## Study Protocol Cover Page

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|---|---|
| Official Study Title: | An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension - Spectrum 5 Study |
| NCT Number: | NCT03697811 |
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# DE-117 Protocol
# Study 011711IN

TITLE: **An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension - Spectrum 5 Study**

| SPONSOR: | STUDY DRUG: |
|---|---|
| SANTEN Inc.<br>6401 Hollis St, Suite 125<br>Emeryville, CA 94608 USA | DE-117 Ophthalmic Solution 0.002% |

I have read the 011711IN 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: _____

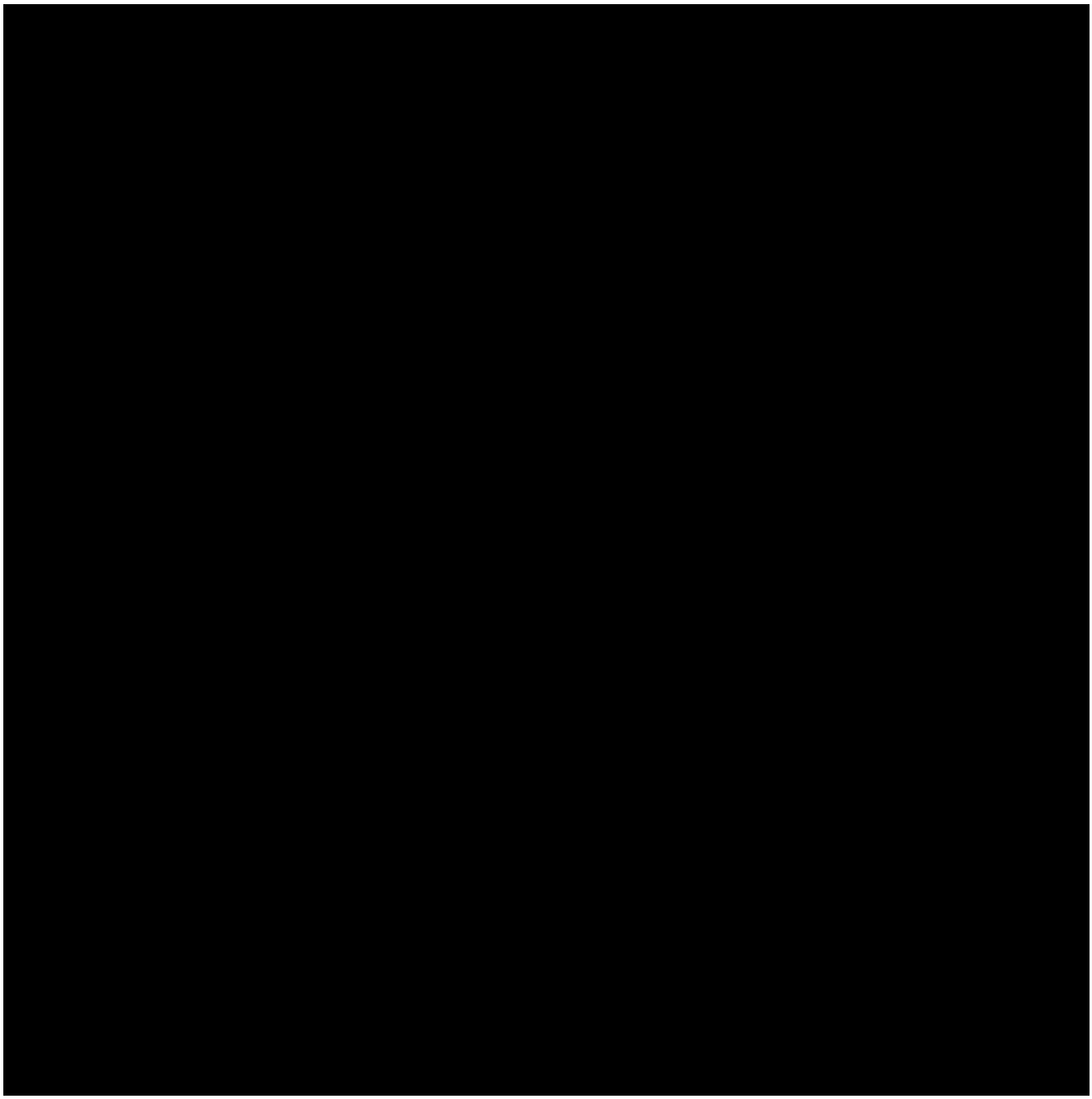
Name: _____

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:**<br>Santen Inc.<br>6401 Hollis Street, Suite 125<br>Emeryville, CA 94608, USA |
| **Name of Investigational Product:** DE-117 Ophthalmic Solution 0.002% |
| **Name of Active Ingredient**:<br>Glycine, *N*-[6-[[[[4-(1*H*-pyrazol-1-yl)phenyl]methyl](3-pyridinylsulfonyl)amino]methyl]-2-pyridinyl]-, 1-methylethyl ester<br>Propan-2-yl 2-[[6-[[(4-pyrazol-1-ylphenyl)methyl-pyridin-3-ylsulfonylamino]methyl]pyridin-2-yl]amino]acetate |
| **Title of Study:**<br>An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension- Spectrum 5 Study |
| **Protocol Number:** 011711IN |
| **Number of Subjects (planned):** Approximately 150 subjects with Primary Open-Angle Glaucoma (POAG) or Ocular Hypertension (OHT) will be enrolled into the Treatment Period with DE-117 ophthalmic solution 0.002% |
| **Number of Sites (planned):** Approximately 25 Sites |
| **Study Period:** Approximately 13 months |
| **Primary objective**:<br>To evaluate the intraocular pressure (IOP) lowering effect of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT. Specifically, the primary efficacy endpoint is the change from baseline (Day 1, Visit 4) in mean diurnal IOP at Month 3 (Visit 7).<br>**Secondary objectives**:<br>To evaluate the IOP lowering efficacy (change, percent change and proportion of responders) of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT at each timepoint.<br>**Safety objective**:<br>To evaluate the safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder |

subjects diagnosed with POAG or OHT.

**Duration of Treatment:** 8-Week Run-in Period with latanoprost ophthalmic solution 0.005% and 3-month Treatment Period with DE-117 ophthalmic solution 0.002%

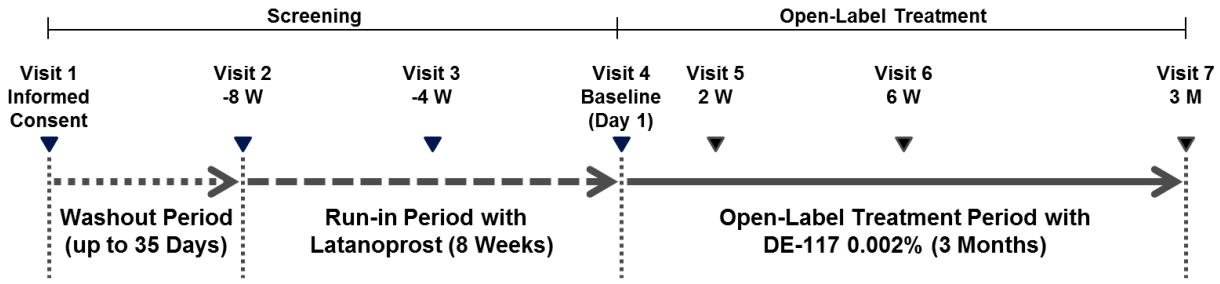
**Methodology**:

This is an open-label multi-center study. Subjects diagnosed with POAG or OHT who meet the eligibility criteria at Visit 1 (Screening) will enter a Washout Period, the duration of which is determined by their current topical IOP-lowering medication(s) if any. After completing the required Washout Period, subjects will return for Visit 2 (Week -8, start of the Run-in Period). Subjects who remain qualified will start a Run-in Period dosing with latanoprost ophthalmic solution 0.005% once daily in the evening in both eyes, and then return for Visit 3 (Week -4, midpoint of the Run-in Period) and Visit 4 (Baseline, Day 1), to confirm ongoing eligibility.

