Study Protocol Cover Page

Official Study Title:	A Phase III, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Glaucoma or Ocular Hypertension - Spectrum 4 Study
NCT Number:	NCT03691662
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DE-117 Protocol
Study 011710IN
Amendment 1

TITLE: **A Phase III, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Glaucoma or Ocular Hypertension - Spectrum 4 Study**

SPONSOR:	STUDY DRUG:
SANTEN Inc. 6401 Hollis St, Suite 125 Emeryville, CA 94608 USA	DE-117 Ophthalmic Solution 0.002% Timolol Maleate Ophthalmic Solution 0.5%

I have read the 011710IN protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form (eCRF) indicates that the data therein has been reviewed and accepted by me as the Investigator.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

Address: _____

_____

Phone: _____

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

2. SYNOPSIS

Name of Sponsor/Company: Santen Inc. 6401 Hollis Street, Suite 125 Emeryville, CA 94608, USA	
Name of Investigational Product: DE-117 Ophthalmic Solution	
Name of Active Ingredient: Glycine, *N*-[6-[[[[4-(1*H*-pyrazol-1-yl)phenyl]methyl](3-pyridinylsulfonyl)amino]methyl]-2-pyridinyl]-, 1-methylethyl ester Propan-2-yl 2-[[6-[[(4-pyrazol-1-ylphenyl)methyl-pyridin-3-ylsulfonylamino]methyl]pyridin-2-yl]amino]acetate	
Title of Study: A Phase III, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Glaucoma or Ocular Hypertension - Spectrum 4 Study	
Protocol Number: 011710IN	
Number of Subjects (planned): Approximately 400 adult subjects (200 in each treatment arm) with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT) and up to 30 pediatric subjects (15 in each treatment arm) with pediatric glaucoma or OHT will be randomized in this study	
Number of Sites (planned): Approximately 35 Sites	
Study Period: Approximately 10 months	**Phase of Development:** Phase III
Primary objective: To determine whether DE-117 Ophthalmic Solution 0.002% given once daily is non-inferior to Timolol Maleate Ophthalmic Solution 0.5% given twice daily in reducing the intraocular pressure (IOP) in subjects with glaucoma or OHT after 3 months of treatment **Secondary objectives**: To determine whether DE-117 Ophthalmic Solution 0.002% is non-inferior to Timolol Maleate Ophthalmic Solution 0.5% in reducing mean diurnal IOP in subjects with glaucoma or OHT after 3 months of treatment To determine whether DE-117 Ophthalmic Solution 0.002% is superior to that of Timolol Maleate Ophthalmic Solution 0.5% in reducing mean diurnal IOP in subjects with glaucoma or	

OHT after 1 week of treatment

Safety objective:

To determine the safety of DE-117 Ophthalmic Solution 0.002% as compared to Timolol Maleate Ophthalmic Solution 0.5% in subjects with glaucoma or OHT

Duration of Treatment: 3 months

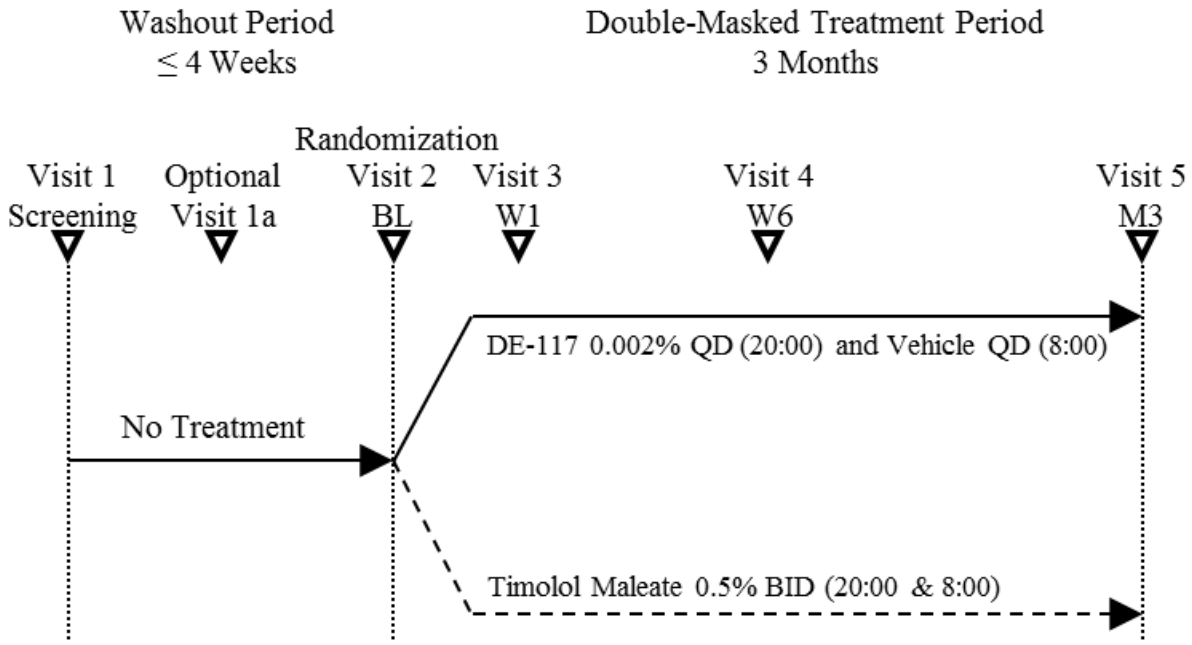
Methodology:

This is a Phase III, randomized, double-masked, active-controlled, parallel-group, multi-center study. Subjects diagnosed with glaucoma or OHT who meet eligibility criteria at Visit 1 (Screening) will washout of their current topical IOP-lowering medication(s), if any. After completing the required washout period, subjects will return for Visit 2 (Baseline, Day 1). Subjects who meet all eligibility criteria at baseline will be randomized to receive treatment for 3 months.

Approximately 400 adult subjects and up to 30 pediatric subjects with glaucoma or OHT who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either:

- DE-117 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- Timolol Maleate Ophthalmic Solution 0.5% BID (20:00 & 08:00).

Study Design



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

At the Screening visit (Visit 1), subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications,

if any, during a washout period as follows (up to +7 days as a window is allowed):

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

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

Final eligibility for randomization will be determined at Visit 2 (Baseline) after all necessary washout from prior IOP-lowering medications have been completed. Subjects who have not used any IOP-lowering medication for the last 28 days, including treatment-naive subjects, must have ≥ 1 day between their screening visit and Visit 2 (Baseline).

At Visit 2, baseline IOP will be measured for both eyes at 08:00 (±60 min), 10:00 (±60 min) and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study, even if only one eye is eligible per IOP inclusion criteria. **For pediatric subjects, if only one eye has a diagnosis of glaucoma or OHT, the fellow eye doesn't have to be treated by the study medications for the duration of the study.**

Double-Masked Treatment Period (3 months):

Approximately 400 eligible adult subjects and up to 30 pediatric subjects will be randomized to receive either DE-117 0.002% QD in the evening and vehicle QD in the morning or Timolol Maleate 0.5% BID in a 1:1 ratio. Subjects will be treated for 3 months with scheduled visits at Visits 2, 3, 4 and 5 (Baseline, Week 1, Week 6 and Month 3).

At Visit 2 (Baseline), subjects will receive their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (±60 min). The next day, subjects will

subsequently dose with their assigned study medication at 08:00 (±60 min), and 20:00 (±60 min). At each scheduled follow-up visit, subjects will receive their morning dose of study medication/eye drops following the 08:00 IOP measurement at the investigative site (the doctor's office).

Timolol Maleate Ophthalmic Solution 0.5% was chosen as the active control because it has previously been proven to be effective for the reduction of elevated IOP in patients with glaucoma or OHT and is approved for these indications.

IOP will be measured at 08:00, 10:00 and 16:00 (±60 min). At these scheduled visits, best-corrected visual acuity (BCVA) and slit-lamp biomicroscopy will be performed just prior to the 08:00 IOP measurement. Ophthalmoscopy (fundus examination) will be performed after the 16:00 IOP measurement. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at visit 1, and approximately 08:00 for Visits 2, and 5 before the morning dose.

Pharmacogenomics/Genomics:

Subjects who consent to the optional pharmacogenomics/genomics laboratory study will provide a blood sample for future testing. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

Masking:

This is a double-masked study. The subjects, Investigators, Examiners and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member who is not the Investigator or Examiner at the investigative site will dispense and collect study medication(s) and will query about dosing compliance. Subjects will be instructed not to show the eye drop bottles or discuss the eye drop to either the Investigator or the Examiner or other study subjects. The active control treatment (Timolol Maleate) containers will be over-labeled and packaged in the same secondary package (e.g., cardboard carton) as the investigational treatment (DE-117). All subjects will receive a bottle labeled "morning" for the morning dose and a bottle labeled "evening" for the evening dose. However, the DE-117/Vehicle arm will receive the vehicle (i.e., "morning" bottle) at the morning dose, while the Timolol Maleate arm receives the active treatment (i.e., "morning" bottle) at the morning dose. Each eligible subject will be assigned to receive a numbered study medication kit as assigned by Central randomization via Interactive Response Technology (Medidata BALANCE) at Visit 2 (Baseline) and at Visit 4 (Week 6).

Inclusion Criteria for ADULT subjects:

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

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF).
2. Be 18 years of age or older on the date of signing the ICF and be able and willing to comply with all treatment and follow-up study procedures.
3. If a subject is a female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of

surgery]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).

- Abstinence
- Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
- Placement of a copper-containing IUD
- Condom with spermicidal foam/gel/film/cream/suppository
- Vasectomized male partner (surgery at least 6 months prior)

Male subjects capable of fathering children should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraceptive method deemed adequate by the investigator throughout the course of the study (as well as for 12 weeks following last dose in study).

4. Must have a diagnosis of OAG (including Pigmentary Glaucoma or Pseudoexfoliative Glaucoma) or OHT in both eyes, or one eye with OAG and the other with OHT.
5. BCVA of +0.60 logMAR (Snellen equivalent 20/80) or better in each eye.
6. Central corneal thickness ≥ 480 μm and ≤ 600 μm in each eye.
7. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition to continuing to meet inclusion criterion 5 (BCVA), the subject must meet the following criteria at Visit 2 (Baseline, Day 1):

8. Completed the required wait/washout period.
9. At all time points of IOP measurements (08:00, 10:00 and 16:00) at Visit 2 (Baseline, Day 1), have IOP of ≥ 22 mmHg in at least one eye (the same eye), and ≤ 34 mmHg in both eyes.

Exclusion Criteria for ADULT subjects:

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

General

1. Females who are pregnant, nursing or planning a pregnancy.
2. Subjects with known or suspected drug or alcohol abuse.
3. Current or planned participation in any other clinical trial involving an investigational product or device within 4 weeks prior to Visit 1 (Screening) or at any time during this trial.
4. Subjects who have been exposed to DE-117 prior to Visit 1 (Screening).

Medications / Therapies

5. Intended or current use of the following prohibited medications/therapies during the study duration:
    - All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications.
    - All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
    - Any ocular, periocular, inhaled, nasal or systemic corticosteroids including for joint injection, etc.
    - Lacrimal/punctal occlusion via plug (s) or cautery.
6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
7. 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]). Subjects using the above medications must be on a stable dose use for at least 30 days prior to Visit 1 (Screening) and during the study duration.
8. Use of contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
9. Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.
10. History of ocular surgery specifically intended to lower IOP (e.g., laser trabeculoplasty, filtering surgery, tube shunt, Minimally Invasive Glaucoma Surgery (MIGS), or trabeculotomy) in either eye.
11. History of keratorefractive surgery (e.g., RK, PRK, LASIK) in either eye.
12. Allergy, hypersensitivity or contraindications to EP2 receptor agonists, beta-blockers, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications. This also includes subjects with a history or presence of contraindications to beta-blocker therapy, such as chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema), bronchial asthma, second or third degree atrioventricular block, uncontrolled congestive heart failure.

