0.5% contains the active ingredient, Timolol 5 mg/ml, and the preservative BAK 0.01%. Other ingredients include monobasic and dibasic sodium phosphate and purified water. The pH is adjusted to 6.5 to 7.5 with sodium hydroxide.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Study Medication Packaging and Labeling

DE-126 ophthalmic solution, 0.002%, and DE-126 vehicle ophthalmic solution will be supplied as [redacted]

Timolol Maleate Ophthalmic Solution 0.5% will be supplied as a 5 mL solution in a 5 mL white low density polyethylene bottle.

Each eye drop bottle will be placed in a unit carton. Four DE-126 eye drop bottles/unit cartons of study medication will be placed in one DE-126 kit. Two Timolol eye drop bottles/unit cartons of study medication will be placed in one Timolol kit. The eye drop bottles, unit cartons, and the kit will be labeled with the protocol number, kit number, storage conditions, and dosing instructions.

Kits dispensed at Visit 2 (Baseline, Day 1) and Visit 4 (Week 6) will contain “morning” eye drop bottles and “evening” eye drop bottles of DE-126 study medication, or “morning/evening” Timolol maleate eye drop bottles of Timolol maleate study medication.

An authorized unmasked study staff member, other than the Investigator or Examiner, will dispense and collect study medications. When collecting the study medications, the kit containing all the used and unused eye drop bottles will be sealed.

6.2.2. Study Medication Storage

All study medication will be provided by Santen and will be stored in an appropriate secure area at the investigational site.

Study medications should be stored under refrigeration at 2° to 8°C (36° to 46°F), protected from light, and stored upright. During the refrigeration storage, the Investigator (or his/her designee) will verify and record that the temperature was maintained at 2° to 8°C (36° to 46°F) using temperature recorder. In the event of a temperature excursion or any study medications damaged during storage, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee).

Subjects will be reminded to store all dispensed eye drop bottles under refrigeration, protected from light, and kept in unit cartons in an upright position. Study medications should not be frozen.

6.2.3. Study Medication Preparation

The study medications will arrive at the site prepared for instillation.

6.2.4. Study Medication Administration

During the Double-Masked Treatment Period, subjects will instill one drop of study medication in each eye at approximately 20:00 (±60min) and 08:00 (±60min) daily for 3 months.

6.2.5. Study Medication Accountability

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The temperature chart recorder from the shipment will be deactivated, and the Investigator (or his/her designee) will verify that the temperature was maintained at 2° to 8°C (36° to 46°F) during transit. In the event of a temperature excursion or any study medications damaged during transit, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee). The receipt of clinical supplies form should be completed, signed, dated, and returned as directed. A copy must be maintained at the site for the Investigator's records.

The Investigator (or his/her designee) will keep a current record of the inventory, storage conditions and dispensing of all study medications. This record will be made available to Santen (or designee) for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigational site must be accounted for and in no case will study medications be used in any unauthorized situation. It is the responsibility of the Investigator to ensure that any used and unused supplies are available to Santen (or designee) for accountability purposes throughout the study.

6.2.6. Study Medication Handling and Disposal

The used study medication kits will be stored at room temperature and the unused study medication kits will be refrigerated until final study medication accountability has been completed by Santen (or designee). Following final study medication accountability and

reconciliation by Santen (or designee), all used and unused study medication will be returned to the assigned central drug depot, or destroyed at the site at the direction of Santen.

6.2.7. Study Supplies

Customized blood sample collection kits for the PGx and urine pregnancy kit will be provided by Santen (or designee).

6.3. Concomitant Medications or Therapies

Medication or therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator. Subjects may continue participation in the study if the instituted medication or therapy will not interfere with the evaluation of the study medication. Whenever possible, medications should be administered in dosages that remain constant throughout the study. Any treatment other than the study medication during the study duration will be considered as a concomitant treatment. The information of concomitant treatment must be recorded in the subject's source documents and on the eCRF.

- Concomitant medication: name of medication, route of administration, treated eye(s) (if applicable), dose, frequency, indication, start date, and stop date.
- Concomitant therapy: name of therapy, treated eye(s) (if applicable), indication, start date, and stop date.

6.3.1. Prohibited Medications or Therapies

- All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications during the study duration.
  - If artificial sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents, Vitamin B_{12} formulation, over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of **at least 10 minutes** between use of the study medication and these ocular medications (the study medication to be given first).
- All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol) during the study duration.
- Any ocular, periocular, inhaled, nasal, or systemic corticosteroids (excluding joint injection), etc. during the study duration.
- Lacrimal/punctual occlusion via plug (s) or cautery during the study duration.
- Initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, ACE inhibitors, and ARB) within the first 28 days prior to Visit 2 (Baseline, Day 1) and during the study duration.

- Contact lenses within 1-2 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye (1 week for soft contact lens wearers, and/or 2 weeks for rigid contact lens wearers).
- Any ocular surgery or ocular laser treatment within 180 days prior to Visit 2 (Baseline, Day 1) and throughout the study in either eye.
- Participation in other investigational drugs (oral or topical therapy) or device clinical trials within 28 days prior to Visit 2 (Baseline, Day 1) and/or participation in other investigational drugs (intravitreal injection therapy) within 3 months or 5 half-lives (whichever is longer) prior to Day 1 or planning to participate in other investigational drug or device clinical trials during a time which would overlap with the duration of the study. This includes both ocular and no-ocular clinical trials. Exposure to investigational biologics should be discussed with the medical monitor.

The decision to administer a prohibited medication or therapy should be made with the safety of the subject as the primary consideration. Whenever possible, Medical Monitor or designee should be notified before any prohibited medication or therapy is administered. There may be additional prohibited therapies not mentioned above. Medical Monitor or designee should be contacted if the permissibility of a specific medication or therapy is in question.

6.4. Treatment Compliance

To obtain reliable efficacy and safety data, the following precautions will be taken to ensure compliance with the treatment regimen during the study:

- Subjects will receive verbal and written instructions for proper instillation of the study medication, the dosing regimen, and the conditions of the study medication storage.
- Subject will record daily medication instillation into paper subject diary.
- Subjects will be reminded at study visits to consistently dose at the same time of the day
  - Twice daily at 08:00 and 20:00 [±60min] through Visit 2 (Baseline, Day 1) to Visit 5 (Month 3).
- Subjects will be reminded of the evening instillation of the study drug on the day before Visit 3 (Week 2) through Visit 5 (Month 3)/Early Termination respectively.
- Subjects will be reminded that the morning instillation of the study drug at each visit through Visit 3 (Week 2) to 5 (Month 3) will be done at the site.
- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 (Week 2) through Visit 5 (Month 3)/Early Termination.
- Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%.
- A subject's dosing compliance for a specific period is determined by the total number of days that subject followed the proper dosing procedures and dosing schedule. Stoppage of study medication use, overdosing of study medication, incorrect time of

study medication administration, will be noted as non-compliance. The subject's dosing compliance will be recorded in the subject's source documents at Visit 3 (Week 2) through Visit 5 (Month 3)/Early Termination.

- Subjects may be discontinued from the study at the discretion of the Investigator if the subject cannot be brought into compliance.

6.5. Randomization and Masking

A stratified permuted-block randomization will be employed to randomize eligible subjects in a 1:1 ratio to either DE-126/Vehicle arm or Timolol Maleate arm. The randomization will be stratified by mean diurnal IOP in the study eye at baseline visit (Visit 2): <25 mmHg vs. ≥25 mmHg.

The randomization schedule will be generated and implemented using central randomization via Interactive Response Technology (Medidata Rave RTSM). Each randomized subject will receive numbered study medication kits as assigned by Medidata Rave RTSM.

This is a double-masked study. The subjects, Investigators, Examiners, and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member at the investigative site who is not the Investigator or Examiner will dispense and collect study medication(s) and will query about dosing compliance.

Subjects will be instructed not to show the eye drop bottles or discuss the eye drop to either the Investigator or the Examiner or other study subjects. The active control treatment (Timolol Maleate) containers will be over-labeled and packaged in the same secondary package (e.g., cardboard kit carton) as the investigational treatment (DE-126). Subjects on DE-126/Vehicle arm will receive a kit containing 2 bottles labeled "morning" for the morning dose and 2 bottles labeled "evening" for the evening dose. Subjects on Timolol arm will receive a kit containing 2 bottles labeled morning/evening for the BID dosing.

Each eligible subject will receive a numbered study medication kit assigned by Central randomization via Interactive Response Technology (Medidata Rave RTSM) at Visit 2 (Baseline, Day 1) and at Visit 4 (Week 6).

In case of a medical emergency, the Principal Investigator may reveal the treatment information by unmasking through Medidata Rave RTSM to know which treatment the subject has received. The Principal Investigator (or his/her designee) should contact Santen, or Santen's designee, before taking this measure, if there is sufficient time. Santen, or Santen's designee, must be informed of all instances where the code is broken and of the reasons for such instances.

Additionally, the AE or SAE for which study treatment was unmasked should be reported to Santen Pharmacovigilance.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Subject Early Discontinuation/Withdrawal from the Study

An early termination occurs when a subject who provides written informed consent ceases participation in the study, regardless of circumstances, before the completion of the study. Subjects may be voluntarily discontinued from study medication or withdrawn from the study at any time for any reason. In addition, the Principal Investigator or Medical Monitor or designee may discontinue the study drug administration or terminate a subject's study participation due to any of the following reasons:

- AE (e.g., not compatible with study continuation)
- Non-compliance with study drug
- Lack of efficacy (e.g., IOP exceeds 34 mmHg in either eye after randomization)
- Progressive disease
- Protocol deviation (e.g., not fulfilling eligibility criteria)
- Pregnancy
- Voluntary withdrawal by subject at any time for any reason
- Lost to follow-up (e.g., no contact is possible)
- Death
- Other

If the study drug administration is discontinued prior to Visit 5, they should be encouraged to still participate in all follow-up study visits until Visit 5 on an observational basis.

If the study drug administration is discontinued prior to Visit 5, then to the extent possible, all procedures for Early Termination will be performed on the day of early drug discontinuation as per Table 3. Subjects who are discontinued from the study early will not be replaced.

7.2. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local

equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or discontinuation of the study is handled as indicated in Section 10.8.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Visit Details

The Schedule of Events and Procedures Table 3 provides a high-level overview of the visits. The sections below provide visit guidance/details by visit.