Subjects who meet all eligibility criteria at Visit 4 (Baseline, Day 1), will enter the Treatment Period and will be treated with DE-117 ophthalmic solution 0.002 % once daily in the evening in both eyes for 3 months. During the 3-month Treatment Period, three follow-up visits will be scheduled: Visit 5 (Week 2), Visit 6 (Week 6) and Visit 7 (Month 3).

Approximately 150 subjects with POAG or OHT who meet all eligibility criteria are planned to enter the Treatment Period and be treated with DE-117 ophthalmic solution 0.002%.

Study Design




This study will consist of a Screening Period which includes a Washout Period of up to 35 days (28 days + 7 days window) and an additional 8-Week Latanoprost Run-in Period; followed by a 3-month Open-Label Treatment Period with DE-117 0.002% ophthalmic solution.

At Visit 1 (Screening; start of the Washout Period [if applicable]), subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications during the 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
- Prostaglandins 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 at the latest 1 week before Visit 2 (Week -8, start of the Run-in Period). An interim safety visit may be performed during the washout period, Visit 1a (optional, mid-washout visit), if in the Investigator's opinion, a subject's IOP may be of concern. If subjects are treated with a topical CAI during the washout period, Visit 1a (optional, mid-washout visit) is recommended to be performed.

Subjects who have not used an IOP-lowering medication for the last 28 days, will need a wait period of ≥ 1 day before Visit 2 (Week -8, start of the Run-in Period).

At Visit 2 (Week -8, start of the Run-in Period), continuing eligibility will be determined based on non-treated IOP:

- IOP ≥ 22 mmHg in at least one eye
- IOP ≤ 34 mmHg in both eyes at all measurement time points

Subjects who are qualified at Visit 2, will begin the 8-Week Run-in Period, dosing with one drop of latanoprost ophthalmic solution 0.005% every evening at 20:00 (±60min) in both eyes.

Visit 3 will take place at Week -4 (midpoint of the Run-in Period) to check the following IOP criteria:

- The same eye meeting criteria at Visit 2 (Week -8, start of the Run-in Period), must meet the following criteria: percent decrease of IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 25% at all measurement time points
  - Visit 3 8:00 IOP should be compared with Visit 2 8:00 IOP;
  - Visit 3 12:00 IOP should be compared with Visit 2 12:00 IOP;
  - Visit 3 16:00 IOP should be compared with Visit 2 16:00 IOP.
- IOP in both eyes of ≤ 34 mmHg at all measurement time points

Subjects who are qualified at Visit 3 (Week -4, midpoint of the Run-in Period), will complete the remainder of the 8-Week Run-in Period, continuing dosing with one drop of latanoprost ophthalmic solution 0.005% every evening at 20:00 (±60min) in both eyes.

Visit 4 (Baseline, Day 1) will take place at the end of the Run-in Period and is considered the

baseline for the analyses. The following criteria have to be met to initiate the Treatment Period with DE-117 ophthalmic solution 0.002%:

- The same eye meeting criteria at Visit 3 (Week -4, midpoint of the Run-in Period) must meet the following criteria: percent decrease of IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 15% at all measurement time points
  - Visit 4 8:00 IOP should be compared with Visit 2 8:00 IOP;
  - Visit 4 12:00 IOP should be compared with Visit 2 12:00 IOP;
  - Visit 4 16:00 IOP should be compared with Visit 2 16:00 IOP.
- IOP in both eyes of ≤ 34 mmHg at all measurement time points

Subjects who are qualified at Visit 4 (Baseline, Day 1), will be enrolled into study and begin the 3-month Treatment Period, dosing with one drop of DE-117 ophthalmic solution 0.002% every evening at 20:00 (±60min) in both eyes. Follow-up visits will be scheduled at Week 2 (Visit 5), Week 6 (Visit 6) and Month 3 (Visit 7).

IOP will be measured at 8:00, 12:00 and 16:00 (±60 min) at all visits except at Visit 1 (Screening) and Visit 1a (optional, mid-washout visit) when one measurement at any time will suffice. The study eye will be the eye that qualifies per eligibility criteria through Visit 4 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher diurnal IOP (calculated as the average of IOP measurements at 3 time points) at Visit 4 (Baseline, Day 1) will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye.

At the scheduled visits, query of adverse events (AEs), best-corrected visual acuity (BCVA) and slit lamp biomicroscopy will be performed before the first IOP measurement. Ophthalmoscopy (fundus examination) will be performed after the last IOP measurement for the day. Additional procedures are explained in Section 7.4.

**Pharmacogenomics/Genomics:**

Subjects who consent to the optional pharmacogenomics/genomics laboratory study will provide a blood sample for future testing after subject is enrolled and study drug, DE-117 ophthalmic solution 0.002%, dosing has begun. 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 an open label study; masking will not be applied.

**Inclusion Criteria**:

At Visit 1 (Screening, start of the Washout Period), the subject 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 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]), subject 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 or 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 POAG or OHT in both eyes, or one eye with POAG 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.

At Visit 2 (Week -8, start of the Run-in Period), the subject must meet the following criteria:

8. Completed the required wait/washout period.
9. At all time points of IOP measurements (08:00, 12:00 and 16:00 ± 60 min), have IOP of ≥ 22 mmHg in at least one eye (the same eye), and ≤ 34 mmHg in both eyes.

At Visit 3 (Week -4, midpoint of the Run-in Period) the following IOP criteria have to be met:

10. Percent decrease in IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 25% at all measurement time points in the eye meeting criteria at Visit 2 (Week -8, start of the Run-in Period).
11. IOP in both eyes ≤ 34 mmHg at all measurement time points.

At Visit 4 (Baseline, Day 1) the following IOP criteria have to be met:

12. Percent decrease in IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 15% at all measurement time points in the eye meeting criteria at Visit 3 (Week -4, midpoint of the Run-in Period).
13. IOP in both eyes ≤ 34 mmHg at all measurement time points.

**Exclusion Criteria**:

From Visit 1 (Screening) to Visit 4 (Baseline, Day 1), subjects with any of the following ocular conditions in any eye or non-ocular conditions or characteristics are not eligible to participate in the study:

**General**

1. Females who are pregnant, nursing or planning a pregnancy.
2. Subjects with known or suspected drug or alcohol abuse.
3. Current or planned participation in any other clinical trial involving an investigational product or device within 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. Usage of more than two active ingredients to lower IOP prior to Washout Period.
6. Intended or current use of the following prohibited medications/therapies during the study:
    - 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.
7. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
8. 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 have a stable dose use for at least 30 days prior to Visit 1 (Screening) and throughout the study.
9. Use of contact lenses within 2-3 weeks prior to Visit 2 (Week -8, start of the Run-in Period) until end of treatment in either eye (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
10. Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.
11. 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.

12. History of keratorefractive surgery (e.g. Radial Keratotomy [RK], Refractive Keratectomy [PRK], Laser-Assisted-in-Situ Keratomileusis [LASIK]) in either eye.
13. Allergy, hypersensitivity or contraindications to latanoprost, EP2 receptor agonists, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications.

**Diseases**

14. Presence of advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
15. 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.
16. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
17. Presence or history of macular edema or known risk factors for macular edema in either eye.
18. History of severe ocular trauma in either eye.
19. History of iritis and/or uveitis, corneal inflammatory conditions, and/or viral infections such as herpes virus in either eye; history of adenovirus is not an exclusion provided no associated inflammation was observed within 6 months prior to screening.
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, 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**:

During the 8-Week Run-in Period, all subjects will dose with one drop of latanoprost ophthalmic solution 0.005% in both eyes once daily in the evening at 20:00 (±60min). During the 3-month Treatment Period, all subjects will dose one drop of DE-117 ophthalmic solution 0.002% in both eyes once daily in the evening at 20:00 (±60min).

