Study Protocol Cover Page

Official Study Title:	A Phase III, Randomized, Observer-Masked, Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Compared with Latanoprost Ophthalmic Solution 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension-PEONY Study
NCT Number:	NCT02981446
Date of the document:	28 Jun 2016

DE-117

Protocol 01171505

Original

TITLE: **A Phase III, Randomized, Observer-Masked, Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Compared with Latanoprost Ophthalmic Solution 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension- PEONY Study**

SPONSOR:	STUDY DRUG:
Santen Pharmaceutical Co., Ltd. Grand Front Osaka Tower A, 4-20, Ofukacho, Kita-ku, Osaka, Japan	0.002% DE-117 Ophthalmic Solution 0.005% Latanoprost Ophthalmic Solution

I have read the 01171505 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 Ethics Committee (EC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form indicates that the data therein has been reviewed and accepted by me as the Investigator. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

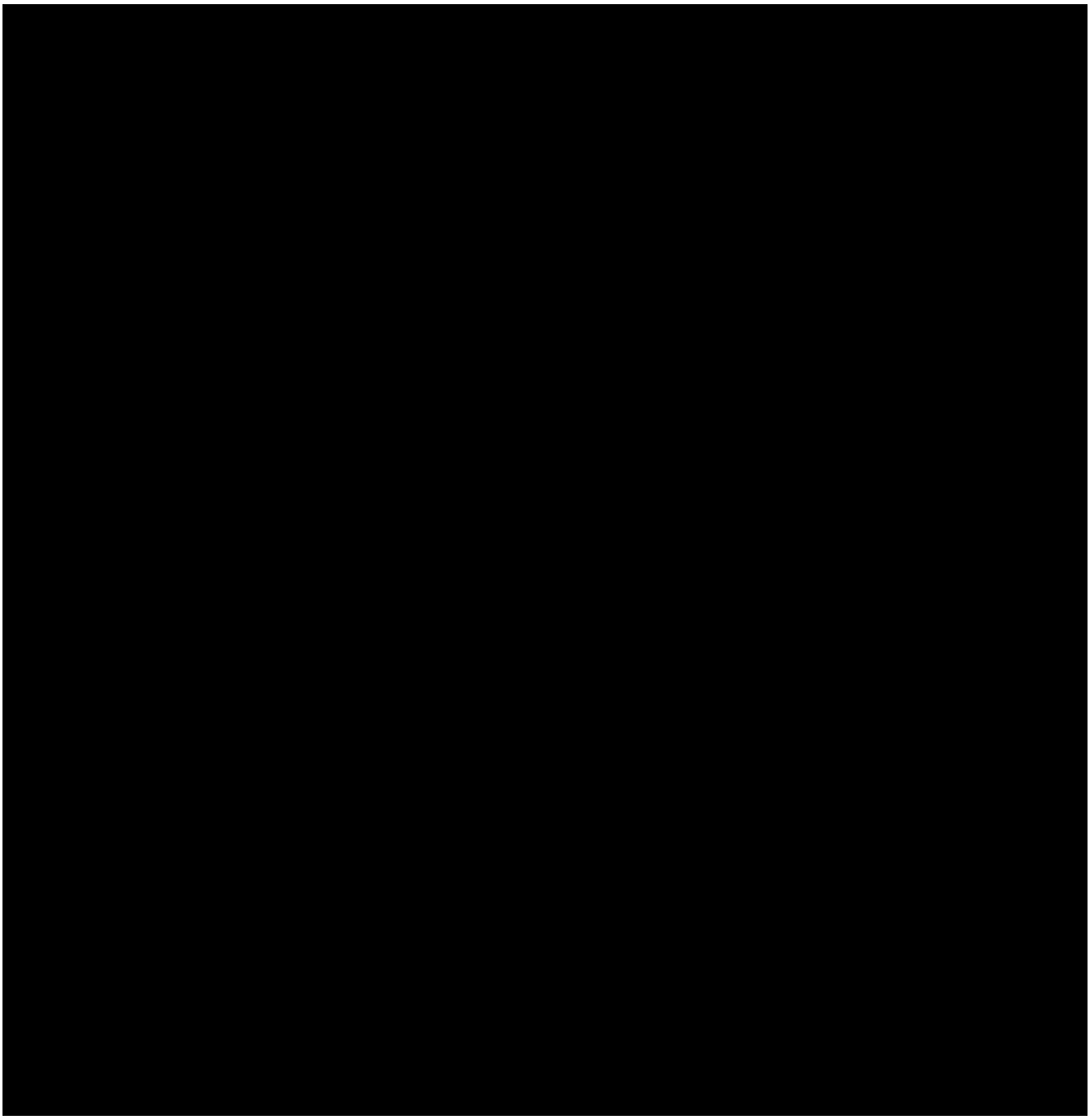
(PRINT OR TYPE)

Address: _____

_____

Phone: _____

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



2. SYNOPSIS

Name of Sponsor/Company:	Santen Pharmaceutical Co., Ltd. Grand Front Osaka Tower A, 4-20, Ofukacho, Kita-ku, Osaka, Japan
Name of Investigational Product: DE-117 Ophthalmic Solution	
Name of Active Ingredient: Isopropyl 2-{[6-({*N*-[4-(1*H*-pyrazol-1-yl)benzyl]pyridine-3-sulfonamido}methyl)pyridine-2-yl]amino}acetate	
Title of Study: A Phase III, Randomized, Observer-Masked, Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Compared with Latanoprost Ophthalmic Solution 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension- **PEONY Study**	
Study centers: Approximately 30 sites in Asian countries including Singapore, India, Taiwan and Korea.	
Study period: Estimated date of first subject screened: Oct 2016 Estimated date last subject completed: Dec 2018	**Phase of development:** III

Primary Objective: To determine if the mean diurnal intraocular pressure (IOP) reduction with DE-117 ophthalmic solution 0.002% is non-inferior to Latanoprost ophthalmic solution 0.005% at Month 3 in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT).