8.1.1. Visit 1 (Screening)

- Explain the purpose and conduct of the study to the subject and obtain written individual informed consent. Informed consent for the optional PGx consent may sign at screening yet laboratory research study must be obtained after subject Visit 2 (Baseline, Day 1) at any visit. Ensure the subject understands that if he/she does not wish to provide a blood sample for the PGx laboratory research study that their decision will have no influence on their participation in the main study.
- Prepare the list of screening/registration of subjects.
- Obtain demographics.
- Obtain medications, procedures/therapies, and medical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 5 years, diagnosis, ocular surgical history, current ocular, and systemic conditions.
- Obtain urine and perform a urine pregnancy test, if the subject is a female of child-bearing potential.
- Query the subject regarding AEs
- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - Vital signs (blood pressure/pulse rate)
  - Refraction
  - BCVA (before IOP measurement)
  - Slit-lamp biomicroscopy (before IOP measurement)
  - IOP
  - Pachymetry (after IOP measurement)
  - Gonioscopy (only if no gonioscopy was performed within 3 months [90 days] prior to screening and documented in the subject's records). If needed, gonioscopy will be performed after IOP measurement.
  -
  - Visual field (only if no visual field test was performed within 3 months [90 days] prior to screening and documented in the subject's records). If needed, visual field test will be performed before IOP, pachymetry, and gonioscopy (if applicable).
  - Ophthalmoscopy with pupil dilation (after IOP measurement)

- Determine if the subject meets eligibility criteria.
- If the subject meets eligibility criteria and is still willing to continue the study, discontinue current IOP-lowering medications, if any, according to the following schedule (up to +7 days as a window is allowed):
  - Miotics: 7 days
  - Oral/topical CAIs: 7 days
  - Alpha agonists: 14 days
  - Alpha/beta agonists: 14 days
  - Alpha antagonists (α1 blocker): 28 days
  - Beta antagonists (β blocker, including αβ blockers): 28 days
  - Prostaglandin Analogs: 28 days
  - Rho kinase inhibitor: 28 days
  - Combination drugs: The longest washout period of the individual component will be used. Please note: Subjects are only allowed to be treated with a maximum of two active ingredients for IOP reduction prior to screening.
- During the required washout period, subjects who discontinue their current treatment may, if the Investigator deems it necessary for safety, be treated with a topical CAI, e.g., brinzolamide or dorzolamide eye drops, one drop twice daily. Topical CAI treatment must stop 7 days before the randomization at Visit 2 (Baseline, Day 1).
- An interim safety visit, mid-washout visit (Optional Visit 1a), may be performed during the washout period if, in the Investigator's opinion, a subject's IOP causes any safety concerns during the washout period. If subjects are to be treated with topical CAI in the week before Visit 2 (Baseline, Day 1), mid washout visit (Optional Visit 1a) is recommended to be performed.
- The eligibility visit (Visit 2 (Baseline, Day 1)) will be scheduled at the end of the washout period for those subjects on prior IOP-lowering medications.
- Subjects who have not used an IOP-lowering medication for the last 28 days, including treatment-naïve subjects, may be combined Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) into one visit. Subjects must fulfill on the day of this combined visit; in particular, full diurnal IOP measurements (at 08:00, 10:00, 16:00) must be taken.
  - If a subject does not require washout from an IOP-lowering medication, but they use contact lenses in either eye, they will need a wait period of ≥ 1-2 weeks (1 week for soft contact lens wearers, and 2 weeks for rigid contact lens wearers) with no contact use before their Visit 2 (Baseline, Day 1).
- Schedule the eligible subject to return for Visit 2 (Baseline, Day 1) after the required wait/washout period.

- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.

8.1.2. Optional Visit 1a

- Optional Visit 1a is an interim safety visit (referred to as mid-washout visit) that may be performed during the washout period if, in the Investigator's opinion, a subject's IOP causes any safety concern during washout period.
- Update concomitant medications and procedures/therapies.
- Query the subject regarding AEs.
- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before IOP measurement)
  - Slit-lamp biomicroscopy (before IOP measurement)
  - IOP

8.1.3. Visit 2 (Baseline, Day 1)

- Update concomitant medications and procedures/therapies.
- Confirm the subject has complied with the required wait/washout period for ocular hypotensive medication(s), or contact lenses use, if required.
- Query the subject regarding AEs.
- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 (±60 min) IOP measurement).
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Slit-lamp biomicroscopy (before the 08:00 (±60 min) IOP measurement).
  - Perform vital signs (blood pressure/pulse rate) measurements (before the 08:00 (±60 min) IOP measurement).
  - Obtain urine and perform a urine pregnancy test, if the subject is a female of childbearing potential (before the 08:00 (±60 min) IOP measurement).
- Perform IOP measurement at 08:00 (±60 min).
- If subject meets the 08:00 IOP eligibility requirements, schedule additional IOP measurements at 10:00.
- Perform IOP measurement at 10:00 (±60 min).
- If subject meets the 08:00 and 10:00 IOP eligibility requirements, schedule additional IOP measurements at 16:00.

- Perform GQL-15 questionnaire at any time during this visit prior to 16:00 IOP measurement.
- Perform IOP measurement at 16:00 (±60 min).
- Perform pupil dilation in both eyes after the 16:00 (±60 min) IOP measurement.
- Perform ophthalmoscopy with pupil dilation in both eyes immediately after the 16:00 (±60 min) IOP measurement.
- Perform final review of eligibility criteria after the 16:00 (±60 min) IOP measurement. The subject will then be randomized, via Medidata Rave RTSM.
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- After the subject has been randomized to a treatment arm, and assigned a treatment kit by Medidata Rave RTSM, an authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Dispense the assigned kit to the subject which will contain the following:
    - Two bottles of study drug labeled "morning" and
    - Two bottles of study drug labeled "evening"
      OR
    - Two bottles of study drug labeled morning/evening.
  - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage.
  - Provide paper subject diary to subject and provide instructions to record daily medication instillation.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.
- Instruct the subject to instill the study medicine daily in both eyes, starting from this evening ("evening" dose) (20:00).
- Schedule the subject to return on Visit 3 (Week 2, Day 14 ±3).
- Inform the subjects they will be reminded of the evening instillation of the study medication by a phone call a few days before Visit 3 (Week 2).
- Remind the subjects that the morning dose of Visit 3 (Week 2) will be done at the site.

8.1.4. Visit 3 (Week 2, Day 14 ±3)

- Update concomitant medications and procedures/therapies.
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance, check the subject paper diary

of daily medication recording, and ensure subject has sufficient study medication to complete dosing through Visit 4 (Week 6).

- Query the subject regarding AEs.
- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 (±60 min) IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Slit-lamp biomicroscopy (before the 08:00 (±60 min) IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes. Authorized unmasked study staff should make sure the instillation is performed. Record the morning medication in the subject diary.
- Perform IOP measurement at 10:00 (±60 min), and 16:00 (±60 min).
- If the subject provided written consent to provide a blood sample for a future PGx laboratory research study, collect the sample at this visit or subsequent visit prior to exit from the study.
  - Note: If a blood sample cannot be collected at this visit, it may be collected at any one of the following visits, for example, Visit 4, 5, or unscheduled or early termination visit, provided the subject has written consent prior to collection of the sample.
- Schedule the subject to return on Day 42±3 for Visit 4 (Week 6).
- Remind the subject to continue dosing according to the written instructions.
- Inform the subjects they will be reminded of the evening instillation of the study medication by a phone call a few days before Visit 4 (Week 6).
- Remind the subjects that the morning dose of Visit 4 (Week 6) will be done at the site.
- Remind the subject to bring all used and unused study medication and subject diary at Visit 4 (Week 6).

8.1.5. Visit 4 (Week 6, Day 42 ±3)

- Update concomitant medications and procedures/therapies.
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance and check the subject paper diary of daily medication recording.
- Query the subject regarding AEs.

- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 (±60 min) IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Slit-lamp biomicroscopy (before the 08:00 (±60 min) IOP measurement)
  - Obtain urine and perform a urine pregnancy test if the subject is a female of childbearing potential (before the 08:00 (±60 min) IOP measurement).
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes. Authorized unmasked study staff should make sure the instillation is performed. Record the morning medication in subject diary.
- Perform IOP measurement at 10:00 (±60 min), and 16:00 (±60 min).
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused bottles of study medication.
  - Collect the paper subject diary.
- Dispense the assigned kit (from Medidata Rave RTSM) to the subject which will contain the following:
    - Two bottles of study drug labeled “morning” and
    - Two bottles of study drug labeled “evening”
      OR
    - Two bottles of study drug labeled morning/evening.
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.
  - Provide paper subject diary to subject and provide instructions to record daily medication instillation.
- If the subject provided written consent to provide a blood sample for a future PGx laboratory research study, the sample may be collected at this visit or subsequent visit prior to exit from the study, if not collected at the previous visit.
- Schedule the subject to return on Day 90±7 for Visit 5 (Month 3).
- Remind the subject to continue dosing according to the written instructions.
- Inform the subjects they will be reminded of the evening instillation of the study medication by a phone call a few days before Visit 5 (Month 3).

- Remind the subjects that the morning dose of Visit 5 (Month 3) will be done at the site.
- Remind the subject to bring all used and unused study medication and subject diary at Visit 5 (Month 3).

8.1.6. Visit 5 (Month 3, Day 90 ±7) / Study Exit/ Early Termination

- Update concomitant medications and procedures/therapies.
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance and check the subject paper diary of daily medication recording.
- Query the subject regarding AEs.
- As per Schedule of Events and Procedures (Table 3), perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 (±60 min) IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Slit-lamp biomicroscopy (before the 08:00 (±60 min) IOP measurement)
  - Perform vital signs (blood pressure/pulse rate) measurements (before the 08:00 (±60 min) IOP measurement).
  - Obtain urine and perform a urine pregnancy test, if the subject is a female of childbearing potential (before the 08:00 (±60 min) IOP measurement).
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes. Authorized unmasked study staff should make sure the instillation is performed. Record the morning medication in subject diary.
- Perform IOP measurement at 10:00 (±60 min), and 16:00 (±60 min).
- Perform pupil dilation in both eyes after the 16:00 (±60 min) IOP measurement.
- Perform ophthalmoscopy with pupil dilation in both eyes immediately after the 16:00 IOP measurement.
- Perform GQL-15 questionnaire at any time during this visit.
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused bottles of study medication.
  - Collect the paper subject diary.

- If the subject provided written consent to provide a blood sample for a future PGx laboratory research study, the sample must be collected at this visit, if not collected at the previous visits.
- Exit the subject from the study.
- Inform the subjects they will be contacted to confirm AEs by phone call approximately 2 weeks post last study drug administration.

Note:

- **If the study drug administration is discontinued prior to Visit 5, then to the extent possible, all procedures for Study Exit/Early Termination as per Table 3 will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.**
- **If subject requires an unscheduled visit, procedures and assessments will be performed as needed.**

8.1.7. Follow-up (2 Weeks +7 days Post Last Study Drug Administration)

- After 2 weeks post last study drug administration, a follow-up phone call visit will be conducted.

8.2. Study Termination

Santen may stop this study at any time by appropriate notification.

8.3. Efficacy Parameter

The IOP (mmHg) measured in the study eye (identified by the IOP values at baseline visit) is the efficacy measure for this study. The IOP at each scheduled time point (08:00, 10:00, and 16:00) will be evaluated at each post-baseline visit. Besides observed IOP measurements, change and percent change from baseline in IOP at each scheduled time point as well as the change and percent change from baseline in mean diurnal IOP will also be derived and evaluated.

8.4. Safety Parameters

In addition to observed values, changes from baseline will be evaluated at relevant post baseline visits. For a safety outcome measure, the baseline value will be the last observation of that outcome measure prior to the first dose of study medication.