**Product to be used during Run-in Period:**

Latanoprost ophthalmic solution 0.005% (Greenstone®)

**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 additio [redacted]

[redacted]

**Route of Administration of Investigational Product:** Topical ocular

**Duration of the Study:** The study duration includes a Screening Period which includes a Washout Period of up to 35 days (28 days + 7 days window) and an additional 8-Week Run-in with Latanoprost; followed by a 3-month Open-Label Treatment Period with DE-117 0.002% ophthalmic solution.

**Criteria for Evaluation:**

**Efficacy:**

Efficacy will be assessed by evaluating IOP at each scheduled time point as follows: 08:00, 12:00, and 16:00 (± 60 min) at the scheduled visits with the exception of Visit 1 (Screening) and Visit 1a (optional, mid-washout visit).

**Safety:**

Safety assessments will be composed of AEs, BCVA, slit-lamp biomicroscopy, ophthalmoscopy, and iris color/eyelash/eyelid examination.

**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**

- Change from baseline in mean diurnal IOP at Month 3 (Visit 7)

**Secondary Efficacy Endpoints**

- Percent change from baseline in mean diurnal IOP at Month 3 (Visit 7)
- Change and percent change from baseline (Visit 4) in mean diurnal IOP at Week 2 (Visit 5) and 6 (Visit 6)
- Change and percent change from baseline in IOP for each post-baseline timepoint/visit
- Having a mean diurnal IOP reduction ≥ 10%, ≥ 15%, ≥ 20%, ≥ 25%, or ≥ 30% from baseline (Visit 4) at Month 3 (Visit 7)

- Having a mean diurnal IOP ≤ 18 mmHg at Month 3 (Visit 7)

**Safety Endpoints**

Safety will be evaluated by the following parameters:

- Incidence of ocular and systemic AEs
- 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**:

Using one sample t-test with a significance level of 5%, a sample size of 150 will have 90% power to detect a mean diurnal IOP reduction of 1.0 mmHg from baseline with a standard deviation of 3.5 mmHg, after taking into account of up to 12% dropouts.

| | Washout Period | | Run- in Period | | Treatment Period | | | |
|---|---|---|---|---|---|---|---|---|
| | **Visit 1 (Screening)** | **Washout Period (up to 4 weeks) Optional Visit 1a [b]** | **Visit 2 Week -8 (Day -56±3)** | **Visit 3 Week -4 (Day -28±3)** | **Visit 4 Baseline (Day 1)** | **Visit 5 Week 2 (Day 15±3)** | **Visit 6 Week 6 (Day 43±5)** | **Visit 7 Month 3 (Day 91±7) Exit or Early Termination** |
| Informed Consent(s) including the consent for pharmacogenomics / genomics laboratory research study[a] | X | | | | | | | |
| Inclusion/Exclusion Criteria | X | | X | X | X | | | |
| Demographics and Medical History, including prior PGA[c] | X | | | | | | | |
| Concomitant Medications/ Therapies | X | X | X | X | X | X | X | X |
| Dosing Compliance | | | | X | X | X | X | X |
| AEs | | X | X | X | X | X | X | X |
| Pregnancy Test[d] | X | | | | X | | | X |
| Refraction[e] | X | | | | | | | |
| BCVA[e] | X | X | X (08:00) | X (08:00) | 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) | X (08:00) | X (08:00) |
| IOP[g] | X (any time) | X (any time) | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 |
| Pachymetry[h] | X | | | | | | | |
| 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 | X | | X | |
| Collect Study Medication | | | | X | X | | X | X |
| Phone call to remind subject to take evening dose on the day before each visit | | | | X | X | 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. An interim safety visit may be performed during the washout period Visit 1a (optional, mid-washout visit), if in the Investigator's opinion a subject's IOP may be of concern. If subjects are treated with a topical CAI during the washout period, Visit 1a (optional, mid-washout visit) is recommended to be performed.
c. The previous use of prostaglandin analogs should be confirmed by either subject's medical records or subject history.
d. A urine pregnancy test will be conducted for all female subjects of childbearing potential.
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 (±60 min).
f. Biomicroscopy examination must be completed before IOP is measured at 08:00 (±60 min). Aqueous flare and cell evaluation will be performed before fluorescein instillation.
g. IOP measurements will be performed at 08:00, 12:00 and 16:00 (±60 min) at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit).
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening).
i. Eye photograph will be taken at Visits 4 (Baseline, Day 1) and 7 (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, 4 and 7 (i.e., Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Screening and Visit 7 (Month 3)/Study 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 is obtained, subject is enrolled and study drug, DE-117 ophthalmic solution 0.002%, dosing has begun.

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

## TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# 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 |
| 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 |
| CAI | Carbonic Anhydrase inhibitor |
| CV | Curriculum Vitae |
| dB | Decibel |
| DUES | Deepening of the Upper Eyelid Sulcus |
| 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 Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug Application |
| IOP | Intraocular Pressure |
| IRB | Institutional Review Board |
| IUDs | Intrauterine Devices |

**Table 2: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Definition |
|---|---|
| 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 |
| 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 |
| $PGE_2$ | Prostaglandin E2 |
| POAG | Primary Open-Angle Glaucoma |
| PPS | Per-Protocol Set |
| PRK | Refractive Keratectomy |
| PT | Preferred Term |
| QD | Once a day |
| RK | Radial Keratotomy |
| SAE | Serious Adverse Event |

**Table 2: Abbreviations and Specialist Terms (Continued)**

| Abbreviation or Specialist Term | Definition |
|---|---|
| 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 open-angle glaucoma (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.

While adequate IOP-lowering can be achieved by currently available pharmacotherapies in some patients, not all patients are adequately treated and additional IOP-lowering may provide for further slowing of disease progression. 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 an open-label, multi-center study. The total duration of this study is 13 months. The objective is to investigate the efficacy and safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT.

# 6. TRIAL OBJECTIVES AND PURPOSE

## 6.1. Primary Objective

To evaluate the intraocular pressure (IOP) lowering effect of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT. Specifically, the primary efficacy endpoint is the change from baseline (Day 1, Visit 4) in mean diurnal IOP at Month 3 (Visit 7).

## 6.2. Secondary Objectives

To evaluate the IOP lowering efficacy (change, percent change and proportion of responders) of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT at each timepoint.

## 6.3. Safety Objective

To evaluate the safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT.

# 7. INVESTIGATIONAL PLAN

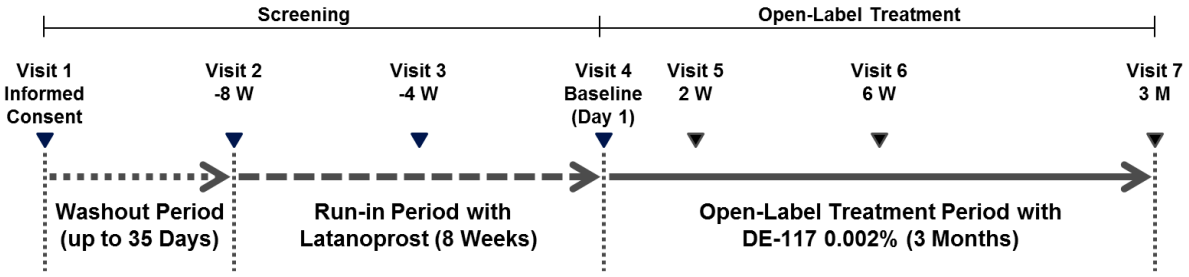
## 7.1. Overall Study Design

This is an open-label and multi-center study investigating the efficacy and safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT.

See the study design diagram in Figure 1. This study will consist of a Screening Period which includes a Washout Period of up to 35 days (28 days + 7 days window) and an additional 8-Week Latanoprost Run-in Period; followed by a 3-month Open-Label Treatment Period with DE-117 0.002% ophthalmic solution.

Approximately 150 subjects with POAG or OHT who meet all eligibility criteria are planned to enter the Treatment Period and be treated with DE-117 ophthalmic solution 0.002%.

