Study Protocol Cover Page

Official Study Title:	A Phase IIb Safety and Efficacy Study of DE-126 Ophthalmic Solution in Primary Open-Angle Glaucoma or Ocular Hypertension- Angel Study
NCT Number:	NCT03216902
Date of the document:	16 June 2017

DE-126

Protocol 012601IN

Amendment 1

TITLE: **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**

SPONSOR:	STUDY DRUG:
Santen Inc. 6401 Hollis Street, Suite 125, Emeryville, CA 94608, USA	Vehicle of DE-126 ophthalmic solution 0.0005% DE-126 Ophthalmic Solution 0.001% DE-126 Ophthalmic Solution 0.002% DE-126 Ophthalmic Solution 0.003% DE-126 Ophthalmic Solution 0.005% Latanoprost Ophthalmic Solution

I have read the 012601IN 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 indicates that the data therein has been reviewed and accepted by me as the Investigator. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____
(PRINT OR TYPE)

Address: _____

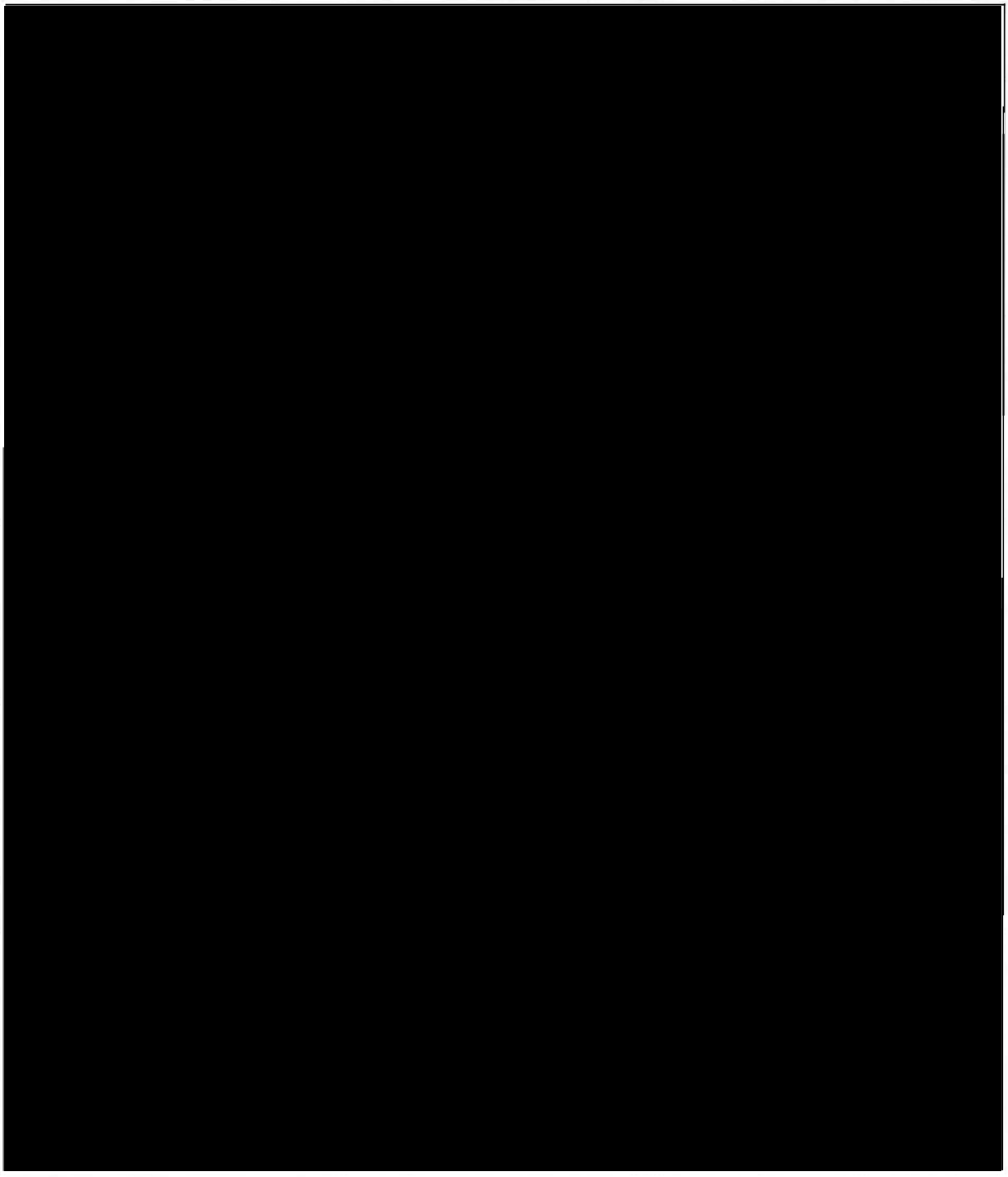
_____

Phone: _____

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

1. PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information



2. SYNOPSIS

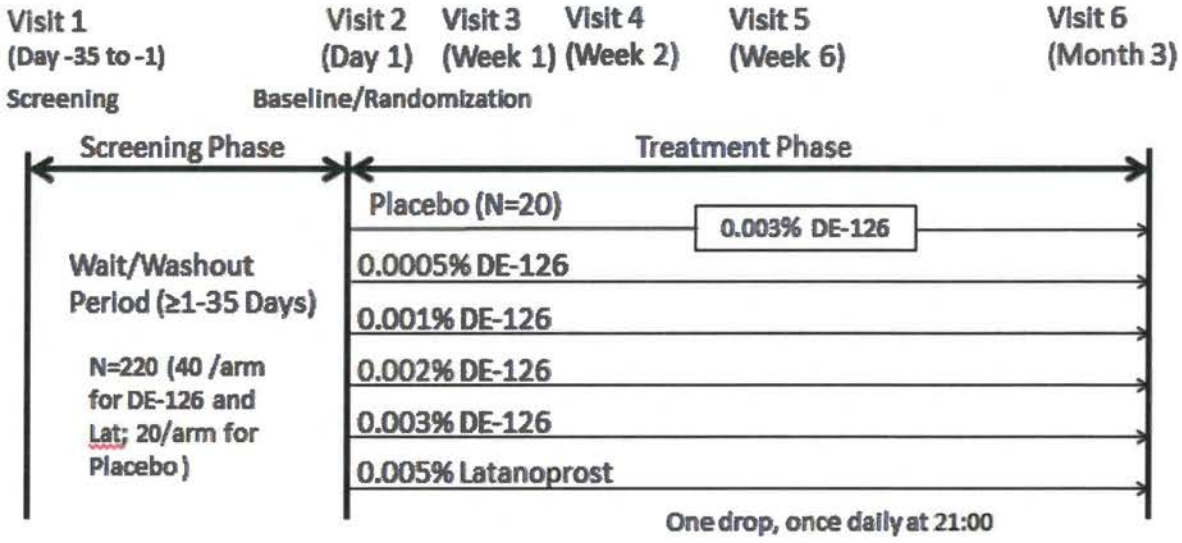
Name of Sponsor/Company:	Santen Inc. 6401 Hollis Street, Suite 125 Emeryville, CA 94608
Name of Investigational Product: DE-126 Ophthalmic Solution	
Name of Active Ingredient: Propan-2-yl 4-{(3*S*,5a*R*,6*R*,7*R*,8a*S*)-6- [(1*E*,3*R*)-4-(2,5-difluorophenoxy)-3- hydroxybut-1-en-1-yl]-7-hydroxyoctahydro- 2*H*-cyclopenta[*b*]oxepin-3-yl}butanoate	
Title of Study: 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**	
Study centers: Approximately 40 sites in the U.S. and Japan	
Study period: Estimated date of first subject screened: July 2017 Estimated date last subject completed: February 2018	**Phase of development:** IIb
Primary objective: To determine the optimal dose of DE-126 by investigating the safety and efficacy of four (4) concentrations of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002%, and 0.003%) when compared to latanoprost (0.005% latanoprost) at Month 3 in subjects with primary open-angle glaucoma or ocular hypertension. **Secondary objective:** To determine if any one of four (4) concentrations of DE-126 (0.0005%, 0.001%, 0.002% and 0.003%) is superior to the placebo (vehicle of DE-126) in mean IOP reduction at each specified time point (09:00, 13:00 and 17:00) at Week 6 compared to baseline. To investigate the dose response of four (4) concentrations of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002% and 0.003%). **Safety objective:** To determine the safety of DE-126 ophthalmic solutions (0.0005%, 0.001%, 0.002% and 0.003%) given once daily as compared to 0.005% latanoprost given once daily in this population.	
Methodology: This is a phase IIb, randomized, observer-masked, placebo-and active-controlled, parallel-group, multinational, multi-center study. Approximately 220 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 up to 3 months. Subjects in the placebo arm will receive placebo eye drops for 6 weeks and then switch to DE-126 0.003% ophthalmic solution for the remaining 6 weeks till study exit.

Approximately 220 subjects with POAG or OHT will be randomized to one of the six (6) treatment arms in a 1:2:2:2:2:2 ratio, as follows:

- Placebo (Vehicle of DE-126 ophthalmic solution)→0.003% DE-126 at Week 6
- 0.0005% DE-126 Ophthalmic Solution
- 0.001% DE-126 Ophthalmic Solution
- 0.002% DE-126 Ophthalmic Solution
- 0.003% DE-126 Ophthalmic Solution
- 0.005% Latanoprost Ophthalmic Solution

Study Design



The study will consist of a screening phase of up to 35 days including a washout period of up to 28 days and a 3-month 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 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
- Beta antagonists (β blocker, including αβ blockers): 28 days
- Alpha antagonists (α1 blocker): 28 days
- Prostaglandins Analogs (PGA): 28 days

- Rho kinase inhibitor: 28 days

For combination drugs, the longest washout period of the individual component will be used. 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 1 week before the randomization at Visit 2 (Baseline, Day 1). An interim safety visit, mid washout visit (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 by 1 week before the randomization at Visit 2 (Baseline, Day 1), mid washout visit (Visit 1a) is recommended to be performed.

Final eligibility will be determined at Visit 2 (Baseline) after all necessary washout from prior IOP-lowering medications has been completed. Subjects who have not used an IOP-lowering medication for the last 28 days prior to the screening visit, including treatment-naive subjects, must have at least one day between their screening visit and Visit 2 (Baseline).

At Visit 2, baseline IOP will be measured for both eyes at 09:00, 13:00 and 17:00 (±60 minutes). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet eligibility criteria, the eye with the higher diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye. In cases where only one eye is fully qualified for the study, both eyes can be treated for the duration of the study. Approximately 220 eligible subjects will be randomized to one of the six (6) treatment arms. Forty (40) subjects per treatment arm will be randomized to each DE-126 and Latanoprost arms, and 20 subjects will be randomized to the Placebo arm. Central randomization via Interactive Response Technology (Medidata BALANCE) will be used to allocate the subjects to each of the six treatment arms in the U.S. and Japan separately. Each eligible subject will be assigned to receive a study medication kit numbered as allocated by the randomization schedule and assigned by BALANCE.

The study eye drops will be given once daily at 21:00 (±60 minutes), starting on the evening of Visit 2 and continuing through the evening prior to Visit 6 (Month 3). During the 3-month treatment period Subjects will return for Visits 3,4, 5, and 6 (Weeks 1, 2, 6 and Month 3) and IOP will be measured at 09:00, 13:00 and 17:00 (±60 minutes). At these scheduled visits corrected visual acuity and slit lamp biomicroscopy will be performed at 09:00 immediately prior to IOP measurement, and corneal thickness measurement (pachymetry) and ophthalmoscopy (fundus examination) will be performed at 17:00 immediately after IOP measurement.

Subjects will be invited to separately consent to provide a saliva sample for a future pharmacogenomics/genomics laboratory research study, however providing such consent is not a prerequisite to participating in the main study. The purpose of this exploratory research is to identify possible genetic markers associated with the study drug(s) and/or ocular conditions.

Number of subjects (planned):

Approximately 220 subjects in the U.S. and Japan in a 1:1 ratio.