8.4.1. Ocular Assessments

Ocular assessments include:

- BCVA
- Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitate, lens, anterior synechiae of iris, posterior synechiae of iris, iris color abnormalities, eyelash abnormalities, and eyelid abnormalities

- Ophthalmoscopy variables: glaucomatous optic nerve

8.4.2. Non-ocular Assessments

Non-Ocular assessments include:

- Vital Signs (blood pressure and pulse rate)

8.5. Other Assessments

8.5.1. Demographic and Other Assessments

Subject demographics, medical history, concomitant medications, and exposure to study medication will be summarized.

8.5.2. Pharmacogenomics/Genomics

For future exploratory research, blood sample will be collected from the participants who have consented to participate in the collection.

8.5.3. Glaucoma Quality of Life (GQL-15) Questionnaire

The GQL-15 (Section 12.6, Appendix F) is a 15-item questionnaire assessing the quality of life in glaucoma patients by measuring the severity of visual disability. The GQL-15 will be completed by the subject at Baseline (Visit 2, Day 1) and Month 3 (Visit 5). The GQL-15 questionnaire will be used as an exploratory outcome in this study.

8.6. Assessment of Safety

8.6.1. Adverse Events and Serious Adverse Events

8.6.1.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE does not necessarily have a causal relationship with the study medication. For this study, the investigational products are DE-126, DE-126 vehicle, and Timolol. Regardless of relationship to the study medication, an AE can be a clinically relevant unintended sign (including an abnormal laboratory finding), symptom, or disease.

Any significant change in a subject's condition from the time that written informed consent is obtained, regardless of causality, is to be considered an AE. A clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE.

An elective surgical procedure scheduled or planned prior to study entry that does not require overnight hospitalization is not considered an AE, and the underlying diagnosis for the procedure should be captured in the medical history as a pre-existing condition. The surgical procedure should also include the term "elective" in all reports. An elective or planned hospitalization must be reported as an SAE.

The lack of efficacy of the study medication for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Investigator.

8.6.1.2. Assessment of Adverse Events

Investigators will seek information on AEs at each subject contact. Subjects should be asked using a general, non-direct question if there has been any change in their general health. Direct questioning and examination should then be performed as appropriate.

Severity of the AE should be assessed according to the following criteria:

> **Mild:** No interference with the subject's daily activities; no medical intervention/therapy required.
>
> **Moderate:** Possible interference with the subject's daily activities; no or minimal medical intervention/therapy required.
>
> **Severe:** Considerable interference with the subject's daily activities; medical intervention/therapy required.

Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions and reporting of serious adverse events (SAEs) in Section 12.4, Appendix D.

An Investigator who is medically qualified must make the determination of relationship (related or not related) to the investigational product for each AE or SAE. When determining relationship to study medication, the Investigator will consider any investigational products that a subject could be exposed to in this clinical trial. The Investigator should decide whether there is a reasonable possibility that the study medication caused the event, taking into account the following: a) evidence, b) science-based rationale, c) medical and clinical judgment, d) mechanisms of action, e) biologic plausibility, f) confounding risk factors (i.e., medical history, concomitant medications), g) temporal relationship, h) dechallenge/rechallenge, and i) lack of alternative explanation.

- The event may be recorded as Related to investigational product or
- Reporting the event as Not Related to study medication be considered

8.6.1.3. Reporting Adverse Events

AEs, whether spontaneously reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE eCRF. Each recorded AE will be described by its duration (represented in dates), affected eye(s) (if applicable), maximum severity of the AE, seriousness criteria, suspected relationship to the study medication, actions taken with the study medication, and the study participation, outcome of the AE, and any other attributable causes of the AE.

Regardless of relationship to the clinical study, AEs that occur at any time after the subject has provided written informed consent until subject withdrawal or the scheduled exit visit, must be recorded. To improve the quality and precision of acquired AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms and /or laboratory or test findings (e.g., record congestive heart

failure rather than dyspnea, rales, and cyanosis, and enlarged heart on chest x-ray). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).

- If the diagnosis is not known, then record the leading component sign, symptom, or test finding and describe the other clinically related findings in the narrative description of the case. A suspected diagnosis can be used and described as such (e.g., record suspected or probable myocardial infarction); this has to be updated in the clinical database once the diagnosis is confirmed.

  AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term. If a primary AE is recorded, events occurring secondary to the primary event should be described in the narrative description of the case. For example:

  The subject developed orthostatic hypotension and subsequently fainted and fell to the floor wherein she experienced a head trauma and neck pain.

  The primary AE in this example is orthostatic hypotension. The fall, head trauma, and neck pain should be described in the narrative description of the case.

- For intermittent events (e.g., intermittent headache), the event onset date should be recorded as the date the subject first started to experience the event and resolution date should reflect when the last occurrence resolved or stopped. Separate AEs for each event should not be recorded. For example, if a subject experienced headache on 14SEP2015 lasting for three hours, then subsequently experienced intermittent episodes of headache every day for approximately 3 hours until 21SEP2015, then the AE date of onset is 14SEP2015 and the resolution date is 21SEP2015.
- For intermittent events, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate.
- For intermittent hospitalizations occurring for a primary AE (e.g., in a subject with multiple sclerosis, commonly known for its relapsing and remitting course, in some cases leading to multiple hospital confinements), the subsequent hospitalizations should be described in the narrative description of the case.
- If treatment was initiated, include the treatment and duration of the medication(s) in the eCRF.

8.6.2. Serious Adverse Events

8.6.2.1. Assessment of Serious Adverse Events

An AE is considered serious if it fulfills one or more of the following criteria:

- Death (i.e., the AE caused or led to death).

- It was life threatening (i.e., immediately life-threatening).
- It required or prolonged inpatient hospitalization.
- It resulted in a persistent or significant disability/incapacity (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- It resulted in a congenital anomaly/birth defect in the offspring of a study subject who was exposed to study therapy prior to conception or during pregnancy.
- It is a medically significant event(s), which may include "sight-threatening events" that may not meet any of the above serious criteria but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.
  - Sight threatening event: A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event.

8.6.2.2. Reporting Serious Adverse Events

The SAE eCRF must be completed with as much information as is available within 24 hours of knowledge of the event.

To improve the quality and precision of acquired SAE data, Investigators should observe the following guidelines:

- Death: Death is an outcome of an event. The event that resulted in the death should be recorded and reported as the SAE.
- Hospitalizations for Surgical or Diagnostic Procedures: The illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the case narrative as part of the action taken in response to the illness.

Depending on the nature and seriousness of the AE, Santen may request additional documentation, for example, copies of the ophthalmic and medical records as well as results of laboratory tests. If the subject was hospitalized, a copy of the discharge summary may be requested.

8.6.2.3. Expedited Reporting of Serious Adverse Events

Santen (or designee) will provide the Principal Investigator with a reporting cover letter and a masked expedited safety report for expedited reporting of SAEs to the IRB or IEC. The Principal Investigator is responsible for receiving and reviewing expedited safety reports, submitting expedited safety reports to the IRB or IEC, and maintaining copies of expedited safety reports in the study records.

8.6.3. Events of Special Interest

The following are considered Events of Special Interests (ESIs) and should be reported on the appropriate eCRF with as much information as available within 24 hours of knowledge of the event:

- Pregnancy:
  - There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 4 weeks for female subjects of childbearing potential and 12 weeks for male subjects capable of fathering children after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject will be discontinued from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.
- Medication administration errors
  - Study medication administration errors determined to be **significant** by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: incorrect dose of study medication and administration of study medication from an incorrect kit. An AE does not necessarily need to have occurred to count as a study medication administration error. A medication administration error is an unintended failure in the process of treatment with a medicinal product that leads to, or has the potential to lead to harm of the subject.

8.6.4. Pregnancy Testing, Monitoring, and Reporting

8.6.4.1. Pregnancy Testing

If the subject is a female of childbearing potential, urine samples will be collected for pregnancy tests as specified in Schedule of Events and Procedures (Table 3). Urine samples will be analyzed at the site with results available prior to administration of Study Medication.

8.6.4.2. Pregnancy Monitoring and Reporting Procedures

A urine pregnancy test will be conducted using a commercially available test kit at Visit 1 (Screening), Visit 2 (Baseline, Day 1), Visit 4 (Week 6) and Visit 5 Study Exit/Early Termination for all females of childbearing potential.

Although not considered an AE or SAE, pregnancy is an ESI and requires careful monitoring and follow up. If pregnancy is reported by a study subject (or in the partner of a study subject), the investigator must:

- Inform Santen within 24 hours of learning of the pregnancy.
- If the pregnancy has occurred in a study subject, discontinue further study medication administration and/or withdraw the subject from the study.
- Report pregnancy information on the eCRF following instructions.
- Follow the pregnancy until outcome is known. Santen will request specific follow-up on a case-by-case basis.

Additional details regarding collection, reporting, and follow-up of pregnancy is provided below:

Female subjects who become pregnant: The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Santen within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to Santen. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an ESI. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study medication by the investigator will be reported to Santen. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting. Any female subject who becomes pregnant while participating in the study will discontinue study medicaiton and be withdrawn from the study.

Male subjects with partners who become pregnant: The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Santen within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Santen. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.6.5. Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be monitored for and collected at the time points specified in Schedule of Events and Procedures (Table 3), from the signing of the ICF until the subject withdrawal or the scheduled exit visit. (Note: Although AEs will be monitored for and collected prior to study medication administration, the statistical data analysis will determine and summarize treatment-emergent AEs, i.e., those AEs that began or worsened in severity after the first study medication administration.)

All SAEs will be recorded and reported to Santen or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 12.4, Appendix D. The investigator will submit any updated SAE data to Santen within 24 hours of it being available.

Investigators are not obligated to monitor for new AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study medication or study participation, the investigator must promptly notify Santen.

8.6.6. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 12.4, Appendix D. During the double-masked period, regardless of the source of the reported occurrence of an AE in a subject, the masked investigator will assess the causality of the AE.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.6.7. Follow-up of Adverse Events

All reported AEs (related and unrelated) should be followed until resolution or until the subject's participation in the study ends. Subjects with the following types of events should be followed by the Investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained.

Independent of whether a subject has already had their scheduled study exit visit or not, any ongoing following types of event should be followed by the investigator until the event is determined to be resolved, irreversible, stable, the subject withdraws consent, or no further information is available.

- On-going SAEs
- On-going ESIs, including pregnancy and medication errors resulting in AE's
- Early termination and withdrawal from the study due to study medication related AEs
- The other types of related AEs should be also followed by the same manner as SAEs in principle, and this follow up should be continued, as needed, up until the time database lock. Generally, the status/resolution of the AE should be confirmed via an on-site visit, frequency as per investigator's judgement. However, in cases where the investigator considers an on-site visit is not necessary, such as with an AE based on subjective symptoms, the Investigator may confirm the outcome of the AE by telephone, email, etc.
- The other types of unrelated AE should be followed until resolution or the scheduled exit visit

If the information requested by Santen is not part of the eCRF, or when database lock has already been completed, the site's response to follow-up requests should be emailed, faxed, or reported in writing to Santen Global Pharmacovigilance of Emergency Contact Information.