Diseases

13. Presence of advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
14. Presence of any corneal abnormality or other conditions interfering with or preventing reliable Goldmann applanation tonometry (e.g., Fuch's dystrophy or significant corneal

surface abnormality) in either eye.

15. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
16. Presence or history of macular edema or known risk factors for macular edema in either eye.
17. History of severe ocular trauma in either eye.
18. History of iritis and/or uveitis in either eye.
19. History of retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may be progressive during the time course of the study in either eye.
20. Presence or history of any disease or condition that in the opinion of the study Investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (e.g., recurrent corneal erosion syndrome, uncontrolled cardiovascular disease etc.).
21. Any decision by the Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

Inclusion Criteria Specific for PEDIATRIC subjects:

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

1. Parent/legal guardian signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and patient assent has been given as applicable.
2. The patient and parent/legal guardian should agree to comply with study restrictions, treatment plan, procedures and keep scheduled visits.
3. Be ≥ 1 year and less than 18 years old on the date of signing the ICF.
4. If a subject is a female of childbearing potential, she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
    - Abstinence
    - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
    - Placement of a copper-containing IUD
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Vasectomized male partner (surgery at least 6 months prior)

    Male subjects capable of fathering children should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6

months prior) or other contraceptive method deemed adequate by the investigator throughout the course of the study (as well as for 12 weeks following last dose in study).

5. Must have a diagnosis of pediatric glaucoma or OHT in one or both eyes, including primary (congenital and juvenile open angle glaucoma) and secondary glaucoma. For a child with pediatric glaucoma due to secondary causes, the Investigator or study site should discuss the case with the Medical Monitor prior to subject enrollment.
6. Must have elevated IOP to such a level that investigator deems pharmacologic intervention with IOP-lowering medication to be clinically necessary in at least one eye.
7. Must have a sufficiently clear cornea that allows for a complete ophthalmic examination.
8. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye, based on gonioscopy performed at Visit 1 (Screening), or historical gonioscopy performed within 12 months prior.

In addition to continuing to meet inclusion criteria 6 (elevated IOP) and 7 (clear cornea), the subject must meet the following criterion at Visit 2 (Baseline, Day 1):

9. Completed the required wait/washout period.

Exclusion Criteria Specific for PEDIATRIC subjects:

At Visit 1 (Screening) and Visit 2 (Baseline, Day 1), subjects with any of the following ocular conditions in either eye or with any of the following non-ocular conditions or characteristics are not eligible to participate in the study. Exception: criteria 8, 9 and 10 only apply to the eye being considered for study treatment. E.g. if only the non-treated eye has a history of LASIK, the other eye may still qualify for participation and treatment in the study if the subject meets all other criteria.

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 4 weeks prior to Visit 1 (Screening) or at any time during this trial.
4. Subjects who have been exposed to DE-117 prior to Visit 1 (Screening).

Medications / Therapies

5. Intended or current use of the following prohibited medications/therapies during the study duration:
    - All ocular medications other than sodium chloride/potassium chloride ophthalmic

solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications.

- All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
- Any ocular, periocular, inhaled, nasal or systemic corticosteroids including joint injection, etc.
- Lacrimal/punctal occlusion via plug (s) or cautery.

6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
7. 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]). Subjects using the above medications must be on a stable dose use for at least 30 days prior to Visit 1 (Screening) and during the study duration.
8. Use of contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
9. Any ocular surgery (including goniotomy or glaucoma surgery) or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study.
10. History of keratorefractive surgery (e.g. RK, PRK, LASIK).
11. Allergy, hypersensitivity or contraindications to EP2 receptor agonists, beta-blockers, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications. This also includes subjects with a history or presence of contraindications to beta-blocker therapy, such as chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema), bronchial asthma, second or third degree atrioventricular block, uncontrolled congestive heart failure.

Diseases

12. Presence of advanced glaucoma in either eye.
13. Presence of any corneal abnormality or other conditions interfering with or preventing reliable tonometric measurement (e.g. Fuch's dystrophy or significant corneal surface abnormality) in either eye.
14. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
15. Presence or history of macular edema or known risk factors for macular edema in either eye.
16. Aphakia or pseudophakia

17. Single sighted subject
18. History of severe ocular trauma in either eye.
19. History of iritis and/or uveitis in either eye.
20. 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.
21. Presence or history of any disease or condition that, in the opinion of the study Investigator, may put the subject at significant risk (such as contraindication to the use of Timolol Maleate Ophthalmic Solution 0.5%), 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 Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

Investigational product, dosage and mode of administration:

Subjects will be assigned in a 1:1 ratio to the DE-117/Vehicle arm and Timolol Maleate arms as follows:

Investigational Product:

DE-117 Ophthalmic Solution contains 0.002% DE-117. Each 2.5 mL bottle of DE-117 Ophthalmic Solution 0.002% contains 50 µg of DE-117. In addition [redacted]

Vehicle:

The vehicle is identical to the investigational product but does not contain the active ingredient in DE-117. [redacted]

Comparator:

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

Each subject will be instructed to instill one drop of study medication from bottle labeled "evening" in each eye at 20:00 and one drop of study medication from bottle labeled "morning" in each eye at 08:00 starting the evening of Visit 2 (Baseline, Day 1) through the morning

before Visit 5 (Month 3).
Route of Administration of Investigational Product: Topical ocular
Duration of the Study: The study duration includes up to 5 week Screening Period, and a 3-month Double-Masked Treatment Period.
Criteria for Evaluation: **Efficacy:** Efficacy will be assessed by evaluating IOP at scheduled time points (08:00, 10:00 and 16:00) at all scheduled visits with the exception of the Screening visit. **Safety:** Safety will be assessed by adverse events (AEs), BCVA, slit-lamp biomicroscopy, ophthalmoscopy, iris color/eyelash/eyelid examination, resting blood pressure and pulse rate. **Other:** Subject demographics, baseline characteristics, medical history, concomitant medications, exposure to study medication, and pregnancy for females of childbearing potential will be summarized.
Efficacy Endpoints: **Primary Efficacy Endpoint** The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00 and 16:00 at Week 1, Week 6 and Month 3 (Visits 3, 4 and 5). **Key Secondary Efficacy Endpoints** • Mean diurnal IOP in the study eye at Month 3 (Visit 5) • Mean diurnal IOP in the study eye at Week 1 (Visit 3) **Other Secondary Efficacy Endpoints** • Change and percent change from baseline in IOP at each timepoint/post-baseline visit • Change and percent change from baseline in mean diurnal IOP at each post-baseline visit • Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2) at each post-baseline visit • Having a mean diurnal IOP ≤ 18 mmHg at each post-baseline visit **Safety Endpoints** Safety will be evaluated by the following parameters: • Incidence of ocular and systemic AEs

- Blood pressure and pulse rate
- BCVA
- Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, lens, anterior synechiae of iris, posterior synechiae of iris
- Ophthalmoscopy
- Iris color/eyelash/eyelid

Statistical Methods:

The sample size calculation was based on a two-sided Type I error rate of 5% and a non-inferiority margin of 1.5 mmHg. Assuming a between-treatment difference of 0 mmHg, a standard deviation (SD) of 4.0 mmHg, and a correlation coefficient of 0.6 among repeated measures, approximately 400 adult subjects in total (200 subjects per treatment arm) will provide 90% power to demonstrate non-inferiority of DE-117 Ophthalmic Solution 0.002% to Timolol Maleate Ophthalmic Solution 0.5%.

A mixed-effects model for repeated measures (MMRM) will be fitted and 95% confidence interval for least square mean difference between the DE-117/Vehicle arm and the Timolol Maleate arm at each scheduled time point of each post-baseline visit up to Month 3 will be estimated. Non-inferiority is achieved if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (0.002% DE-117 - Timolol Maleate) is $\leq$ 1.5 mmHg at all nine time points and $\leq$ 1.0 mmHg in majority (5 or more) of the 9 time points.

Separate statistical analysis for pediatric subjects may be performed depending on the number of pediatric subjects enrolled in this study.

Schedule of Events and Procedures for ADULT Subjects

	Washout Period		Double-Masked Treatment Period			
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43 ±3)	Visit 5 Month 3 (Day 91±7) Exit or Early Termination [n]
Informed Consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study [a]	X					
Inclusion/Exclusion Criteria	X		X			
Demographics and Medical History, including prior PGA [b]	X					
Concomitant Medications/ Therapies	X	X	X	X	X	X
Dosing Compliance				X	X	X
AEs		X	X	X	X	X
Pregnancy Test [c]	X		X			X
Vital Signs (blood pressure/pulse rate) [d]	X		X (08:00)			X (08:00)
Refraction [e]	X					
BCVA[e]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy [f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
IOP [g]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00
Pachymetry [h]	X					
Instill study medication after IOP measurement				X (08:00)	X (08:00)	X (08:00)
Iris color, eyelash, eyelid [i]			X (photo)			X (photo)
Gonioscopy [j]	X					
Visual Field [k]	X					
Ophthalmoscopy [l]	X (pupil dilation)		X (16:00)			X (16:00, pupil dilation)
Blood Sampling for Pharmacogenomics/genomics [m]				X		
Dispense Study Medication			X		X	
Collect Study Medication					X	X
Phone call to remind subject to take evening dose on the day before each visit				X	X	X

a. Informed Consent Form 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's medical records or subject history.
c. A urine pregnancy test will be conducted for all female subjects of childbearing potential.
d. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and Visit 5 before the morning dose.
e. Refraction will be performed at the screening visit. If more than 10 letters in BCVA are lost compared to the screening visit, then refraction should be performed again. BCVA examination will be completed before IOP measurement at 08:00.
f. Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before fluorescein instillation.
g. IOP measurements will be performed at 08:00, 10:00 and 16:00 (±60 min) at all visits except for Visit 1 and the optional Visit 1a (screening and mid-washout).
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening).
i. Eye photograph will be taken at Visits 2 (Baseline) and 5 (Month 3).

j. If gonioscopy was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary. Gonioscopy will be performed after IOP measurement at Visit 1 (Screening).
k. If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.
l. Ophthalmoscopy will be performed at Visits 1, 2 and 5 (i.e. Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Visit 1 and Visit 5/exit or early termination. Dilation of the pupil will be performed after the 16:00 IOP measurement.
m. Blood sampling for the pharmacogenomics/genomics laboratory research study may be performed at any visit after pharmacogenomics/genomics informed consent obtained, subject randomized and study drug dosing has begun.
n. Optional at unscheduled visit, required for early terminated subjects.