Masking:

The appearance of the bottles used for the 4 active DE-126 groups and the placebo group will be identical. However, due to differences in appearance between the containers used for the test treatments (DE-126 and placebo) and the commercially available active control treatment (0.005% latanoprost) this study is classified as observer-masked. In order to maintain masking of investigators, examiners and sponsor personnel involved in the conduct of the study, only an authorized study staff member who is not the investigator or examiner at the investigative site will be permitted to dispense and collect study medication. Subjects will be instructed not to show the bottles to either the investigator or the examiner or other study subjects. The active control treatment containers will be overlabeled and packaged in the same secondary package (e.g., cardboard carton) as the test treatments.

Masking of treatment for subjects assigned to the placebo group, will be maintained when they are switched to 0.003% DE-126 at the Week 6 visit, since the appearance of the 0.003% DE-126 bottles will be identical to the placebo bottles.

Diagnosis and main criteria for inclusion:

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

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
2. Be 20 years or older in Japan and 18 years of age or older in the U.S. (or meets specific state requirement for legal age if that is greater than 18 years of age) on the date of signing the ICF and 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 surgically sterile [less than 6 months]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during, and for 28 days following the study.
    - Abstinence
    - Hormonal contraceptive method- oral and 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

    The male partner of the female subject of childbearing potential should use/practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraception deemed adequate by the investigator throughout the course of the study.
    Male subjects, with a female partner of childbearing potential, should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraception deemed adequate by the investigator

throughout the course of the study.

4. Subjects must have a diagnosis of POAG or OHT in both eyes (excluding pseudoexfoliation syndrome).
5. Corrected visual acuity of +0.60 logMAR (Snellen equivalent 20/80, Decimal visual acuity 0.3) or better in each eye.
6. Central corneal thickness ≥ 480 µm and ≤ 620 µm in each eye.
7. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition, the subject must meet the inclusion criterion #3 again if applicable and the following criteria at Visit 2 (Baseline, Day 1):

8. Completed the required wait/washout period if applicable.
9. At all IOP measurement time-points (09:00, 13:00 and 17:00), IOP must be ≥ 22 mmHg in at least one eye and ≤ 34 mmHg in both eyes.

Exclusion Criteria:

A subject with any of the following ocular conditions in any eye or 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. Current or planned participation in any other clinical trial involving an investigational product or device within 30 days prior to Visit 1 (Screening) or at any time during this trial.
4. Subjects who have been exposed to DE-126 prior to Visit 1 (Screening).

Medications / Therapies-

5. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
6. 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 [ARB]) within the first 30 days prior to Visit 1 (Screening), or anticipated change in such therapy during the study.
7. Intended or current use of the following prohibited medications during the study:
   - All ocular medications other than artificial tear, cataract treatment agents, and Vitamin B_{12} formulation, and study medications during the study.
   - All systemically administered ocular hypotensive medication (e.g., oral or intravenous CAI, oral glycerol).
   - Any ocular, periocular, inhaled, nasal or systemic corticosteroids.
8. Known allergy, hypersensitivity or contraindications to prostaglandins, benzalkonium chloride (BAK) or any other components of the study medications or other study related procedures/medications.
9. History of ocular surgery specifically intended to lower IOP (e.g., laser trabeculoplasty, filtering surgery, Minimally Invasive Glaucoma Surgery [MIGS], or trabeculotomy) in either eye.
10. History of keratorefractive surgery in either eye.

11. Use of contact lenses within one week prior to Visit 2 (Baseline, Day 1) until end of treatment.
12. Any ocular surgery or ocular laser treatment within 90 days prior to Visit 1 (Screening) and throughout the study in either eye.

Diseases-

13. Advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
14. Any corneal abnormality or other condition interfering with or preventing reliable Goldmann applanation tonometry (e.g., Fuch's dystrophy, band-shaped keratopathy, Avellino corneal dystrophy or significant corneal surface abnormality) in either eye.
15. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
16. History of iritis and/or uveitis, corneal inflammatory conditions, and/or viral infections such as herpes virus in either eye; history of adenovirus is not an exclusion provided no associated inflammation was observed within 6 months prior to screening.
17. Pseudophakic 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 or within 90 days after ocular surgery) for macular edema in either eye
18. 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.
19. Subjects with a history of severe ocular trauma in either eye.
20. Subjects with any condition that prevents clear visualization of the fundus in either eye.
21. Presence or history of any ocular or systemic disease, clinical laboratory test abnormality 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.).
22. Any decision by the Principal Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any reason.

Investigational product/reference therapy, dosage and mode of administration:

Subjects will be randomly assigned in a 1:2:2:2:2:2 ratio to receive one of the following treatments:

- Placebo (Vehicle of DE-126 ophthalmic solution) → 0.003% DE-126 at Week 6.
- 0.0005% DE-126 Ophthalmic Solution
- 0.001% DE-126 Ophthalmic Solution
- 0.002% DE-126 Ophthalmic Solution
- 0.003% DE-126 Ophthalmic Solution
- 0.005% Latanoprost Ophthalmic Solution

Each subject will be instructed to instill one drop of study medication in each eye at 21:00 daily during the Treatment Phase of the study.

Route of administration: Topical ocular

Duration of treatment: 3 months

Criteria for evaluation:

Safety:

Safety assessments will be composed of adverse events, vital signs, clinical laboratory tests, corrected visual acuity, ocular symptoms, slit lamp biomicroscopy, ophthalmoscopy findings, central corneal thickness measurement (pachymetry), iris color, eyelash and eyelid examination.

Efficacy:

Efficacy will be assessed by evaluating IOP at each scheduled time point as follows: 09:00, 13:00 and 17:00 (plus or minus 60 minutes).

Other:

Subject demographics and baseline characteristics, exposure to study medication and concomitant medications will be summarized.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- IOP in the study eye at each specified time point (09:00, 13:00 and 17:00) at Visit 6 (Month 3).

Key Secondary Efficacy Endpoint:

- IOP in the study eye at each specified time point (09:00, 13:00 and 17:00) at Visit 5 (week 6).

Other Secondary Efficacy Endpoints:

- IOP in the study eye at each specified time point (09:00, 13:00 and 17:00) at Visit 3 and 4 (Week 1 and Week 2).
- Mean diurnal IOP in the study eye at Visits 3, 4, 5, and 6 (Week 1, Week 2, Week 6, and Month 3).
- Change and percent change from baseline (CFB) in mean diurnal IOP in the study eye at each post-baseline visit (Visits 3, 4, 5, and 6 [Week 1, Week 2, Week 6 and Month 3, respectively]).
- Change and percent change from baseline (CFB) in IOP in the study eye at the specified time points: 09:00, 13:00, and 17:00 at each post-baseline visit.
- Proportion of subjects with mean diurnal IOP reduction from baseline $\geq$ 20%, 25% and 30% in the study eye at Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3).
- Proportion of subjects with mean diurnal IOP $\leq$ 18 mmHg in the study eye at Visit 3 (Week1), Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3).

Safety Endpoints:

- Incidence of ocular and systemic adverse events (AEs).
- Corrected visual acuity.
- Ocular symptoms.
- Slit-lamp biomicroscopy: conjunctival hyperemia, corneal staining, aqueous flare and cell etc.
- Ophthalmoscopy.
- Central corneal thickness.

- Iris color/eyelash/eyelid by photographs.
- Vital signs.
- Clinical laboratory tests.

Statistical methods:

The sample size is not planned on the primary efficacy endpoint. For the key secondary endpoint, assuming that the minimal expected treatment difference across all timepoints is -5.1 mmHg between an optimal DE-126 dose and placebo (based on ONO-9054IOU002 and ONO-9054IOU003 studies) and the standard deviation of such a difference is 3.9 mmHg, with a 2:1 ratio, a sample size of 36 for each DE-126 arm and 18 for placebo will provide 92% power to detect the difference at all timepoints using a t-test (2-sided, a=0.0125 adjusted by Bonferroni correction). With 10% dropout rate, the sample size is 40 for each DE-126 arm and 20 for placebo arm.

Moreover, this sample size will provide less than 20% power to claim non-inferiority of DE-126 optimal dose to Latanoprost, assuming no treatment difference and 1.5 mmHg non-inferiority margin.

A mixed-effects model for repeated measures (MMRM) will be fitted and 95% confidence interval for each least-squares mean difference (DE-126 of each dose vs. placebo) will be estimated. To control an overall type I error rate of the study, Hochberg procedure will be used for multiple comparisons between DE-126 and control for the key secondary efficacy endpoint.

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4. 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
AE	Adverse event
AGIS	Advanced Glaucoma Intervention Study
Al-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BAK	Benzalkonium chloride
BUN	Blood urea nitrogen
CAIs	Carbonic Anhydrase inhibitors
Cl	Chlorine
dB	Decibel
eCRF	Electronic case report form
EDC	Electronic data capture
EP3	Prostaglandin E receptor 3
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full analysis set
FP	Prostaglandin F receptor
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUD	Intrauterine Device
K	Potassium
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
µg	Microgram
µm	Micrometer
MIGS	Minimally Invasive Glaucoma Surgery
MMRM	Mixed-effects Model for Repeated Measures
Na	Sodium
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
PACG	Primary Angle Closure Glaucoma
PG	Prostaglandin
PGA	Prostaglandin Analogue
POAG	Primary Open Angle Glaucoma
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SUN	Standardization of Uveitis Nomenclature
WHO-DDE	World Health Organization Drug Dictionary Enhanced
γ-GT	Gamma-glutamyltransferase

5. INTRODUCTION

Glaucoma represents a group of related diseases associated frequently with elevated IOP. When left untreated, glaucoma leads to retinal ganglion cell death and optic nerve damage, resulting in progressive and irreversible loss of vision. Glaucoma is the second leading cause of blindness worldwide, with an estimated prevalence of 60.5 million people in 2010 increasing to an estimated 79.6 million by 2020 (Quigley et al., 2006). It affects one in two hundred people aged fifty or younger and one in ten over the age of eighty (Resnikoff et al., 2004). Similarly in Japan, glaucoma is the first leading cause of blindness and it's prevalence is 5.0% (POAG 3.9%, PACG 0.6%, secondary glaucoma 0.5%) and OHT 0.8% in population over the age of forty (Iwase et al., 2004; Yamamoto et al., 2005).

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.

Several classes of ocular hypotensive medications exist today and are differentiated by their mechanism of action at the cellular/molecular level. These include miotics, β-adrenergic receptor antagonists (β-blockers), carbonic anhydrase inhibitors (CAIs), α-adrenergic receptor agonists (α-agonists), and prostaglandin analogues (PGAs). The pharmacodynamic effect of these medications can differ substantially, as some affect aqueous humor production (β-blockers, α-agonists, and CAIs) while others affect the outflow pathway (miotics, PGs, and α-agonists). In general, PGAs are recommended as the first choice agent for most eyes with ocular hypertension and open-angle glaucoma. The main reasons for this choice include their effective IOP reduction, lack of relevant systemic side effects, convenient once-daily dosing, and good tolerability profile (Alm, 2014).

With first line treatment with PGAs or β-blockers' IOP reduction is very effective; 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 ocular hypertension or open angle glaucoma.

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, and indeed it was proven such compounds exhibit more potent IOP reduction than latanoprost. Among the 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.

Three clinical studies (ONO-9054IOU001, ONO-9054IOU002, ONO-9054IOU003) were conducted 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.

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

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To determine the optimal dose of DE-126 by investigating the safety and efficacy of four (4) concentrations of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002%, and 0.003%) when compared to latanoprost (0.005% latanoprost) at Month 3 in subjects with primary open-angle glaucoma or ocular hypertension.

6.2. Secondary Objective

To determine if any one of four (4) concentrations of DE-126 (0.0005%, 0.001%, 0.002% and 0.003%) is superior to the placebo (vehicle of DE-126) in mean IOP reduction at each specified time point (09:00, 13:00 and 17:00) at Week 6 compared to baseline.

To investigate the dose response of four (4) concentrations of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002% and 0.003%).