In addition, on a case by case basis, Santen (or designee) may request follow up beyond the scheduled exit visit.

The follow-up information on an individual SAE or AE (or ESI) will be entered into the eCRF prior to database lock. If the information requested by Santen is not part of the eCRF, or when database lock has already been completed, the site's response to follow-up requests should be emailed to globalPVAmericas@santen.com or reported in writing and fax to +1-415-276-5882 (in the US).

8.6.8. Manual Back-Up Reporting Procedures

This study is utilizing an EDC system for data entry. In the event that the EDC system is unavailable for electronic reporting, the manual back-up reporting procedures below should be followed.

- Complete an AE Form, SAE Form, Pregnancy Form, Medication Error Form, or ESI Form as appropriate.
- Attach a cover sheet with your contact information and address to Santen (or its designee) (Table 1).
- Email (preferred) or Fax the cover sheet and the completed form(s) to Santen (or its designee) (Table 1) at 'globalPVAmericas@santen.com' or fax number +1-415-276-5882 (in the US).

When the EDC system becomes available, the EDC system should be updated with all previously reported information.

8.6.9. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Santen of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

Santen has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Santen will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Santen will prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Santen policy and forward them to investigators as necessary. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Santen will review and then file it along with the Investigational Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9. STATISTICAL CONSIDERATIONS

This section outlines topics related to the statistical methods used in the design and analysis of the study. A more detailed description of all the analyses and methods is provided in the SAP.

9.1. Interim Analysis

There is no planned interim analysis for this study.

9.2. Final Analysis

An unmasked final analysis will be performed after all subjects completed Month 3 or discontinued prematurely. The analysis will evaluate the efficacy and safety of DE-126 Ophthalmic Solution 0.002% once daily compared with Timolol Maleate Ophthalmic Solution 0.5% twice daily.

9.3. General Considerations

Descriptive statistics, unless otherwise noted, will include the number of subjects (N), mean, SD, median, minimum, and maximum for continuous variables and N and percent for categorical variables.

The study eye will be defined as the eye that qualifies per inclusion criteria at Visit 2 (Baseline, Day 1). For example, IOP must be ≥ 22 mmHg at all IOP measurement time-points (08:00, 10:00, and 16:00). See Section 5.1 and Section 5.2 for all inclusion/exclusion criteria. If both eyes qualify, the eye with the higher mean diurnal IOP at Visit 2 (Baseline, Day 1) will be the study eye. If both eyes have the same mean diurnal IOP at baseline, then the right eye will be designated as the study eye.

Additional considerations will be described in SAP which will be finalized prior to unmasking the data.

9.3.1. Sample Size

The sample size calculation was based on a two-sided Type I error rate of 5% and a non-inferiority margin of 1.5 mmHg. Assuming a between-treatment difference of 0 mmHg, SD of 4.0 mmHg and a correlation coefficient of 0.6 among repeated measures, approximately 280 adult subjects in total (140 subjects per treatment arm) will provide 70% power to demonstrate non-inferiority of DE-126 Ophthalmic Solution 0.002% to Timolol maleate ophthalmic solution 0.5%. Assuming a drop-out rate of 5%, the final needed sample size will be 294 in total, i.e. 147 subjects/arm.

9.3.2. Statistical Hypotheses and Level of Significance

The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00, and 16:00 at Week 2, Week 6, and Month 3 visits.

For the primary endpoint, a MMRM will be used to test the following hypotheses:

$$H_0: \mu_T - \mu_C > \Delta \text{ versus } H_A: \mu_T - \mu_C \leq \Delta$$

Where μ_T and μ_C denote the mean values of the primary endpoint in DE-126/Vehicle arm and Timolol Maleate arm, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg.

Treatment difference between the DE-126/Vehicle arm and Timolol Maleate arm at each specified time point of each post-baseline visit up to Month 3 will be reported along with 95% confidence intervals. Non-inferiority is established if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (DE-126/Vehicle - Timolol Maleate) is ≤ 1.5 mmHg at all nine time points and ≤ 1.0 mmHg in majority (5 or more) of the time points. If the upper limit of the 95% confidence interval for the difference is < 0 at all nine time points, superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% will be claimed for the primary endpoint.

If non-inferiority in the primary endpoint is achieved, then the key secondary endpoint will be tested: Mean diurnal IOP in the study eye at Month 3.

The corresponding hypothesis is:

$$H_{0S}: \mu_{Ts} - \mu_{Cs} > \Delta \text{ versus } H_{AS}: \mu_{Ts} - \mu_{Cs} \leq \Delta$$

Where μ_{Ts} and μ_{Cs} denote the mean diurnal IOP at Month 3 in DE-126/Vehicle arm and Timolol Maleate arm, respectively; and Δ denotes the non-inferiority margin of 1.5 mmHg. Non-inferiority is established if the upper limit of the two-sided 95% confidence interval for the difference between DE-126/Vehicle arm and Timolol Maleate arm (DE-126/Vehicle – Timolol Maleate) in the mean diurnal IOP at Month 3 is ≤ 1.5 mmHg. If the upper limit of the 95% confidence interval for the difference is < 0 mmHg, superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the key secondary endpoint will be claimed.

9.3.3. Multiple Comparisons/Multiplicity

Fixed sequence procedure will be applied to control the overall Type I error rate across the four hypotheses in the primary and key secondary endpoints at the 0.05 level. Fixed sequence procedure tests hierarchically ordered hypotheses at level 0.05 until the first non-rejection.

The fixed sequence for the four hypotheses in this study is as follows:

1. Hypothesis of non-inferiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the primary endpoint, IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 2, Week 6, and Month 3.
2. Hypothesis of non-inferiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the key secondary endpoint, mean diurnal IOP at Month 3.
3. Hypothesis of superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the key secondary endpoint, mean diurnal IOP at Month 3.
4. Hypothesis of superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the primary endpoint, IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 2, Week 6, and Month 3.

9.4. Study Populations

9.4.1. Safety Population

The Safety Population will include all randomized subjects who received at least one dose of the study medication. The safety analysis will be performed on the Safety Population by actual treatment received.

9.4.2. Full Analysis Set

The FAS will include all randomized subjects who received at least one dose of study medication and provided at least one post-baseline IOP measurement. The efficacy analysis will be performed on the FAS or a subset of the FAS by planned treatment.

9.4.3. Per-Protocol Set

The PPS is a subset of the FAS, restricted to the subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment. It will be the analysis population for some sensitivity analyses. More details will be provided in SAP.

9.5. Handling of Missing Values

The primary analysis of continuous IOP endpoints will be performed using the MMRM analysis on observed cases. As sensitivity analyses, a PMM approach may be applied to evaluate the impact of missing data on the primary analysis results.

For medical events including AEs and medical history, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. Similar rules will be followed to impute the completely or partially missing start and end dates of non-study medications.

Unless specified otherwise, descriptive summaries will be based on observed cases.

More details on handling of missing data will be provided in the SAP.

9.6. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized with descriptive statistics by treatment.

Concurrent diseases will be coded using the latest version of MedDRA. Subjects with any concurrent diseases will be tabulated by primary SOC and PT specified in the MedDRA.

Subjects using any prior medications that has been used for glaucoma or OHT within 28 days before Screening (Visit 1) will be tabulated by Anatomical Therapeutic Chemical (ATC) levels and PT specified in the latest version of World Health Organization Drug Dictionary Enhanced (World Health Organization Drug Dictionary, 2011).

9.7. Efficacy Analyses

Unless specified otherwise, for subjects who discontinue from the study medication per protocol before the Study Exit, the IOP data collected after the study medication discontinuation with any use of non-study IOP lowering medication or surgery will be censored from all efficacy analyses.

9.7.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00, and 16:00 at Week 2 (Visit 3), Week 6 (Visit 4), and Month 3 (Visit 5).

A MMRM will be carried out on observed cases up to Month 3. At each scheduled time point of each visit, least square mean IOP of each treatment arm and 95% confidence interval for the difference in least square means between DE-126/Vehicle arm and Timolol Maleate arm will be estimated. Non-inferiority is established if the upper limit of the 95% confidence interval for the difference is ≤ 1.5 mmHg for all nine time points and ≤ 1.0 mmHg for at least 5 out of the 9 time points.

The primary analysis will be based on the FAS. The same analysis will be repeated on the PPS population as a sensitivity analysis. More details on the model specifications will be provided in the SAP.

9.7.2. Analysis of Secondary Efficacy Endpoints

9.7.2.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is mean diurnal IOP in the study eye at Month 3 (Visit 5).

A MMRM will be carried out on observed cases up to Month 3. The least square mean diurnal IOP of each treatment arm and 95% confidence interval for the difference in least square means between DE-126/Vehicle arm and Timolol Maleate arm at Month 3 will be estimated. If non-inferiority in the primary endpoint is achieved, then the key secondary endpoint will be tested at the 0.05 significance level (2-sided).

The primary analysis will be based on the FAS. The same analysis will be repeated on the PPS population as a sensitivity analysis. More details on the model specifications will be provided in the SAP.

9.7.2.2. Other Secondary Efficacy Endpoints

Other secondary endpoints to be assessed include:

- Mean diurnal IOP in the study eye at Week 2 (Visit 3) and Week 6 (Visit 4)
- Change and percent change from Baseline (Visit 2, Day 1) in IOP in the study eye at each timepoint of each post-baseline visit
- Change and percent change from Baseline (Visit 2, Day 1) in mean diurnal IOP in the study eye at each post-baseline visit
- Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2, Day 1) in the study eye at each post-baseline visit

- Having a mean diurnal IOP ≤ 18mmHg in the study eye at each post-baseline visit

The continuous secondary endpoints will be analyzed using MMRM on observed cases. More details on the model specifications will be provided in the SAP.

The binary secondary endpoints will be analyzed using the Pearson's chi-square test for a 2×2 contingency table. The Fisher's Exact test may be conducted as a sensitivity analysis.

Subgroup analyses by the two randomization strata (baseline IOP in the study eye <25 mmHg vs. ≥25 mmHg) be performed for secondary endpoints using descriptive statistics.

9.8. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs, BCVA, slit-lamp biomicroscopy, ophthalmoscopy, and vital signs (blood pressure and pulse rate).

AEs will be coded using the latest version of MedDRA. Subjects with any AEs will be tabulated by primary SOC and PT specified in the MedDRA. Similarly, subjects with any ocular and non-ocular AEs will be tabulated separately. AEs, ocular, and non-ocular will also be summarized by relationship to treatment and maximum severity. In addition, SAEs and discontinuations due to AEs will be summarized.

Safety parameters listed in Section 8.4.1 and Section 8.4.2 will be summarized using descriptive statistics by actual treatment received. Changes from baseline in these safety parameters will also be summarized by treatment.

9.9. Exploratory Analyses

The GQL-15 total score and each domain score will be summarized descriptively by actual treatment received. The 4 domains are central and near vision, outdoor mobility, peripheral vision, and dark adaption and glare.