Schedule of Events and Procedures Specially for PEDIATRIC Subjects

	Washout Period		Double-Masked Treatment Period			
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43 ±3)	Visit 5 Month 3 (Day 91±7) Exit or Early Termination [n]
Informed Consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study [a]	X					
Inclusion/Exclusion Criteria	X		X			
Demographics and Medical History, including prior PGA [b]	X					
Concomitant Medications/ Therapies	X	X	X	X	X	X
Dosing Compliance				X	X	X
AEs		X	X	X	X	X
Pregnancy Test [c]	X		X			X
Vital Signs (blood pressure/pulse rate) [d]	X		X (08:00)			X (08:00)
Refraction [e]	X					
BCVA[e]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy [f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
IOP [g]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00
Pachymetry [h]	X					
Instill study medication after IOP measurement				X (08:00)	X (08:00)	X (08:00)
Iris color, eyelash, eyelid [i]			X (photo)			X (photo)
Gonioscopy [j]	X					
Visual Field [k]	X					
Ophthalmoscopy [l]	X (pupil dilation)		X (16:00)			X (16:00 pupil dilation)
Blood Sampling for Pharmacogenomics/genomics [m]				X		
Dispense Study Medication			X		X	
Collect Study Medication					X	X
Phone call to remind subject to take evening dose on the day before each visit				X	X	X

a. Informed Consent Form and the Assent Form 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's medical records or subject history.
c. A urine pregnancy test will be conducted for all female subjects of childbearing potential.
d. Vital signs (resting blood pressure and pulse rate) will be collected in anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and Visit 5 before the morning dose.
e. Refraction will be performed at the screening visit if the pediatric subject is able to cooperate. Autorefraction is also acceptable. If more than 10 letters in BCVA are lost compared to the screening visit level, then refraction should be performed again if the pediatric subject is able to cooperate. BCVA examination will be completed before IOP measurement at 08:00. BCVA will be performed for the pediatric subjects who are able to cooperate using an age-appropriate eye chart and method (e.g. ETDRS chart, LEA symbols chart with logMAR notation, Tumbling E's with logMAR notation, Landolt's broken rings with LogMAR notation, fix and follow) under normal room illumination. Same eye chart should be used for a given subject throughout the study.

f. Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before instillation of fluorescein.
g. IOP measurements will be performed at 08:00, 10:00 and 16:00 (±60 min) at all visits except for Visit 1 and the optional Visit 1a (screening and mid-washout). IOP will be measured with age-appropriate tonometers (e.g. Goldmann applanation tonometer, a Perkins tonometer, or a tonopen, or iCare tonometer etc.) to the extent the subject is able to cooperate.
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening) if the subject is able to cooperate. Subject must have sufficiently clear cornea that allows for a complete ophthalmic exam to be enrolled if pachymetry is not able to be obtained.
i. Eye photograph will be taken at Visits 2 (Baseline), and 5 (Month 3) if the subject is able to cooperate.
j. Gonioscopy will be performed at Visit 1 (Screening) if the subject is able to cooperate. If unable to cooperate, historical gonioscopy performed within 12 months prior to screening and documented in the subject's records is acceptable. Gonioscopy performed at Visit 1 (Screening) should occur after IOP measurement.
k. Visual field test will be performed if the subject is able to cooperate. If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.
l. Ophthalmoscopy will be performed if the subject is able to cooperate. Ophthalmoscopy will be performed at Visits 1, 2, and 5 (i.e. Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Visit 1 and visit 5/exit or early termination. Dilation of the pupil will be performed after the 16:00 IOP measurement.
m. Blood sampling for the pharmacogenomics/genomics laboratory research study may be performed at any visit after the pharmacogenomics/genomics informed consent is obtained, subject is randomized and study drug dosing has begun.
n. Optional at unscheduled visit, required for early terminated subjects.

Guidance for the visual acuity and IOP measurements in pediatric subjects are shown in Section 21.4.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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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
ACE	Angiotensin-Converting Enzyme
ADR	Adverse Drug Reaction
AE	Adverse Event
AGIS	Advanced Glaucoma Intervention Study
ARB	Angiotensin II Receptor Blockers
ATC	Anatomical Therapeutic Chemical
BAK	Benzalkonium Chloride
BCVA	Best-Corrected Visual Acuity
BID	Twice a Day
CAI	Carbonic Anhydrase inhibitor
CV	Curriculum Vitae
D	Diopter
dB	Decibel
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMGT	Early Manifest Glaucoma Trial
EP2	Prostaglandin E receptor Subtype 2
ESI	Events of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Prostaglandin F Receptor
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUDs	Intrauterine Devices
LASIK	Laser-Assisted-in-Situ Keratomileusis
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µm	Micrometer
mg	Milligram
MIGS	Minimally Invasive Glaucoma Surgery
min	Minute
mL	Milliliter
mmHg	Millimeters of Mercury
MMRM	Mixed-effects Model for Repeated Measures
N	Number of subjects
NDA	New Drug Application
OAG	Open-Angle Glaucoma
OCT	Optical Coherence Tomography
OD	Right Eye
OHT	Ocular Hypertension
OHTS	Ocular Hypertension Treatment Study
OS	Left Eye
OU	Both Eyes
PACG	Primary Angle Closure Glaucoma
PCR	Polymerase Chain Reaction
PG	Prostaglandin
PGA	Prostaglandin Analogue
PMM	Pattern Mixture Model
POAG	Primary Open-Angle Glaucoma
PPS	Per-Protocol Set
PRK	Refractive Keratectomy

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
PT	Preferred Term
QD	Once a day
RK	Radial Keratotomy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SUN	Standardization of Uveitis Nomenclature
UKGTS	United Kingdom Glaucoma Treatment Study
WHO-DDE	World Health Organization Drug Dictionary Enhanced

5. INTRODUCTION

Glaucoma represents a group of related diseases frequently associated with elevated IOP. When left untreated, glaucoma can lead 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. In 2013, the global prevalence of glaucoma for population aged 40 to 80 years was 3.54%. The number of people (aged 40 to 80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040 (Tham et al., 2014). 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 OAG, 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), and United Kingdom Glaucoma Treatment Study (UKGTS) (Garway-Heath et al., 2015) 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), 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 OHT and OAG. However as disease progresses and maintaining target IOP becomes difficult, more than one drug is needed to achieve optimum benefit and reach target IOP. Surgical interventions, including laser surgery, shunting of aqueous humor to an appropriate locale, and filtering surgery, are available options for treating insufficiently controlled IOP. In such instances pharmacotherapy may be continued as well.

In some patients, treatment with a single IOP-lowering compound is not sufficient to obtain optimal IOP control. Adjunctive or combination therapy using different classes of drugs is often employed in order to achieve additional IOP-lowering effects. Moreover, consistent lowering of IOP over a 24-hour period has not yet been fully realized. If achieved, this could also contribute to slowing of disease progression. Therefore, new pharmacologic agents with new mechanism of action are needed.

Santen has developed an ophthalmic topical formulation of omidenepag isopropyl (UR-7385) for the reduction of elevated IOP in patients with OHT or OAG. DE-117 is a pro-drug of the pharmacologically active acid metabolite, UR-7276, a synthetic non-prostanoid agonist of prostaglandin E2 (PGE_2) receptor, subtype 2 (EP2). PGE_2 has been shown to markedly reduce IOP when applied topically to human and animal eyes (Bito, 2001). PGE_2, its analogues and receptor agonists are thought to mediate the IOP-lowering effect by relaxing the ciliary muscle

and increasing outflow of aqueous humor through the uveo-scleral pathway (Yamaji et al., 2005). Very recently, Fuwa et al., demonstrated that DE-117 lowers the IOP through a novel meachnism of action: that is, through both conventional and uveoscleral outflows (Fuwa et al., 2017). Currently approved IOP- lowering medications such as latanoprost (Latanoprost Ophthalmic Solution, 0.005%; NDA 20-597) lower IOP by enhancing uveoscleral outflow only, but do so through effects on a receptor for $PGF_2\alpha$. Unlike latanoprost and other approved prostaglandin F receptor (FP) agonists that are synthetic prostanoid analogues, DE-117 is a non-prostanoid chemical compound.

To date, Santen has completed seven clinical studies including three clinical studies (33-001, 33-002, 33-003) in the U.S. and four clinical studies (01171502, 01171503, 01171504, 01171506) in Japan with DE-117 in healthy adult subjects, or subjects with OAG or OHT to evaluate the efficacy and safety of DE-117. DE-117 Ophthalmic Solution 0.002% appeared to be well tolerated and efficacious in IOP lowering. As a result, it was chosen to advance into the phase III clinical development program in the US.

Additional information on DE-117 Ophthalmic Solution, including the results of nonclinical and clinical studies can be found in the Investigator's Brochure.

The proposed study is a randomized, double-masked, active-controlled, parallel group, multi-center, Phase III study. The total duration of treatment is 3 months. The objective is to investigate the efficacy and safety of DE-117 Ophthalmic Solution 0.002% compared with Timolol Maleate Ophthalmic Solution 0.5% in subjects with glaucoma or OHT.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To determine whether DE-117 Ophthalmic Solution 0.002% given once daily is non-inferior to Timolol Maleate Ophthalmic Solution 0.5% given twice daily in reducing the IOP in subjects with glaucoma or OHT after 3 months of treatment

6.2. Secondary Objectives

To determine whether DE-117 Ophthalmic Solution 0.002% is non-inferior to Timolol Maleate Ophthalmic Solution 0.5% in reducing mean diurnal IOP in subjects with glaucoma or OHT after 3 months of treatment

To determine whether DE-117 Ophthalmic Solution 0.002% is superior to that of Timolol Maleate Ophthalmic Solution 0.5% in reducing mean diurnal IOP in subjects with glaucoma or OHT after 1 week of treatment

6.3. Safety Objective

To determine the safety of DE-117 Ophthalmic Solution 0.002% as compared to Timolol Maleate Ophthalmic Solution 0.5% in subjects with glaucoma or OHT.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a Phase III, randomized, double-masked, active-controlled, parallel-group and multi-center study investigating the efficacy and safety of DE-117 Ophthalmic Solution 0.002% in subjects with glaucoma or OHT.

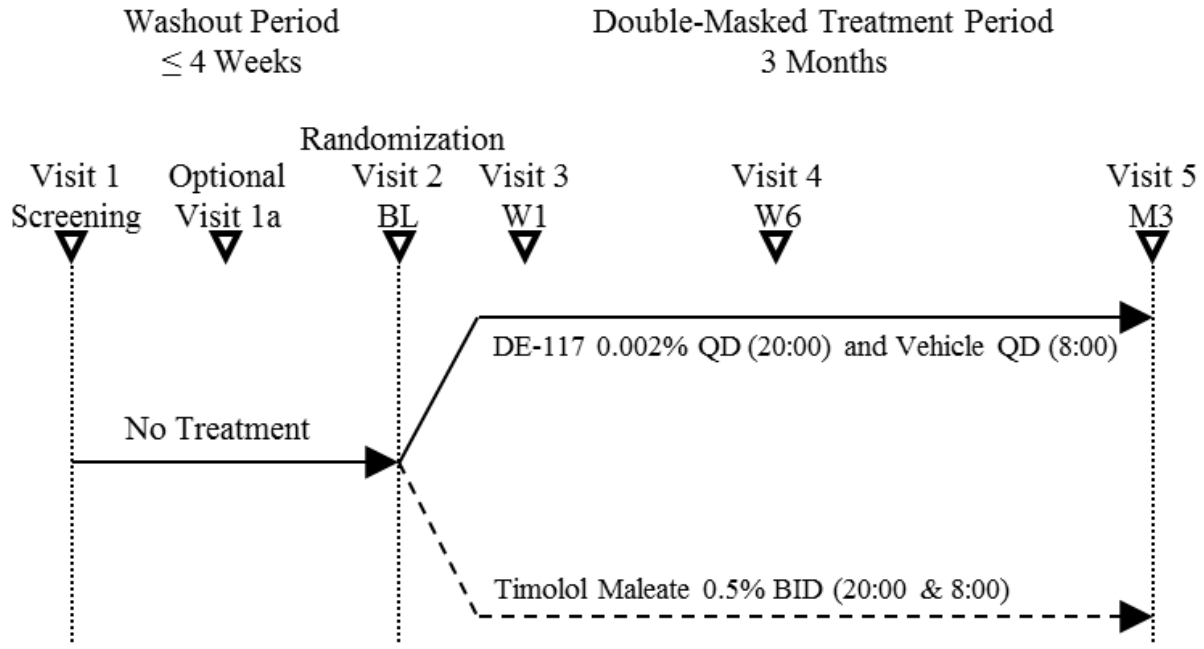
See the study design diagram in Figure 1. This study will consist of a Screening Period of up to 35 days including a washout period of up to 28 days (+ 7 days window) and a 3-month Double-Masked Treatment Period.