Secondary objective :
To determine if the mean diurnal IOP reduction with DE-117 ophthalmic solution 0.002% is superior to that of Latanoprost ophthalmic solution 0.005% at Week 1 in subjects with OAG or OHT.

Safety objective:

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

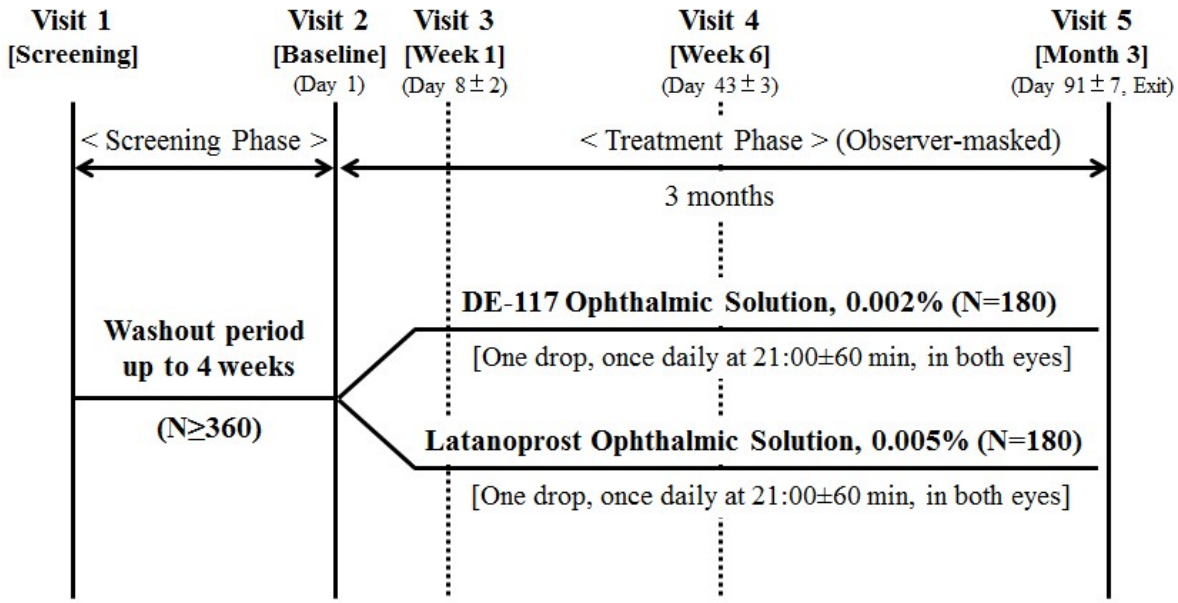
Methodology:

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

Approximately 360 subjects with OAG or OHT will be randomized in a 1:1 ratio to either:

- Arm 1- DE-117 Ophthalmic Solution 0.002%
- Arm 2- Latanoprost Ophthalmic Solution 0.005%

Study Design



The study will consist of a screening phase, a washout period of up to 4 weeks and a 3-month treatment period.

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

- Miotics (cholinergic): 1 week
- Oral/topical carbonic anhydrase inhibitors (CAIs) : 1 week
- Non-selective alpha agonists: 2 weeks
- Alpha-2 agonists: 3 weeks
- Alpha-1 antagonists: 4 weeks
- Beta antagonists (β blocker) : 4 weeks
- Prostaglandins analogs (PGA): 4 weeks
- Rho kinase inhibitor: 4 weeks
- Combination drugs: The longest washout period of the individual component will be used.
- No prior IOP-lowering medications: Subjects who have not used an IOP-lowering medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).

An interim safety visit, mid washout visit (Visit 1a), may be scheduled during the washout period at the investigator's opinion if a patient's IOP might be getting too high, or if investigators are concerned that this will occur over the washout.

The eligibility visit (Visit 2) will be scheduled at the end of the washout period for those subjects on prior IOP-lowering medications. Subjects who have not used an IOP-lowering

medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).

At Visit 2, baseline IOP will be measured for both eyes at 9:00 (±60min), 13:00 (±60min) and 17:00 (±60min). The study eye will be the eye that qualifies per inclusion/exclusion criteria at Visit 2. If both eyes meet the inclusion criteria, the eye with the higher mean diurnal IOP at Visit 2 will be the study eye. If both eyes meet the inclusion criteria and have the same mean diurnal IOP, the right eye will be the study eye. Even if only one eye is qualified for the study, both eyes will be treated for the duration of the study. Eligible subjects will be randomized via IWRS (Interactive Web Response System) to DE-117 ophthalmic solution 0.002% once daily at 21:00 (±60min) or Latanoprost ophthalmic solution 0.005% once daily at 21:00 (±60min) for 3 months. The first dose will be instilled at 21:00 the evening of Visit 2 and continued through the night right before Visit 5 (Month 3). Subjects will return for Visits 3, 4 and 5 (Weeks 1, 6 and Month 3) after the eligibility visit (Visit 2). IOP will be measured at 9:00, 13:00 and 17:00 at the scheduled visits. Slit-lamp biomicroscopy will be performed right before the 9:00 IOP measurement, and corneal thickness measurement will be performed right after the 9:00 IOP measurement.

If there are no regulatory restrictions, subjects who consent will provide a saliva sample for a future pharmacogenetic laboratory research study. The purpose of this exploratory research is to identify possible genetic markers associated with the study drug(s) and/or ocular conditions.