10. SUPPORTING DOCUMENTAITON AND OPERATIONAL CONSIDERATIONS

The Principal Investigator will allow representatives of Santen's monitoring team (or designee), the governing IRB or IEC, and other applicable regulatory agencies to inspect all study records, eCRFs, recruitment materials, and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the eCRF, and compliance with the International Conference on Harmonization (ICH)- Good Clinical Practice (GCP) or other regulatory agency regulations.

10.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Santen (or designee) will evaluate the investigational study site to:

- Determine the adequacy of the study facilities.
- Review with the Principal Investigator and his/her designee their responsibilities with regard to protocol procedures adherence, and the responsibilities of Santen (or designee).

During the study, Santen (or designee) will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Assess adherence to the protocol and ICH-GCP.
- Perform investigational product accountability checks and quality control procedures.
- Ensure the on-going implementation of accurate data entry in the eCRF.
- Perform source data verification, including a comparison of the data in the eCRFs with the subject's medical records and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Santen.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.
- Confirm sites have a complete record of all study International New Drug Application (IND) Safety Reports and filed them with the IRB or IEC.

Santen (or designee) may remotely access the eCRFs at any time during the study for centralized monitoring. Santen (or designee) will be available between visits if authorized study staff need study related information or support.

10.2. Audits and Inspections

The Principal Investigator will allow Santen (or designee), the governing IRB or IEC, and applicable regulatory agencies to audit and inspect any aspect of the study, including all study records, eCRFs, recruitment materials, and corresponding portions of the subject's charts and medical records at any time during the study. These study records must be retained at the study site and made available for audits and inspections. The purpose of these audits and inspections is to verify adherence to the protocol, completeness, and accuracy of the eCRF data, and compliance with ICH-GCP guidelines and applicable regulatory requirements.

The Principal Investigator (or his/her designee) will notify Santen (or designee) should the site be audited or inspected by the governing IRB or IEC, and applicable regulatory agencies. Santen (or designee) will also notify the investigational site of any known pending site audits or inspections planned by Santen (or designee), governing IRB or IEC, and regulatory agencies.

10.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The Principal Investigator must obtain IRB/IEC approval for the study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the subject consent form, written information provided to subjects, and recruitment materials must be maintained by the Principal Investigator and made available for inspection.

10.4. Quality Control and Quality Assurance

10.4.1. Quality Control

Santen (or designee) will provide instructional material to the study sites, as appropriate; including but not limited to instruction on the protocol, the eCRFs completion guidelines, and study procedures. Santen (or designee) will communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic visits to the study site. During those visits, Santen
(or designee) will perform source data verification with the subject's medical records and other records relevant to the study. Upon receiving the eCRFs, Santen (or designee) will review and evaluate eCRF data and use standard system edits and may use centralized monitoring to detect errors in data collection.

10.4.2. Quality Assurance

Santen (or designee) may conduct a quality assurance audit at any time. See Section 10.2.

10.5. Ethics

10.5.1. Ethics Review

The final study protocol and the final version of the ICF, for the main study and the ICF for the PGx study, assent form, and other study related material, as appropriate, must be approved in writing by an IRB or IEC as appropriate. If an IRB or IEC does not approve the collection of blood samples for optional future PGx research, this will not affect the approvals for conducting

the main study. The Principal Investigator must submit written IRB or IEC approval to Santen (or designee) before study initiation. Refer to Section 12.1, Appendix A for a list of obligations of Investigators.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local regulations and guidelines. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments.

The Principal Investigator is also responsible for providing the IRB or IEC with progress reports and notifications of any reportable serious adverse drug reactions from the investigational product.

10.5.2. Ethical Conduct of the Study

This study will be conducted in compliance with IRB or IEC, and regulatory requirements. This study will also be conducted in compliance with the protocol, GCP guidelines, International ICH guidelines, and the Declaration of Helsinki.

10.6. Written Informed Consent

The Principal Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and possible benefit of the study and participation in the collection of blood samples for future PGx research studies. If the subject does not wish to provide a blood sample for the biomarker research study this will not affect the subject's enrollment in this clinical trial. Subjects must also be notified that they are free to withdraw from either study at any time. Subjects should be given the opportunity to ask questions and allowed time to consider the information provided. Before participating in any study-related activity, voluntary informed consent must be documented by the use of a written ICF approved by the IRB or IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The original signed and dated ICF will be retained with the study records, and a copy of the signed ICF will be given to the subject or the subject's legally authorized representative. See Section 12.2, Appendix B.

10.7. Data Handling and Recordkeeping

10.7.1. Inspection of Records

The Principal Investigator will allow Santen (or designee), the governing IRB or IEC, and applicable regulatory agencies to inspect any aspect of the study, including all study records, eCRFs, and corresponding portions of the subject's charts and medical records at any time during the study. The purpose of these inspections is to verify adherence to the protocol, completeness, and accuracy of the eCRF data, and compliance with ICH-GCP guidelines and applicable regulatory requirements.

10.7.2. Retention of Records

All records relating to the conduct of this study are to be retained by the Principal Investigator until notified by Santen (or designee) that the records may be destroyed.

10.7.3. Source Documents

The Principal Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents include subject medical records, hospital charts, clinic charts, medication dosing diaries, study files, as well as the results of diagnostic tests (e.g., visual field test printouts).

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number
- The study protocol number and the name of Santen
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures, and/or evaluations)
- The dates of all study-related subject visits (scheduled and unscheduled)
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study medication accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination
- If unmasking at the site occurred, proper documentation and notifications were made

10.7.4. Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data should be accurate, legible, contemporaneous, original, attributable, complete and consistent. Source data is documented in source documents which may be both electronic and on paper.

The Investigator(s) should be aware about the location of the source data and consistent in recording them. The intended location should be clearly defined prior to subject enrollment. One way of achieving this is to generate a source data location list. The source data location list will be prepared by the site and will be signed and dated by the Principal Investigator. The list will be filed in the Investigator's trial master file.

10.7.5. Data Collection

The Principal Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened and randomized subjects will be entered into eCRFs. eCRFs should be completed within 3 business days of each subject visit as much as possible. A review of the eCRFs will be completed remotely by Santen (or designee). At designated intervals, a study monitor will perform Source Data Verification on site. During those visits, Santen (or designee)

will monitor the subject data recorded in the eCRF against source documents at the study site. Santen (or designee) will review and evaluate eCRF data and use standard system edits, and may use centralized monitoring evaluations, to detect errors in data collection. At the end of the study, a copy of the completed eCRFs will be sent to the site to be maintained as study records.

10.8. Study and Site Closure

Santen's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Santen. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Santen or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Santen's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further development of the investigational product

10.9. Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied that is indicated as confidential. Information pertaining to this study will be published on www.clinicaltrials.gov.

The data generated by this clinical study are the property of Santen and should not be disclosed without the prior written permission of Santen. These data may be used by Santen now and in the future for presentation or publication at Santen's discretion or for submission to governmental regulatory agencies. Santen reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the Principal Investigator agrees to the release of the data from this study and acknowledges the above publication policy.

11. REFERENCES

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11.2. Study Reports

1. Data on File: ONO-9054IOU001. A Double-masked, Placebo-controlled, Single-dose Escalation Study To Evaluate The Safety, Tolerability, And Pharmacokinetics Of ONO-9054 In Healthy Adult Subjects
2. Data on File: ONO-9054IOU002. A Double-Masked, Placebo-Controlled, Dose-Escalation Stusy And Double-Masked, Two-sequence, Crossover Study To Evaluate The Safety, Tolerability, Pharmacokinetics, And Pharmacodynamics of ONO-9054 In Patients With Ocular Hypertension Or Mild Openangle Glaucoma
3. Data on File: ONO-9054IOU003. A 28-Day, Double-masked, Randomized, Parallel-group, Active-controlled Study of ONO-9054 Ophthalmic Solution in Subjects With Ocular Hypertension or Open-angle Glaucoma
4. 012601IN - A Phase IIb, Randomized, Observer-Masked, Placebo- and Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-126 Ophthalmic Solution in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension – Angel Study

12. APPENDICES

12.1. Appendix A - Obligations of Investigators

In summary, the Principal Investigator has agreed to the following obligations:

- Obtaining informed consent from every subject before the subject's participation in any study-related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the IRB or IEC before involving any subject in any study-related activity; submitting verification of the approval to Santen; submitting periodic progress reports (at least annually) and final report to IRB or IEC.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing Santen of all deviations from the protocol.
- Informing the IRB or IEC of all protocol amendments/modifications; sending Santen a copy of the letter from the IRB or IEC approving the amendment/modification.
- Reporting to Santen any AEs and reporting to the IRB or IEC any reportable AEs that occur in the course of the investigation.
- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB or IEC and of all action by the IRB or IEC regarding the study.
- Making study records available for inspection by Santen and representatives of regulatory agencies and the IRB or IEC; keeping records until notified by Santen that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to Santen. See I, II, and III as listed below.

I. Before the Beginning of the Study Providing Santen the following:

  - A signed Form FDA 1572, Statement of Investigator, if applicable.
  - A signed Financial Disclosure Form.
  - A current curriculum vitae (CV) if not submitted to Santen previously or if updated.
  - CVs for all Sub-Investigators.
  - A letter from the IRB or IEC indicating that the protocol was approved, including the name and address of the IRB or IEC.
  - A copy of the consent form approved by the IRB or IEC.
  - A list of current members of the IRB or IEC.
  - A copy of the source data location list.

- A copy of delegation list/log.
- A copy of training log.

II. While the Study is in Progress

- Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
- eCRFs for each subject enrolled in the study.
- Information regarding all deviations from the protocol.
- Information regarding all AEs occurring to a subject while enrolled in the study.
- Annual progress report (if study is on-going for more than one year). Letter from the IRB or IEC indicating approval of the annual progress report.

III. Once the Study is Completed

- Disposition of all used and/or unused test and control articles, as well as documentation of all and drug accountability.
- Providing Santen a final study report.

12.2. Appendix B - Elements of Informed Consent

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent as required by ICH-GCP and/or local regulations. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written ICF.

A. The trial involves research.

B. The purpose of the trial.

C. Name of the Investigator (s) and IRB/IEC

D. The trial treatment(s) and the probability for random assignment to each treatment.

E. The trial procedures to be followed, including all invasive procedures.

F. The subject's responsibilities.

G. Those aspects of the trial that are experimental.

H. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

I. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

J. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

K. The compensation and/or treatment available to the subject in the event of trial-related injury.

L. The anticipated prorated payment, if any, to the subject for participating in the trial.

M. The anticipated expenses, if any, to the subject for participating in the trial.

N. That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

O. That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

P. That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

Q. That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.

R. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

S. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.