Approximately 400 adult subjects and up to 30 pediatric subjects s with glaucoma or OHT who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either:

- DE-117 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- Timolol Maleate Ophthalmic Solution 0.5% BID (20:00 & 08:00).

In the Double-Masked Treatment Period, Timolol Maleate Ophthalmic Solution 0.5% will be used as active control.

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, if any, during a washout period as follows (up to +7 days as a window is allowed):

- Miotics: 7 days
- Oral/topical Carbonic Anhydrase Inhibitors (CAIs): 7 days

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

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

Final eligibility for randomization will be determined at Visit 2 (Baseline) after all necessary washouts from prior IOP-lowering medications have been completed. Subjects who have not used any IOP-lowering medication for the last 28 days, including treatment-naive subjects, must have ≥ 1 day between their screening visit and Visit 2 (Baseline).

At Visit 2, baseline IOP will be measured for both eyes at 08:00 (±60 min), 10:00 (±60 min) and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study, even if only one eye is eligible per IOP inclusion criteria. **For pediatric subjects, if only one eye has a diagnosis of glaucoma or OHT, the fellow eye doesn't have to be treated by the study medications for the duration of the study.**

Double-Masked Treatment Period (3 months):

Approximately 400 eligible adult subjects and up to 30 pediatric subjects will be randomized to receive either DE-117 0.002% QD in the evening and vehicle QD in the morning or Timolol Maleate 0.5% BID in a 1:1 ratio. Subjects will be treated for 3 months with scheduled visits at Visits 2, 3, 4 and 5 (Baseline, Week 1, Week 6 and Month 3).

At Visit 2 (Baseline), subjects will receive their first dose of study medication (study eye drops) as per their assigned/randomized study treatment at 20:00 (±60 min). The next day, subjects will subsequently dose with their assigned study medication at 08:00 (±60 min), and 20:00 (±60 min). At each scheduled follow-up visit, subjects will receive their morning dose of study medication/eye drops following the 08:00 IOP measurement at the investigative site (the doctor's office).

Timolol Maleate Ophthalmic Solution 0.5% was chosen as the active control because it has previously been proven to be effective for the reduction of elevated IOP in patients with glaucoma or OHT and is approved for these indications.

IOP will be measured at 08:00, 10:00 and 16:00 (±60 min). At these scheduled visits, BCVA and slit-lamp biomicroscopy will be performed just prior to the 08:00 IOP measurement. Ophthalmoscopy (fundus examination) will be performed after the 16:00 IOP measurement. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1, and approximately 08:00 for Visits 2, and 5 before the morning dose.

Pharmacogenomics/genomics:

Subjects who consent to the optional pharmacogenomics/genomics laboratory study will provide a blood sample for future testing. The purpose of this exploratory research is to identify possible genetic markers associated with the study medication(s) and/or ocular conditions.

7.2. Number of Subjects

Approximately 400 adult subjects and up to 30 pediatric subjects are planned to be enrolled in this study.

7.3. Treatment Assignment

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

- DE-117 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00)
- Timolol Maleate Ophthalmic Solution 0.5% BID (20:00 & 08:00)

7.4. Schedule of Events and Procedures

Table 3: Schedule of Events and Procedures for ADULT subjects

	Washout Period		Double-Masked Treatment Period			
	Visit 1 Screening	**Washout Period (up to 4 weeks) Optional Visit 1a**	**Visit 2 Eligibility/Baseline (Day 1)**	**Visit 3 Week 1 (Day 8±2)**	**Visit 4 Week 6 (Day 43 ±3)**	**Visit 5 Month 3 (Day 91±7) Exit or Early Termination [n]**
Informed Consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study [a]	X					
Inclusion/Exclusion Criteria	X		X			
Demographics and Medical History, including prior PGA [b]	X					
Concomitant Medications/ Therapies	X	X	X	X	X	X
Dosing Compliance				X	X	X
AEs		X	X	X	X	X
Pregnancy Test [c]	X		X			X
Vital Signs (blood pressure/pulse rate) [d]	X		X (08:00)			X (08:00)
Refraction [e]	X					
BCVA[e]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy [f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
IOP [g]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00
Pachymetry [h]	X					
Instill study medication after IOP measurement				X (08:00)	X (08:00)	X (08:00)
Iris color, eyelash, eyelid [i]			X (photo)			X (photo)
Gonioscopy [j]	X					
Visual Field [k]	X					
Ophthalmoscopy [l]	X (pupil dilation)		X (16:00)			X (16:00, pupil dilation)
Blood Sampling for Pharmacogenomics/genomics [m]				X		
Dispense Study Medication			X		X	
Collect Study Medication					X	X
Phone call to remind subject to take evening dose on the day before each visit				X	X	X

a. Informed Consent Form 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's medical records or subject history.
c. A urine pregnancy test will be conducted for all female subjects of childbearing potential.
d. Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and Visit 5 before the morning dose.
e. Refraction will be performed at the screening visit. If more than 10 letters in BCVA are lost compared to the screening visit, then refraction should be performed again. BCVA examination will be completed before IOP measurement at 08:00.
f. Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before fluorescein instillation.
g. IOP measurements will be performed at 08:00, 10:00 and 16:00 (±60 min) at all visits except for Visit 1 and the optional Visit 1a (screening and mid-washout).
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening).
i. Eye photograph will be taken at Visits 2 (Baseline) and 5 (Month 3).
j. If gonioscopy was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary. Gonioscopy will be performed after IOP measurement at Visit 1 (Screening).
k. If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.
l. Ophthalmoscopy will be performed at Visits 1, 2 and 5 (i.e. Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Visit 1 and Visit 5/exit or early termination..Dilation of the pupil will be performed after the 16:00 IOP measurement.
m. Blood sampling for the pharmacogenomics/genomics laboratory research study may be performed at any visit after pharmacogenomics/genomics informed consent obtained, subject randomized and study drug dosing has begun.
n. Optional at unscheduled visit, required for early terminated subjects.

Table 4: Schedule of Events and Procedures for PEDIATRIC subjects

	Washout Period		Double-Masked Treatment Period			
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a	Visit 2 Eligibility/Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43 ±3)	Visit 5 Month 3 (Day 91±7) Exit or Early Termination [n]
Informed Consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study [a]	X					
Inclusion/Exclusion Criteria	X		X			
Demographics and Medical History, including prior PGA [b]	X					
Concomitant Medications/ Therapies	X	X	X	X	X	X
Dosing Compliance				X	X	X
AEs		X	X	X	X	X
Pregnancy Test [c]	X		X			X
Vital Signs (blood pressure/pulse rate) [d]	X		X (08:00)			X (08:00)
Refraction [e]	X					
BCVA[e]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy [f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)
IOP [g]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00
Pachymetry [h]	X					
Instill study medication after IOP measurement				X (08:00)	X (08:00)	X (08:00)
Iris color, eyelash, eyelid [i]			X (photo)			X (photo)
Gonioscopy [j]	X					
Visual Field [k]	X					
Ophthalmoscopy [l]	X (pupil dilation)		X (16:00)			X (16:00 pupil dilation)
Blood Sampling for Pharmacogenomics/genomics [m]				X		
Dispense Study Medication			X		X	
Collect Study Medication					X	X
Phone call to remind subject to take evening dose on the day before each visit				X	X	X

a. Informed Consent Form and the Assent Form 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's medical records or subject history.

c. A urine pregnancy test will be conducted for all female subjects of childbearing potential.

d. Vital signs (resting blood pressure and pulse rate) will be collected in anytime at Visit 1 (Screening), and approximately 08:00 for Visit 2 (Baseline), and Visit 5 before the morning dose.

e. Refraction will be performed at the screening visit if the pediatric subject is able to cooperate. Autorefraction is also acceptable. If more than 10 letters in BCVA are lost compared to the screening visit level, then refraction should be performed again if the pediatric subject is able to cooperate. BCVA examination will be completed before IOP measurement at 08:00. BCVA will be performed for the pediatric subjects who are able to cooperate using an age-appropriate eye chart and method (e.g. ETDRS chart, LEA symbols chart with logMAR notation, Tumbling E's with logMAR notation, Landolt's broken rings with LogMAR notation, fix and follow) under normal room illumination. Same eye chart should be used for a given subject throughout the study.

f. Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before instillation of fluorescein.

g. IOP measurements will be performed at 08:00, 10:00 and 16:00 (±60 min) at all visits except for Visit 1 and the optional Visit 1a (screening and mid-washout). IOP will be measured with age-appropriate tonometers (e.g. Goldmann applanation tonometer, a Perkins tonometer, or a tonopen, or iCare tonometer etc.) to the extent the subject is able to cooperate.
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening) if the subject is able to cooperate. Subject must have sufficiently clear cornea that allows for a complete ophthalmic exam to be enrolled if pachymetry is not able to be obtained.
i. Eye photograph will be taken at Visits 2 (Baseline), and 5 (Month 3) if the subject is able to cooperate.
j. Gonioscopy will be performed at Visit 1 (Screening) if the subject is able to cooperate. If unable to cooperate, historical gonioscopy performed within 12 months prior to screening and documented in the subject's records is acceptable. Gonioscopy performed at Visit 1 (Screening) should occur after IOP measurement.
k. Visual field test will be performed if the subject is able to cooperate. If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.
l. Ophthalmoscopy will be performed if the subject is able to cooperate. Ophthalmoscopy will be performed at Visits 1, 2, and 5 (i.e. Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Visit 1 and Visit 5/exit or early termination. Dilation of the pupil will be performed after the 16:00 IOP measurement.
m. Blood sampling for the pharmacogenomics/genomics laboratory research study may be performed at any visit after the pharmacogenomics/genomics informed consent is obtained, subject is randomized and study drug dosing has begun.
n. Optional at unscheduled visit, required for early terminated subjects.

Guidance for the visual acuity and IOP measurements in pediatric subjects are shown in Section 21.4.

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 pharmacogenomics/genomics laboratory research study may be obtained at any visit prior to blood sampling. Ensure the subject understands that if he/she does not wish to provide a blood sample for the pharmacogenomics/genomics laboratory research study that their decision will have no influence on their participation in the main study.

  For pediatric subjects, written informed consent must be provided by the parent/legal guardian, and assent should be provided by the pediatric subjects. The evaluation of whether or not a child can give assent should not solely be based on chronological age, but should also depend on factors such as developmental stage, intellectual capacity and disease experience/understanding.

- Prepare the list of screening/registration of subjects.
- Obtain demographics.
- Obtain medications, procedures/therapies and medical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 5 years, diagnosis, ocular surgical history, current ocular and systemic conditions.
- Obtain urine and perform urine pregnancy test, if the subject is a female of child-bearing potential.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - Vital signs (blood pressure/pulse rate)
  - Refraction
  - BCVA (before IOP measurement)
  - Biomicroscopy (before IOP measurement)
  - IOP
  - Pachymetry (after IOP measurement)
  - Ophthalmoscopy with pupil dilation (after IOP measurement)
  - Gonioscopy
  - Visual field
- Determine if the subject meets eligibility criteria.
- If the subject meets eligibility criteria and is still willing to continue the study, discontinue any current IOP-lowering medications if any according to the following schedule (up to +7 days as a window is allowed):
  - Miotics: 7 days

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

- 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 concerns during the washout period. If subjects are to be treated with topical CAI in the week before Visit 2 (Baseline, Day 1), mid washout visit (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 for adult subjects or in the eye being considered for study treatment for pediatric subjects, they will need a wait period of ≥ 2-3 weeks (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers) with no contact use before their Visit 2 (Baseline, Day 1).
- Schedule the eligible subject to return for Visit 2 (Baseline, Day 1) after the required wait/washout period.
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.