Number of subjects (planned):

Approximately 360 subjects (180 in each treatment arm) in Asian countries including Singapore, India, Taiwan and Korea.

Diagnosis and main criteria for inclusion:

At Visit 1 (Screening) and Visit 2 (Baseline, Day 1), 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 able and willing to comply with all treatment and follow-up study procedures.
3. If a subject is a female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or surgically sterile [less than 6 months]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study.
    - Abstinence
    - Hormonal contraceptive method- oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 28 days prior
    - Placement of a copper-containing IUD
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Vasectomized male partner (surgery at least 6 months prior)
4. Subjects must have a diagnosis of OAG (Primary Open Angle Glaucoma [POAG], Pigmentary Glaucoma, or Pseudoexfoliative Glaucoma) or OHT in both eyes.
5. Corrected visual acuity of +0.60 logMAR (Snellen equivalent 20/80) or better in each

eye.
6. Central corneal thickness ≥ 480 μm and ≤ 600 μm in each eye.
7. Anterior chamber angle grade ≥ 2 (Shaffer scale) in each eye.

In addition, the subject must meet the following criteria at Visit 2 (Baseline, Day 1):
8. Completed the required wait/wash-out period.
9. At all time points of IOP measurements (9:00, 13:00 and 17:00), have IOP of ≥ 22 mmHg in either eye and ≤ 34 mmHg in both eyes.

Exclusion Criteria:

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

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

Medications / Therapies-
5. Intended or current use of the following prohibited medications during the study:
    - All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B12 formulation (e.g., cyanocobalamine) 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.
6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/wash-out period.
7. Subjects who will be required to initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARB]).
8. Use of contact lenses within one week prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye.
9. Any ocular surgery or ocular laser treatment within 90 days prior to Visit 1 (Screening) and throughout the study in either eye.
10. History of ocular surgery specifically intended to lower IOP (e.g. laser trabeculoplasty, filtering surgery, Minimally Invasive Glaucoma Surgery (MIGS), or trabeculotomy) in either eye.
11. History of keratorefractive surgery in either eye.
12. Allergy, hypersensitivity or contraindications to prostaglandins, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications.

Diseases-

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

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

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

- DE-117 Ophthalmic Solution 0.002%
- Latanoprost Ophthalmic Solution 0.005%

Each subject will be instructed to instill one drop of study medication in each eye at 21:00 (±60min) daily during the Treatment Phase of the study.

Route of administration: Topical ocular

Duration of treatment: 3 months

Criteria for evaluation:

Safety:
Safety assessments will be composed of adverse events, corrected visual acuity, slit lamp biomicroscopy, central corneal thickness, ophthalmoscopy, iris color, eyelash and eyelid.

Efficacy:
Efficacy will be assessed by evaluating IOP at each scheduled time point as follows: 9:00, 13:00 and 17:00.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Mean diurnal IOP (average of IOP at three time points: 9:00, 13:00 and 17:00) in the study eye at Visit 5 (Month 3).

Key Secondary Efficacy Endpoint:

- Mean diurnal IOP in the study eye at Visit 3 (Week 1)

Other Secondary Efficacy Endpoints:

- Mean diurnal IOP in the study eye at Visit 4 (Week 6).
- Proportion of subjects with mean diurnal IOP reduction from baseline ≥ 20%, 25 % and 30% in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).
- Proportion of subjects with mean diurnal IOP ≤ 18 mmHg in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).
- Change and percent change from baseline (CFB) in mean diurnal IOP in the study eye at each post-baseline visit (Visit 3, 4, and 5 [Week 1, Week 6 and Month 3, respectively]).
- IOP in the study eye at the specified time points: 9:00, 13:00, and 17:00 at each post-baseline visit.
- Change and percent change from baseline (CFB) in IOP in the study eye at the specified time points: 9:00, 13:00, and 17:00 at each post-baseline visit.
- Overall (grand) mean diurnal IOP (average of 4 visits) in the study eye.

Safety Endpoints:

- Incidence of ocular and systemic adverse events (AEs).
- Corrected visual acuity.
- Slit-lamp biomicroscopy.
- Ophthalmoscopy.
- Central corneal thickness.
- Iris color/eyelash/eyelid.

Statistical methods:

The standard deviations of mean diurnal intraocular pressure in the latanoprost group and DE-117 0.002% group ranged from 2.59 mmHg to 4.40 mmHg in Study 33-003. Assuming a difference of 0 mmHg and a standard deviation of 4.0 mmHg for the comparison between the DE-117 group and the latanoprost group, a total of 151 subjects per treatment group will provide 90% power to demonstrate the non-inferiority of the DE-117 group to the latanoprost group (two-sided $\alpha = 0.05$ and non-inferiority margin of 1.5 mmHg). Assuming that 16% subjects will prematurely discontinue the study, a total of 360 subjects (180 subjects per group) are to be randomized.

A mixed-effect model analysis for repeated measures (MMRM) will be carried out and 95% confidence interval for the difference in means (0.002% DE-117 vs. latanoprost) will be estimated. Non-inferiority is established if the upper limit of the 95% confidence interval for the difference is less than or equal to 1.5mmHg for mean diurnal IOP at Month 3.

If non-inferiority in the primary endpoint is achieved, then superiority will be tested for the key secondary endpoint. Accordingly, superiority is shown if the upper limit of the 95% confidence interval for the difference is less than 0 mmHg at Week 1.