T. The expected duration of the subject's participation in the trial.

U. The approximate number of subjects involved in the trial.

V. Clinical trial information has been or will be available on http://www.clinicaltrials.gov.

II. Additional Elements of Informed Consent for Optional Future Pharmacogenomics/genomics Laboratory Research Study

The following information must be provided to each subject in obtaining informed consent for the future PGx laboratory research study:

1. The location of storage of their sample.
2. The duration of storage of their sample.
3. What group(s) within Santen will be using their sample in research study.
4. What use restrictions are assigned to their sample.
5. Destruction of their sample if they withdraw prior to its use, and retention of the sample data if they withdraw after its use.

The informed consent requirements in this protocol are not intended to preempt any applicable local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in this protocol is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable local laws.

12.3. Appendix C - Procedures for Assessments

12.3.1. Refraction

Refraction will be performed for each eye at Visit 1 (Screening). At Visit 2 (Baseline, Day 1) to 5 (Month 3) Exit/Early Termination, if the prescription is not up to date within 12 months at the screening visit. Refraction will be performed at study visits after Screening if more than 10 letters lost compared to the screening visit.

12.3.2. Demographics, Medication/Therapy, and Medical History

Demographics, Medication/Therapy, and Medical History will be obtained through subject interviews at Visit 1 (Screening) to determine if the subject meets eligibility criteria.

Demographics

Demographics include age, sex, race, prostaglandin analogs naïve status, and ethnicity. They must be confirmed and recorded in the source documents.

Medical and Surgical History

Followings must be confirmed.

- Non-ocular medical history including diagnosis and relevant treatments within 5 years before the date of Visit 1 (Screening)
- All lifetime ocular medical history including diagnosis and relevant treatments
- All current ocular and systemic conditions

Following details must be recorded in the source documents.

- Diagnosis and treatment(s), affected eye(s) (if applicable), start date, and resolved date.

Medications

Followings must be confirmed.

- Prior medications that have been used for POAG or OHT within 28 days before the date of Visit 1 (Screening)
- All current concomitant medications (including over-the-counter)

Following details must be recorded in the source documents.

- Name of medication, route of administration, treated eye(s) (if applicable), dose, frequency, indication, start date and stop date

Therapies

Followings must be confirmed.

- Prior therapies that have been used for POAG or OHT within 28 days before the date of Visit 1 (Screening)

- All current concomitant therapies

Following details must be recorded in the source documents.

- Name of therapy, treated eye(s) (if applicable), indication, start date and stop date

Surgical procedures occurring during the study

Following details must be recorded in the source documents.

- Name of surgical procedure, treated eye(s) (if applicable), indication, start date and stop date

12.3.3. Pregnancy Test

A urine pregnancy test will be conducted using a commercially available test kit at Visit 1 (Screening), Visit 2 (Baseline, Day 1), Visit 4 (Week 6) and Visit 5 (Month 3) Exit/Early Termination for all females of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 12 months since last menses occurred), is without a uterus or without both ovaries, or has had a bilateral tubal ligation. To perform the pregnancy test, follow instructions provided by the manufacturer of the urine pregnancy test kit. Urine samples will be analyzed at the site with results available prior to administration of study medication.

12.3.4. Vital signs (Blood pressure/Pulse rate)

Systolic blood pressure, diastolic blood pressure, and pulse rate will be measured at Visit 1 (Screening), Visit 2 (Baseline, Day 1), and Visit 5 (Month 3) Exit/Early Termination. Vital signs (resting blood pressure and pulse rate) will be collected anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline, Day 1), and Visit 5 (Month 3) Exit/Early Termination before the morning dose.

Vital signs will be collected in a sitting position after keeping quiet for more than 5 minutes.

12.3.5. Best-Corrected Visual Acuity

BCVA will be measured for each eye prior to the 08:00 IOP measurement at all visits except Visit 1 (Screening)/1a (Optional visit) under normal room illumination using visual acuity chart (Early Treatment Diabetic Retinopathy Study [ETDRS] chart) and the logMAR scoring and will be recorded in the subject's source document. For Visit 1 (Screening)/1a (Optional visit), the corrected visual acuity should be performed prior to IOP measurement. If ETDRS chart is used, the following procedure should be followed.

12.3.5.1. ETDRS Visual Acuity Scoring

The Examiner records each letter identified correctly by circling the corresponding letter on an appropriate visual acuity worksheet. The Examiner records a letter read incorrectly, or a letter for which the subject made no guess, by crossing the letter out with an "x" or a line. Each letter read incorrectly is scored as one point. The last line in which a letter is read correctly will be taken as the Base logMAR line.

The total number of letters that have an "x" or a line through them (letters read incorrectly or not at all) down to and including the Base logMAR line and multiply the total number by 0.02. Add this value to the Base logMAR value to obtain the logMAR score.

Example:

Subject correctly reads 4 of 5 letters on the +0.2 line, and 2 of 5 letters on the +0.1 line, and zero letters on the 0.0 line

Base logMAR value = +0.1 (last line in which a letter was read correctly)

Total number of letters missed = 4 (number of letters missed on the +0.2 line plus the number missed on the +0.1 line)

LogMAR score = +0.1 + (4 x 0.02) = 0.18

Table 4: LogMAR Scoring Grid for ETDRS Eye Chart

		Total Number of Letters Missed										
Snellen	**Base LogMAR**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
20/200	**+1.0**	1.00	1.02	1.04	1.06	1.08	---	---	---	---	---	---
20/160	**+0.9**	0.90	0.92	0.94	0.96	0.98	1.00	1.02	1.04	1.06	1.08	1.10
20/125	**+0.8**	0.80	0.82	0.84	0.86	0.88	0.90	0.92	0.94	0.96	0.98	1.00
20/100	**+0.7**	0.70	0.72	0.74	0.76	0.78	0.80	0.82	0.84	0.86	0.88	0.90
20/80	**+0.6**	0.60	0.62	0.64	0.66	0.68	0.70	0.72	0.74	0.76	0.78	0.80
20/63	**+0.5**	0.50	0.52	0.54	0.56	0.58	0.60	0.62	0.64	0.66	0.68	0.70
20/50	**+0.4**	0.40	0.42	0.44	0.46	0.48	0.50	0.52	0.54	0.56	0.58	0.60
20/40	**+0.3**	0.30	0.32	0.34	0.36	0.38	0.40	0.42	0.44	0.46	0.48	0.50
20/32	**+0.2**	0.20	0.22	0.24	0.26	0.28	0.30	0.32	0.34	0.36	0.38	0.40
20/25	**+0.1**	0.10	0.12	0.14	0.16	0.18	0.20	0.22	0.24	0.26	0.28	0.30
20/20	**0.0**	0.00	0.02	0.04	0.06	0.08	0.10	0.12	0.14	0.16	0.18	0.20
20/16	**-0.1**	-0.10	-0.08	-0.06	-0.04	-0.02	0.00	0.02	0.04	0.06	0.08	0.10
20/12.5	**-0.2**	-0.20	-0.18	-0.16	-0.14	-0.12	-0.10	-0.08	-0.06	-0.04	-0.02	0.00
20/10	**-0.3**	-0.30	-0.28	-0.26	-0.24	-0.22	-0.20	-0.18	-0.16	-0.14	-0.12	-0.10

12.3.6. Slit-Lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the 08:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1 (Screening)/1a (Optional visit), the biomicroscopy examinations should be performed prior to IOP measurement. If Investigator evaluates for possible torn posterior lens capsule by biomicroscopy under dilation in subjects with pseudophakic eye(s) based on his/her decision at Visit 1 (Screening), please dilate pupil and evaluate after all other ocular procedures have been completed.

Anterior chamber cells and flare will be observed and graded using the SUN scale, before fluorescein instillation.

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) = None

(1) = Faint

(2) = Moderate (iris/lens details clear)

(3) = Marked (iris/lens details hazy)

(4) = Intense (fibrin/plastic aqueous)

The lid, conjunctiva, cornea, lens, and iris will be observed and graded on a 4-point scale (0-3 scale).

Lid Hyperemia

None	(0) =	Normal
Mild	(1) =	Redness of most or all the lid(s) margin OR skin
Moderate	(2) =	Redness of most or all the lid(s) margin AND skin
Severe	(3) =	Marked diffuse redness of both lid(s) margin AND skin

Lid Edema

None	(0) =	Normal
Mild	(1) =	Localized to a small region of the lid(s)
Moderate	(2) =	Diffuse, most or all the lid(s) but not prominent/protruding
Severe	(3) =	Diffuse, most or all the lid(s) AND prominent/protruding

Conjunctival (Palpebral and Bulbar) Hyperemia

None	(0) =	Normal
Mild	(1) =	Slight localized injection
Moderate	(2) =	Pink color, confined to palpebral OR bulbar conjunctiva

Severe (3) = Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Chemosis

None (0) = Normal

Mild (1) = Slight localized swelling

Moderate (2) = Mild/medium localized swelling or mild diffuse swelling

Severe (3) = Moderate diffuse swelling

Corneal Edema

None (0) = Normal

Mild (1) = Mild, diffuse stromal haze

Moderate (2) = Dense, diffuse stromal haze or bullae

Severe (3) = Dense, diffuse bullae or stromal haze AND stromal edema

Corneal Staining (with fluorescein)

None (0) = Normal

Mild (1) = Localized, occasional punctate staining

Moderate (2) = Localized, dense OR diffuse occasional punctate staining

Severe (3) = Diffuse, dense punctate staining which may be confluent staining

Keratic Precipitate

None (0) = Normal

Mild (1) = Slight pigmentation or keratic precipitate

Moderate (2) = Moderate pigmentation or keratic precipitate

Severe (3) = Dense pigmentation or keratic precipitate

Lens

The lens will be noted as phakic, aphakic, or pseudophakic. Phakic lens will be graded as described below:

None (0) = No lens discoloration nor opacification

Mild (1) = Yellow lens discoloration or small lens opacity (axial or peripheral)

Moderate (2) = Amber lens discoloration or medium lens opacity (axial or peripheral)

Severe (3) = Brunescent lens discoloration or complete lens opacification (no red reflex)

Anterior Synechiae of Iris

None (0) = No anterior synechiae of iris is found

Mild (1) = <25% anterior synechiae of iris is found

Moderate (2) = 25% to 50% anterior synechiae of iris is found

Severe (3) = >50% anterior synechiae of iris is found

Posterior Synechiae of Iris

None (0) = No posterior synechiae of iris is found

Mild (1) = <25% posterior synechiae of iris is found

Moderate (2) = 25% to 50% posterior synechiae of iris is found

Severe (3) = >50% posterior synechiae of iris is found

The presence and severity of iris color abnormalities, eyelash abnormalities, and eyelid abnormalities will be observed and graded on a 4-point scale (0-3 scale).

Iris Color Abnormalities (e.g., increased pigmentation)

The presence and severity will be assessed. If present, further specification is required.

None (0) = No iris color abnormalities are found

Mild (1) = Slight iris color abnormalities are found

Moderate (2) = Moderate iris color abnormalities are found

Severe (3) = Severe iris color abnormalities are found

Eyelash Abnormalities (e.g., thickening, increased pigmentation/length/number, trichiasis)

The presence and severity will be assessed. If present, further specification is required.