7.4.2. Visit 1a (Optional, Washout Period)

- Visit 1a is an interim safety visit (referred to as mid-washout visit) that may be performed during the washout period if, in the Investigator's opinion, a subject's IOP causes any safety concern during washout period.
- Update concomitant medications and procedures/therapies.

- Query the subject regarding AEs.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before IOP measurement)
  - Biomicroscopy (before IOP measurement)
  - IOP

7.4.3. Visit 2 (Baseline, Day 1)

- Update concomitant medications and procedures/therapies.
- Confirm the subject has complied with the required wait/washout period for ocular hypotensive medication(s), or contact lenses use, if required.
- Query the subject regarding AEs.
- Perform vital signs (blood pressure/pulse rate) measurements at approximately 08:00.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (before the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- If subject meets the 08:00 IOP eligibility requirements, schedule additional IOP measurements at 10:00.
- Perform IOP measurement at 10:00 (±60 min).
- If subject meets the 08:00 and 10:00 IOP eligibility requirements, schedule additional IOP measurements at 16:00
- Perform IOP measurement at 16:00 (±60 min).
- Perform ophthalmoscopy in both eyes immediately after the 16:00 IOP measurement.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments at any time during this visit.
  - Iris color, eyelash, eyelid assessment, with sets of front view and side view photographs of each eye individually. The following six (6) photos are required at this visit as follows:

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

- Perform final review of eligibility criteria after the 16:00 IOP measurement. The subject will then be randomized, via Interactive Response Technology (Medidata BALANCE).
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- After the subject has been randomized to a treatment arm, and assigned a treatment kit by BALANCE, an authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Dispense the assigned kit to the subject which will contain the following;
    - Two (2) bottles of study drug labeled “morning”
    - Two (2) bottles of study drug labeled “evening”
  - 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 including the Investigator or Examiner, or other study subjects.
- Instruct the subject to instill the study medicine daily, starting from this evening (“evening” dose) (20:00).
- Schedule the subject to return on Day 8 ±2 for Visit 3 (Week 1).
- Inform the subjects they will be reminded of the evening instillation of the study medication by phone call a few days before Visit 3.
- Remind the subjects that the morning dose of Visit 3 will be done at the clinic.
- 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 procedures/therapies.
- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance and ensure subject has sufficient study medication to complete dosing through Visit 4.
- Query the subject regarding AEs.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (before the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes (for pediatric subjects, the investigator may elect to dose only one eye). An authorized unmasked study staff should make sure the instillation is performed.
- Perform IOP measurement at 10:00, and 16:00 (±60 min).
- If the subject provided written consent to provide a blood 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 blood sample cannot be collected at this visit, it may be collected at any one of the following Visits, for example, Visits 4, 5 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 43±3 for Visit 4 (Week 6).
- Remind the subject to continue dosing according to the written instructions.
- Inform the subjects they will be reminded of the evening instillation of the study medication by phone call a few days before Visit 4.
- Remind the subjects that the morning dose of Visit 4 will be done at the clinic.
- Remind the subject to bring all used and unused study medication at Visit 4.

7.4.5. Visit 4 (Week 6, Day 43 ±3)

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

- Query the subject regarding AEs.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (before the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes **(for pediatric subjects, the investigator may elect to dose only one eye, the study eye).** An authorized unmasked study staff should make sure the instillation is performed.
- Perform IOP measurement at 10:00, and 16:00 (±60 min).
- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused bottles of study medication.
- Dispense the assigned kit (from BALANCE) to the subject which will contain the following;
    - Two (2) bottles of study drug labeled "morning"
    - Two (2) bottles of study drug labeled "evening"
  - Instruct the subject not to show or discuss their study medication with other study staff including the Investigator or Examiner, or other study subjects.
- If the subject provided written consent to provide a blood 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 91±7 for Visit 5 (Month 3).
- Remind the subject to continue dosing according to the written instructions.
- Inform the subjects they will be reminded of the evening instillation of the study medication by phone call a few days before Visit 5.
- Remind the subjects that the morning dose of Visit 5 will be done at the clinic.
- Remind the subject to bring all used and unused study medication at Visit 5.

7.4.6. Visit 5 (Month 3, Day 91 ±7) Study Exit/Early Termination

- Update concomitant medications and procedures/therapies.

- An authorized unmasked study staff member, other than the Investigator or Examiner should query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Perform vital signs (blood pressure/pulse rate) measurements at approximately 08:00.
- As per Schedule of Events and Procedures Table 3 (for adult subjects**) or Table 4 (for pediatric subjects),** perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (before the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (before the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes **(for pediatric subjects, the investigator may elect to dose only one eye, the study eye).** An authorized unmasked study staff should make sure the instillation is performed.
- Perform IOP measurement at 10:00, and 16:00 (±60 min).
- Perform pupil dilation in both eyes after the 16:00 IOP measurement.
- Perform ophthalmoscopy with pupil dilation in both eyes immediately after the 16:00 IOP measurement.
- As per Schedule of Events and Procedures Table 3 (for adult subjects) **or Table 4 (for pediatric subjects),** perform the following procedures or assessments at any time during this visit.
  - Assess any changes from baseline in Iris color, Eyelash, Eyelid and take front view and side view photographs of each eye. The following six (6) photos are required at this visit as follows:

[redacted]

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

- An authorized unmasked study staff member, other than the Investigator or Examiner, must:
  - Collect all used and unused bottles of study medication.
- If the subject provided written consent to provide a blood sample for a future pharmacogenomics/genomics laboratory research study, the sample must be collected at this visit, if not collected at the previous visits.
- Exit the subject from the study.

Note:

- **If the study drug administration is discontinued prior to Visit 5, the subject should be encouraged to still participate in follow-up study visits until Visit 5 on an observational basis.**
- **If the study drug administration is discontinued prior to Visit 5, then to the extent possible, all procedures for Study Exit/Early Termination as per Table 3 (for adult subjects) or Table 4 (for pediatric subjects) will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.**

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.

8.1. Subject Inclusion Criteria for ADULT Subjects

Inclusion Criteria Specific for ADULT Subjects:

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

1. Provide signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF).
2. Be 18 years of age or older on the date of signing the ICF and be able and willing to comply with all treatment and follow-up study procedures.
3. If a subject is a female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of surgery]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
   - Abstinence
   - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
   - Placement of a copper-containing IUD
   - Condom with spermicidal foam/gel/film/cream/suppository
   - Vasectomized male partner (surgery at least 6 months prior)

   Male subjects capable of fathering children should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraceptive method deemed adequate by the investigator throughout the course of the study (as well as for 12 weeks following last dose in study).
4. Must have a diagnosis of OAG (including Pigmentary Glaucoma or Pseudoexfoliative Glaucoma) or OHT in both eyes, or one eye with OAG and the other with OHT.
5. BCVA of +0.60 logMAR (Snellen equivalent 20/80) or better in each eye.
6. Central corneal thickness ≥ 480 μm and ≤ 600 μm in each eye.
7. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition to continuing to meet inclusion criterion 5 (BCVA), the subject must meet the following criteria at Visit 2 (Baseline, Day 1):

8. Completed the required wait/washout period.

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

8.2. Subject Exclusion Criteria for ADULT Subjects

Exclusion Criteria Specific for ADULT Subjects:

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

General

1. Females who are pregnant, nursing or planning a pregnancy.
2. Subjects with known or suspected drug or alcohol abuse.
3. Current or planned participation in any other clinical trial involving an investigational product or device within 4 weeks prior to Visit 1 (Screening) or at any time during this trial.
4. Subjects who have been exposed to DE-117 prior to Visit 1 (Screening).

Medications / Therapies

5. Intended or current use of the following prohibited medications/therapies during the study duration:

All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications.
All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
Any ocular, periocular, inhaled, nasal or systemic corticosteroids including joint injection, etc.
Lacrimal/punctal occlusion via plug (s) or cautery.

6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
7. 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]). Subjects using the above medications must be on a stable dose use for at least 30 days prior to Visit 1 (Screening) and during the study duration.

8. Use of contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
9. Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.
10. History of ocular surgery specifically intended to lower IOP (e.g., laser trabeculoplasty, filtering surgery, tube shunt, Minimally Invasive Glaucoma Surgery (MIGS), or trabeculotomy) in either eye.
11. History of keratorefractive surgery (e.g., RK, PRK, LASIK) in either eye.
12. Allergy, hypersensitivity or contraindications to EP2 receptor agonists, beta-blockers, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications. This also includes subjects with a history or presence of contraindications to beta-blocker therapy, such as chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema), bronchial asthma, second or third degree atrioventricular block, uncontrolled congestive heart failure.

Diseases

13. Presence of advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
14. Presence of any corneal abnormality or other conditions interfering with or preventing reliable Goldmann applanation tonometry (e.g. Fuch's dystrophy or significant corneal surface abnormality) in either eye.
15. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
16. Presence or history of macular edema or known risk factors for macular edema in either eye.
17. History of severe ocular trauma in either eye.
18. History of iritis and/or uveitis in either eye.
19. History of retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may be progressive during the time course of the study in either eye.
20. Presence or history of any disease or condition that in the opinion of the study Investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (e.g., recurrent corneal erosion syndrome, uncontrolled cardiovascular disease etc.).
21. Any decision by the Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

8.3. Subject Inclusion Criteria for PEDIATRIC Subjects

Inclusion Criteria Specific for PEDIATRIC Subjects:

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

1. Parent/legal guardian signed written informed consent on the Institutional Review Board (IRB)/Ethics Committee (EC) approved Informed Consent Form (ICF) and patient assent has been given as applicable.
2. The patient and parent/legal guardian should agree to comply with study restrictions, treatment plan, procedures and keep scheduled visits.
3. Be ≥1 year and less than 18 years old on the date of signing the ICF.
4. If a subject is a female of childbearing potential she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).
   - Abstinence
   - Hormonal contraceptive method (including oral or transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
   - Placement of a copper-containing IUD
   - Condom with spermicidal foam/gel/film/cream/suppository
   - Vasectomized male partner (surgery at least 6 months prior)

   Male subjects capable of fathering children should use/ practice an acceptable contraceptive method, such as abstinence, condom or vasectomy (surgery at least 6 months prior) or other contraceptive method deemed adequate by the investigator throughout the course of the study (as well as for 12 weeks following last dose in study).
5. Must have a diagnosis of pediatric glaucoma or OHT in one or both eyes, including primary (congenital and juvenile open angle glaucoma) and secondary glaucoma. For a child with pediatric glaucoma due to secondary causes, the Investigator or study site should discuss the case with the Medical Monitor prior to subject enrollment.
6. Must have elevated IOP to such a level that investigator deems pharmacologic intervention with IOP-lowering medication to be clinically necessary in at least one eye.
7. Must have a sufficiently clear cornea that allows for a complete ophthalmic examination.
8. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye, based on gonioscopy performed at Visit 1 (Screening), or historical gonioscopy performed within 12 months prior.