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
AE	Adverse event
AGIS	Advanced Glaucoma Intervention Study
ATC	Anatomical Therapeutic Chemical
BAK	Benzalkonium chloride
CAIs	Carbonic Anhydrase inhibitors
dB	Decibel
eCRF	Electronic case report form
EDC	Electronic data capture
EP_2	Prostaglandin E receptor 2
ESI	Events of special interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full analysis set
FP	Prostaglandin F receptor
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IUD	Intrauterine Device
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram

Table 2: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Definition
min	Minute
mL	Milliliter
mm	Millimeter
mmHg	Millimeters of mercury
µg	Microgram
µm	Micrometer
MIGS	Minimally Invasive Glaucoma Surgery
MMRM	Mixed-effects Model for Repeated Measures
OAG	Open Angle Glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
PG	Prostaglandin
PGA	Prostaglandin Analogue
PGE_2	Prostaglandin E_2
POAG	Primary Open Angle Glaucoma
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SITA	Swedish Interactive Threshold Algorithm
SUN	Standardization of Uveitis Nomenclature
WHO-DDE	World Health Organization Drug Dictionary Enhanced

5. INTRODUCTION

Glaucoma comprises a group of related diseases typically associated with elevated intraocular pressure (IOP). The common factors of this group of diseases are 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 is 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 and younger and one in ten over the age of eighty (Resnikoff et al., 2004).

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

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

[redacted]

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 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). Currently approved IOP- lowering medications such as latanoprost (Latanoprost Ophthalmic Solution, 0.005%) also lower IOP by enhancing uveoscleral outflow, 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. Based on animal and clinical data, a greater response than with currently marketed FP agonists, is expected with topical ocular administration of DE-117.

Santen has conducted three randomized, observer-masked, placebo-and-active-controlled, parallel-group, multi-center clinical studies (33-001, 33-002 and 33-003) with DE-117 in subjects with POAG or OHT in the US.

Study 33-001 was a Phase I/II study investigating the safety and efficacy of DE-117 and DE-117 in combination with tafluprost 0.0015% compared with placebo and tafluprost (0.003%, 0.01% and 0.03% DE-117, 0.003%, 0.01% and 0.03% DE-117 with 0.0015% tafluprost, 0.0015% tafluprost and placebo). The IOP reduction in the lower concentration (0.003% DE-117) appeared to be greater than the higher concentration (0.01% DE-117). The most common adverse events reported were photophobia, followed by conjunctival hyperaemia, eye pain and iritis, occurred more frequently in the DE-117 treatment arms compared to tafluprost and placebo.

Study 33-002 was a Phase II study, assessing the safety and efficacy of four concentrations of DE-117 ophthalmic solution (0.0003%, 0.001%, 0.002% and 0.003%), compared with latanoprost ophthalmic solution 0.005% and placebo. The efficacy result showed that 0.002% DE-117 and latanoprost ophthalmic solution 0.005% performed similarly and were superior to the remaining four arms. The lowest dose of DE-117 tested (0.0003%) performed slightly better than placebo throughout the study. AEs experienced in the 0.002% and 0.003% DE-117 arms, the most frequent ocular AEs reported were conjunctival hyperaemia, followed by ocular hyperemia and photophobia. All AEs were mild, and resolved without intervention.

Study 33-003 was a Phase II, assessor-masked, parallel-group, comparative study conducted in patients with POAG or OHT, to investigate the efficacy and safety of five different concentrations of DE-117 ophthalmic solution (0.0012%, 0.0016%, 0.002%, 0.0025%, and 0.003%.) compared with latanoprost ophthalmic solution 0.005%, and to determine the optimal concentration of DE-117 ophthalmic solution. All groups of DE-117 ophthalmic solution demonstrated the IOP-lowering effect. The change from baseline in the mean diurnal IOP was comparably largest in the DE-117 0.0025% group and the DE-117 0.003% group, followed by the DE-117 0.002% group. Most of the reported ocular adverse events were mild, and none of the ocular adverse events were serious. Common ocular adverse events in the DE-117 ophthalmic solution groups were conjunctival hyperaemia, eye pain, and photophobia. The incidence of ocular adverse events was highest in the DE-117 0.003% group, then comparable across the DE-117 0.0025% and 0.002% groups and the latanoprost group.

In addition to the US clinical studies, Santen has been conducting a Phase II/III (01171503) study which consists of the stage 1 and stage 2 in Japan. The stage 1, Phase II, conducted in patients with POAG or OHT, to investigate the efficacy and safety of two different concentrations of DE-117 ophthalmic solution (0.002%, 0.0025%) compared with placebo. Both groups of DE-117 ophthalmic solution demonstrated the intraocular pressure-lowering efficacy. The change from baseline in the mean diurnal IOP was comparable between 0.002% and 0.0025% groups, but with slightly in favor of the DE-117 0.002% group. In addition, the 0.002% group numerically outperformed the 0.0025% group in terms of the responder rates including ≥20%, ≥25% and ≥30% IOP reduction. Common ocular adverse events in the DE-117 ophthalmic solution groups were conjunctival hyperaemia and corneal thickening. All ocular AEs were mild and were promptly resolved. The incidence of ocular adverse events was slightly higher in the DE-117 0.0025% group compared to the DE-117 0.002% group. The objective of

the Stage 2 (phase III) in Japan is to evaluate the safety and efficacy of DE-117 ophthalmic solutions (the optimal dose from Stage 1) compared with latanoprost ophthalmic solution.

With the consideration of the clinical findings above, DE-117 0.002% was selected to advance into the stage 2 (phase III) in Japan and this Asian Phase III clinical investigation.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

To determine if the mean diurnal intraocular pressure (IOP) reduction with DE-117 ophthalmic solution 0.002% is non-inferior to Latanoprost ophthalmic solution 0.005% at Month 3 in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT).

6.2. Secondary Objective

To determine if the mean diurnal IOP reduction with DE-117 ophthalmic solution 0.002% is superior to that of Latanoprost ophthalmic solution 0.005% at Week 1 in subjects with OAG or OHT.