6.3. Safety Objective

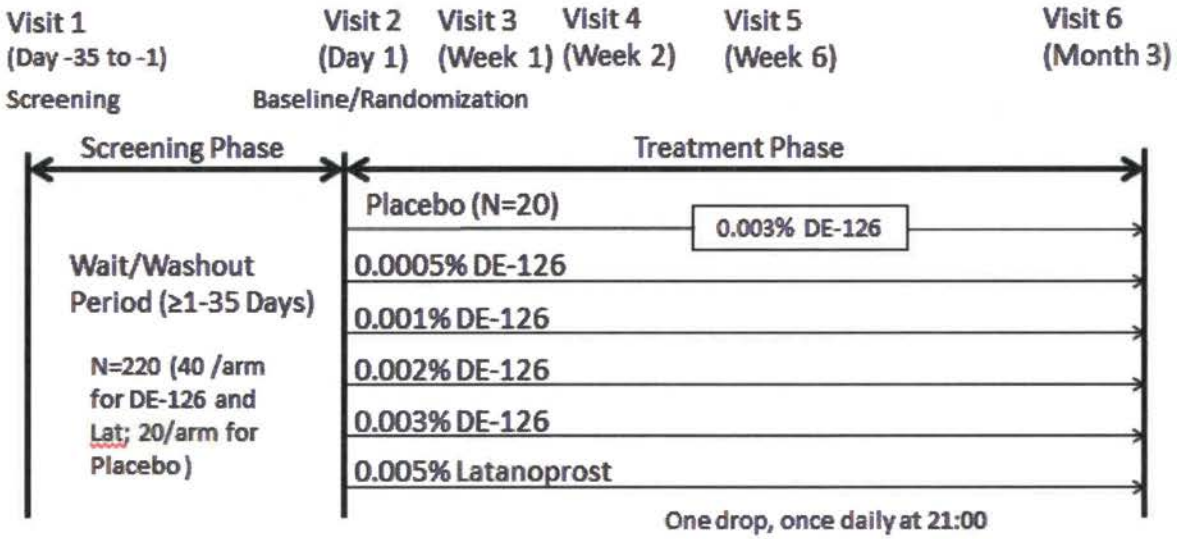
To determine the safety of DE-126 ophthalmic solutions (0.0005%, 0.001%, 0.002% and 0.003%) given once daily as compared to 0.005% latanoprost given once daily in this population.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, observer-masked, placebo- and active-controlled, parallel-group, multinational and multicenter study assessing the safety and efficacy of four (4) concentration of DE-126 ophthalmic solution (0.0005%, 0.001%, 0.002%, and 0.003%) in subjects with POAG or OHT. Latanoprost ophthalmic solution 0.005% will be used as active control. This study will consist of a screening phase of up to 35 days, including a washout period of up to 28 days (up to 7 additional days allowed prior to baseline visit) and a 3-month treatment period (Figure 1). If subject does not require washout of any medication, a minimum of 1 day is required between screening and baseline visits (or minimum of 7 days if subject uses contact lenses).

Figure 1: Study Design



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 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
- Beta antagonists (β blocker, including αβ blockers): 28 days

- Alpha antagonists (α1 blocker): 28 days
- Prostaglandins Analogs (PGA): 28 days
- Rho kinase inhibitor: 28 days

For combination drugs, the longest washout period of the individual component will be used.

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 1 week before the randomization at Visit 2 (Baseline, Day 1).

An interim safety visit, mid washout visit (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 by 1 week before the randomization at Visit 2 (Baseline, Day 1), mid washout visit (Visit 1a) is recommended to be performed.

Final eligibility will be determined at Visit 2 (Baseline) after all necessary washout from prior IOP-lowering medications has been completed. Subjects who have not used an IOP-lowering medication for the last 28 days prior to the screening visit, including treatment-naive subjects, must have at least one day between their screening visit and Visit 2 (Baseline).

At Visit 2, baseline IOP will be measured for both eyes at 09:00, 13:00 and 17:00 (±60 minutes). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet eligibility criteria, the eye with the higher diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye.

In cases where only one eye is fully qualified for the study, both eyes can be treated for the duration of the study. Approximately 220 eligible subjects will be randomized to one of the six (6) treatment arms. Forty (40) subjects per treatment arm will be randomized to each DE-126 and Latanoprost arm, and 20 subjects will be randomized to the Placebo arm. Central randomization via Interactive Response Technology (Medidata BALANCE) will be used to allocate the subjects to each of the six treatment arms in the U.S. and Japan separately. Each eligible subject will be assigned to receive a study medication kit number as allocated by the randomization schedule and assigned by BALANCE.

The study eye drops will be given once daily at 21:00 (±60 minutes), starting on the evening of Visit 2 and continuing through the evening prior to Visit 6 (Month 3). During the 3-month treatment period, subjects will return for Visits 3, 4, 5, and 6 (Weeks 1, 2, 6 and Month 3) and IOP will be measured at 09:00, 13:00 and 17:00 (±60 minutes). At these scheduled visits, corrected VA and slit lamp biomicroscopy will be performed at 09:00 immediately prior to IOP measurement. Corneal thickness measurement (pachymetry) and ophthalmoscopy (fundus examination) will be performed at 17:00 immediately after IOP measurement.

Subjects will be invited to separately consent to provide a saliva sample for a future pharmacogenomics/genomics laboratory research study, however providing such consent is not a prerequisite to participating in the main study. The purpose of this exploratory research is to identify possible genetic markers associated with the study drug(s) and/or ocular conditions.

7.2. Number of Subjects

Approximately 220 subjects in the U.S. and Japan in a 1:1 ratio.

7.3. Treatment Assignment

Subjects will be randomly assigned in a 1:2:2:2:2:2 ratio to receive one of the following treatments:

- Placebo (Vehicle of DE-126 ophthalmic solution) → 0.003% DE-126 at Week 6.
- 0.0005% DE-126 Ophthalmic Solution
- 0.001% DE-126 Ophthalmic Solution
- 0.002% DE-126 Ophthalmic Solution
- 0.003% DE-126 Ophthalmic Solution
- 0.005% Latanoprost Ophthalmic Solution

7.4. SCHEDULE OF EVENTS AND PROCEDURES

	Screening Phase		Treatment Phase				
	Visit 1 Screening	**Washout Period (optional Visit 1a)**	**Visit 2 Baseline (Day 1)**	**Visit 3 Week 1 (Day 8±2)**	**Visit 4 Week 2 (Day 15±2)**	**Visit 5 Week 6 (Day 43±3)**	**Visit 6 Month 3 (Day 91±3, Exit) or Early Term**
Informed Consent(s)[a]	X						
Inclusion/Exclusion Criteria	X		X				
Demographics and Medical History (incl. Prostaglandin Analogs naïve[b])	X						
Concomitant Medications/Therapies	X	X	X	X	X	X	X
Dosing Compliance				X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Pregnancy Test[c]	X		X				X
Urinalysis	X						X
Hematology and Serum Biochemistry	X						X
Vital signs (Blood pressure/heart rate)[d]	X		X				X
Refraction[e]	X		X	X	X	X	X
Corrected VA[f]	X	X	X (09:00)	X (09:00)	X (09:00)	X (09:00)	X (09:00)
Ocular Symptoms questionnaire[g]	X		X	X	X	X	X
Biomicroscopy (including conjunctival hyperemia, aqueous flare, cells)[f]	X	X	X (09:00)	X (09:00)	X (09:00)	X (09:00)	X (09:00)
Intraocular Pressure (IOP[f])[h]	X	X	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00	09:00 13:00 17:00

7.4 SCHEDULE OF EVENTS AND PROCEDURES (Continued)

	Screening Phase		Treatment Phase				
	Visit 1 Screening	**Washout Period (optional Visit 1a)**	**Visit 2 Baseline (Day 1)**	**Visit 3 Week 1 (Day 8±2)**	**Visit 4 Week 2 (Day 15±2)**	**Visit 5 Week 6 (Day 43±3)**	**Visit 6 Month 3 (Day 91±3, Exit) or Early Term**
Pachymetry (Central Corneal Thickness)[i]	X		X (17:00)			X (17:00)	X (17:00)
Iris, Eyelash, Eyelid assessment and photograph[j]			**X**			**X**	**X**
Gonioscopy[k]	**X**						
Visual Field[k]	**X**						
Ophthalmoscopy[l]	**X**		**X (17:00)**			**X (17:00)**	**X (17:00)**
Pharmacogenomics/genomics[m]			**X**				
Dispense Study Medication			**X**			**X**	
Collect Study Medication						**X**	**X**

[a] Informed Consent and authorization as appropriate for local privacy regulations must be signed and dated before study procedures are performed. Informed consent for the optional pharmacogenomics/genomics laboratory research study may be obtained at any visit prior to study exit.
[b] 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 medical records or subject history.
[c] A urine pregnancy test will be conducted for all female subjects of childbearing potential.
[d] Vital signs should be recorded at same timepoint at each visit, where possible.
[e] Refraction will be required if the prescription is not up to date within 12 months at the screening visit. If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction must be performed.
[f] Corrected VA and biomicroscopy examination will be completed before IOP is measured at 09:00. Aqueous flare and cell evaluation will be performed before fluorescein instillation. 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.
[g] Ocular symptoms questionnaire should be performed at the screening visit, and at the beginning of each post-screening visit (Visits 2 to 6).
[h] IOP Measurements will be taken at 09:00 ±60min, 13:00 ±60min and 17:00 ±60min at all visits except for Visit 1 (Screening).
[i] Pachymetry will be performed after IOP measurement at Visit 1 (if pachymetry is contact type), and after the 17:00 IOP measurement at Visits 2, 5, and 6.
[j] Iris, eyelash and eyelid photograph will be maintained as source documentation.
[k] Gonioscopy and visual field measurement will be performed if not done within 3 months prior to Visit 1. Gonioscopy will be performed after IOP measurement.

[l] Ophthalmoscopy will be performed after IOP measurement at Visit 1 and after the 17:00 IOP measurement at Visits 2, 5, and 6. If investigator performs ophthalmoscopy under dilation based on his/her decision, please dilate pupil and perform after all other ocular procedures have been completed.
[m] Saliva collection for the pharmacogenomics/genomics laboratory research study may be collected at any visit after informed consent obtained and subject randomized.

7.4.1. 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 pharmacogenetic laboratory research study may be obtained at any visit prior to study exit. Ensure that the subject understands that if they do not wish to provide a saliva sample for the pharmacogenomics/genomics laboratory research study that it will not affect the subject's enrollment in main study.

- Prepare the list of screening/registration of subjects.

- Obtain demographics.

- Obtain medications, ocular procedures/therapies and medical history including all ocular medical history, any other medical history within 5 years, POAG or OHT diagnosis, ocular surgical history, current ocular and systemic conditions.

- Obtain urine and perform urine pregnancy test, if the subject is a women of child-bearing potential.

- Perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):

    - Vital signs (at same timepoint at each visit, where possible)

    - Refraction (if it has not been performed in the previous twelve months)

    - Corrected visual acuity (before IOP measurement)

    - Ocular symptoms questionnaire

    - Biomicroscopy (before 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, please dilate pupil and evaluate after all other ocular procedures have been completed)

    - IOP

    - Pachymetry (if pachymetry is contact type, central corneal thickness is measured after IOP measurement)

    - Gonioscopy (if it has not been performed in the previous three months, after IOP measurement)

    - Visual field (if it has not been performed in the previous three months)

- Ophthalmoscopy (after IOP measurement. If investigator performs ophthalmoscopy under dilation based on his/her decision, please dilate pupil and perform after all other ocular procedures have been completed)
- Urinalysis
- Hematology and serum biochemistry

- Determine if the subject meets eligibility criteria.
- If the subject meets eligibility criteria and will continue in the study, discontinue any current IOP medication according to the following schedule (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
  - Beta antagonists (β blocker, including αβ blockers): 28 days
  - Alpha antagonists (α1 blocker): 28 days
  - Prostaglandins Analogs (PGA): 28 days
  - Rho kinase inhibitor: 28 days
- For combination drugs, the longest washout period of the individual component will be used. 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 1 week before the randomization at Visit 2 (Baseline, Day 1).
- An interim safety visit, mid washout visit (Visit 1a), may be performed during the washout period if, in the investigator's opinion, a subject's IOP causes any safety concern during the washout period. If subjects are treated with a topical CAI by 1 week before the randomization at Visit 2 (Baseline, Day 1), mid washout visit (Visit 1a) is recommended to be performed.
- The eligibility visit (Visit 2) 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-naive subjects, will need a wait period of ≥ 1 day before their Visit 2 (Baseline, Day 1).
  - 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 ≥ 7 days 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.