In addition to continuing to meet inclusion criteria 6 (elevated IOP) and 7 (clear cornea), the

subject must meet the following criterion at Visit 2 (Baseline, Day 1):

9. Completed the required wait/washout period.

8.4. Subject Exclusion Criteria for PEDIATRIC Subjects

Exclusion Criteria Specific for PEDIATRIC Subjects:

At Visit 1 (Screening) and Visit 2 (Baseline, Day 1), subjects with any of the following ocular conditions in either eye or with any of the following non-ocular conditions or characteristics are not eligible to participate in the study. Exception: criteria 8, 9 and 10 only apply to the eye being considered for study treatment. E.g. if only the non-treated eye has a history of LASIK, the other eye may still qualify for participation and treatment in the study if the subject meets all other criteria.

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 4 weeks prior to Visit 1 (Screening) or at any time during this trial.
4. Subjects who have been exposed to DE-117 prior to Visit 1 (Screening).

Medications / Therapies

5. Intended or current use of the following prohibited medications/therapies during the study duration:

All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications.
All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
Any ocular, periocular, inhaled, nasal or systemic corticosteroids including joint injection, etc.
Lacrimal/punctal occlusion via plug (s) or cautery.

6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
7. 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]). Subjects using the above medications must be on a stable dose use for at least 30 days prior to Visit 1 (Screening) and during the study duration.

8. Use of contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
9. Any ocular surgery (including goniotomy or glaucoma surgery) or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study.
10. History of keratorefractive surgery (e.g. RK, PRK, LASIK).
11. Allergy, hypersensitivity or contraindications to EP2 receptor agonists, beta-blockers, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications. This also includes subjects with a history or presence of contraindications to beta-blocker therapy, such as chronic obstructive pulmonary disease (e.g. chronic bronchitis, emphysema), bronchial asthma, second or third degree atrioventricular block, uncontrolled congestive heart failure.

Diseases

12. Presence of advanced glaucoma in either eye.
13. Presence of any corneal abnormality or other conditions interfering with or preventing reliable tonometric measurements (e.g., Fuch's dystrophy or significant corneal surface abnormality) in either eye.
14. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
15. Presence or history of macular edema or known risk factors for macular edema in either eye.
16. Aphakia or pseudophakia
17. Single sighted subject
18. History of severe ocular trauma in either eye.
19. History of iritis and/or uveitis in either eye.
20. 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.
21. Presence or history of any disease or condition that, in the opinion of the study Investigator, may put the subject at significant risk (such as contraindication to the use of Timolol Maleate Ophthalmic Solution 0.5%), 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 Investigator or Medical Monitor to terminate a subject in screening or declare any subject ineligible for any sound medical reason.

8.5. 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 discontinue the study drug administration or terminate a subject's study participation due to any of the following reasons:

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

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

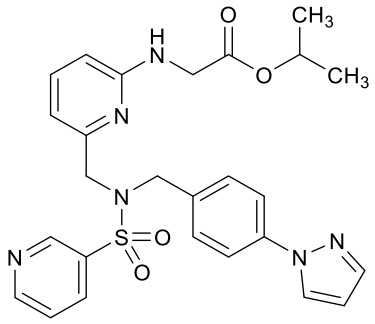
If the study drug administration is discontinued prior to Visit 5, then to the extent possible, all procedures for Early Termination will be performed on the day of early drug discontinuation as per Table 3 (for adult subjects) or Table 4 (for pediatric subjects). Subjects who are discontinued from the study early will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Medication

DE-117 Ophthalmic Solution 0.002% is an aqueous solution containing DE-117. [redacted]

Figure 2: DE-117 Structure



Investigational Product:

- DE-117 Ophthalmic Solution 0.002% contains 0.02 mg/mL DE-117

Active Control:

- Timolol Maleate Ophthalmic Solution 0.5% contains the active ingredient, timolol 5 mg/mL. See Section 21.5.

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 other than the study medication during the study duration will be considered as a concomitant treatment. The information of concomitant treatment must be recorded in the subject's source documents and on the eCRF.

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

9.2.1. Prohibited Medications or Therapies

- All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B12 formulation (e.g., cyanocobalamine), over-the-counter dry eye artificial tears/drops, and study medications during the study duration.

  - If artificial sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents, Vitamin B_{12} formulation, over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of **at least 5 minutes** between use of these ocular medications and use of the study medication.
- All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol) during the study duration.
- Any ocular, periocular, inhaled, nasal or systemic corticosteroids including joint injection, etc. during the study duration.
- Lacrimal/punctal occlusion via plug (s) or cautery during the study duration.
- Initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, ACE inhibitors, and ARB) within the first 30 days prior to Visit 1 (Screening) and during the study duration.
- Contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye for adult subjects or in the eye being considered for study treatment for pediatric subjects (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
- Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye for adult subjects or in the eye being considered for study treatment for pediatric subjects.
- Participation in any other clinical trial involving an investigational product within 4 weeks prior to Visit 1 (Screening) and during the study.

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

- Subjects will receive verbal and written instructions for proper instillation of the study medication, the dosing regimen, and the conditions of the study medication storage.
- Subjects will be reminded at study visits to consistently dose at the same time of the day
  - Twice daily at 08:00 and 20:00 [±60min] through Visit 2 to 5
- Subjects will be reminded of the evening instillation of the study drug on the day before Visit 3 through Visit 5/Early Termination respectively.

- Subjects will be reminded that the morning instillation of the study drug at each visit through Visit 3 to 5 will be done at the clinic.
- For adult subjects, since subjects must have a diagnosis of OAG or OHT in both eyes, both eyes should be treated for the duration of the study, even if only one eye is eligible per IOP inclusion criteria.
  For pediatric subjects, if only one eye has a diagnose of glaucoma or OHT, the fellow eye doesn't have to be treated by the study medications for the duration of the study.
- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 through Visit 5/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 through Visit 5/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

A stratified permuted-block randomization will be employed to randomize eligible subjects in a 1:1 ratio to either DE-117/Vehicle arm or Timolol Maleate arm. Two strata will be constructed based on age (adult: ≥ 18 years; pediatric: < 18 years).

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

This is a double-masked study. The subjects, Investigators, Examiners and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member who is not the Investigator or Examiner at the investigative site will dispense and collect study medication(s) and will query about dosing compliance. Subjects will be instructed not to show the eye drop bottles or discuss the eye drop to either the Investigator or the Examiner or other study subjects. The active control treatment (Timolol Maleate) containers will be over-labeled and packaged in the same secondary package (e.g., cardboard carton) as the investigational treatment (DE-117). All subjects will receive a bottle labeled "morning" for the morning dose and a bottle labeled "evening" for the evening dose. However, the DE-117/Vehicle arm will receive the vehicle (i.e., "morning" bottle) at the morning dose, while the Timolol Maleate arm receives the active treatment (i.e., "morning" bottle) at the morning dose.

In case of a medical emergency, the Principal Investigator may reveal the treatment information by unmasking through 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 AE or SAE 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

DE-117 Ophthalmic Solution contains 0.002% or 0.02 mg/mL DE-117. Each 2.5 mL bottle of DE-117 Ophthalmic Solution 0.002% contains 50 µg of DE-117. In addition,

[redacted]

10.1.2. Vehicle

The vehicle is identical to the investigational product but does not contain the active ingredient in DE-117. [redacted]

10.1.3. Active Control

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

Timolol Maleate Ophthalmic Solution 0.5% contains the active ingredient, timolol 5 mg/mL and the preservative BAK 0.01%. Other ingredients include monobasic and dibasic sodium phosphate and purified water. The pH is adjusted to 6.5 to 7.5 with sodium hydroxide. See Section 21.5.

10.2. Study Medication Packaging and Labeling

DE-117 Ophthalmic Solution 0.002% and DE-117 vehicle ophthalmic solution will be supplied as [redacted]

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

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

Kits dispensed at Visit 2 and Visit 4 (double-masked portion) will contain two (2) “morning” eye drop bottles and two (2) “evening” eye drop bottles of study medication.

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

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. During the refrigeration storage, the Investigator (or his/her designee) will verify and record that the temperature was maintained at 2° to 8°C (36° to 46°F) using temperature recorder at least once every seven days at the investigational site, until the last subject has exited the study at the site. In the event of a temperature excursion or any study medications damaged during storage, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee).

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

10.4. Study Medication Preparation

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

10.5. Study Medication Administration

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

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 and customized blood 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 (08:00, 10:00 and 16:00) will be evaluated at each post-baseline visit. Besides observed IOP measurements, change and percent change from baseline in IOP at each scheduled time point as well as the change and percent change from baseline in mean diurnal IOP will also be derived and evaluated.

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 medication. For this study, the investigational products are DE-117, DE-117 vehicle and Timolol. Regardless of relationship to the study medication, an AE can be a clinically relevant unintended sign (including an abnormal laboratory finding), symptom, or disease.

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

An elective surgical procedure scheduled or planned prior to study entry that does not require 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 medication 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 subject withdrawal or the scheduled exit visit, must be recorded. To improve the quality and precision of acquired AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms and /or laboratory or test findings (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis, and enlarged heart on chest x-ray). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).

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

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

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

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

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

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:

- 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. Events of Special Interest

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

- Pregnancy:
  - There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 4 weeks for female subjects of childbearing potential and 12 weeks for male subjects capable of fathering children after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject will be discontinued from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.

- Medication administration errors
  - Study medication administration errors determined to be **significant** by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: incorrect dose of study medication and administration of study medication from an incorrect kit. An AE does not necessarily need to have occurred to count as a study medication administration error. A medication administration error is an unintended failure in the process of treatment with a medicinal product that leads to, or has the potential to lead to harm of the subject.
- Macular edema (including cystoid macular edema):
  - Macular edema has been reported in some patients during the DE-117 clinical trials. Any cases of macular edema (including cystoid macular edema) should be reported in the ESI form in eCRF, or in case the EDC system is down, in the manual ESI form. Any cases of macular edema (including cystoid macular edema) will need to be followed until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained as per Section 12.1.4.

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 with the following types of events should be followed by the Investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained.

- On-going SAEs issued after study medication treatment
- On-going ESIs, including pregnancy, medication errors resulting in AE's, and macular edema/cystoid macular edema issued after study medication treatment
- Early termination and withdrawal from the study due to study medication related AEs

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

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

12.1.5. Manual Back-Up Reporting Procedures

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

- Complete an AE Form, SAE Form, pregnancy Form, medication error Form, or ESI Form as appropriate.

- Attach a cover sheet with your contact information and address to Santen (or its designee).
- Email (preferred) or Fax the cover sheet and the completed form(s) to Santen (or its designee) at globalPVAmericas@santen.com or fax number +1-415-276-5882 (in the US).

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

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:

- BCVA
- Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitate, lens, anterior synechiae of iris and posterior synechiae of iris
- Ophthalmoscopy variables: glaucomatous optic nerve
- Iris color/eyelash/eyelid

12.2.2. Non-ocular Assessments

Non-Ocular assessments include:

- Blood pressure and pulse rate

13. OTHER ASSESSMENTS

13.1. Demographic, Baseline Characteristics and Other Assessments

Subject demographics, baseline characteristics, medical history, concomitant medications, exposure to study medication, and pregnancy test for females of childbearing potential will be summarized.

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. Interim Analysis

There is no planned interim analysis for this study.

14.2. Final Analysis

An unmasked final analysis will be performed after all subjects completed Month 3. The analysis will evaluate the efficacy and safety of DE-117 Ophthalmic Solution 0.002% once daily compared with Timolol Maleate Ophthalmic Solution 0.5% twice daily.

14.3. 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 Baseline (Visit 2). For example, IOP must be ≥ 22 mmHg at all IOP measurement time-points (08:00, 10:00 and 16:00). See Section 8.1 and Section 8.2 for all inclusion/exclusion criteria. If both eyes qualify, the eye with the higher mean diurnal IOP at Baseline (Visit 2) will be the study eye. If both eyes have the same mean diurnal IOP at baseline, then the right eye will be designated as the study eye.