**Figure 1: Study Design**




At Visit 1 (Screening; start of the Washout Period [if applicable]), subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications during the 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
- Prostaglandins 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 at the latest 1 week before Visit 2 (Week -8, start of the Run-in Period). An interim safety visit may be performed during the washout period Visit 1a (optional, mid-washout visit) if, in the Investigator's opinion, a subject's IOP may be of concern. If subjects are treated with a topical CAI during the washout period, Visit 1a (optional, mid-washout visit) is recommended to be performed.

Subjects who have not used an IOP-lowering medication for the last 28 days, will need a wait period of ≥ 1 day before their Visit 2 (Week -8, start of the Run-in Period).

At Visit 2 (Week -8, start of the Run-in Period), continuing eligibility will be determined based on non-treated IOP:

- IOP ≥22 mmHg in at least one eye and ≤34 mmHg in both eyes at all measurement time points

Subjects who are qualified at Visit 2, will begin the 8-Week Run-in Period, dosing with one drop of latanoprost ophthalmic solution 0.005% every evening at 20:00 (±60min) in both eyes.

Visit 3 will take place at Week -4 (midpoint of the Run-in Period), to check the following IOP criteria:

- The same eye meeting criteria at Visit 2 (Week -8, start of the Run-in Period), must meet the following criteria: percent decrease of IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 25% at all measurement time points
  - Visit 3 8:00 IOP should be compared with Visit 2 8:00 IOP;
  - Visit 3 12:00 IOP should be compared with Visit 2 12:00 IOP;
  - Visit 3 16:00 IOP should be compared with Visit 2 16:00 IOP.
- IOP in both eyes of ≤ 34 mmHg at all measurement time points

Subjects who are qualified at Visit 3 (Week -4, midpoint of the Run-in Period), will complete the remainder of the 8-Week Run-in Period, continuing dosing with one drop of latanoprost ophthalmic solution 0.005% QD at 20:00 (±60min) in both eyes.

Visit 4 (Baseline, Day 1) will take place at the end of the Run-in Period and is considered the baseline for the analyses. The following criteria have to be met to initiate the Treatment Period with DE-117 ophthalmic solution 0.002%:

- The same eye meeting criteria at Visit 3 (Week -4, midpoint of the Run-in Period) must meet the following criteria: percent decrease of IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 15% at all measurement time points
  - Visit 4 8:00 IOP should be compared with Visit 2 8:00 IOP;
  - Visit 4 12:00 IOP should be compared with Visit 2 12:00 IOP;
  - Visit 4 16:00 IOP should be compared with Visit 2 16:00 IOP.
- IOP in both eyes of ≤ 34 mmHg at all measurement time points

Subjects who are qualified at Visit 4 (Baseline, Day 1), will be enrolled into study and begin the 3-month Treatment Period, dosing with one drop of DE-117 ophthalmic solution 0.002% every evening at 20:00 (±60min) in both eyes. Follow-up visits will be scheduled at Week 2 (Visit 5), Week 6 (Visit 6) and Month 3 (Visit 7).

IOP will be measured at 8:00, 12:00 and 16:00 (± 60 min) at all visits except at Visit 1 (Screening) and Visit 1a (optional, mid-washout visit) when one measurement at any time may suffice. The study eye will be the eye that qualifies per eligibility criteria through Visit 4 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher diurnal IOP (calculated as the average of IOP measurements at 3 time points) at the end of the Run-in Period (Visit 4) 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.

At the scheduled visits, query of AEs, BCVA and slit lamp biomicroscopy will be performed before the first IOP measurement. Ophthalmoscopy (fundus examination) will be performed after the last IOP measurement for the day. Additional procedures are explained in Section 7.4.

**Pharmacogenomics/genomics:**

Subjects who consent to the optional pharmacogenomics/genomics laboratory study will provide a blood sample for future testing after subject is enrolled and study drug, DE-117 ophthalmic solution 0.002%, dosing has begun. 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 150 subjects are planned to be enrolled into the Treatment Period with DE-117 ophthalmic solution 0.002%.

## 7.3. Treatment Assignment

All subjects will receive the following study medications:

- 8-Week Run-in Period: latanoprost ophthalmic solution 0.005% QD (20:00 ±60min)
- 3-month Treatment Period: DE-117 ophthalmic solution 0.002% QD (20:00 ±60min)

## 7.4. Schedule of Events and Procedures

| | Washout Period | | Run-in Period | | Treatment Period | | | |
|---|---|---|---|---|---|---|---|---|
| | **Visit 1 (Screening)** | **Washout Period (up to 4 weeks) Optional Visit 1a[b]** | **Visit 2 Week -8 (Day -56±3)** | **Visit 3 Week -4 (Day -28±3)** | **Visit 4 Baseline (Day 1)** | **Visit 5 Week 2 (Day 15±3)** | **Visit 6 Week 6 (Day 43±5)** | **Visit 7 Month 3 (Day 91±7) Exit or Early Termination** |
| Informed Consent(s) including the consent for pharmacogenomics / genomics laboratory research study[a] | X | | | | | | | |
| Inclusion/Exclusion Criteria | X | | X | X | X | | | |
| Demographics and Medical History, including prior PGA[c] | X | | | | | | | |
| Concomitant Medications/ Therapies | X | X | X | X | X | X | X | X |
| Dosing Compliance | | | | X | X | X | X | X |
| AEs | | X | X | X | X | X | X | X |
| Pregnancy Test[d] | X | | | | X | | | X |
| Refraction[e] | X | | | | | | | |
| BCVA[e] | X | X | X (08:00) | X (08:00) | 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) | X (08:00) | X (08:00) |
| IOP[g] | X (any time) | X (any time) | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 | 08:00 12:00 16:00 |
| Pachymetry[h] | X | | | | | | | |
| 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 | X | | X | |
| Collect Study Medication | | | | X | X | | X | X |
| Phone call to remind subject to take evening dose on the day before each visit | | | | X | X | 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. An interim safety visit may be performed during the washout period Visit 1a (optional, mid-washout visit), if in the Investigator's opinion a subject's IOP may be of concern. If subjects are treated with a topical CAI during the washout period, Visit 1a (optional, mid-washout visit) is recommended to be performed.
c. The previous use of prostaglandin analogs should be confirmed by either subject's medical records or subject history.
d. A urine pregnancy test will be conducted for all female subjects of childbearing potential.
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 (±60 min).
f. Biomicroscopy examination must be completed before IOP is measured at 08:00 (±60 min). Aqueous flare and cell evaluation will be performed before fluorescein instillation.
g. IOP measurements will be performed at 08:00, 12:00 and 16:00 (±60 min) at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit).
h. Pachymetry will be performed after IOP measurement at Visit 1 (Screening).
i. Eye photograph will be taken at Visits 4 (Baseline, Day 1) and 7 (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, 4 and 7 (i.e. Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Screening and Visit 7 (Month 3)/ Study 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 is obtained, subject is enrolled and study drug, DE-117 ophthalmic solution 0.002%, dosing has begun.

### 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 participation in the optional pharmacogenomics/genomics laboratory research will not influence participation in the main study.
- Prepare the list of screening/registration of subjects.
- Obtain demographics.
- Obtain medications including prior prostaglandin analog use, 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 female of child-bearing potential.
- Perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - Refraction

  - BCVA (before IOP measurement)
  - Visual field (will be performed if this has not been performed in the previous three months)
  - Gonioscopy (will be performed after IOP measurement if this has not been performed in the previous three months)
  - Biomicroscopy (before IOP measurement)
  - IOP
  - Pachymetry (after IOP measurement)
  - Ophthalmoscopy with pupil dilation (after IOP measurement)
- Determine if the subject meets eligibility criteria.
- If the subject meets eligibility criteria and is still willing to continue the study, discontinue any current IOP-lowering medication according to the following schedule (up to +7 days as a window is allowed):
  - Miotics: 7 days
  - Oral/topical Carbonic Anhydrase Inhibitors (CAIs): 7 days
  - Alpha agonists: 14 days
  - Alpha/beta agonists: 14 days
  - Alpha antagonists (α1 blocker): 28 days
  - Beta antagonists (β blocker, including αβ blockers): 28 days
  - Prostaglandins 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 Visit 2 (Week -8, start of the Run-in Period).
- An interim safety visit may be performed during the washout period Visit 1a (optional, mid-washout visit) if in the Investigator's opinion, a subject's IOP may be of concern. If subjects are treated with a topical CAI in the week before Visit 2 (Week -8, start of the Run-in Period), Visit 1a (optional, mid washout visit) is recommended to be performed.
- Subjects who have not used an IOP-lowering medication for the last 28 days, will need a wait period of ≥ 1 day before their Visit 2 (Week -8, start of the Run-in Period).