7.4.2. Visit 1a (Optional, Washout Period)

- Visit 1a is an interim safety visit, mid washout visit that may be performed during the washout period if, the investigator's opinion, a subject's IOP causes any safety concern during washout period.
- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding AEs.
- Perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
    - Corrected visual acuity (before IOP measurement)
    - Biomicroscopy (before IOP measurement)
    - IOP measurement

7.4.3. Visit 2 (Baseline, Day 1)

- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding AEs.
- Confirm the subject has complied with the required wait/washout period for ocular hypotensive medication(s), or contact lenses use.
- Complete ocular symptoms questionnaire prior to performing procedures listed below.
- Obtain urine and perform urine pregnancy test, if the subject is a women of child-bearing potential.
- Perform all ophthalmic procedures in both eyes.
- Perform corrected visual acuity and biomicroscopy immediately prior to the 09:00 IOP measurement.
- If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.
- Perform IOP measurement at 09:00 (±60 minutes).

- If subject meets the 09:00 IOP eligibility requirements, schedule additional IOP measurements at 13:00 and perform within ±60 minutes of the scheduled time.
- If subject meets the 09:00 and 13:00 IOP eligibility requirements, schedule additional IOP measurements at 17:00 and perform within ±60 minutes of the scheduled time.
- Perform pachymetry and ophthalmoscopy immediately after the 17:00 IOP measurement.
- Perform vital signs measurement at same timepoint at each visit, where possible.
- Collect Iris, Eyelash, Eyelid photographs at any time during this visit.
- Perform final review of eligibility criteria after the 17:00 IOP measurement. If the subject meets all eligibility criteria, upon completion of the above procedures and assessments, the Investigator will determine the study eye. The subject will then be randomized, via Interactive Response Technology (Medidata BALANCE).
    - The study eye will be the eye that qualifies per inclusion/exclusion criteria at Visit 2. If both eyes meet eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 will be the study eye. If both eyes meet eligibility criteria and have the same mean diurnal IOP, the right eye will be the study eye.
- After the subject has been randomized to a treatment arm, and assigned a treatment kit by BALANCE, an authorized study staff, other than the Investigator or examiner, must:
    - Dispense three bottles of study medication from the assigned subject kit.
    - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage. Instruct the subject not to show or discuss their study medication with other study staff or other study subjects.
- If the subject provided written consent to provide a saliva sample for a future pharmacogenomics/genomics laboratory research study, collect the sample at this visit or subsequent visit prior to exit from the study.
    - Note: If a saliva sample cannot be collected at this visit, it may be collected at any one of the following Visits, for example, Visits 3, 4, 5, 6, or unscheduled or early termination visit, the subject has provided written consent prior to collection of the sample.
- Schedule the subject to return on Day 8 ±2 for Visit 3 (Week 1).

- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- Remind the subject to bring all used and unused study medication at Visit 3.

7.4.4. Visit 3 (Week 1, Day 8 ±2)

- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding dosing compliance. An authorized study staff, other than the Investigator or examiner should ensure subject has sufficient study medication to complete dosing through Visit 4.
- Query the subject regarding AEs.
- Complete ocular symptoms questionnaire prior to performing procedures listed below.
- Perform all ophthalmic procedures in both eyes.
- Perform corrected visual acuity and biomicroscopy immediately prior to the 09:00 IOP measurement.
- If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.
- Perform IOP measurement at 09:00, 13:00, and 17:00 within ±60 minutes of the scheduled time.
- If the subject provided written consent to provide a saliva sample for a future pharmacogenomics/genomics 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 15 ±2 for Visit 4 (Week2).
- Remind the subject to continue dosing according to the written instructions.
- Remind the subject to bring all used and unused study medication at Visit 4.

7.4.5. Visit 4 (Week 2, Day 15 ±2)

- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding dosing compliance. An authorized study staff, other than the Investigator or examiner should ensure subject has sufficient study medication to complete dosing through Visit 5.
- Query the subject regarding AEs.

- Complete ocular symptoms questionnaire prior to performing procedures listed below.
- Perform all ophthalmic procedures in both eyes.
- Perform corrected visual acuity and biomicroscopy immediately prior to the 09:00 IOP measurement.
- If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.
- Perform IOP measurement at 09:00, 13:00, and 17:00 and perform within ±60 minutes of the scheduled time.
- If the subject provided written consent to provide a saliva sample for a future pharmacogenomics/genomics 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 43 ±3 for Visit 5 (Week6).
- Remind the subject to continue dosing according to the written instructions.
- Remind the subject to bring all used and unused study medication at Visit 5.

7.4.6. Visit 5 (Week 6, Day 43 ±3)

- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding dosing compliance. An authorized study staff, other than the Investigator or examiner should ensure subject has sufficient study medication to complete dosing through Visit 6.
- Query the subject regarding AEs.
- Complete ocular symptoms questionnaire prior to performing procedures listed below.
- Perform all ophthalmic procedures in both eyes.
- Perform corrected visual acuity and biomicroscopy immediately prior to the 09:00 IOP measurement.
- If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.
- Perform IOP measurement at 09:00, 13:00, and 17:00 and perform within ±60 minutes of the scheduled time.

- Perform pachymetry and ophthalmoscopy immediately after the 17:00 IOP measurement.
- Collect Iris, Eyelash, Eyelid photographs at any time during this visit.
- Assess any changes from baseline in Iris, Eyelash, Eyelid at any time during this visit.
- An authorized study staff member, other than the Investigator or examiner, must:
    - Collect all used and unused bottles of study medication.
    - Dispense three bottles of study medication. Instruct the subject not to show or discuss their study medication with other study staff or other study subjects.
- If the subject provided written consent to provide a saliva sample for a future pharmacogenomics/genetics 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 91 ±3 for Visit 6 (Month 3) Study Exit.
- Remind the subject to continue dosing according to the written instructions.
- Remind the subject to bring all used and unused study medication at Visit 6.

7.4.7. Visit 6 (Month 3, Day 91±3) Study Exit/Early Termination

- An authorized study staff member, other than the Investigator or examiner, must collect all used and unused bottles of study medication.
- Update concomitant medications and ocular procedures/therapies.
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Complete ocular symptoms questionnaire prior to performing laboratory tests and procedures listed below.
- Obtain urine and perform urine pregnancy test, if the subject is a women of child-bearing potential.
- Perform urinalysis, hematology, and serum biochemistry.
- Perform all ophthalmic procedures in both eyes.
- Perform corrected visual acuity and biomicroscopy immediately prior to the 09:00 IOP measurement.

- If more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.
- Perform IOP measurement at 09:00, 13:00, and 17:00 and within ±60 minutes of scheduled time.
- Perform pachymetry and ophthalmoscopy immediately after the 17:00 IOP measurement.
- Perform vital signs measurement at same timepoint at each visit, where possible.
- Collect Iris, Eyelash, Eyelid photographs at any time during this visit.
- Assess any changes from baseline in Iris, Eyelash, Eyelid at any time during this visit.
- If the subject provided written consent to provide a saliva sample for a future pharmacogenomics/genomics laboratory research study, and the sample was not collected a previous visit, it must be collected at this visit.
- Exit the subject from the study.

Note: If a subject's study participation is terminated prior to Visit 6, then, to the extent possible, all scheduled Visit 6 procedures will be performed on the day of early termination.

Note: If subject requires an unscheduled visit, procedures and assessments will be performed as needed.

7.5. Study Termination

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

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Subjects must meet all eligibility (inclusion and exclusion) criteria described in Sections 8.1 and 8.2.

8.1. Subject Inclusion Criteria

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

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.

2. Be 20 years or older in Japan and 18 years of age or older in the U.S. (or meets specific state requirement for legal age if that is greater than 18 years of age) on the date of signing the ICF and 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 surgically sterile [less than 6 months]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during, and for 28 days following the study.

    - Abstinence
    - Hormonal contraceptive method- oral and 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

    The male partner of the female subject of childbearing potential should use/practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraception deemed adequate by the investigator throughout the course of the study.

    Male subjects, with a female partner of childbearing potential, should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraception deemed adequate by the investigator throughout the course of the study.

4. Subjects must have a diagnosis of POAG or OHT in both eyes (excluding pseudoexfoliation syndrome).

5. Corrected visual acuity of +0.60 logMAR (Snellen equivalent 20/80, Decimal visual acuity 0.3) or better in each eye.

6. Central corneal thickness ≥ 480 µm and ≤ 620 µm in each eye.

7. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition, the subject must meet the inclusion criterion #3 again if applicable and the following criteria at Visit 2 (Baseline, Day 1):

8. Completed the required wait/washout period if applicable.
9. At all IOP measurement time-points (09:00, 13:00 and 17:00), IOP must be ≥ 22 mmHg in at least one eye and ≤ 34 mmHg in both eyes.

8.2. Subject Exclusion Criteria

A subject with any of the following ocular conditions in any eye or 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. Current or planned participation in any other clinical trial involving an investigational product or device within 30 days prior to Visit 1 (Screening) or at any time during this trial.

4. Subjects who have been exposed to DE-126 prior to Visit 1 (Screening).

Medications / Therapies-

5. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.

6. 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 [ARB]) within the first 30 days prior to Visit 1 (Screening), or anticipated change in such therapy during the study.

7. Intended or current use of the following prohibited medications during the study:

    - All ocular medications other than artificial tear, cataract treatment agents, and Vitamin B12 formulation, and study medications during the study.

- All systemically administered ocular hypotensive medication (e.g., oral or intravenous CAI, oral glycerol).
- Any ocular, periocular, inhaled, nasal or systemic corticosteroids.

8. Known allergy, hypersensitivity or contraindications to prostaglandins, benzalkonium chloride (BAK) or any other components of the study medications or other study related procedures/medications.

9. History of ocular surgery specifically intended to lower IOP (e.g., laser trabeculoplasty, filtering surgery, Minimally Invasive Glaucoma Surgery [MIGS], or trabeculotomy) in either eye.

10. History of keratorefractive surgery in either eye.

11. Use of contact lenses within one week prior to Visit 2 (Baseline, Day 1) until end of treatment.

12. Any ocular surgery or ocular laser treatment within 90 days prior to Visit 1 (Screening) and throughout the study in either eye.

Diseases-

13. Advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.

14. Any corneal abnormality or other condition interfering with or preventing reliable Goldmann applanation tonometry (e.g., Fuch's dystrophy, band-shaped keratopathy, Avellino corneal dystrophy or significant corneal surface abnormality) in either eye.

15. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.

16. History of iritis and/or uveitis, corneal inflammatory conditions, and/or viral infections such as herpes virus in either eye; history of adenovirus is not an exclusion provided no associated inflammation was observed within 6 months prior to screening.

17. Pseudophakic 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 or within 90 days after ocular surgery) for macular edema in either eye.

18. 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.

19. Subjects with a history of severe ocular trauma in either eye.

20. Subjects with any condition that prevents clear visualization of the fundus in either eye.

21. Presence or history of any ocular or systemic disease, clinical laboratory test abnormality 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.).

22. Any decision by the Principal Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

8.3. Subject Withdrawal Criteria

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 may terminate a subject's study participation due to any of the following reasons:

- Adverse Event (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., any contact is not possible)
- Death
- Other

- If a subject is voluntarily discontinued from study drug administration, he or she will be discontinued from the study.

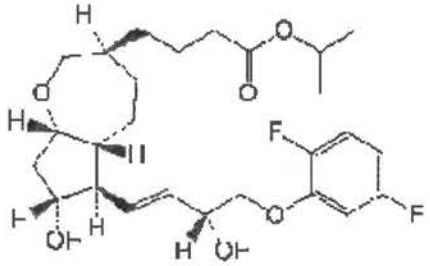
- If a subject's study participation is terminated prior to Visit 6, then to the extent possible, all scheduled Visit 6 procedures will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Medication

DE-126 ophthalmic solution is an aqueous solution containing DE-126. Benzalkonium chloride 0.005% is added as a preservative.

Figure 2: DE-126 Structure



Investigational Product:

- DE-126 ophthalmic solution 0.0005% contains 0.005 mg/mL DE-126.
- DE-126 ophthalmic solution 0.001% contains 0.01 mg/mL DE-126.
- DE-126 ophthalmic solution 0.002% contains 0.02 mg/mL DE-126.
- DE-126 ophthalmic solution 0.003% contains 0.03 mg/mL DE-126.