Statistical analyses for pediatric subjects may be performed separately depending on the number of pediatric subjects enrolled in this study.

More details on the statistical methods will be described in SAP which will be finalized prior to unmasking the data.

14.3.1. Sample Size

The sample size calculation was based on a two-sided Type I error rate of 5% and a non-inferiority margin of 1.5 mmHg. Assuming a between-treatment difference of 0 mmHg, SD of 4.0 mmHg and a correlation coefficient of 0.6 among repeated measures, approximately 400 adult subjects in total (200 subjects per treatment arm) will provide 90% power to demonstrate non-inferiority of DE-117 Ophthalmic Solution 0.002% to Timolol Maleate Ophthalmic Solution 0.5%.

14.3.2. Statistical Hypotheses and Level of Significance

The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00 and 16:00 at Week 1, Week 6 and Month 3 visits.

For the primary endpoint, a Mixed Effect Model for Repeated Measurement (MMRM) will be used to test the following hypotheses:

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

where μ_T and μ_C denote the mean values of the primary endpoint in DE-117/Vehicle arm and Timolol Maleate arm, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg.

Treatment difference between the DE-117/Vehicle arm and Timolol Maleate arm at each specified time point of each post-baseline visit up to Month 3 will be reported along with 95% confidence intervals. Non-inferiority is established if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (0.002% DE-117 - Timolol Maleate) is ≤ 1.5 mmHg at all nine time points and ≤ 1.0 mmHg in majority (5 or more) of the time points. If the upper limit of the 95% confidence interval for the difference is ≤ 0 at all nine time points, superiority of DE-117 to Timolol will be claimed.

If non-inferiority in the primary endpoint is achieved, then the following two key secondary endpoints will be tested sequentially according to hierarchical fixed sequence procedure:

1. Mean diurnal IOP in the study eye at Month 3

The corresponding hypothesis is:

$$H_{0S1}: \mu_{Ts1} - \mu_{Cs1} > \Delta \text{ versus } H_{AS1}: \mu_{Ts1} - \mu_{Cs1} \leq \Delta$$

where μ_{Ts1} and μ_{Cs1} denote the mean diurnal IOP at Month 3 in DE-117/Vehicle arm and Timolol Maleate arm, respectively; and Δ denotes the non-inferiority margin of 1.5 mmHg.

If the hypothesis is rejected at 0.05 significance level, then the following key secondary endpoint will be tested:

2. Mean diurnal IOP in the study eye at Week 1

The corresponding hypothesis is:

$$H_{0S2}: \mu_{Ts2} = \mu_{Cs2} \text{ versus } H_{AS2}: \mu_{Ts2} \neq \mu_{Cs2}$$

Where μ_{Ts2} and μ_{Cs2} denote the mean diurnal IOP at Week 1 in DE-117/Vehicle arm and Timolol Maleate arm, respectively.

14.4. Study Populations

14.4.1. Safety Population

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

14.4.2. 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 by planned treatment.

14.4.3. Per-Protocol Set

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

14.5. Handling of Missing Values

The primary analysis of continuous IOP endpoints will be performed using the MMRM analysis on observed cases. As sensitivity analyses, a last-observation-carried-forward (LOCF) approach and a Pattern Mixture Models (PMM) approach may be applied to evaluate the impact of missing data on the primary analysis results. For the binary IOP endpoints, the missing data at Month 3 will be imputed using an LOCF approach.

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

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

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

14.6. 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 (SOC) and Preferred Term (PT) specified in the MedDRA.

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

14.7. Efficacy Analyses

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

14.7.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 10:00 and 16:00 at Week 1, Week 6 and Month 3 (Visits 3, 4 and 5).

A MMRM will be carried out on observed cases up to Month 3. At each scheduled time point of each visit, least square mean IOP of each treatment arm and 95% confidence interval for the difference in least square means between DE-117/Vehicle and Timolol Maleate will be estimated. Non-inferiority is established if the upper limit of the 95% confidence interval for the

difference is ≤ 1.5 mmHg for all nine time points and ≤ 1.0 mmHg for at least 5 out of the 9 time points.

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

14.7.2. Analysis of Secondary Efficacy Endpoints

14.7.2.1. Key Secondary Efficacy Endpoints

The key secondary efficacy endpoints are

- Mean diurnal IOP in the study eye at Month 3 (Visit 5), and
- Mean diurnal IOP in the study eye at Week 1 (Visit 3)

A MMRM will be carried out on observed cases up to Month 3. The least square mean diurnal IOP of each treatment arm and 95% confidence interval for the difference in least square means between DE-117/Vehicle and Timolol Maleate at Week 1 and Month 3 will be estimated, respectively. If non-inferiority in the primary endpoint is achieved, then the two key secondary endpoints will be tested sequentially at the 0.05 significance level (2-sided) to control the overall Type I error rate associated with the two comparisons.

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

14.7.2.2. Other Secondary Efficacy Endpoints

Other secondary endpoints to be assessed include:

- Change and percent change from baseline in IOP at each timepoint/post-baseline visit
- Change and percent change from baseline in mean diurnal IOP at each post-baseline visit
- Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2) at each post-baseline visit
- Having a mean diurnal IOP ≤ 18mmHg at each post-baseline visit

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

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

Subgroup analyses may be performed for secondary endpoints using descriptive statistics.

14.8. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs, blood pressure and pulse rate, BCVA, slit-lamp biomicroscopy findings, ophthalmoscopy, iris color, eyelash, and eyelid.

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

Safety parameters listed in Section 12.2.1 and Section 12.2.2 will be summarized using descriptive statistics by actual treatment received. Changes from baseline in these 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 IRB or IEC and other applicable regulatory agencies to inspect all study records, eCRFs, recruitment materials and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the eCRF, and compliance with the 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 IRB or 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 pharmacogenomics study, assent form and other study related material, as appropriate, must be approved in writing by an IRB or IEC as appropriate. If an IRB or IEC does not approve the collection of blood samples for optional future pharmacogenomic 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 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 blood samples for future pharmacogenomic research studies. If the subject does not wish to provide a blood 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.

For the pediatric subjects, written informed consent must be signed in accordance with local regulatory and legal requirements by the patient or parent/legal guardian, and giving of assent by the patient if appropriate, must be documented prior to initiation of any study-related procedures. Subjects and their parents/legal guardians must be provided with adequate time to think over their possible participation in the study, to ask questions from the investigator and/or to discuss the study participation with their family or primary care

physician. No measures whatsoever described in the study protocol shall be undertaken, nor any current medication discontinued without such consent indicating that the patient and/or the parent/legal guardian have been given both verbal and written information about the study and the study treatment. The evaluation of whether or not a child can give assent should not solely be based on chronological age, but should also depend on factors such as developmental stage, intellectual capacities and disease experience/understanding.

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: Santen Study 33-001. A Phase I/II, Randomized, Observer-masked, Placebo-and-active-controlled, Parallel-group, Multi-center Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension
2. Data on File: Santen Study 33-002. A Phase II, Randomized, Observer-masked, Placebo- and Active-controlled, Parallel-group, Multi-center Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution Compared with Latanoprost and Placebo in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension
3. Data on File: Santen Study 33-003. A Phase IIb, Randomized, Observer-masked, Active-controlled, Parallel-group, Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution Compared with Latanoprost Ophthalmic Solution, 0.005% in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension – SEE Study
4. Data on File: Santen Study 01171502. A Pharmacokinetic Study of DE-117 Ophthalmic Solution in Healthy Adult Male Subjects - Phase I Study -
5. Data on File: Santen Study 01171503. A Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution in Subjects With Primary Open Angle Glaucoma or Ocular Hypertension -AYAME Study-
6. Data on File: Santen Study 01171504. A Long-term Study of DE-117 Ophthalmic Solution Monotherapy and Concomitant Use of DE-117 Ophthalmic Solution With Timolol Ophthalmic Solution in Patients With OAG or OH: RENGE Study

7. Data on File: Santen Study 01171506. A Study Assessing the Safety and Efficacy of DE-117 in Subjects With POAG or OH Who Are Non-/Low-responders to Latanoprost: FUJI Study

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

The following descriptions are for adult and pediatric subjects, however specific guidance for pediatric subjects is shown in Section 21.4.

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

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

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

Medical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 5 years, diagnosis, ocular surgical history, current ocular and systemic conditions will be confirmed through subject interviews at Visit 1 (Screening) to determine if the subject meets eligibility criteria. Primary diagnosis 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), 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), and Visit 5 Study Exit/Early Termination for all females of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 12 months since last menses occurred), is without a uterus or without both ovaries, or has had a bilateral tubal ligation. To perform the pregnancy test, follow instructions provided by the manufacturer of the urine pregnancy test kit.

21.3.3. Vital signs (Blood pressure/Pulse rate)

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

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

21.3.4. Iris color, Eyelash, Eyelid

Please take photographs of the iris, eyelids and eyelashes of each eye at Visit 2 (Baseline), and Visit 5 Study Exit/Early Termination. Six (6) photos are required at each visit as follows:

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, eyelashes and eyelids at Visit 5 Study Exit/Early Termination. For any changes from baseline in deepening of the upper eyelid sulcus (DUES), the response will be YES or NO.

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

21.3.4.1. Iris Color

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

21.3.4.2. Eyelash

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

21.3.4.3. Eyelid

The Investigator will assess eyelid change at Visit 5 Study Exit/Early Termination (e.g., pigmentation, hair growth and deepening of the upper eyelid sulcus) using the photographs obtained at Visit 2 (Baseline). For any changes from baseline in deepening of the upper eyelid sulcus (DUES), the response will be YES or NO.

21.3.5. Refraction

Refraction will be performed for each eye at Visit 1 (Screening). At Visits 2 to 5, if more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed.

21.3.6. Best-Corrected Visual Acuity

BCVA (Best-Corrected Visual Acuity) will be measured for each eye prior to the 08:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit) under normal room illumination using visual acuity chart (ETDRS chart) and the logMAR scoring will be recorded in the subject's source document. 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.

21.3.6.1. 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 5: 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

Table 5: LogMAR Scoring Grid for ETDRS Eye Chart (Continued)

		Total Number of Letters Missed										
Snellen	**Base LogMAR**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
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

21.3.7. Slit-lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the 08:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1/1a, 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 punctate staining

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

Keratic Precipitate

None (0) = Normal

Mild (1) = Slight pigmentation or keratic precipitate

Moderate (2) = Moderate pigmentation or keratic precipitate

Severe (3) = Dense pigmentation or keratic precipitate

Lens

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

None (0) = No lens discoloration nor opacification

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

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

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

Anterior Synechiae of Iris

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

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

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

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

Posterior Synechiae of Iris

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

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

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

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

21.3.8. Intraocular Pressure

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

IOP will be measured using calibrated manual Goldmann applanation tonometer. Measurement will be performed preferably by the same Investigator (operator) and the same authorized study staff (recorder) throughout the study. Investigator (operator) who performs the IOP measurement must have at least 2 years of experience in IOP measurement.

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

A single measurement is made as follows:

- The 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 45º, 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.