6.3. Safety Objective

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

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a randomized, observer-masked, active-controlled, parallel-group, multinational and multicenter study assessing the safety and efficacy of DE-117 ophthalmic solution 0.002% compared with Latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT. This study will consist of a screening phase, a washout period of up to 4 weeks and a 3-month treatment period (Figure 1).

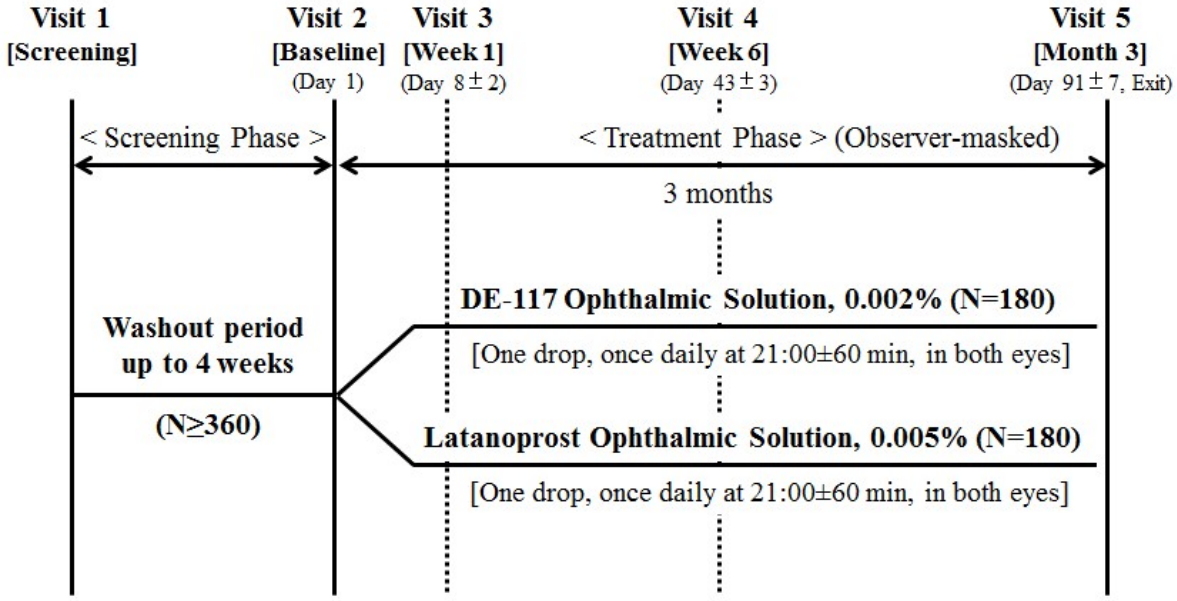


Figure 1: Study Design

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

- Miotics (cholinergic): 1 week
- Oral/topical carbonic anhydrase inhibitors (CAIs) : 1 week
- Non-selective alpha agonists: 2 weeks
- Alpha-2 agonists: 3 weeks
- Alpha-1 antagonists: 4 weeks
- Beta antagonists (β blocker) : 4 weeks
- Prostaglandins analogs (PGA): 4 weeks
- Rho kinase inhibitor: 4 weeks
- Combination drugs: The longest washout period of the individual component will be used.

- No prior IOP-lowering medications: Subjects who have not used an IOP-lowering medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).

An interim safety visit, mid washout visit (Visit 1a), may be scheduled during the washout period at the investigator's opinion if a patient's IOP might be getting too high, or if investigators are concerned that this will occur over the washout.

The eligibility visit (Visit 2) will be scheduled at the end of the washout period for those subjects on prior IOP-lowering medications. Subjects who have not used an IOP-lowering medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).

At Visit 2, baseline IOP will be measured for both eyes at 9:00 (±60min), 13:00 (±60min) and 17:00 (±60min). The study eye will be the eye that qualifies per inclusion/exclusion criteria at Visit 2. If both eyes meet the inclusion criteria, the eye with the higher mean diurnal IOP at Visit 2 will be the study eye. If both eyes meet the inclusion criteria and have the same mean diurnal IOP, the right eye will be the study eye. Even if only one eye is qualified for the study, both eyes will be treated for the duration of the study. Eligible subjects will be randomized via IWRS (Interactive Web Response System) to DE-117 ophthalmic solution 0.002% once daily at 21:00 (±60min) or Latanoprost ophthalmic solution 0.005% once daily at 21:00 (±60min) for 3 months. The first dose will be instilled at 21:00 the evening of Visit 2 and continued through the night right before Visit 5 (Month 3). Subjects will return for Visits 3, 4 and 5 (Weeks 1, 6 and Month 3) after the eligibility visit (Visit 2). IOP will be measured at 9:00, 13:00 and 17:00 at the scheduled visits. Slit-lamp biomicroscopy will be performed right before the 9:00 IOP measurement, and corneal thickness measurement will be performed right after the 9:00 IOP measurement.

If there are no regulatory restrictions, subjects who consent will provide a saliva sample for a future pharmacogenetic laboratory research study. The purpose of this exploratory research is to identify possible genetic markers associated with the study drug(s) and/or ocular conditions.

7.2. Number of Subjects

Approximately 360 subjects (180 in each treatment arm) in Asian countries including Singapore, India, Taiwan and Korea.

7.3. Treatment Assignment

Each subject will be assigned randomly in a 1:1 ratio to either DE-117 ophthalmic solution 0.002% or Latanoprost ophthalmic solution 0.005%.