Active Control:

- Latanoprost ophthalmic solution 0.005% contains 0.05 mg/mL latanoprost.

Placebo:

- DE-126 vehicle ophthalmic solution.

9.2. 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 taken in addition to the study medication during the study duration will be considered as a concomitant treatment. The following information of concomitant treatment must be recorded in the subject's source documents.

- 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.

9.2.1. Prohibited Medications or Therapies

- All ocular medications other than artificial tear, cataract treatment agents, and Vitamin B_{12} formulation, and study medications, must be discontinued after Visit 1 (Screening).
  - If artificial tear, cataract treatment agents, and Vitamin B_{12} formulation 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.
- All systemically administered ocular hypotensive medications (e.g., oral or intravenous CAI, oral glycerol) during the study duration.
- Any ocular, periocular, inhaled, nasal or systemic corticosteroids 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, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARB]) within the first 30 days prior to Visit 1 (screening) and during the study duration.
- Contact lens wear must be discontinued at least one week prior to Visit 2 (Baseline, Day 1) and is prohibited during the remainder of the study.
- Any ocular surgery or ocular laser treatment will not be allowed within 90 days prior to Visit 1 (Screening) and throughout the study in either eye.
- Participation in any other clinical trial involving an investigational product within 30 days prior to Visit 1 (Screening) and during the study is not allowed.

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 should be notified before any prohibited medication or therapy is administered. There may be additional prohibited therapies not mentioned above. Medical monitor should be contacted if the permissibility of a specific medication or therapy is in question.

9.3. Treatment Compliance

To obtain reliable safety and efficacy 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 study medication storage. Subjects will be reminded at Visit 2 (Baseline, Day 1), Visit 3 (Day 8 ±2), Visit 4 (Day 15 ±2), and Visit 5 (Day 43 ±3) to consistently dose at the same time of the day (once daily at 21:00 [±60min]). Since subjects must have a diagnosis of POAG or OHT in both eyes, both eyes will be treated for the duration of the study, even if only one eye is eligible per IOP inclusion criteria.

- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 (Day 8 ±2),Visit 4 (Day 15 ±2), Visit 5 (Day 43 ±3), and Visit 6 (Day 91 ±3) Study Exit/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 (Day 8 ±2), Visit 4 (Day 15 ±2), Visit 5 (Day 43 ±3), and Visit 6 (Day 91 ±3) Study Exit/Early Termination. Subjects may be discontinued from the study at the discretion of the Investigator if the subject cannot be brought into compliance.

9.4. Randomization and Masking

Subjects will be randomized to one of the six (6) treatment arms. Forty (40) subjects per treatment arm will be randomized to each DE-126 and Latanoprost arms, and 20 subjects will be randomized to the Placebo arm. Central randomization via Interactive Response Technology (Medidata BALANCE) will be used to allocate the subjects to each of the six treatment arms in the U.S. and Japan separately. Each eligible subject will be assigned to receive a study medication kit numbered as allocated by the randomization schedule.

The appearance of the bottles used for the 4 active DE-126 groups and the placebo group will be identical. However, due to differences in appearance between the containers used for the test treatments (DE-126 and placebo) and the commercially available active control treatment (0.005% latanoprost), this study is classified as observer-masked. In order to maintain masking of investigators, examiners and sponsor personnel involved in the conduct of the study, only an authorized study staff member who is not the investigator or examiner at the investigative site will be permitted to dispense and collect study medication. Subjects will be instructed not to show the bottles to either the investigator or the examiner or other study subjects. The active control treatment containers will be overlabeled and packaged in the same secondary package (e.g., cardboard carton) as the test treatments.

Masking of treatment for subjects assigned to the placebo group, will be maintained when they are switched to 0.003% DE-126 at the week 6 visit, since the appearance of the 0.003% DE-126 bottles will be identical to the placebo bottles.

In case of a medical emergency, the Principal Investigator may reveal the treatment information by unmasking through Interactive Response Technology (Medidata BALANCE) 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 adverse event or serious adverse event for which study treatment was unmasked should be reported to Santen Pharmacovigilance.

10. STUDY MEDICATION MATERIALS AND MANAGEMENT

10.1. Study Medication

10.1.1. Investigational Product

Each 2.5 mL of DE-126 ophthalmic solution 0.0005%, 0.001%, 0.002% and 0.003% contains 12.5, 25, 50 and 75 µg of DE-126, respectively. In addition, the formulation contains excipients required to produce a stable ophthalmic solution dosage form. The solution is preserved with benzalkonium chloride (BAK) at 0.005%. Other inactive ingredients are polysorbate 80, sodium citrate, mannitol, edetate disodium, sodium hydroxide, hydrochloric acid and purified water.

10.1.2. Active Control

The active control used in this clinical study, Latanoprost ophthalmic solution 0.005% is supplied as a sterile, isotonic, buffered aqueous solution.

Latanoprost ophthalmic solution 0.005%

Each 2.5 mL of Latanoprost ophthalmic solution 0.005% contains 125 µg of latanoprost. Benzalkonium chloride 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. See Section 21.4, Appendix D.

10.1.3. Placebo

The formulation contains excipients required to produce a stable ophthalmic solution dosage form. The solution is preserved with benzalkonium chloride (BAK) at 0.005%. Other inactive ingredients are polysorbate 80, sodium citrate, mannitol, edetate disodium, sodium hydroxide, hydrochloric acid and purified water.

10.2. Study Medication Packaging and Labeling

DE-126 ophthalmic solution 0.0005%, 0.001%, 0.002%, 0.003% and DE-126 vehicle ophthalmic solution will be supplied as a 2.5 mL solution in a 5 mL clear polypropylen bottle.

Latanoprost ophthalmic solution 0.005% will be supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle.

Four eye drop bottles of study medication will be placed in one kit. The eye drop bottles and the kit will be labeled with the protocol number, kit number, storage conditions, and dosing instructions.

Three eye drop bottles of study medication in one kit will be dispensed at Visit 2 (Day 1, Baseline) and Visit 5 (Day 43 ±3), respectively. An authorized study staff, other than the

Investigator or examiner, will dispense and collect study medications. When collecting the study medications, the kit containing the all used and unused eye drop bottles will be sealed.

10.3. 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. Undispensed kits should be stored under refrigeration at 2° to 8°C (36° to 46°F) until dispensed. After 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 of the investigational site thereafter, until the last subject has exited the study. 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, protection from light and upright. Study medications should not be frozen.

10.4. Study Medication Preparation

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

10.5. Study Medication Administration

Subjects will instill one drop of study medication in each eye at approximately 21:00 (±60min) daily for 3 months.

10.6. 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.

10.7. 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.

10.8. Study Supplies

Commercial urine pregnancy test kits, laboratory test kits and customized saliva sample collection kits for the pharmacogenomics/genomics will be provided by Santen (or designee).

11. ASSESSMENT OF EFFICACY

11.1. Efficacy Parameter

The IOP (mmHg) measured in the study eye (identified at the baseline visit) is the efficacy measure for this study. The IOP at each scheduled time point (09:00, 13:00 and 17:00) will be evaluated at each post-baseline visit. Besides observed IOP measurements, change from baseline in IOP, and percent changes from baseline in IOP at each scheduled time point as well as the change from baseline in mean diurnal IOP will also be calculated and evaluated.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events and Serious Adverse Events

12.1.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical trial subject. An AE does not necessarily have a causal relationship with the study treatment. For this study, the investigational products are DE-126 vehicle, DE-126 and latanoprost. Regardless of relationship to the study treatment, 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 written informed consent, 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 an 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 treatment for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Investigator.

12.1.1.1. 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 12.1.2.

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 if:
  - There is a plausible temporal relationship between the onset of the AE and administration of the study medication
  - The AE abates or resolves upon discontinuation of the study medication or dose reduction and, if applicable, reappears upon rechallenge
  - The AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies
  - The AE follows a known pattern of response to the investigational product
- Reporting the event as **Not Related** to study medication may be considered if:
  - There is good evidence that the AE has an etiology other than the investigational product (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication)
  - The AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study medication)

12.1.1.2. 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 electronic case report form (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 the last study procedure is performed, 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.

12.1.2. Serious Adverse Events

12.1.2.1. Assessment of Serious Adverse Events

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

- It resulted in 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.

12.1.2.2. 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.

12.1.2.3. 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.

12.1.3. Reporting Pregnancy

There are no controlled data with the investigational product in human pregnancy. It is required that women of childbearing potential use effective contraception during, and for 28 days following the study. Any pregnancy in a subject occurring during study treatment should be reported on the appropriate eCRF with as much information as available within 24 hours of knowledge of the event and the subject removed from the study. The subject should be followed until the end of pregnancy.

12.1.4. Follow-up of Adverse Events

All reported AEs should be followed until resolution or until the subject's participation in the study ends. Subjects who have an on-going study medication-related SAE at study completion or at early termination from the study will be followed by the Investigator until the event is resolved or determined to be irreversible, chronic, or stable.

In addition, on a case by case basis, Santen (or designee) may request follow up beyond the end of the study.

If Santen Pharmacovigilance requests follow-up on an individual SAE or AE, the response will be entered into the eCRF, as appropriate. If the information requested from Santen Pharmacovigilance is not part of the SAE or AE eCRF, the information will be sent to Santen Pharmacovigilance.

12.1.5. Manual Back-Up Reporting Procedures

This study is utilizing an electronic data capture (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 and an SAE Form and/or pregnancy form.
- Attach a cover sheet with your contact information and address to Santen (or its designee).
- Email (preferred) or Fax the cover sheet and the completed form(s) to Santen (or its designee) at santensafety@santen.com or fax number +81-6-6359-3843 (in JP) and +1-415-276-5882 (in US).

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

12.2. 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.

12.2.1. Ocular Assessments

Ocular assessments include:

- Ocular symptoms: burning/stinging, foreign body sensation, tearing, itching, photophobia, and pain
- Corrected visual acuity
- 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
- Central corneal thickness
- Ophthalmoscopy variables: glaucomatous optic nerve
- Iris color/eyelash/eyelid

13. OTHER ASSESSMENTS

13.1. Demographic, Baseline Characteristics and Other Assessments

Subject demographics and baseline characteristics will be recorded. Subject demographics include age, sex, race, and ethnicity. Baseline characteristics include iris color, concurrent disease, prior medications especially IOP-lowering medications, and baseline IOP.

Other assessments include exposure (number of days on study medication) and concomitant medications/therapies.

14. STATISTICAL METHODS

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 Statistical Analysis Plan (SAP).

14.1. Analysis Time Points

A single analysis at the end of the study will be performed.

14.1.1. Interim Analysis

There are no interim analyses planned during this study.

14.1.2. Final Analysis

An unmasked final analysis will be performed to evaluate the safety and efficacy of DE-126 ophthalmic solution in each dose (0.0005%, 0.001%, 0.002% and 0.003%) compared with placebo and latanoprost ophthalmic solution 0.005%.

14.2. General Considerations

Descriptive statistics, unless otherwise noted, will include the number of subjects (N), mean, standard deviation (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. If both eyes qualify, the eye with the higher mean diurnal IOP at baseline (Visit 2) will be the study eye, although both eyes may receive study drug. If both eyes have the same mean diurnal IOP at baseline, then the right eye will be designated as the study eye.

The SAP with more details on the statistical methods will be finalized prior to unmasking the data. Unless otherwise stated, all analyses will be implemented using SAS® v9.

14.2.1. Sample Size

The sample size is not planned on the primary efficacy endpoint. For the key secondary endpoint, assuming that the minimal expected treatment difference across all timepoints is -5.1 mmHg between an optimal DE-126 dose and placebo (based on ONO-9054IOU002 and ONO-9054IOU003 studies) and the standard deviation of such a difference is 3.9 mmHg, with a 2:1 ratio, a sample size of 36 for each DE-126 arm and 18 for placebo will provide 92% power to detect the difference at all timepoints using a t-test (2-sided, a=0.0125 adjusted by Bonferroni correction). With 10% dropout rate, the sample size is 40 for each DE-126 arm and 20 for placebo arm.

Moreover, this sample size will provide less than 20% power to claim non-inferiority of DE-126 optimal dose to Latanoprost, assuming no treatment difference and 1.5 mmHg non-inferiority margin.