  - If a subject does not require washout from an IOP-lowering medication, but they use contact lenses in either eye, they will need a wait period of ≥ 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 (Week -8).
- Schedule the eligible subject to return for Visit 2 (Week -8) 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, mid-washout visit)

- 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. If subjects are treated with a topical CAI in the week before Visit 2 (Week -8, start of the Run-in Period), Visit 1a (optional, mid-washout visit) is recommended to be performed.
- Update concomitant medications and procedures/therapies.
- Query the subject regarding AEs.
- 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 (Week -8, start of the Run-in Period)

- Confirm the subject has complied with the required wait/washout period for ocular hypotensive medication(s), or contact lenses use, if required.
- Update concomitant medications and procedures/therapies.
- Query the subject regarding AEs.
- Perform the following procedures or assessments immediately before the 08:00 (± 60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy
- Perform IOP measurement at 08:00 (±60 min).
- If subject meets the 08:00 (±60 min) IOP eligibility requirements, schedule additional IOP measurements at 12:00 (±60 min).

- Perform IOP measurement at 12:00 (±60 min).
- If subject meets the 08:00 and 12:00 (±60 min) IOP eligibility requirements, schedule additional IOP measurements at 16:00 (±60 min).
- Perform IOP measurement at 16:00 (±60 min).
- Perform final review of eligibility criteria after the 16:00 (±60 min) IOP measurement.
- If the subject meets all eligibility criteria upon completion of the above procedures and assessments, the subject will be assigned a treatment kit via Interactive Response Technology. A study staff member will:
  - Dispense one (1) bottle of latanoprost ophthalmic solution 0.005% from the assigned kit to the subject
  - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage.
- Schedule the subject to return for Visit 3 (Week -4, midpoint of the Run-in Period)
- Inform the subjects they will be reminded of the evening instillation of the study medication the day before Visit 3 through a phone call.
- Remind the subject to bring all study medication at Visit 3 (Week -4, midpoint of the Run-in Period).
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.

#### 7.4.4. Visit 3 (Week -4, midpoint of the Run-in Period)

- Update concomitant medications and procedures/therapies.
- Collect study medication
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Perform the following procedures or assessments immediately before the 08:00 (± 60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy
- Perform IOP measurement at 08:00 (±60 min).
- If subject meets the 08:00 (±60 min) IOP eligibility requirements, schedule additional IOP measurements at 12:00 (±60 min).
- Perform IOP measurement at 12:00 (±60 min).

- If subject meets the 08:00 and 12:00 (±60 min) IOP eligibility requirements, schedule additional IOP measurements at 16:00 (±60 min).
- Perform IOP measurement at 16:00 (±60 min).
- Determine if subject meets eligibility criteria after the 16:00 IOP measurement.
- If the subject meets all eligibility criteria upon completion of the above procedures and assessments, the subject will be assigned a treatment kit via Interactive Response Technology. A study staff member will:
  - Dispense one (1) bottle of latanoprost ophthalmic solution 0.005% from the assigned kit to the subject
  - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage.
- Schedule the subject to return on Visit 4 (Baseline, Day 1).
- Inform the subjects they will be reminded of the evening instillation of the study medication the day before Visit 4 through a phone call.
- Remind the subject to bring all study medication at Visit 4 (Baseline, Day 1).
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.

### 7.4.5. Visit 4 (Baseline, Day 1)

- Update concomitant medications and procedures/therapies.
- Collect study medication
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Obtain urine and perform urine pregnancy test, if the subject is female of child-bearing potential.
- Perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy
- Perform IOP measurement at 08:00 (±60 min).
- If subject meets the 08:00 IOP eligibility requirements, schedule additional IOP measurements at 12:00 (±60 min).
- Perform IOP measurement at 12:00 (±60 min).

- If subject meets the 08:00 and 12:00 (±60 min) IOP eligibility requirements, schedule additional IOP measurements at 16:00 (±60 min).
- Perform IOP measurement at 16:00 (±60 min).
- Perform ophthalmoscopy in both eyes immediately after the 16:00 (±60 min) IOP measurement.
- Perform iris color, eyelash, eyelid assessment at any time during this visit, 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:

- Perform final review of eligibility criteria after the 16:00 (±60 min) IOP measurement. A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure. If the subject meets all eligibility criteria, upon completion of the above procedures and assessments, the Investigator will determine the study eye. The subject will then be enrolled in the study, via Interactive Response Technology.
  - The study eye will be the eye that qualifies per eligibility criteria at Visit 4 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 4 (Baseline, Day 1) will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye.
- After the subject has been enrolled and assigned a treatment kit through the Interactive Response Technology, a study staff member must:
  - Dispense two (2) bottles of study drug DE-117 ophthalmic solution 0.002% from the assigned kit to the subject
  - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage.
- Schedule the subject to return on Day 15 ± 3 for Visit 5 (Week 2).

- Inform the subjects they will be reminded of the evening instillation of the study medication the day before Visit 5 through a phone call.

### 7.4.6. Visit 5 (Week 2, Day 15 ± 3)

- Update concomitant medications and procedures/therapies.
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.

Biomicroscopy

- Perform IOP measurement at 08:00, 12:00, and 16:00 (±60 min).
- If the subject provided written consent to provide a blood sample for a future pharmacogenomics/genomics laboratory research study, the sample may be collected at this visit or at future visits.
- Remind the subject of proper instillation of the study medication, the dosing regimen, and study medication storage.
- Inform the subjects they will be reminded of the evening instillation of the study medication the day before Visit 6 through a phone call.
- Schedule the subject to return on Day 43 ± 5 for Visit 6 (Week 6).
- Remind the subject to bring all study medication at Visit 6.

### 7.4.7. Visit 6 (Week 6, Day 43 ± 5)

- Update concomitant medications and procedures/therapies.
- Collect study medication.
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy
- Perform IOP measurement at 08:00, 12:00, and 16:00 (±60 min).

- If the subject provided written consent to provide a blood sample for a future pharmacogenomics/genomics laboratory research study, the sample may be collected at this visit or subsequent visit prior to exit from the study, if not collected at the previous visit.
- Dispense two (2) bottles of study drug DE-117 ophthalmic solution 0.002% from the assigned kit to the subject
- Give the subject verbal and written instructions for proper instillation of the study medication, the dosing regimen, and study medication storage.
- Schedule the subject to return on Day 91 ± 7 for Visit 7 (Month 3).
- Inform the subjects they will be reminded of the evening instillation of the study medication the day before Visit 7 through a phone call.
- Remind the subject to bring all study medication at Visit 7.

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

- Update concomitant medications and procedures/therapies.
- Collect all study medication.
- Query the subject regarding dosing compliance.
- Query the subject regarding AEs.
- Obtain urine and perform urine pregnancy test, if the subject is female of child-bearing potential.
- Perform the following procedures or assessments immediately before the 08:00 (±60 min) IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy
- Perform IOP measurement at 08:00, 12:00, and 16:00 (±60 min).
- Assess any changes from baseline in iris color, eyelash, eyelid and take front view and side view photographs of each eye individually. The following six (6) photos are required at this visit as follows:

- Perform pupil dilation in both eyes after the 16:00 (±60 min) IOP measurement.
- Perform ophthalmoscopy with pupil dilation in both eyes immediately after the 16:00 IOP measurement.
- 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 a subject's study participation is terminated prior to Visit 7, then, to the extent possible, all scheduled Visit 7 procedures will be performed at the earliest visit or on the day of early termination.**

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

## 7.5. Study Termination

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

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

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

## 8.1. Subject Inclusion Criteria

At Visit 1 (Screening, start of the Washout Period), the subject 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 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]), subject 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 or 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 POAG or OHT in both eyes, or one eye with POAG 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.