7.4. SCHEDULE OF EVENTS AND PROCEDURES

	Screening Phase		Treatment Phase				
	Visit 1 Screening	Wash-out Period (optional Visit 1a)	Visit 2 Baseline (Day 1)	Visit 3 Week 1 (Day 8±2)	Visit 4 Week 6 (Day 43±3)	Visit 5 Month 3 (Day 91±7, Exit)	Early Term [l]
Informed Consent(s) [a]	X						
Inclusion/Exclusion Criteria	X		X				
Demographics and Medical History	X						
Medications/Therapies	X	X	X	X	X	X	X
Dosing Compliance				X	X	X	X
Adverse Events		X	X	X	X	X	X
Pregnancy Test [b]	X		X			X	X
Biomicroscopy [c]	X	X	X (9:00)	X (9:00)	X (9:00)	X (9:00)	X (9:00)
IOP [d]	X	X	9:00 13:00 17:00	9:00 13:00 17:00	9:00 13:00 17:00	9:00 13:00 17:00	9:00 13:00 17:00
Central corneal thickness [e]	X		X (9:00)	X (9:00)	X (9:00)	X (9:00)	X (9:00)
Corrected visual acuity	X	X	X	X	X	X	X
Iris, Eyelash, Eyelid			X (Photo)	X	X	X	X
Ophthalmoscopy [f]	X		X			X	X
Gonioscopy [g]	X						
Visual Field [h]	X						
Randomization via IWRS			X				
Dispense Study Medication [i]			X		X		
Collect Study Medication [j]					X	X	X
[redacted]							

[a] Informed Consent and authorization as appropriate for local privacy regulations must be signed and dated before study procedures are performed. [redacted]

[b] Urine pregnancy test will be conducted for all female subjects of childbearing potential.

[c] Biomicroscopy examination will be completed right before the 9:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1/1a, the biomicroscopy examination should be performed before IOP measurement.

[d] IOP Measurements will be taken at 9:00±60min, 13:00±60min and 17:00±60min at all visits except Visit 1/1a (Screening or mid washout visit).

[e] Central corneal thickness measurements will be performed right after the 9:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1, central corneal thickness measurement should be performed after IOP measurement.

[f] Ophthalmoscopy (fundus) examination will be performed without pupil dilation.

[g] Gonioscopy will be performed if not done within the prior 3 months of Visit 1.

[h] Visual field measurement will be performed if not done within the prior 3 months of Visit 1.

[i] One kit containing four eye drop bottles of study medication will be dispensed at Visit 2 and Visit 4, respectively. To maintain masking of the Investigator and examiner during this study, an authorized study staff, other than the Investigator or examiner, will dispense and collect study medications.

[j] One kit containing four eye drop bottles of study medication will be collected at Visit 4 and Visit 5 Study Exit/Early Termination, respectively. When collecting the study medications, the kit containing the used and unused four eye drop bottles will be sealed.

[redacted]

[l] The specified examinations and observations will be performed as much as possible.

7.4.1. Visit 1 (Screening)

- Explain the purpose and conduct of the study to the subject and obtain written individual informed consent. Informed consent for the optional pharmacogenetic laboratory research study may be obtained at any visit prior to study exit. Ensure that the subject understands that if they do not wish to provide a saliva sample for the biomarker research study that it will not affect the subject's enrollment in this trial.

- Obtain demographics.

- Obtain medications, therapies and medical history including OAG or OHT diagnosis, surgical history, current ocular and systemic conditions.

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

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

    - Biomicroscopy (before IOP measurement)

    - IOP

    - Central corneal thickness (after IOP measurement)

    - Corrected visual acuity

    - Ophthalmoscopy without pupil dilation

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

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

- Determine if the subject meets eligibility criteria.

- If the subject meets eligibility criteria and will continue in the study, discontinue any current IOP medication according to the following schedule (up to +7 days as a window is allowed):

    - Miotics (cholinergic): 1 week

    - Oral/topical carbonic anhydrase inhibitors (CAIs) : 1 week

    - Non-selective alpha agonists: 2 weeks

    - Alpha-2 agonists: 3 weeks

- Alpha-1 antagonists: 4 weeks
- Beta antagonists (β blocker) : 4 weeks
- Prostaglandins analogs (PGA): 4 weeks
- Rho kinase inhibitor: 4 weeks
- Combination drugs: The longest washout period of the individual component will be used.
- No prior IOP-lowering medications: Subjects who have not used an IOP-lowering medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).

- An interim safety visit, mid washout visit (Visit 1a), may be scheduled during the washout period at the investigator's opinion if a patient's IOP might be getting too high, or if investigators are concerned that this will occur over the washout.
- The eligibility visit (Visit 2) will be scheduled at the end of the washout period for those subjects on prior IOP-lowering medications.
- Subjects who have not used an IOP-lowering medication for the last 4 weeks or treatment-naive subjects will need a wait period of ≥1 day before their Visit 2 (Baseline, Day 1).
  - If the subject who has not used an IOP-lowering medication for the last 4 weeks uses contact lenses in either eye, the subject will need a wait period of ≥7 days before their Visit 2 (Baseline, Day 1).
- If the subject has consented to provide a saliva sample for a future pharmacogenetic laboratory research study, collect the sample.
  - Note: If a saliva sample cannot be collected at this visit, it may be collected at any one of the following Visits, for example, Visits 2, 3, 4, 5, or early termination visit.
- Schedule the eligible subject to return for Visit 2 (Baseline, Day 1) after the required wait/wash-out period.
- A subject who will not continue in the study and/or does not meet eligibility criteria is considered a screen failure.

7.4.2. Visit 1a (Optional, Wash-out Period)

Visit 1a is an interim safety visit, mid washout visit that may be performed during the washout period at the investigator's opinion if a patient's IOP might be getting too high, or if investigators are concerned that this will occur over the washout.