14.2.2. Statistical Hypotheses and Level of Significance

The primary efficacy endpoint is the IOP at each scheduled time point (09:00, 13:00 and 17:00) in the study eye at Visit 6 (Month 3). No formal statistical hypothesis testing will be implemented for the primary endpoint. Descriptive summaries will be provided by groups.

For the key secondary endpoint, the comparison between DE-126 of each dose group and placebo group will be performed with the following pair of testing hypotheses:

H_0: $\mu_P = \mu_T$ versus H_1: $\mu_P \neq \mu_T$

where μ_T and μ_P denote the mean values of the primary endpoint in DE-126 treatment group and placebo group, respectively.

Treatment differences between the DE-126 of each dose group and the placebo group will be reported for each time point along with 95% confidence intervals. Superiority of DE-126 to placebo is established if the upper limit of the 95% confidence interval for the difference is less than 0 mmHg for IOP at all timepoints at Visit 5 (week 6). To control the overall Type I error rate associated with the four comparisons at the 0.05 level (two-sided), the Hochberg procedure will be used, and the statistical significance will be evaluated with the adjusted P-values.

14.3. Study Populations

14.3.1. 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.

14.3.2. Full Analysis Set

The Full Analysis Set (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.

14.3.3. Per-Protocol Population

The Per-Protocol (PP) Population is a subset of the FAS. It includes all FAS subjects without protocol deviations that could affect the primary efficacy endpoint. Subjects excluded from the PP Population will be identified before unmasking the data.

14.4. Handling of Missing Values

Efficacy endpoints will be analyzed using available data at the end of the study. Sensitivity analyses using last observation carried forward (LOCF) may be performed. Details on sensitivity analyses, if any, will be included in the SAP.

14.5. Demographic and Baseline Characteristics

Age, sex, race, ethnicity, iris color, and baseline IOP will be summarized with descriptive statistics by treatment.

Concurrent diseases will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Subjects with any concurrent diseases will be tabulated by primary system organ class and preferred term specified in the MedDRA.

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

14.6. Efficacy Analyses

14.6.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the IOP at each scheduled time point (09:00, 13:00 and 17:00) in the study eye at Visit 6 (Month 3).

An optimal dose of DE-126 will be specified based on the descriptive summary and no statistical hypothesis testing will be implemented.

14.6.2. Analysis of Secondary Efficacy Endpoints

14.6.2.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the mean IOP in the study eye at each specified time point (09:00, 13:00 and 17:00) at Visit 5 (week 6).

A mixed-effect model for repeated measures (MMRM) will be carried out and 95% confidence interval for the difference in means (DE-126 of each dose; 0.0005%, 0.001%, 0.002% and 0.003%, vs. placebo) will be estimated. Superiority of DE-126 to placebo is established if the upper limit of the 95% confidence interval for the difference is less than 0 mmHg for IOP at all timepoints at Week 6.

14.6.2.2. Other Secondary Efficacy Endpoints

- IOP in the study eye at each specified time point (09:00, 13:00 and 17:00) at Visit 3 and Visit 4 (Week 1 and Week 2).

- Mean diurnal IOP in the study eye at Visits 3, 4, 5, and 6 (Week 1, Week 2, Week 6, and Month 3).
- Change and percent change from baseline (CFB) in mean diurnal IOP in the study eye at each post-baseline visit (Visit 3, 4, 5, and 6 [Week 1, Week 2, Week 6 and Month 3, respectively]).
- Change and percent change from baseline (CFB) in IOP in the study eye at the specified time points: 09:00, 13:00, and 17:00 at each post-baseline visit.
- Proportion of subjects with mean diurnal IOP reduction from baseline $\geq$ 20%, 25 % and 30% in the study eye at Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3).
- Proportion of subjects with mean diurnal IOP $\leq$ 18 mmHg in the study eye at Visit 3 (Week 1), Visit 4 (Week 2), Visit 5 (Week 6) and Visit 6 (Month 3).

14.7. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs, corrected visual acuity, ocular symptoms, slit-lamp biomicroscopy findings, central corneal thickness, ophthalmoscopy variables, iris color, eyelash, and eyelid by photographs, vital sign and clinical laboratory tests.

AEs will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Subjects with any AEs will be tabulated by primary system organ class and preferred term 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.

Ocular safety parameters listed in Section 12.2.1 will be summarized using descriptive statistics by treatment. Changes from baseline in these ocular safety parameters will also be summarized by treatment.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Principal Investigator will allow representatives of Santen's monitoring team (or designee), the governing institutional review board (IRB) or independent ethics committee (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 ICH-GCP or other regulatory agency regulations.

15.1. 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

- Confirm sites have a complete record of all study 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.

15.2. 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.

15.3. 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.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. 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 completion of eCRFs, 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.

16.2. Quality Assurance

Santen (or designee) may conduct a quality assurance audit at any time. See Section 15.2.

17. ETHICS

17.1. Ethics Review

The final study protocol and the final version of the informed consent form (ICF), for the main study and the ICF for the pharmacogenetics study, 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 saliva samples for optional future pharmacogenetic 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 21.1, 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.

17.2. 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 Conference on Harmonization (ICH) guidelines, and the Declaration of Helsinki.

17.3. 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 saliva samples for future pharmacogenetic research studies. If the subject does not wish to provide a saliva sample for the biomarker research study that it 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 21.2, Appendix B.

18. DATA HANDLING AND RECORDKEEPING

18.1. 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.

18.2. 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.

18.2.1. 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

18.2.2. 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.

18.2.3. 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. 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.

19. 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.

20. REFERENCES

20.1. Literature

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20.2. Study Data

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

21. APPENDICES

21.1. 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 drug accountability.
- Providing Santen a final study report.

21.2. 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 pharmacogenomics/genomics 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.

21.3. Appendix C - Procedures for Assessments

21.3.1. Demographics, Medication/Therapy and Medical History

Demographics including age, sex, race, prostaglandin analogs naïve status, and ethnicity will be obtained through subject interviews at Visit 1 (Screening).

Medications and ocular procedures/therapies will be confirmed through subject interviews during the study.

Following details of prior medication that has been used for POAG or OHT within 28 days before the date of Visit 1, or any concomitant medication, must be recorded in the subject's source documents.

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

Following details of prior ocular procedure/therapy that has been received for POAG or OHT within 28 days before the date of Visit 1, or any concomitant ocular procedure/therapy, must be recorded in the subject's source documents.

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

Medical history including all ocular medical history, any other medical history within 5 years, POAG or OHT diagnosis, ocular surgical history, current ocular and systemic conditions will be confirmed through subject interviews at Visit 1 (Screening) to determine if the subject meets eligibility criteria. Primary diagnosis, POAG or OHT, and the affected eye must be recorded in the subject's source documents.

Name of concurrent disease, and affected eye(s) (if applicable) will be confirmed at Visit 1 (Screening) and Visit 2 (Baseline, Day 1), and recorded in the subject's source documents.

21.3.2. Pregnancy Test

A urine pregnancy test will be conducted using a commercially available test kit at Visit 1 (Screening), Visit 2 (Baseline, Day 1) and Visit 6 (Day 91 ±3) Study Exit/Early Termination for all women 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.

21.3.3. Urinalysis, Hematology, and Serum Biochemistry

Blood and urine samples will be collected at the Visit 1 and 6 for urinalysis, hematology, and serum biochemistry. The amount of one blood sample is 5.5 mL and the amount of one urine

sample is 6 mL. Urine to be used is midstream urine. Detailed procedures are listed in the Central Laboratory Services Manual.

Urinalysis

Urine glucose (qualitative), urine protein (qualitative), and urobilinogen (qualitative)

Hematology

Erythrocytes, leukocytes, hemoglobin, hematocrit, platelet count, leukocyte differentiation (neutrophil, eosinophil, basophil, monocyte, and lymphocyte)

Serum Biochemistry

AST, ALT, γ-GT, Al-P, LDH, total bilirubin, total protein, albumin, cholesterol (total, HDL, LDL and triglycerides), BUN, creatinine, uric acid, Na, K, and Cl

21.3.4. Vital signs (Blood pressure/heart rate)

Systolic blood pressure, diastolic blood pressure, and heart rate will be measured at same timepoint at each visit, where possible, after keeping quiet in a sitting position for more than 5 minutes.

21.3.5. Ocular Symptoms

Ocular Symptoms will be graded on 4-point scales prior to performing any other procedures at each visit except Visit 1, as described below:

Burning/Stinging

Burning or stinging sensation involving ocular structures.

None	(0) =	Absent.
Mild	(1) =	Subject aware of ocular discomfort.
Moderate	(2) =	Subject experiencing intermittent burning sensation causing a desire to rub, and tearing over the lid margin.
Severe	(3) =	Constant burning for extended period of time causing tearing, hyperemia, swelling, etc.

Foreign Body Sensation

Sensation of grittiness or having something under the eyelid or on the ocular surface.

None	(0) =	Absent.
Mild	(1) =	Similar to the sensation of fine dust or powder in the eye.

Moderate (2) = Similar to the sensation of sand or dust in the eye, resulting in moderate tearing and blinking.

Severe (3) = Similar to the sensation of a hot cinder in the eye, associated with constant tearing and blepharospasm.

Tearing

None (0) = Absent.

Mild (1) = Positive sensation of fullness of the conjunctival sac without tears spilling over the lid margin.

Moderate (2) = Infrequent or intermittent spilling of tears over the lid margin.

Severe (3) = Constant or nearly constant spilling of tears over the lid margin, associated with blowing nose.

Itching

Sensation of the need to scratch or rub the eyelids or the periorbital area.

None (0) = Absent.

Mild (1) = Subject aware of intermittent sensation. Not severe enough to rub.

Moderate (2) = Intermittent sensation with desire to rub.

Severe (3) = Constant awareness of sensation with tearing and rubbing, resulting in disruption of normal schedule.

Photophobia

None (0) = Absent.

Mild (1) = Very minimal light intolerance which may require some degree of sunglass protection to eliminate the symptom, noticed primarily in sunlight.

Moderate (2) = Infrequent or intermittent discomfort in the globe associated with exposure to room light or sunlight which is only partially relieved by dark glasses or subdued light. The symptoms still persist to some degree even with sunglasses.

Severe (3) = Constant or nearly constant exquisite pain in the eye that is not relieved by sunglasses and is only relieved by total occlusion of the eye with an eye patch or by closing the eyes. This sensation is so significant that

frequently bed rest and occasionally, systemic sedation is required to relieve this severe grade of symptoms.

Pain

Sensation in the periocular region of the external eye including burning, itching around the eye, headache, orbital aching etc.

None	(0) =	Absent.
Mild	(1) =	Awareness of one's eyes, difficulty in describing specific type of discomfort, e.g., fullness or heaviness, diffuse foreign body sensation, mild aching.
Moderate	(2) =	Ability to describe the pain modality in specific terms, e.g., burning, itching, focal foreign body sensation, moderate aching.
Severe	(3) =	Exquisite ocular, periocular, or radiating pain, e.g., throbbing headache, which may be accompanied by nausea and vomiting requiring analgesia and/or sedation.

21.3.6. Iris, Eyelash, Eyelid

The investigator (or his/her designee) will take frontview and sideview photograph of each eye at Visit 2, Visit 5, and Visit 6. The photographs must include iris, eye lids and eyelashes of each eye. The photographs taken at Visit 2 (Baseline) will be used to help the Investigator assess iris color (e.g., brown, yellow-brown, green-brown, green with slightly brown, green, blue/gray-brown, blue/gray with slightly brown, blue/gray) and any changes from baseline (decreased/no change/increased) in iris color, eyelash and eyelid at Visit 5 and Visit 6 Study Exit/Early Termination.

Each photograph will be labeled with subject number, OD or OS, and Visit number, and kept with the subject's source document.

21.3.6.1. Iris Color

The investigator will assess the iris color and any change (e.g., pigmentation) at Visit 5 and Visit 6 Study Exit/Early Termination using the photographs obtained at Visit 2 (Baseline).

21.3.6.2. Eyelash

The investigator will assess eyelash change at Visit 5 and Visit 6 Study Exit/Early Termination (e.g., length, thickness, pigmentation and number) using the photographs obtained at Visit 2 (Baseline).