At Visit 2 (Week -8, start of the Run-in Period), the subject must meet the following criteria:

8. Completed the required wait/washout period.
9. At all time points of IOP measurements (08:00, 12:00 and 16:00 ±60 min), have IOP of ≥ 22 mmHg in at least one eye (the same eye), and ≤ 34 mmHg in both eyes.

At Visit 3 (Week -4, midpoint of the Run-in Period) the following IOP criteria have to be met:

10. Percent decrease in IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤ 25% at all measurement time points in the eye meeting criteria at Visit 2 (Week -8, start of the Run-in Period).
11. IOP in both eyes ≤ 34 mmHg at all measurement time points.

At Visit 4 (Baseline, Day 1) the following IOP criteria have to be met:

12. Percent decrease in IOP from Visit 2 (Week -8, start of the Run-in Period) of ≤15% at all measurement time points in the eye meeting criteria at Visit 3 (Week -4, midpoint of the Run-in Period).
13. IOP in both eyes ≤34 mmHg at all measurement time points.

## 8.2. Subject Exclusion Criteria

From Visit 1 (Screening) to Visit 4 (Baseline, Day 1), subjects with any of the following ocular conditions in any eye or non-ocular conditions or characteristics are not eligible to participate in the study:

**General**

1. Females who are pregnant, nursing or planning a pregnancy.
2. Subjects with known or suspected drug or alcohol abuse.
3. Current or planned participation in any other clinical trial involving an investigational product or device within 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. Usage of more than two active ingredients to lower IOP prior to Washout Period.
6. Intended or current use of the following prohibited medications/therapies during the study:
    - 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.
7. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.

8. 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 have a stable dose use for at least 30 days prior to Visit 1 (Screening) and throughout the study.
9. Use of contact lenses within 2-3 weeks prior to Visit 2 (Week -8, start of the Run-in Period) until end of treatment in either eye (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
10. Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.
11. 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.
12. History of keratorefractive surgery (e.g., Radial Keratotomy [RK], Refractive Keratectomy [PRK], Laser-Assisted-in-Situ Keratomileusis [LASIK]) in either eye.
13. Allergy, hypersensitivity or contraindications to latanoprost, EP2 receptor agonists, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications.

**Diseases**

14. Presence of advanced glaucoma (e.g., visual field mean deviation worse than -12 dB) in either eye.
15. 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.
16. Presence of any active severe external ocular disease, inflammation, or infection of the eye and/or eyelids in either eye.
17. Presence or history of macular edema or known risk factors for macular edema in either eye.
18. History of severe ocular trauma in either eye.
19. History of iritis and/or uveitis, corneal inflammatory conditions, and/or viral infections such as herpes virus in either eye; history of adenovirus is not an exclusion provided no associated inflammation was observed within 6 months prior to screening.
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, 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.

## 8.3. Subject Withdrawal Criteria

An early termination occurs when a subject who provides written informed consent ceases participation in the study after enrollment (Visit 4 Baseline [Day 1]), regardless of circumstances, and 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 enrollment)
- 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 DE-117 study drug administration is discontinued prior to last scheduled visit, Visit 7, the subject should be encouraged to continue participating in all remaining follow-up study visits/procedures on an observational basis.

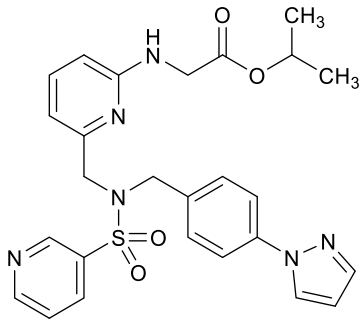
If subject participation is terminated prior to Visit 7, then to the extent possible, all Visit 7 procedures will be performed on the day of early termination or at the earliest opportunity possible. Subjects who are terminated from the study early will not be replaced.

# 9. TREATMENT OF SUBJECTS

## 9.1. Description of Study Medication

DE-117 ophthalmic solution 0.002% is an aqueous solution containing DE-117. Benzalkonium chloride 0.005% is added as a preservative.

**Figure 2: DE-117 Structure**



Investigational Product:

- DE-117 ophthalmic solution 0.002% contains 0.02 mg/mL DE-117

Product to be used during Run-in Period:

- Latanoprost ophthalmic solution 0.005% (Greenstone®) contains the active ingredient, latanoprost 0.05 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 taken besides 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 $B_{12}$

formulation (e.g., cyanocobalamine); over-the-counter dry eye artificial tears/drops; and study medications during the study duration.

  - If artificial sodium chloride/potassium chloride ophthalmic solution; cataract treatment agents; Vitamin $B_{12}$ formulation; over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of **at least 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 (Week -8, start of the Run-in Period) until end of treatment in either eye (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.
- 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.
  - once daily at 20:00 [±60min] through Visit 2 to 7.

- Subjects will be reminded of the evening instillation of the study drug on the days before Visit 3 (Week -4, midpoint of the Run-in Period) through Visit 7/Early Termination respectably.
- Since subjects must have a diagnosis of POAG 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.
- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 (Week -4, midpoint of the Run-in Period) through Visit 7/Early Termination.
- Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%.
- A subject's dosing compliance for a specific period is determined by the total number of days that subject followed the proper dosing procedures and dosing schedule. Stoppage of study medication use, overdosing of study medication, incorrect time of study medication administration, will be noted as non-compliance. The subject's dosing compliance will be recorded in the subject's source documents at Visit 3 (Week -4, midpoint of the Run-in Period) through Visit 7/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

This is an open label study; masking will not be applied. There will be no randomization for this study.

# 10. STUDY MEDICATION MATERIALS AND MANAGEMENT

## 10.1. Study Medication

### 10.1.1. 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,

### 10.1.2. Product to be used during Run-in Period

The product to be used during the Run-in Period, latanoprost ophthalmic solution 0.005%, is supplied as a sterile, isotonic, buffered aqueous solution.

Latanoprost ophthalmic solution 0.005% contains the active ingredient, latanoprost 0.05 mg/mL and the preservative BAK 0.02%. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection. The latanoprost solution has a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. See Section 21.5.

## 10.2. Study Medication Packaging and Labeling

DE-117 ophthalmic solution 0.002% will be supplied as [redacted] Each DE-117 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.

Latanoprost ophthalmic solution 0.005% will be supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle with a clear polyethylene dropper tip, a turquoise high density polyethylene screw cap, and a tamper-evident clear low density polyethylene overcap. Each latanoprost eye drop bottle will be in a unit carton, consistent with commercial packaging. The unit carton will be labeled with the protocol number and kit number.

## 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

Subjects will instill one drop of study medication in each eye at approximately 20:00 (±60min) daily for a total of 5 months. During the 8-Week Latanoprost Run-in Period, subjects will dose with one drop of latanoprost ophthalmic solution 0.005% every evening at 20:00 (±60min) in both eyes. During the 3-month Open-Label Treatment Period, subjects will dose one drop of DE-117 ophthalmic solution 0.002% every evening at 20:00 (±60min) in both eyes.