None (0) = No eyelash abnormalities are found

Mild (1) = Slight eyelash abnormalities are found

Moderate (2) = Moderate eyelash abnormalities are found

Severe (3) = Severe eyelash abnormalities are found

Eyelid Abnormalities (e.g. increased pigmentation/hair growth)

The presence and severity will be assessed. If present, further specification is required.

None (0) = No Eyelid Abnormalities are found

Mild (1) = Slight eyelid abnormalities are found

Moderate (2) = Moderate eyelid abnormalities are found

Severe (3) = Severe eyelid abnormalities are found

12.3.7. Intraocular Pressure

IOP will be performed at each visit. At visit 1 (Screening)/1a (Optional visit), IOP can be measured at any time. For Visit 2 (Baseline, Day 1) to Visit 5 (Month 3) Exit/Early Termination, IOP measurements will be scheduled for 08:00 (±60min), 10:00 (±60min), and 16:00 (±60min).

IOP will be measured using calibrated manual Goldmann applanation contact tonometer with the subject in a sitting position. The same Goldmann contact tonometer employing the investigator's standard technique will be used throughout the study. Measurement will be performed preferably by the same authorized study staff throughout the study. Study staff who performs the IOP measurement must have at least 2 years of experience in IOP measurement.

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a determination of IOP. Each IOP measurement and the clock time of IOP measurement will be recorded in the subject's source document.

A single measurement is made as follows:

- The study staff adjusts the force on the tonometer dial to an initial setting corresponding to 10 mmHg. The slit-lamp magnification is set at 10X. The light source is positioned at an angle of approximately 45°, and the aperture is maximally opened. A cobalt blue filter is employed.
- After instillation of a topical anesthetic, a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic (Fluress, Barnes Hind) may be instilled. The study staff should use the same technique each time, be it a paper strip or a pre-mixed eye drop.
- The subject and slit-lamp are adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The subject is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the study staff holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The subject is cautioned not to hold his breath.
- The study staff looks through the slit-lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.
- The study staff adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.
- The study staff removes the tip from the cornea, and records the reading on the dial, rounded to the next highest integer. For example, if the measurement indicated is

between 16 and 17, then 17 is recorded as the measurement in the subject's source document.

- If corneal astigmatism is greater than 3.0 D, the prism is rotated so that the red line corresponds to the orientation of the longer axis of the elliptical applanated area.

The above procedure is then repeated for the same eye, and that second measurement is also recorded in the subject's source document.

- If the two measurements differ by less than 3 mmHg, then the average of the two measurements becomes the recorded IOP. For example, if the two measurements are 22 and 23, then 22.5 is the final recorded IOP.
- However, if the two measurements differ by 3 mmHg or more, then a third measurement is made, and the median of the three measurements becomes the recorded IOP (the median is the middle measurement after ordering the measurements from low to high). For example, if the three measurements are 15, 19, and 16, then 16 is the final recorded IOP.

The IOP in the left eye is then measured using the same technique.

12.3.7.1. Goldmann Applanation Tonometer Calibration

Every tonometer being used in the study must be calibrated for accuracy before the first subject undergoes screening (mandatory), and then check calibration monthly until the last subject has exited the study. For checking calibration, follow the manufacturer's instructions. If the variation is within ±2 mmHg, the tonometer is considered adequately calibrated. However, if the variation exceeds this amount, the tonometer should be sent for repair and a different, adequately calibrated instrument should be used for IOP measurement. The date of each calibration, along with the name and signature (or initials) of the person who performed the calibration, will be documented. The tonometer calibration record will be retained as a part of the study record.

12.3.8. Gonioscopy

Gonioscopy will be performed to examine the angle of the anterior chamber after IOP measurement at Visit 1 (Screening) if it has not been performed within 3 months (90 days). The Shaffer scale will be used to rate the degree of angle closure.

(0) = approximately 5 degrees or less, complete or partial closure

(1) = approximately 10 degrees

(2) = approximately 20 degrees

(3) = approximately 30 degrees

(4) = approximately 40 degrees or more

12.3.9. Pachymetry (Central Corneal Thickness)

The central corneal thickness (μm) of each eye using any pachymeter including optical pachymeter, ultrasound pachymeter, OCT (optical coherence tomography), etc. will be measured and recorded after IOP measurement at Visit 1 (Screening). Pachymetry will be performed after IOP measurement.

12.3.10. Visual Field

Visual field examinations will be performed using a static or dynamic perimeter (Humphrey or Octopus) without pupil dilation at Visit 1 (Screening), if it has not been performed within 3 months (90 days) or the previous visual field test(s) indicates low subject reliability (e.g., due to fixation losses, false positive errors, or false negative errors). Glaucomatous visual field loss will be evaluated by the Investigator as presence or absence (mean deviation, pattern SD, glaucoma hemifield test, and type of glaucomatous visual field loss).

Visual field tests that, in the Investigator's opinion, indicate low subject reliability (e.g., due to fixation losses, false positive errors, or false negative errors) can be repeated once more; if still low reliability then the subject should be excluded. A copy of the computer printout from the visual field test(s) will be attached to the subject's source documents.

12.3.11. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination with pupil dilation will be performed for each eye at Visit 1 (Screening), Visit 2 (Baseline, Day 1), and Visit 5 (Month 3) Exit/Early Termination, and graded as described below. The examination will be performed with pupil dilated at Visit 1 (Screening) and Visit 5 (Month 3) Exit. Dilate pupil and ophthalmoscopy examination will be performed after all other ocular procedures have been completed. Cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will also be evaluated.

Glaucomatous Optic Nerve Findings

The optic nerve will be evaluated using a 4-point scale (0-3 scale).

None	(0) =	No damage
Mild	(1) =	Optic nerve damage, secondary to glaucoma including any rim loss (sloping or thinning)
Moderate	(2) =	Optic nerve damage, including cupping to disc margin at one or more points
Severe	(3) =	Optic nerve damage, nearly total cupping, only nasal rim or less present

12.3.12. Blood Sample for Pharmacogenomics/genomics Study

All subjects participating in the study will have the option to participate in blood sampling for PGx and this will be consented to collect this optional test. Subjects who do not wish to participate in the PGx sampling may still participate in the study. For PGx, one whole blood sample (approximately 10 mL) will be collected on Visit 3 (Week 2) but may be collected at any time during the study, as shown in Schedule of Events and Procedures (Table 3). The blood samples will be coded to protect the subject's private information. DNA will be extracted from the blood sample and stored in the DNA repository for potential future PGx research. The samples will be coded to protect the participant's private information. Sample handling, storage, and shipment will be defined in a separate procedure manual.

If conducted, PGx research will be performed by appropriate assay platforms such as Polymerase Chain Reaction (PCR), hybridization, and sequencing. Individual subjects' results from the research testing of their sample will not be communicated to investigator and participants.

12.4. Appendix D- Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (and not related to progression of underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Sight threatening event: A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event.
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Santen in lieu of completion of the Santen/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Santen. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Santen.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

Severity of the AE should be assessed according to the following criteria:

Mild: No interference with the subject's daily activities; no medical intervention/therapy required.

Moderate: Possible interference with the subject's daily activities; no or minimal medical intervention/therapy required.

Severe: Considerable interference with the subject's daily activities; medical intervention/therapy required.

- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality Note: During the double-masked period, regardless of the source of the reported occurrence of an AE in a subject, the masked investigator will assess the causality of the AE.

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The following criterial can be used to make a causality judgment:
- Related (possibly or probably)
  - There is a clinically plausible time sequence between onset of the AE and investigational product administration/protocol procedure; and/or
  - There is a biologically plausible mechanism for investigational product causing or contributing to the AE; and
  - The AE may or may not be attributed to concurrent/underlying illness, other drugs, or protocol procedures.
- Not Related

- A clinically plausible temporal sequence is inconsistent with the onset of the AE and Investigational product administration/protocol procedure; and/or
- A causal relationship is considered biologically implausible. The investigator will use clinical judgment to determine the relationship.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigational Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Santen. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to Santen.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Procedures for Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Santen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Santen with a copy of any post--mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to Santen within 24 hours of receipt of the information.

4. Reporting of SAEs

SAE Reporting to Santen via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Santen will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form to Santen Global Pharmacovigilance (Table 1). • Contacts for SAE reporting can be found in Table 1. • For SAE supporting information (i.e. X-ray reports, hospital summaries, etc.) that are not included in the EDC format, follow a procedure analogous to the manual SAE reporting process.
SAE Reporting to Santen via Paper CRF (If Electronic Data Collection Tool is Unavailable)
• Complete both the paper AE and SAE Forms (located in your site regulatory binder). • Attach a Fax Cover Sheet with your contact information and fax to Santen Global Pharmacovigilance (Table 1). • In the rare circumstance of the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper AE and SAE forms sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Table 1.

12.5. Appendix E- Adverse Event Case Report Form Items and Terms

Concise Description of Event:	A concise description of the signs, symptoms, complaints, or diagnosis of the subject's problem (e.g., nasal congestion). Complete one AE form for related symptoms that can be grouped as one condition (e.g., If a subject complains of sneezing, nasal congestion, watery eyes, the AE is described as cold symptoms). If two independent events occur at the same time, separate AE forms must be completed for each event.
Affected Eye(s):	Indicate if ocular event is OD, OS, or OU. Non-ocular events should be recorded as N/A.
Adverse Event Serious/Event of Special Interest:	If AE is serious or an Event of Special Interest, Santen must be notified immediately (within 24 hours). Complete both the AE and the SAE eCRFs in the EDC system. In the event the EDC system is unavailable, and your site needs to report an SAE, please follow the manual process described in the body of the protocol under "Reporting of SAEs."
Date of Event Onset:	The date the event started.
Maximum Severity of Event:	Record the severity of the AE according to the following definitions: Mild: Aware or unaware of event, but easily tolerated Moderate: Discomfort enough to cause interference with usual activity Severe: Incapacitating; unable to work or perform usual activity For intermittent events, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate. Record that the severity of the headaches ranged from mild to moderate in the comment section of the form. If an event occurs with each administration (e.g., eyes burn mild to moderate for 5 minutes after every administration), record the maximum severity of the individual incident. In the example above, the severity is moderate. Record that the severity of the event ranged from mild to moderate in the comment section of the form.
Action Taken as Related to this AE:	Indicate the action taken as a result of the AE. If the frequency of Investigational product administration was changed or discontinued temporarily or if surgery was required, provide more detailed explanation in the comment section of the form. If "Other" is indicated, specify the action taken.

Outcome of Event:	Indicate the outcome of the AE and provide resolution date or date of death. For intermittent events (e.g., intermittent headache) and events that occur with each administration (e.g., eyes burn for 5 minutes after every administration), the date should reflect when the last occurrence resolved or stopped. For example, if a subject has an intermittent headache from 12/14/2010 until 12/21/2010 and each individual headache lasts 3 hours a day, then the date of resolution is 12/21/2010 (NOT 12/14/2010). If treatment was initiated, then include the treatment and duration in the comments section (e.g., subject took acetaminophen for headache on 12/14/2010, 12/17/2010, and 12/20/2010).
Relationship to Study Drug/Investigational Product:	Indicate if there is a reasonable possibility that the AE may have been caused by the study drug/investigational product with a Yes or No response. A "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug/investigational product and the AE. If response is No, select the possible alternative explanation of the event from the list provided.