21.3.6.3. Eyelid

The investigator will assess eyelid change at Visit 5 and Visit 6 Study Exit/Early Termination (e.g., pigmentation and hair growth) using the photographs obtained at Visit 2 (Baseline).

21.3.7. Refraction

Refraction will be performed for each eye at Visit 1, if it has not been performed in the previous 12 months. At Visits 2 to 6, if more than 10 letters in corrected visual acuity were lost compared to the screening visit, then refraction should be performed.

21.3.8. Corrected Visual Acuity

Corrected visual acuity will be measured for each eye immediately prior to the 09:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit) under normal room illumination using visual acuity chart (e.g., ETDRS chart, Snellen chart) and the logMAR scoring will be recorded in the subject's source document (ETDRS only – if Snellen chart is used the logMAR score will be converted by the sponsor). For Visit 1/1a, the corrected visual acuity should be performed prior to IOP measurement. If ETDRS chart is used, the following procedure should be followed.

21.3.8.1. 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 3: 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

21.3.9. Slit-lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the 09:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1/1a, 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 Standardization of Uveitis Nomenclature (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 punctuate 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

21.3.10. Intraocular Pressure

IOP will be performed at each visit. At visit 1/1a, IOP can be measured at any time. For Visit 2, Visit 3, Visit 4, Visit 5, and Visit 6 Study Exit/Early Termination, IOP measurements will be scheduled for 09:00 (±60min), 13:00 (±60min) and 17:00 (±60min).

IOP will be measured using calibrated Goldmann applanation tonometer. Measurement will be performed preferably by the same Investigator (operator) and the same authorized study staff (recorder) throughout the study.

The right eye is always tested first. At least two, and sometimes three, consecutive measurements are made to obtain a determination of intraocular pressure. 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 Investigator 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 Investigator 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 Investigator 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 investigator 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 Investigator 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 Investigator removes the tip from the cornea, and the authorized study staff (recorder) 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.

  - The Investigator may be recorder instead of the authorized study staff, if he/she is not assigned.

- 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.

21.3.10.1. Tonometer Calibration

The tonometer must be calibrated for accuracy before the first subject undergoes screening (mandatory), and then in accordance with the site's established procedure and frequency for

calibration maintenance, until the last subject has exited the study (as much as possible). 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.

21.3.11. 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 immediately after the 17:00 IOP measurement at Visit 2, Visit 5 and Visit 6 Study Exit/Early Termination. For Visit 1 (Screening), pachymetry should be performed after IOP measurement (if pachymetry is contact type).

21.3.12. 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. 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

21.3.13. Visual Field

Visual field examinations will be performed using a static or dynamic perimeter (Humphrey, Octopus, or KOWA perimeter) without pupil dilation at Visit 1 (Screening), if it has not been performed within 3 months 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 standard deviation, 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) should be excluded. A copy of the computer printout from the visual field test(s) will be attached to the subject's source documents.

21.3.14. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination will be performed for each eye at Visit 1, Visit 2, Visit 5, and Visit 6 Study Exit/Early Termination, and graded as described below. If investigator performs ophthalmoscopy under dilation based on his/her decision, please dilate pupil and perform 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

21.3.15. Saliva Sample for Pharmacogenomics/genomics Study

At sites which elect to participate and for subjects who agree to provide a saliva sample, an exploratory biomarker laboratory research study will be performed to evaluate the association of possible genetic biomarkers with the study drug(s) and/or ophthalmologic conditions. Approximately 2 mL of saliva will be collected for genetic analysis from the subject and stored in a refrigerator or room temperature until shipment. Please refer to the separate Central Laboratory Services manual for sample handling, storage, and shipment. The samples will be coded to protect the participants' private information. Nucleic acids will be extracted from saliva sample and stored in the repository for future pharmacogenomics/genomics studies performed by appropriate assay platforms such as PCR (Polymerase Chain Reaction), hybridization, and sequencing on the genes involved in the study drug(s) and/or ophthalmologic conditions. Individual subjects' results from the research testing on their samples will not be communicated to them.

Samples collected and stored, and relevant documents (the list of screening/registration of subjects only for documents to be retained by the medical institution) will be retained for the period agreed in the IC. Upon completion of analyses or the retention period, they will be anonymized and disposed. If the subject withdraws the consent, samples will be immediately disposed, and the applicable subject will be informed in writing.

For any other matters not specified in the protocol, a written procedure will be defined separately.

21.4. Appendix D - Latanoprost Ophthalmic Solution, 0.005% Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALATAN safely and effectively. See full prescribing information for XALATAN.

XALATAN® (latanoprost ophthalmic solution) 0.005%
Initial U.S. Approval: 1996

INDICATIONS AND USAGE

XALATAN is a prostaglandin $F_{2\alpha}$ analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

DOSAGE AND ADMINISTRATION

One drop in the affected eye(s) once daily in the evening. (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing 50 mcg/mL latanoprost (0.005%). (3)

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product. (4)

WARNINGS AND PRECAUTIONS

- Pigmentation: pigmentation of the iris, periorbital tissue (eyelid) and eyelashes can occur. Iris pigmentation likely to be permanent. (5.1)
- Eyelash Changes: gradual change to eyelashes including increased length, thickness and number of lashes. Usually reversible. (5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥4%) from clinical trials are blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, punctate epithelial keratopathy, and upper respiratory tract infection/cold/flu. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer at 1-800-438-1985 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

***In vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used, they should be administered at least 5 minutes apart. (7)**

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Pigmentation
5.2 Eyelash Changes
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5.4 Macular Edema
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XALATAN Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

2 DOSAGE AND ADMINISTRATION

The recommended dosage is one drop in the affected eye(s) once daily in the evening. If one dose is missed, treatment should continue with the next dose as normal.

The dosage of XALATAN should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including XALATAN is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure (IOP) lowering effect or cause paradoxical elevations in IOP.

Reduction of the IOP starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

XALATAN may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. Contact lenses should be removed prior to the administration of XALATAN, and may be reinserted 15 minutes after administration

3 DOSAGE FORMS AND STRENGTHS

Sterile ophthalmic solution containing 50 mcg/mL latanoprost.

4 CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in this product.

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

XALATAN has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. Beyond 5 years the effects of increased pigmentation are not known *[see Clinical Studies (14.2)]*.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with XALATAN can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [*see Patient Counseling Information (17.1)*].

5.2 Eyelash Changes

XALATAN may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment [*see Patient Counseling Information (17.2)*].

5.3 Intraocular Inflammation

XALATAN 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 because inflammation may be exacerbated.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. XALATAN should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Herpetic Keratitis

Reactivation of Herpes Simplex keratitis has been reported during treatment with XALATAN. XALATAN should be used with caution in patients with a history of herpetic keratitis. XALATAN should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

5.6 Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface [*see Patient Counseling Information (17.3)*].

5.7 Use with Contact Lenses

Contact lenses should be removed prior to the administration of XALATAN, and may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions were reported in postmarketing experience and are discussed in greater detail in other sections of the label:

- Iris pigmentation changes [see *Warnings and Precautions (5.1)*]
- Eyelid skin darkening [see *Warnings and Precautions (5.1)*]
- Eyelash changes (increased length, thickness, pigmentation, and number of lashes) [see *Warnings and Precautions (5.2)*]
- Intraocular inflammation (iritis/uveitis) [see *Warnings and Precautions (5.3)*]
- Macular edema, including cystoid macular edema [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

XALATAN was studied in three multicenter, randomized, controlled clinical trials. Patients received 50 mcg/mL XALATAN once daily or 5 mg/mL active-comparator (timolol) twice daily. The patient population studied had a mean age of 65±10 years. Seven percent of patients withdrew before the 6-month endpoint.

Table 1: Ocular Adverse Reactions and ocular signs/symptoms reported by 5–15% of patients receiving Latanoprost

	Adverse Reactions (incidence (%))	
Symptom/Finding	Latanoprost (n=460)	Timolol (n=369)
Foreign body sensation	13	8
Punctate epithelial keratopathy	10	9
Stinging	9	12
Conjunctival hyperemia	8	3
Blurred vision	8	8
Itching	8	8
Burning	7	8
Increased pigmentation of the iris	7	0

Less than 1% of the patients treated with XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

Table 2: Adverse Reactions that were reported in 1–5% of patients receiving Latanoprost

	Adverse Reactions (incidence (%))	
	Latanoprost (n=460)	Timolol (n=369)
Ocular Events/Signs and Symptoms		
Excessive tearing	4	6
Lid discomfort/pain	4	2
Dry eye	3	3
Eye pain	3	3
Lid crusting	3	3
Lid erythema	3	2
Photophobia	2	1
Lid edema	1	3
Systemic Events		
Upper respiratory tract infection/cold/flu	3	3

	Adverse Reactions (Incidence (%))	
	Latanoprost (n=460)	Timolol (n=369)
Muscle/joint/back pain	1	0.5
Rash/allergic skin reaction	1	0.3

6.2 Postmarketing Experience

The following reactions have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include:

Nervous System disorders: dizziness, headache, and toxic epidermal necrolysis

Eye Disorders: eyelash and vellus hair changes (increased length, thickness, pigmentation, and number); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; misdirected eyelashes sometimes resulting in eye irritation; periorbital and lid changes resulting in deepening of the eyelid sulcus

Respiratory, Thoracic and Mediastinal Disorders: asthma and exacerbation of asthma; dyspnea

Skin and Subcutaneous Tissue Disorders: eyelid skin darkening

Infections and Infestations: Herpes keratitis

7 DRUG INTERACTIONS

In vitro studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins, or prostaglandin analogs including XALATAN is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose.

There are no adequate and well-controlled studies in pregnant women. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XALATAN is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

10 OVERDOSAGE

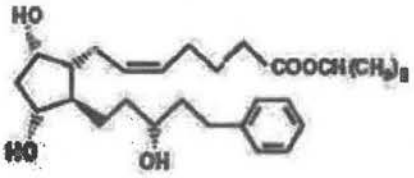
Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

If overdosage with XALATAN occurs, treatment should be symptomatic.

11 DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:

M.W. 432.58



Latanoprost is a colorless to slightly yellow oil that is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol, and octanol. It is practically insoluble in water.

XALATAN (latanoprost ophthalmic solution) 0.005% is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of XALATAN contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. One drop contains approximately 1.5 mcg of latanoprost.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist that is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow. Elevated IOP represents a major risk factor for glaucomatous field loss. The higher the level of IOP, the greater the likelihood of optic nerve damage and visual field loss.

12.2 Pharmacodynamics

Reduction of the IOP in man starts about 3–4 hours after administration and maximum effect is reached after 8–12 hours. IOP reduction is present for at least 24 hours.

12.3 Pharmacokinetics

Absorption

Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Metabolism

Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Excretion

The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}$ = 17 min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical and intravenous dosing, respectively.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 mcg/kg/day (approximately 2800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Latanoprost was not mutagenic in bacteria, in mouse lymphoma, or in mouse micronucleus tests. Chromosome aberrations were observed *in vitro* with human lymphocytes. Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative.

Latanoprost has not been found to have any effect on male or female fertility in animal studies.

14 CLINICAL STUDIES

14.1 Elevated Baseline IOP

Patients with mean baseline IOP of 24 – 25 mmHg who were treated for 6 months in multi-center, randomized, controlled trials demonstrated 6 – 8 mmHg reductions in IOP. This IOP reduction with XALATAN 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

14.2 Progression of Increased Iris Pigmentation

A 3-year open-label, prospective safety study with a 2-year extension phase was conducted to evaluate the progression of increased iris pigmentation with continuous use of XALATAN once-daily as adjunctive therapy in 519 patients with open-angle glaucoma. The analysis was based on observed-cases population of the 380 patients who continued in the extension phase.

Results showed that the onset of noticeable increased iris pigmentation occurred within the first year of treatment for the majority of the patients who developed noticeable increased iris pigmentation. Patients continued to show signs of increasing iris pigmentation throughout the five years of the study. Observation of increased iris pigmentation did not affect the incidence, nature, or severity of adverse events (other than increased iris pigmentation) recorded in the study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

16 HOW SUPPLIED/STORAGE AND HANDLING

XALATAN is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 mcg/mL). It is supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap.