21.3.8.1. Goldmann Applanation Tonometer Calibration

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

21.3.9. Pachymetry (Central Corneal Thickness)

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

21.3.10. Gonioscopy

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

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

(1) = approximately 10 degrees

(2) = approximately 20 degrees

(3) = approximately 30 degrees

(4) = approximately 40 degrees or more

21.3.11. Visual Field

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

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

21.3.12. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination will be performed for each eye at Visit 1, Visit 2, and Visit 5 Study Exit/Early Termination, and graded as described below. The examination will be performed with pupil dilated at Visit 1 and Visit 5/Study Exit. 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

21.3.13. Blood Sample for Pharmacogenomics/genomics Study

At sites which elect to participate and for subjects who agree to provide a blood 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 10 mL of blood will be collected for genetic analysis from the subject and stored in a refrigerator until shipment. Please refer to the separate procedure manual for sample handling, storage, and shipment. The samples will be coded to protect the participants' private information. Nucleic acids will be extracted from blood 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 discarded. 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 - Guidance for Visual Acuity and Intraocular Pressure Measurement for Pediatric Subjects

Distance Visual Acuity Assessment for Pediatric Subjects *(Pediatric Ophthalmology and Strabismus, 2017-2018 Basic and Clinical Science Course, AAO)*

Visual acuity assessment requires different eye charts or approaches depending on the age and cooperativeness of the child. The cognitively highest test type that the child is capable of performing should be used. The following age-appropriate eye charts or methods used for visual acuity testing serve as a guide only.

[redacted]

- The same type of eye chart or vision test and lighting conditions (e.g., room illumination) should be used throughout the course of the study.
- A child who has corrective glasses should be tested wearing them. The used refraction should also be recorded.
- In subjects who could not be tested using the manufacturer's recommended test distance, the actual test distance should be recorded in the eCRF.

[redacted]

[redacted]

Intraocular Pressure Measurement for Pediatric Subjects

IOP is the primary endpoint of the study. Every effort should be made to perform IOP measurement to have the diurnal curve. IOP will be measured with age-appropriate tonometers (e.g. Goldmann applanation tonometer, a Perkins tonometer, a tonopen, iCare tonometer etc.) to the extent the subject is able to cooperate. The same tonometer to measure IOP should be used at all visits for a given subject. Investigator or IOP examiner should follow the standard procedures used in their office to measure IOP.

For pediatric subjects who are old enough and can sit at the slit lamp for applanation and are able to cooperate with the IOP measurement, Goldmann applanation tonometer is preferred. Otherwise, handheld tonometers, for example, Perkins applanation tonometer, iCare tonometer or tonopen tonometer are also acceptable. Follow the manufacturing guidance on the use of each handheld tonometer. For pediatric subjects who resist anesthetic eye drops, iCare tonometer can be tried.

21.5. Appendix E - Timolol Maleate Ophthalmic Solution 0.5% Package Insert

Timolol Maleate Ophthalmic Solution USP
0.25% and 0.5%
(equivalent to timolol maleate
3.4 mg/mL and 6.8 mg/mL) — Sterile

TL00N Rev. 06/05

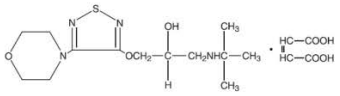
℞ only

DESCRIPTION

Timolol maleate ophthalmic solution is a non-selective beta-adrenergic receptor blocking agent. Its chemical name is (-)-1-(*tert*-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate (1:1) (salt). Timolol maleate possesses an asymmetric carbon atom in its structure and is provided as the levo-isomer. The nominal optical rotation of timolol maleate is:

$[\alpha]_{405\ nm}^{25^\circ}$ in 0.1N HCl (C=5%)=-12.2°. (-11.7° to -12.5°)

Its molecular formula is $C_{13}H_{24}N_4O_3S \cdot C_4H_4O_4$ and its structural formula is:



Timolol maleate has a molecular weight of 432.50. It is a white, odorless, crystalline powder which is soluble in water, methanol, and alcohol. Timolol maleate ophthalmic solution is stable at room temperature.

Timolol maleate ophthalmic solution is supplied as a sterile, isotonic, buffered, aqueous solution of timolol maleate in two dosage strengths.

Timolol Maleate Ophthalmic Solution, 0.25%
Each mL contains:
Active: timolol maleate 3.4 mg, equivalent to 2.5 mg timolol (0.25%).
Preservative: benzalkonium chloride 0.1 mg (0.01%).
Inactives: sodium phosphate dibasic, sodium phosphate monobasic, sodium hydroxide may be added to adjust pH (6.5 to 7.5), and purified water USP.

Timolol Maleate Ophthalmic Solution, 0.5%
Each mL contains:
Active: timolol maleate 6.8 mg, equivalent to 5 mg timolol (0.5%).
Preservative: benzalkonium chloride 0.1 mg (0.01%).
Inactives: sodium phosphate dibasic, sodium phosphate monobasic, sodium hydroxide may be added to adjust pH (6.5 to 7.5), and purified water USP.

CLINICAL PHARMACOLOGY

Mechanism of Action

Timolol maleate is a $beta_1$ and $beta_2$ (non-selective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic (membrane-stabilizing) activity.

reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

Cardiac Failure

Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure

continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure timolol should be discontinued.

Obstructive Pulmonary Disease

Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which timolol is contraindicated [see **CONTRAINDICATIONS**]) should, in general, not receive beta-blockers, including timolol.

Major Surgery

The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have experienced protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of adrenergic agonists.

Diabetes Mellitus

Beta-adrenergic blocking agents should be administered with caution in patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis

Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS

General

Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with timolol, alternative therapy should be considered.

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 **PRECAUTIONS,** *Information for Patients.*)

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Beta-adrenergic receptor blockade reduces cardiac output in both healthy subjects and patients with heart disease. In patients with severe impairment of myocardial function beta-adrenergic receptor blockade may inhibit the stimulatory effect of the sympathetic nervous system necessary to maintain adequate cardiac function.

Beta-adrenergic receptor blockade in the bronchi and bronchioles results in increased airway resistance from unopposed parasympathetic activity. Such an effect in patients with asthma or other bronchospastic conditions is potentially dangerous.

Timolol maleate ophthalmic solution, when applied topically on the eye, has the action of reducing elevated as well as normal intraocular pressure, whether or not accompanied by glaucoma. Elevated intraocular pressure is a major risk factor in the pathogenesis of glaucomatous visual field loss. The higher the level of intraocular pressure, the greater the likelihood of glaucomatous visual field loss and optic nerve damage.

The onset of reduction in intraocular pressure following administration of timolol maleate ophthalmic solution can usually be detected within one-half hour after a single dose. The maximum effect usually occurs in one to two hours and significant lowering of intraocular pressure can be maintained for periods as long as 24 hours with a single dose. Repeated observations over a period of one year indicate that the intraocular pressure-lowering effect of timolol is well maintained.

The precise mechanism of the ocular hypotensive action of timolol is not clearly established at this time. Tonography and fluorophotometry studies in man suggest that its predominant action may be related to reduced aqueous formation. However, in some studies a slight increase in outflow facility was also observed.

Pharmacokinetics
In a study of plasma drug concentration in six subjects, the systemic exposure to timolol was determined following twice daily administration of timolol maleate ophthalmic solution 0.5%. The mean peak plasma concentration following morning dosing was 0.46 ng/mL and following afternoon dosing was 0.35 ng/mL.

Clinical Studies
In controlled multiclinic studies in patients with untreated intraocular pressures of 22 mm Hg or greater, timolol 0.25 percent or 0.5 percent administered twice a day produced a greater reduction in intraocular pressure than 1, 2, 3, or 4 percent pilocarpine solution administered four times a day or 0.5, 1, or 2 percent epinephrine hydrochloride solution administered twice a day.

In these studies, timolol was generally well tolerated and produced fewer and less severe side effects than either pilocarpine or epinephrine. A slight reduction of resting heart rate in some patients receiving timolol (mean reduction 2.9 beats/minute standard deviation 10.2) was observed.

INDICATIONS AND USAGE
Timolol maleate ophthalmic solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS
Timolol maleate is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see **WARNINGS**); (4) sinus bradycardia; (5) second or third degree atrio-ventricular block; (6) overt cardiac failure (see **WARNINGS**); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS
As with other topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. Timolol maleate should not be used alone in the treatment of angle-closure glaucoma.

Anaphylaxis: While taking beta-blockers, patients with a history of atopy or a history of severe anaphylactic reactions to a variety of allergens may be more reactive to repeated accidental, diagnostic, or therapeutic challenge with such allergens. Such patients may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

Information for Patients
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures.

Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can 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 **PRECAUTIONS,** *General.*)

Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See **CONTRAINDICATIONS**.)

Patients should be advised that timolol maleate ophthalmic solution contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following timolol maleate ophthalmic solution administration.

Drug Interactions
Although timolol used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with timolol and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and timolol should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as timolol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Quinidine: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with quinidine and timolol, possibly because quinidine inhibits the metabolism of timolol via the P-450 enzyme, CYP2D6.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable Epinephrine: **(**See **PRECAUTIONS,** *General, Anaphylaxis***)**

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: Teratogenic Effects:
Pregnancy Category C. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **PRECAUTIONS**, *General*); and tinnitus.

UROGENITAL
Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/-Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital***:** Urination difficulties.

OVERDOSAGE
There have been reports of inadvertent overdosage with timolol maleate ophthalmic solution resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also **ADVERSE REACTIONS**).

Overdosage has been reported with timolol maleate tablets. A 30 year old female ingested 650 mg of timolol maleate tablets (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

Significant lethality was observed in female rats and female mice after a single dose of 900 and 1190 mg/kg (5310 and 3570 mg/m^2) of timolol, respectively.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION
Timolol Maleate Ophthalmic Solution USP is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent solution in the affected eye(s) twice a day. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) twice a day.

Since in some patients the pressure-lowering response to timolol may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with timolol maleate ophthalmic solution.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of a 0.5 percent timolol maleate ophthalmic solution twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See **PRECAUTIONS,** *Drug Interactions, Beta-adrenergic blocking agents.*)

HOW SUPPLIED
Timolol maleate ophthalmic solution USP is a clear,

doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

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

Nursing Mothers
Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS
The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE
Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR
Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE
Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC
Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC
Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN
Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY
Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash.

RESPIRATORY
Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough, and upper respiratory infections.

ENDOCRINE
Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS**).

SPECIAL SENSES
Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances

HOW SUPPLIED
Timolol maleate ophthalmic solution USP is a clear, colorless to light yellow solution supplied in a white, opaque, plastic dropper bottle in two strengths as follows:

Timolol Maleate Ophthalmic Solution USP, 0.25% (equivalent to timolol maleate 3.4 mg/mL)

NDC 17478-289-25, 2.5 mL
NDC 17478-289-10, 5 mL
NDC 17478-289-11, 10 mL
NDC 17478-289-12, 15 mL

Timolol Maleate Ophthalmic Solution USP, 0.5% (equivalent to timolol maleate 6.8 mg/mL)

NDC 17478-288-25, 2.5 mL
NDC 17478-288-10, 5 mL
NDC 17478-288-11, 10 mL
NDC 17478-288-12, 15 mL

Storage: Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.

Protect from freezing.

WARNING — KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

TL00N Rev. 06/05

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21.6. Appendix F - Summary of Changes

V1.0 to V1.1

- Text regarding the use of general anesthesia and/or conscious sedation descriptions was removed from:
  - Schedule of Events and Procedures for PEDIATRIC Subjects - Synopsis and Section 7.4
  - Pediatric Subject Exclusion Criterion #21 - Synopsis and Section 8.4 (Subject Exclusion Criteria Specific for PEDIATRIC subjects)
  - Section 21.4 Intraocular Pressure Measurement for Pediatric Subjects
- To be consistent with the instruction for subject exclusion, the descriptions of "in either eye" were removed from Pediatric Subject Exclusion Criteria #8, 9 and 10 - Synopsis and Section 8.4.
- To require recording of non-ocular procedures/therapies (as well as ocular procedures/therapies) in the subject's source documents, the descriptions of "ocular procedures/therapies" were updated to "procedures/therapies" in:
  - Section 7.4 Schedule of Events and Procedures
  - Section 21.3.1 Demographics, Medication/Therapy and Medical History