- Update concomitant medications/therapies.
- Query the subject regarding adverse events (AEs).
- Perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
    - Biomicroscopy (before IOP measurement)
    - IOP
    - Corrected visual acuity

7.4.3. Visit 2 (Baseline, Day 1)

- Update concomitant medications/therapies.
- Query the subject regarding adverse events (AEs).
- Determine if the subject has complied with the required wait/wash-out period for ocular hypotensive medication(s).
- Obtain urine and perform urine pregnancy test, if the subject is a women of child-bearing potential.
- All ophthalmic procedures to be performed in both eyes.
- Perform biomicroscopy right before the 9:00 IOP measurement.
- Perform IOP measurement at 9:00 (±60 minutes).
- Perform central corneal thickness measurement right after the 9:00 IOP measurement.
- If subject met the 9:00 IOP eligibility requirements, schedule additional IOP measurements at 13:00 and 17:00 and perform within ±60 minutes of the scheduled time.
- Perform the following procedures and assessments at any time during this visit.
    - Corrected visual acuity
    - Iris, Eyelash, Eyelid photographs
    - Ophthalmoscopy without pupil dilation
- Perform final review of inclusion/exclusion criteria after the 17:00 IOP measurement. If the subject has met all eligibility criteria, upon completion of the

above procedures and assessments, the Investigator will determine the study eye. The subject will then be randomized, via IWRS (Interactive Web Response System).

  - The study eye will be the eye that qualifies per inclusion/exclusion criteria at Visit 2. If both eyes meet the inclusion criteria, the eye with the higher mean diurnal IOP at Visit 2 will be the study eye. If both eyes meet the inclusion criteria and have the same mean diurnal IOP, the right eye will be the study eye.

- After the subject has been randomized to a treatment arm, an authorized study staff, other than the Investigator or examiner, must:
  - Dispense one kit containing four eye drop bottles of study medication.
  - Give the subject verbal and written instructions including medication dosing diary for proper instillation of the study medication, the dosing regimen, and study medication storage.
- Schedule the subject to return on Day 8 ±2 for Visit 3 (Week 1).
- A subject who will not continue in the study and/or does not meet eligibility criteria is considered a screen failure.

7.4.4. Visit 3 (Week1, Day 8 ±2)

- Update concomitant medications/therapies.
- Query the subject regarding AEs.
- Query the subject regarding dosing compliance reviewing the medication dosing diary.
- All ophthalmic procedures to be performed in both eyes.
- Perform biomicroscopy right before the 9:00 IOP measurement.
- Perform IOP measurement at 9:00 (±60 minutes).
- Perform central corneal thickness measurement right after the 9:00 IOP measurement.
- Schedule additional IOP measurements at 13:00 and 17:00 and perform within ±60 minutes of the scheduled time.
- Perform the following procedures and assessments at any time during this visit.
  - Corrected visual acuity

- Iris, Eyelash, Eyelid

- Schedule the subject to return on Day 43 ±3 for Visit 4 (Week6).
- Remind the subject to continue dosing according to the written instructions and to complete the medication dosing diary.
- Remind the subject to bring all used and unused study medication placed in the kit at Visit 4.

7.4.5. Visit 4 (Week6, Day 43 ±3)

- Update concomitant medications/therapies.
- Query the subject regarding AEs.
- Query the subject regarding dosing compliance reviewing the medication dosing diary.
- All ophthalmic procedures to be performed in both eyes.
- Perform biomicroscopy right before the 9:00 IOP measurement.
- Perform IOP measurement at 9:00 (±60 minutes).
- Perform central corneal thickness measurement right after the 9:00 IOP measurement.
- Schedule additional IOP measurements at 13:00 and 17:00 and perform within ±60 minutes of the scheduled time.
- Perform the following procedures and assessments at any time during this visit.
  - Corrected visual acuity
  - Iris, Eyelash, Eyelid
- An authorized study staff, other than the Investigator or examiner, must:
  - Collect used and unused four eye drop bottles placed in sealed kit by the subject or the authorized study staff.
  - Dispense one kit containing four eye drop bottles of study medication.
- Schedule the subject to return on Day 91 ±7 for Visit 5 (Month 3) Study Exit.
- Remind the subject to continue dosing according to the written instructions and to complete the medication dosing diary.

- Remind the subject to bring all used and unused study medication placed in the kit at Visit 5.

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

- An authorized study staff, other than the Investigator or examiner, must collect used and unused four eye drop bottles placed in sealed kit by the subject or the authorized study staff.
- Update concomitant medications/therapies.
- Query the subject regarding AEs.
- Query the subject regarding dosing compliance reviewing the medication dosing diary.
- Obtain urine and perform urine pregnancy test, if the subject is a women of child-bearing potential.
- All ophthalmic procedures to be performed in both eyes.
- Perform biomicroscopy right before the 9:00 IOP measurement.
- Perform IOP measurement at 9:00 (±60 minutes).
- Perform central corneal thickness measurement right after the 9:00 IOP measurement.
- Schedule additional IOP measurements at 13:00 and 17:00 and perform within ±60 minutes of the scheduled time.
- Perform the following procedures and assessments at any time during this visit.
    - Corrected visual acuity
    - Iris, Eyelash, Eyelid
    - Ophthalmoscopy without pupil dilation
- Exit the subject from the study.

7.4.7. Early Termination

- An authorized study staff, other than the Investigator or examiner, must collect used and unused four eye drop bottles placed in sealed kit by the subject or the authorized study staff.
- Update concomitant medications/therapies.