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle: NDC 0013-8303-04

2.5 mL fill, 0.005% (50 mcg/mL): Multi-pack of 3 bottles: NDC 0013-8303-01

Storage: Protect from light. Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to the patient, the bottle may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.

17 PATIENT COUNSELING INFORMATION

17.1 Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Inform patients about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XALATAN [*see Warnings and Precautions (5.1)*].

17.2 Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XALATAN. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

17.3 Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions [*see Warnings and Precautions (5.6)*].

17.4 When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

17.5 Use with Contact Lenses

Advise patients that XALATAN contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of XALATAN.

17.6 Use with Other Ophthalmic Drugs

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

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22. PROTOCOL AMENDMENT 1 SUMMARY OF CHANGES

Table 4: Protocol Amendment 1 Summary of Changes (Continued)

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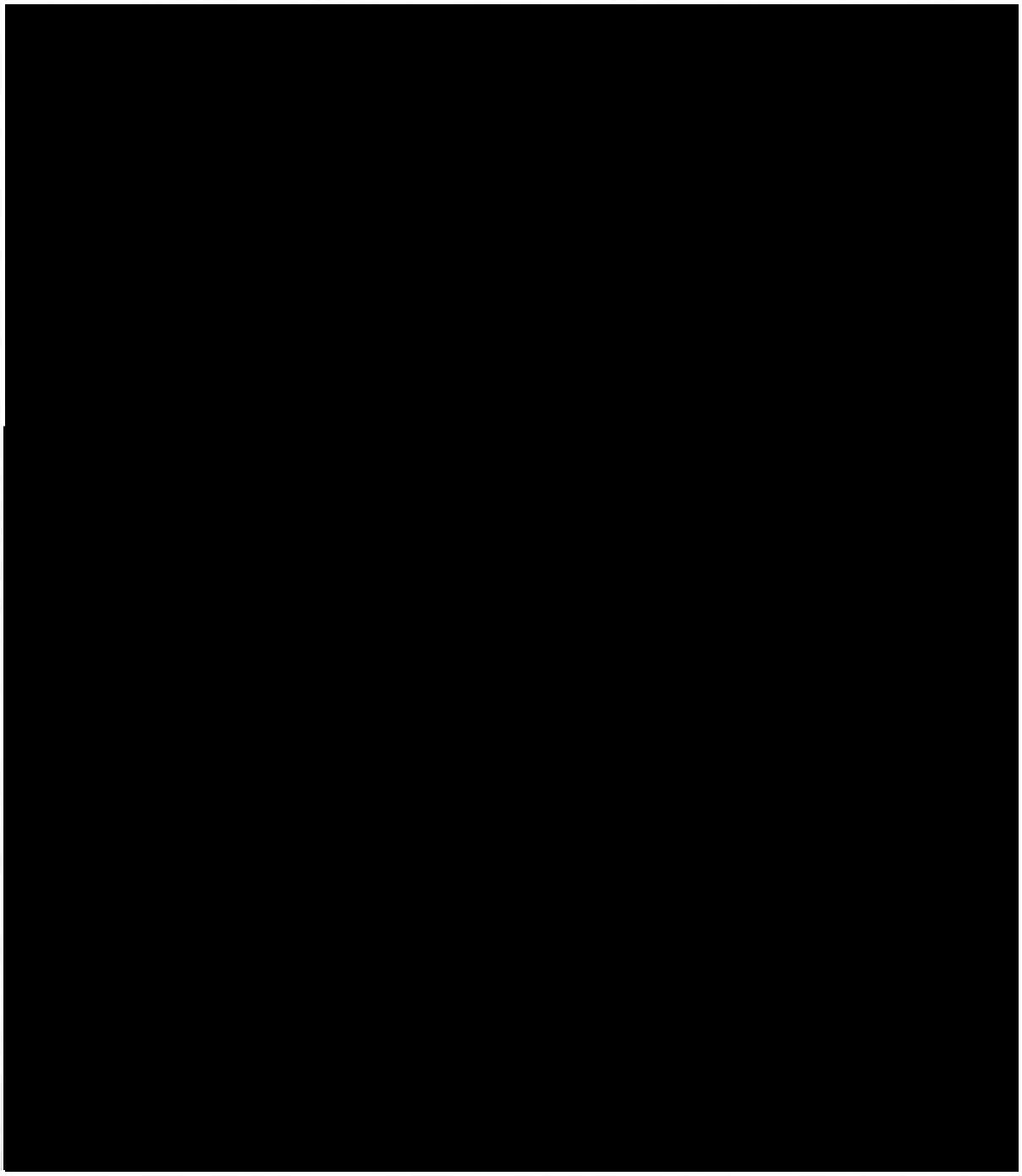

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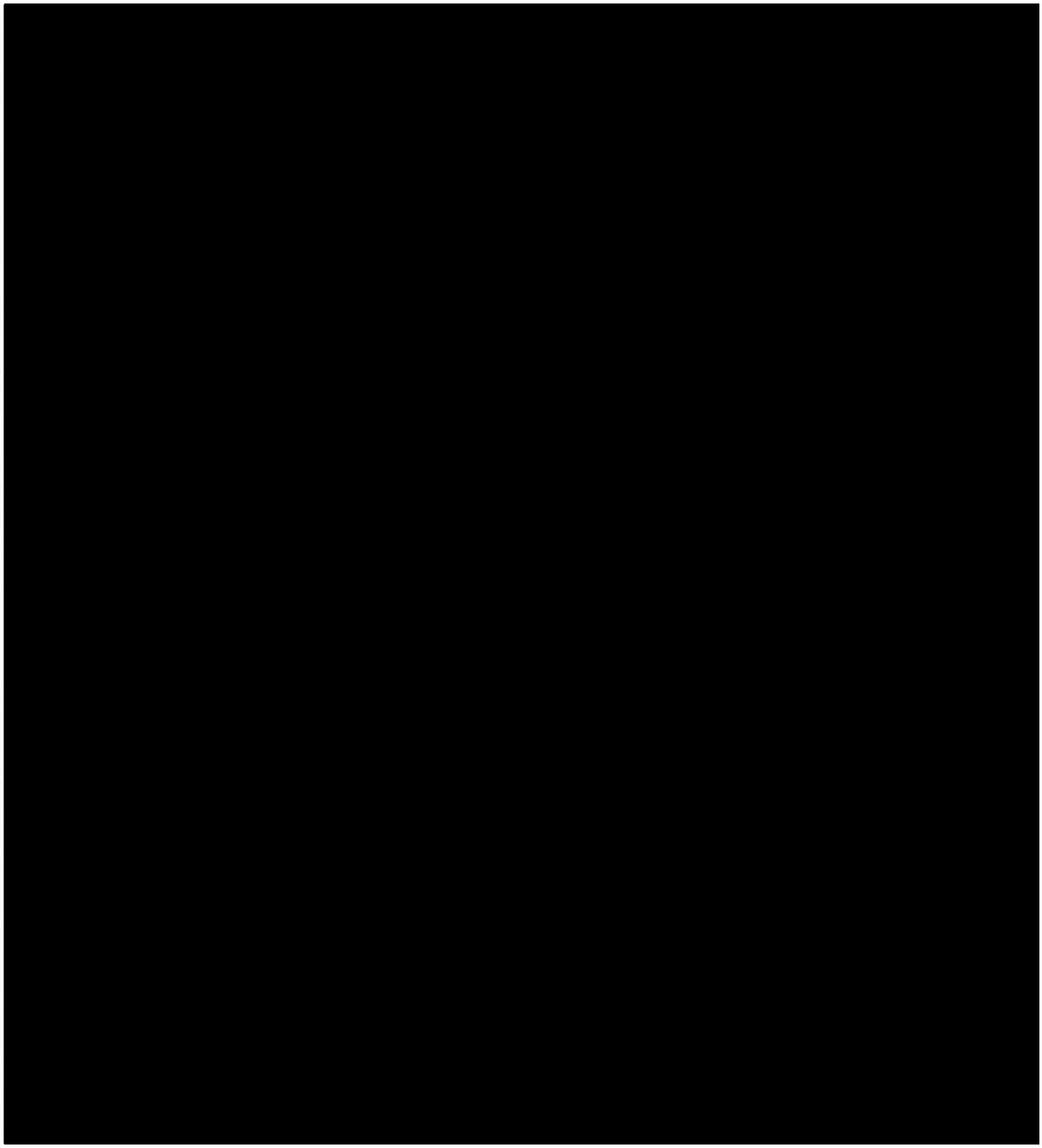

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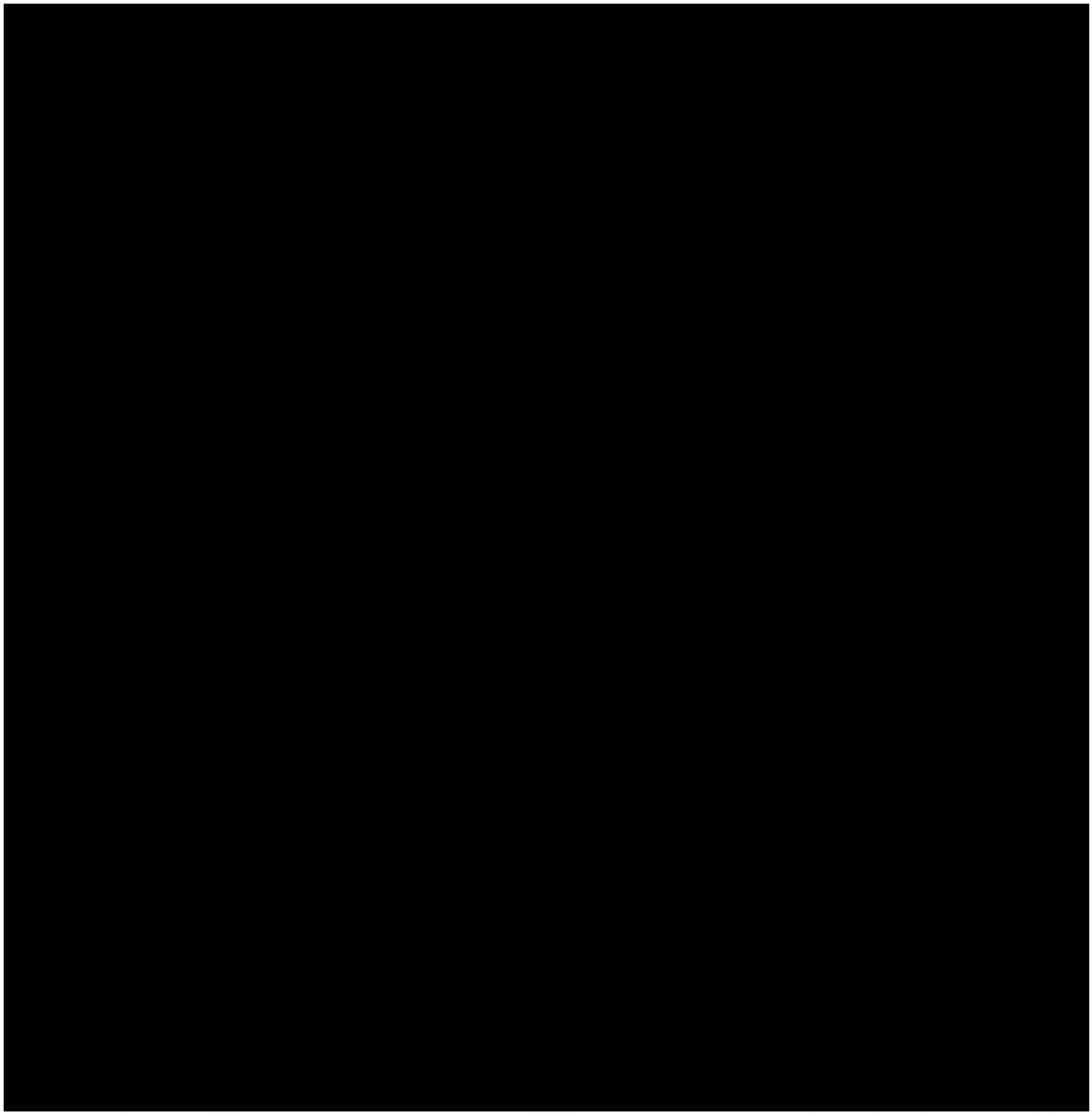

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