## 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, 12:00 and 16:00 ±60 min) will be evaluated at each post-baseline visit. Besides observed IOP measurements, change from baseline in IOP, and percent changes from baseline in IOP at each scheduled time point as well as the change from baseline in mean diurnal IOP will also be 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 and latanoprost. 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 a serious adverse event (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 events of special interests (ESIs) and should be reported on the appropriate eCRF with as much information as available within 24 hours of knowledge of the event:

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

- Medication administration errors
  - Study medication administration errors determined to be **significant** by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: incorrect dose of study medication and administration of study medication from an incorrect kit. An AE does not necessarily need to have occurred to count as a study medication administration error. A medication administration error is an unintended failure in the process of treatment with a medicinal product that leads to, or has the potential to lead to harm of the subject.
- 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 electronic data capture (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 precipitates, lens, anterior synechiae of iris, posterior synechiae of iris
- Ophthalmoscopy variables: glaucomatous optic nerve
- Iris color/eyelash/eyelid

# 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

The final analysis will be performed after all subjects completed Month 3 (Visit 7). The analysis will evaluate the efficacy and safety of DE-117 ophthalmic solution 0.002% once daily in latanoprost low/non-responders.

## 14.3. General Considerations

Descriptive statistics, unless otherwise noted, will include the number of subjects (n), mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentage for categorical variables.

The study eye will be defined as the eye that qualifies per eligibility criteria at Baseline (Visit 4). If both eyes qualify, the eye with the higher mean diurnal IOP at baseline 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.

The statistical testing will be conducted at a significance level of 0.05 (two-sided) and the 95% confidence interval will be shown, unless specified otherwise. No statistical testing will be conducted for safety measures.

More details on the statistical methods will be described in the SAP.

### 14.3.1. Sample Size

Using one sample t-test with a significance level of 5%, a sample size of 150 will have 90% power to detect a mean diurnal IOP reduction of 1.0mmHg from baseline with a standard deviation of 3.5 mmHg, after taking into account of up to 12% dropouts.

### 14.3.2. Statistical Hypotheses and Level of Significance

The primary endpoint (the mean diurnal IOP change from baseline at Month 3) will be evaluated according to the following testing hypotheses:

$$H0: \mu i = \mu j$$

versus

$$H1: \mu i \neq \mu j$$

where $\mu i$ and $\mu j$ are the mean diurnal IOP at Baseline and Month 3, respectively.

Paired t-test will be used to compare the difference in diurnal IOP between Baseline (Visit 4) and Month 3 (Visit 7). The mean difference in diurnal IOP will be reported along with 95% confidence intervals.

## 14.4. Study Populations

### 14.4.1. Safety Population

The Safety Population will include all subjects who signed informed consent, met the eligibility criteria at baseline, and received at least one dose of the study medication. The safety analysis will be performed on the Safety Population.

### 14.4.2. Full Analysis Set

The Full Analysis Set (FAS) will include all Safety population who had at least one post-baseline IOP measurement. The efficacy analysis will be performed on the FAS or a subset of the FAS.

### 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 the SAP.

## 14.5. Handling of Missing Values

The primary analysis of IOP will be based on observed cases. As a sensitivity analysis, missing IOP data at Month 3 will be imputed by last observed post-baseline IOP. Sensitivity analyses using other imputation methods may be performed and detailed in the SAP.

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.

Additional 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.

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 OAG or OHT within 28 days before Visit 1 (Screening) will be tabulated by Anatomical Therapeutic Chemical (ATC) levels, and PT specified in the latest version of World Health Organization Drug Dictionary Enhanced (WHO-DDE, 2011).

## 14.7. Efficacy Analyses

### 14.7.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in mean diurnal IOP at Month 3 (Visit 7).

The primary analysis will be performed on the FAS. Paired t-test will be used to compare the difference in diurnal IOP between Baseline (Visit 4) and Month 3 (Visit 7). The mean difference in diurnal IOP will be reported along with the 95% confidence intervals.

### 14.7.2. Analysis of Secondary Efficacy Endpoints

#### 14.7.2.1. Secondary Efficacy Endpoints

The following secondary efficacy endpoints will be analyzed:

- Percent change from baseline in mean diurnal IOP at Month 3 (Visit 7)
- Change and percent change from baseline (Visit 4) in mean diurnal IOP at Week 2 (Visit 5) and 6 (Visit 6)
- Change and percent change from baseline in IOP for each post-baseline timepoint/visit
- Having a mean diurnal IOP reduction ≥ 10%, ≥ 15%, ≥ 20%, ≥ 25%, or ≥ 30% from baseline (Visit 4) at Month 3 (Visit 7)
- Having a mean diurnal IOP ≤ 18 mmHg at Month 3 (Visit 7)

For change and percent change in mean diurnal IOP from baseline, descriptive statistics will be provided including the number of subjects (n), mean, standard deviation, median, minimum and maximum. For binary secondary efficacy endpoints, results will be tabulated using frequencies and percentages.

## 14.8. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs, BCVA, slit-lamp biomicroscopy findings, ophthalmoscopy variables, and iris color, eyelash, 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 study drug and maximum severity. In addition, SAEs and AEs leading to discontinuations will be summarized. More details will be provided in the SAP.

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

# 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/genomics study, and other study related material, as appropriate, must be approved in writing by an IRB or IEC as appropriate. If an IRB or IEC does not approve the collection of blood samples for optional future pharmacogenomics/genomic 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 pharmacogenomics/genomic 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.

# 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

### 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 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

### 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 POAG or OHT within 28 days before the date of Visit 1 (Screening), 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 POAG or OHT within 28 days before the date of Visit 1 (Screening), 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 4 (Baseline, Day 1), and recorded in the subject's source documents.

### 21.3.2. Pregnancy Test

A urine pregnancy test will be conducted using a commercially available test kit at Visit 1 (Screening), Visit 4 (Baseline, Day 1), and Visit 7 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. Iris color, Eyelash, Eyelid

Please take photographs of the iris, eyelids and eyelashes of each eye at Visit 4 (Baseline, Day 1), and Visit 7 (Month 3), Study Exit/Early Termination. Six (6) photos are required at each visit as follows:

The photographs taken at Visit 4 (Baseline, Day 1) 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 7 (Month 3) 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.

#### 21.3.3.1. Iris Color

The Investigator will assess the iris color and any change (e.g., pigmentation) at Visit 7 (Month 3) Study Exit/Early Termination using the photographs obtained at Visit 4 (Baseline, Day 1).

#### 21.3.3.2. Eyelash

The Investigator will assess eyelash change at Visit 7 (Month 3) Study Exit/Early Termination (e.g., length, thickness, pigmentation and number) using the photographs obtained at Visit 4 (Baseline, Day 1).

#### 21.3.3.3. Eyelid

The Investigator will assess eyelid change at Visit 7 (Month 3) Study Exit/Early Termination (e.g., pigmentation, hair growth and deepening of the upper eyelid sulcus) using the photographs obtained at Visit 4 (Baseline, Day 1). For any changes from baseline in deepening of the upper eyelid sulcus (DUES), the response will be YES or NO.

### 21.3.4. Refraction

Refraction will be performed for each eye at Visit 1 (Screening). At Visits 2 to 7, if more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed.

### 21.3.5. Best-Corrected Visual Acuity

BCVA (Best-Corrected Visual Acuity) will be measured for each eye prior to the 08:00 (±60 min) IOP measurement at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit). For Visit 1 (Screening) and Visit 1a (optional, mid-washout visit), BCVA will be performed prior to IOP measurement. BCVA will be measured under normal room illumination

using visual acuity chart (ETDRS chart) and the logMAR scoring will be recorded in the subject's source document. If ETDRS chart is used, the following procedure should be followed.

#### 21.3.5.1. ETDRS Visual Acuity Scoring

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

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

Example:

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

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

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

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

**Table 3: LogMAR Scoring Grid for ETDRS Eye Chart**

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

### 21.3.6. Slit-lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the 08:00 (±60 min) IOP measurement at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit). For Visit 1 (Screening) and Visit1a (optional, mid-washout visit), the biomicroscopy examinations should be performed prior to IOP measurement. If an Investigator decides to evaluate a subject with pseudophakic eye(s) for possible tears in the posterior lens capsule by biomicroscopy under dilation at Visit 1 (Screening), pupil dilation must occur 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

### 21.3.7. Intraocular Pressure

IOP will be performed at each visit. At Visit 1 (Screening) and Visit 1a (optional, mid-washout visit), IOP can be measured at any time. For Visit 2 to Visit 7 Study Exit/Early Termination, IOP measurements will be scheduled for 08:00 (±60min), 12:00 (±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 member (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 also be the recorder instead of an authorized study staff member, if a study staff member was 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.