For SAE supporting information (i.e., X-ray reports, hospital summaries, etc.) that are not included in the EDC format, follow the same reporting process as for manual SAE reporting.

12.6. Appendix F – The Glaucoma Quality of Life-15 Questionnaire

The Glaucoma Quality of Life-15 Questionnaire

List of daily activities with the strongest relationship with visual field loss in glaucoma

Patient instruction: Please, circle the correct answer on the scale ranging from 1 to 5 where [1] stands for no difficulty, [2] for a little bit of difficulty, [3] for some difficulty, [4] for quite a bit of difficulty, and [5] for severe difficulty. If you do not perform any of the activities for other than visual reasons please circle [0].

Does your vision give you any difficulty, even with glasses, with the following activities?

	None	A little bit	Some	Quite a lot	Severe	Do not perform for non-visual reasons
Reading newspapers	1	2	3	4	5	0
Walking after dark	1	2	3	4	5	0
Seeing at night	1	2	3	4	5	0
Walking on uneven ground	1	2	3	4	5	0
Adjusting to bright lights	1	2	3	4	5	0
Adjusting to dim lights	1	2	3	4	5	0
Going from light to dark room or vice versa	1	2	3	4	5	0
Tripping over objects	1	2	3	4	5	0
Seeing objects coming from the side	1	2	3	4	5	0
Crossing the road	1	2	3	4	5	0
Walking on steps / stairs	1	2	3	4	5	0
Bumping into objects	1	2	3	4	5	0
Judging distance of foot to step / curb	1	2	3	4	5	0
Finding dropped objects	1	2	3	4	5	0
Recognizing faces	1	2	3	4	5	0

12.7. Appendix G - Protocol Amendment 1 Summary of Changes

Global Changes:	• Herein is a summary of changes made to original protocol dated 16 October 2020 and reflected in Amendment 1 dated 18 February 2021. New text is identified in ***bold and italicized*** and deleted text with **bold/strikethrough**. • Updated Contact Information. • Updated exploratory objective. • Added Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, D 1) may be combined into one visit for treatment-naïve subjects. • Updated Exclusion # 6, bullet two by adding excluding join injections. • Added Aphakia to the Exclusion # 16. • Added new exclusion for the use of marijuana excluding 28 days prior to Day 1 visit. • Updated visit window for post-study follow-up phone call from +/- 7 days to + 7 days. • Added evaluation of the presence and severity of iris color abnormalities, eyelash abnormalities, and eyelid abnormalities graded on a 4-point scale (0-3 scale).

Section:	Synopsis, Section 3.4 Exploratory objectives
Original Text:	To achieve the response from subjects on the Glaucoma Quality of Life (GQL)–15 Questionnaire.
Revised Text:	To **~~achieve the response from~~** ***explore Quality of Life in*** subjects ***with POAG or OHT when given DE-126 or Timolol for 3 months*** **~~on the Glaucoma Quality of Life (GQL)–15 Questionnaire~~**.
Rationale:	Clarified of Exploratory Objectives.

Section:	Synopsis, Section 4.1 Overall Study Design
Original Text:	*Please note: that prior to trial, subjects are allowed to have used at a maximum of two active ingredients for IOP reduction.*
Revised Text:	*Please note:* ~~**that prior to trial, s**~~***S****ubjects are* ***only*** *allowed* ***to be treated with*** ~~**have used at**~~ a *maximum of two active ingredients for IOP reduction* ***prior to screening.***
Rationale:	Clarified that subjects are only allowed to be treated with maximum of two active ingredients for IOP reduction prior to Screening Visit.

Section:	Synopsis, Section 4.1 Overall Study Design
Original Text:	Final eligibility for randomization will be determined at Visit 2 (Baseline, Day 1) after all necessary washout from prior IOP-lowering medications have been completed. Subjects who have not used any IOP-lowering medication for the last 28 days, including treatment-naive subjects, must have ≥ 1 day between their screening visit and Visit 2 (Baseline, Day 1).
Revised Text:	Final eligibility for randomization will be determined at Visit 2 (Baseline, Day 1) after all necessary washout from prior IOP-lowering medications have been completed. ~~**Subjects who have not used any IOP-lowering medication for the last 28 days, including treatment-naive subjects, must have ≥ 1 day between their screening visit and Visit 2 (Baseline, Day 1).**~~
Rationale:	Removed the statement and clarified in a new paragraph that both Screening and Day 1 may be combined for treatment-naïve subjects.

Section:	Synopsis, Section 4.1 Overall Study Design, Table 3 footnote
Original Text:	N/A
Revised Text:	***Please note: Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) may be combined into one visit for treatment-naïve subjects as long as the additional requirements of Visit 2 (Eligibility/Baseline, Day 1) are fulfilled on the day of this combined visit; in particular, full diurnal IOP measurements (at 08:00, 10:00, 16:00) must be taken.***
Rationale:	Added to allow subjects to skip unnecessary visits and reduces subject wait time to receive the treatment.

Section:	Synopsis, Section 4.1 Pharmacogenomics/Genomics
Original Text:	Subjects who consent to the optional pharmacogenomics/genomics (PGx) laboratory study will provide a blood sample for future testing. It will be collected at Visit 3 (Week 2) but may be collected at any time during the study. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.
Revised Text:	Subjects who consent to the optional pharmacogenomics/genomics (PGx) laboratory study will provide a blood sample for future testing. ***The earliest this sample is to*** ~~**It will**~~ be collected at Visit 3 (Week 2) but ***it*** may ***also*** be collected at any time ***later*** during the study ***after Visit 2 (Eligibility/Baseline) or at a separate post-study visit, if necessary***. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.
Rationale:	Clarified that the PGx samples can be collected anytime after subject randomized or at a separate unscheduled visit.

Section:	Table 3: Schedule of Events and Procedures
Original Text:	Follow-up Period Visit window in days ±7
Revised Text:	Follow-up Period Visit window in days ~~±~~ +7
Rationale:	Administrative change to provide additional clarity that follow-up phone call should be conducted at least 2 weeks of post last study drug administration with a visit window of +7 days.

Section:	Section 5.1. Subject Inclusion Criteria # 10
Original Text:	Completed the required wait/washout period.
Revised Text:	Completed the required wait/washout period ***(if required per protocol).***
Rationale:	Added if required per protocol for clarity.

Section:	Section 5.2. Subject Exclusion Criteria # 6, third bullet point and Section 6.3.1 Prohibited Medications or Therapies
Original Text:	• Any ocular, periocular, inhaled, nasal, or systemic corticosteroids.
Revised Text:	• Any ocular, periocular, inhaled, nasal, or systemic corticosteroids ***(excluding joint injections).***
Rationale:	Added excluding joint injections to clarify that systemic corticosteroids are allowed for subjects using for joint injections.

Section:	Section 5.2. Subject Exclusion Criteria # 16.
Original Text:	Pseudophakia with a torn posterior lens capsule, history or presence of macular edema or known risk factors (e.g., retinal vein occlusion, diabetic retinopathy, uveitis, age-related macular degeneration) for macular edema in either eye.
Revised Text:	***Aphakia, p***seudophakia with a torn posterior lens capsule, history or presence of macular edema or known risk factors (e.g., retinal vein occlusion, diabetic retinopathy, uveitis, age-related macular degeneration) for macular edema in either eye.
Rationale:	Added Aphakia to clarify that subjects with a history of Aphakia and Pseudophakia with torn posterior lens capsule will be excluded.

Section:	Section 5.2. Subject Exclusion Criteria # 23
Original Text:	N/A
Revised Text:	***Use of marijuana and/or marijuana derivatives within 28 days prior to Visit 2 (Baseline, Day 1); including, but not limited to, cannabidiol topical eye drops.***
Rationale:	Added new exclusion criteria due to marijuana can affect Intra Ocular Pressure, and any use of marijuana and/or marijuana derivatives are excluded.

Section:	Section 6.2.2. Study Medication Storage
Original Text:	Study medications should be stored under refrigeration at 2° to 8°C (36° to 46°F), protected from light, and stored upright. During the refrigeration storage, the Investigator (or his/her designee) will verify and record that the temperature was maintained at 2° to 8°C (36° to 46°F) using temperature recorder at least once every seven days at the investigational site until the last subject has exited the study at the site.
Revised Text:	Study medications should be stored under refrigeration at 2° to 8°C (36° to 46°F), protected from light, and stored upright. During the refrigeration storage, the Investigator (or his/her designee) will verify and record that the temperature was maintained at 2° to 8°C (36° to 46°F) using temperature recorder ~~**at least once every seven days at the investigational site until the last subject has exited the study at the site**~~.
Rationale:	Removed the statement for clarity that temperature monitoring at the site level will be recorded daily during normal business hours.

Section:	Section 6.3.1. Prohibited Medications or Therapies
Original Text:	– If artificial sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents, Vitamin B12 formulation, over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of at least 5 minutes between use of these ocular medications and use of the study medication.
Revised Text:	– If artificial sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents, Vitamin B12 formulation, over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of at least 5 10 minutes between use of the study medication and these ocular medications (the study medication to be given first) and use of the study medication.
Rationale:	Clarified that between the use of any permitted ocular medications and study medication there will be an interval for at least for 10 minutes and study medication will be given first before any allowed ocular medications.

Section:	Section 12.3.6 Slit-Lamp Biomicroscopy
Original Text:	N/A
Revised Text:	***The presence and severity of iris color abnormalities, eyelash abnormalities, and eyelid abnormalities will be observed and graded on a 4-point scale (0-3 scale).*** ***Iris Color Abnormalities (e.g., increased pigmentation)*** ***The presence and severity will be assessed. If present, further specification is required.*** ***None (0) = No iris color abnormalities are found*** ***Mild (1) = Slight iris color abnormalities are found*** ***Moderate (2) = Moderate iris color abnormalities are found*** ***Severe (3) = Severe iris color abnormalities are found*** ***Eyelash Abnormalities (e.g., thickening, increased pigmentation/length/number, trichiasis)*** ***The presence and severity will be assessed. If present, further specification is required.*** ***None (0) = No eyelash abnormalities are found*** ***Mild (1) = Slight eyelash abnormalities are found*** ***Moderate (2) = Moderate eyelash abnormalities are found*** ***Severe (3) = Severe eyelash abnormalities are found*** ***Eyelid Abnormalities (e.g., increased pigmentation/hair growth)*** ***The presence and severity will be assessed. If present, further specification is required.*** ***None (0) = No Eyelid Abnormalities are found*** ***Mild (1) = Slight eyelid abnormalities are found*** ***Moderate (2) = Moderate eyelid abnormalities are found*** ***Severe (3) = Severe eyelid abnormalities are found***
Rationale:	Added evaluation of the presence and severity of iris color abnormalities, eyelash abnormalities, and eyelid abnormalities to monitor any changes. 4-point scale (0-3 scale) included for overall study consistency.