#### 21.3.7.1. Goldmann Applanation Tonometer Calibration

It is mandatory for every tonometer used in the study to be calibrated for accuracy before the first subject undergoes screening. Thereafter, the calibration must be checked monthly until the last subject has exited the study. For calibration checks, the manufacturer's instructions should be followed. 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.

### 21.3.8. 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.

### 21.3.9. 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

### 21.3.10. Visual Field

Visual field examinations will be performed using a static or dynamic perimeter (Humphrey or Octopus) without pupil dilation at Visit 1 (Screening), if this 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.

### 21.3.11. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination will be performed for each eye at Visit 1 (Screening), Visit 4 (Baseline, Day 1), and Visit 7 Study Exit/Early Termination, and graded as described below. Ophthalmoscopy will be performed under dilation at Visit 1 (Screening) and Visit 7 Study Exit/Early Termination. Pupil dilation must be performed after all other ocular procedures have been completed. Cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will also be evaluated.

**Glaucomatous Optic Nerve Findings**

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

None (0) = No damage

| | | |
|---|---|---|
| Mild | (1) = | Optic nerve damage, secondary to glaucoma including any rim loss (sloping or thinning) |
| Moderate | (2) = | Optic nerve damage, including cupping to disc margin at one or more points |
| Severe | (3) = | Optic nerve damage, nearly total cupping, only nasal rim or less present |

### 21.3.12. Blood Sample for Pharmacogenomics/genomics Study

For 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 ICF. 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.

## 21.5. Appendix D - Latanoprost Ophthalmic solution 0.005% Package Insert

**LATANOPROST- latanoprost solution**
**Greenstone LLC**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

**These highlights do not include all the information needed to use latanoprost ophthalmic solution safely and effectively. See full prescribing information for latanoprost ophthalmic solution.**

**Latanoprost ophthalmic solution 0.005%**
**Initial U.S. Approval: 1996**

**INDICATIONS AND USAGE**

Latanoprost ophthalmic solution is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension. (1)

**DOSAGE AND ADMINISTRATION**

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

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

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

**ADVERSE REACTIONS**

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

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

**DRUG INTERACTIONS**

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

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 5/2017**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*

Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

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

**2 DOSAGE AND ADMINISTRATION**

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

The dosage of latanoprost ophthalmic solution should not exceed once daily; the combined use of two or more prostaglandins, or prostaglandin analogs including latanoprost ophthalmic solution is not

recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the intraocular pressure (IOP) lowering effect or cause paradoxical elevations in IOP.

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

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

**3 DOSAGE FORMS AND STRENGTHS**

Sterile ophthalmic solution containing 50 mcg/mL latanoprost.

**4 CONTRAINDICATIONS**

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

**5 WARNINGS AND PRECAUTIONS**

**5.1 Pigmentation**

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

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

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with latanoprost ophthalmic solution can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly *[see Patient Counseling Information (17)]*.

**5.2 Eyelash Changes**

Latanoprost ophthalmic solution may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment *[see Patient Counseling Information (17)]*.

**5.3 Intraocular Inflammation**

Latanoprost ophthalmic solution should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because inflammation may be exacerbated.

**5.4 Macular Edema**

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

**5.5 Herpetic Keratitis**

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

**5.6 Bacterial Keratitis**

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information (17)]*.

**5.7 Use with Contact Lenses**

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

**6 ADVERSE REACTIONS**

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

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

**6.1 Clinical Trials Experience**

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

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

**Table 1: Ocular Adverse Reactions and Ocular Signs/Symptoms Reported by 5–15% of Patients Receiving Latanoprost**

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

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

**Table 2: Adverse Reactions That Were Reported in 1–5% of Patients Receiving Latanoprost**

| | **Adverse Reactions (incidence (%))** | |
|---|---|---|
| | **Latanoprost (n=460)** | **Timolol (n=369)** |
| **Ocular Events/Signs and Symptoms** | | |
| Excessive tearing | 4 | 6 |
| Eyelid discomfort/pain | 4 | 2 |
| Dry eye | 3 | 3 |
| Eye pain | 3 | 3 |
| Eyelid margin crusting | 3 | 3 |
| Erythema of the eyelid | 3 | 2 |
| Photophobia | 2 | 1 |
| Eyelid edema | 1 | 3 |
| **Systemic Events** | | |

| | | |
|---|---|---|
| Upper respiratory tract infection/nasopharyngitis/influenza | 3 | 3 |
| Myalgia/arthralgia/back pain | 1 | 0.5 |
| Rash/allergic skin reaction | 1 | 0.3 |

The ocular event/signs and symptoms of blepharitis have been identified as "commonly observed" through analysis of clinical trial data.

**6.2 Postmarketing Experience**

The following reactions have been identified during postmarketing use of latanoprost ophthalmic solution in clinical practice. Because they are reported voluntarily from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to latanoprost ophthalmic solution, or a combination of these factors, include:

Nervous System Disorders: Dizziness; headache; toxic epidermal necrolysis

Eye Disorders: Eyelash and vellus hair changes of the eyelid (increased length, thickness, pigmentation, and number of eyelashes); keratitis; corneal edema and erosions; intraocular inflammation (iritis/uveitis); macular edema, including cystoid macular edema; trichiasis; periorbital and lid changes resulting in deepening of the eyelid sulcus; iris cyst; eyelid skin darkening; localised skin reaction on the eyelids; conjunctivitis; pseudopemphigoid of the ocular conjunctiva

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

Skin and Subcutaneous Tissue Disorders: Pruritus

Infections and Infestations: Herpes keratitis

Cardiac Disorders: Angina; palpitations; angina unstable

General Disorders and Administration Site Conditions: Chest pain

**7 DRUG INTERACTIONS**

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

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

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

### 8.3 Nursing Mothers

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

### 8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

### 8.5 Geriatric Use

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

## 10 OVERDOSAGE

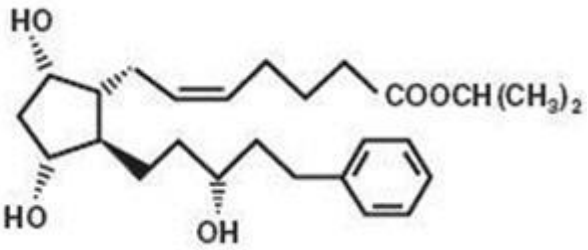
Intravenous infusion of up to 3 mcg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 mcg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

If overdosage with latanoprost ophthalmic solution occurs, treatment should be symptomatic.

## 11 DESCRIPTION

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

M.W. 432.58




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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

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

### 12.3 Pharmacokinetics

Absorption

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

Distribution

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

Metabolism

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

Excretion

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

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

## 14 CLINICAL STUDIES

### 14.1 Elevated Baseline IOP

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

### 14.2 Progression of Increased Iris Pigmentation

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

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

study. IOP reduction was similar regardless of the development of increased iris pigmentation during the study.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

2.5 mL fill, 0.005% (50 mcg/mL): Package of 1 bottle: NDC 59762-0333-2

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

## 17 PATIENT COUNSELING INFORMATION

**Potential for Pigmentation**

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

**Potential for Eyelash Changes**

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

**Handling the Container**

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

**When to Seek Physician Advice**

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

**Use with Contact Lenses**

Advise patients that latanoprost ophthalmic solution contains benzalkonium chloride, which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the

solution. Lenses may be reinserted 15 minutes following administration of latanoprost ophthalmic solution.

**Use with Other Ophthalmic Drugs**

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

This product's label may have been updated. For current full prescribing information, please visit www.greenstonellc.com.

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