- Query the subject regarding AEs.
- Query the subject regarding dosing compliance reviewing the medication dosing diary.
- Obtain urine for urine pregnancy test, if the subject is a women of child-bearing potential.
- All ophthalmic procedures to be performed in both eyes.
- Perform biomicroscopy right before the 9:00 IOP measurement.
- Perform IOP measurement at 9:00 (±60 minutes).
- Perform central corneal thickness measurement right after the 9:00 IOP measurement.
- Schedule additional IOP measurements at 13:00 and 17:00 and perform within ±60 minutes of the scheduled time.
- Perform the following procedures and assessments at any time during this visit.
    - Corrected visual acuity
    - Iris, Eyelash, Eyelid
    - Ophthalmoscopy without pupil dilation
- Exit the subject from the study.

Note: The above specified examinations and observations will be performed as much as possible.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

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

8.1. Subject Inclusion Criteria

At Visit 1 (Screening) and Visit 2 (Baseline, Day 1), 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 able and willing to comply with all treatment and follow-up study procedures.

3. If a subject is a female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or surgically sterile [less than 6 months]), she must have a negative urine pregnancy test and must use at least one of the following acceptable contraceptive methods during the study.

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

4. Subjects must have a diagnosis of OAG (Primary Open Angle Glaucoma [POAG], Pigmentary Glaucoma, or Pseudoexfoliative Glaucoma) or OHT in both eyes.

5. Best-corrected visual acuity of +0.60 logMAR (Snellen equivalent 20/80) or better in each eye.

6. Central corneal thickness $\geq$ 480 µm and $\leq$ 600 µm in each eye.

7. Anterior chamber angle grade $\geq$ 2 (Shaffer scale) in each eye.

In addition, the subject must meet the following criteria at Visit 2 (Baseline, Day 1):

8. Completed the required wait/wash-out period.

9. At all time points of IOP measurements (9:00, 13:00 and 17:00), have IOP of ≥ 22 mmHg in either eye and ≤ 34 mmHg in both eyes.

8.2. Subject Exclusion Criteria

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

General-

1. Females who are pregnant, nursing or planning a pregnancy.

2. Subjects with known or suspected drug or alcohol abuse.

3. Current or planned participation in any other clinical trial involving an investigational product or device within 4 weeks prior to Visit 1 (Screening) or at any time during this trial.

4. Subjects who have been exposed to DE-117 prior to Visit 1 (Screening).

Medications / Therapies-

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

    - All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B12 formulation (e.g., cyanocobalamine) 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.

6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/wash-out period.

7. Subjects who will be required to initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARB]).

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

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

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

11. History of keratorefractive surgery in either eye.

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

Diseases-

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

14. Presence of any corneal abnormality or other condition interfering with or preventing reliable Goldmann applanation tonometry (e.g. Fuch's dystrophy or significant corneal surface abnormality) in either eye.

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

16. Presence of clinically significant macular edema in either eye.

17. History of severe ocular trauma in either eye.

18. History of iritis and/or uveitis in either eye.

19. History of retinal detachment, proliferative diabetic retinopathy, or any retinal disease that may be progressive during the time course of the study in either eye.

20. Presence or history of any disease or condition that in the opinion of the study investigator may put the subject at significant risk, may confound study results, or may interfere significantly with the subject's participation in the study (e.g., recurrent corneal erosion syndrome, uncontrolled cardiovascular disease etc.).

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

8.3. Subject Withdrawal Criteria

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

- Adverse Event (e.g., not compatible with study continuation)

- Lack of efficacy (e.g., IOP exceeds 34 mmHg in either eye after randomization)
- Protocol deviation (e.g., not fulfilling eligibility criteria)
- Pregnancy
- Voluntary withdrawal by subject at any time for any reason
- Lost to follow-up (e.g., any contact is not possible)
- Other

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

If a subject is terminated from the study before completing Month 3 (Visit 5), as much as possible, the specified examinations and observations of the early termination visit will be performed on the day of early termination. Subjects who are discontinued from the study early will not be replaced.

8.4. Study Termination

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

9. TREATMENT OF SUBJECTS

9.1. Description of Study Medication

DE-117 ophthalmic solution is an aqueous solution containing DE-117. [redacted]

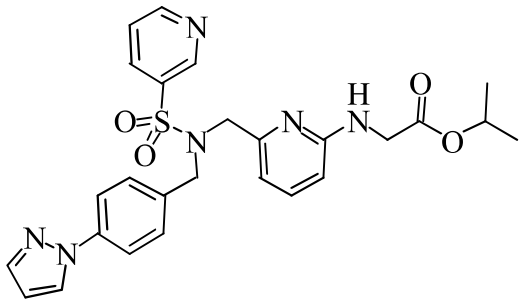


Figure 2: DE-117 Structure

Investigational Product:

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

Active Control:

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

9.2. Concomitant Medications or Therapies

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

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

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

9.2.1. Prohibited Medications or Therapies

- All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B12 formulation (e.g., cyanocobalamine) and study medications, must be discontinued after Visit 1 (Screening).
    - If sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), and/or Vitamin B12 formulation (e.g., cyanocobalamin) 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 during the study duration.
- Initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARB]) during the study duration.
- Contact lens wear must be discontinued at least one week prior to Visit 2 (Baseline, Day 1) and is prohibited during the remainder of the study .
- Any ocular surgery or ocular laser treatment will not be allowed within 90 days prior to Visit 1 (Screening) and throughout the study in either eye.
- Participation in any other clinical trial involving an investigational product within 4 weeks prior to Visit 1 (Screening) and during the study is not allowed.

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

9.3. Treatment Compliance

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

- Subjects will receive verbal and written instructions including medication dosing diary for proper instillation of the study medication, the dosing regimen, and study medication storage. Subjects will be reminded at Visit 2 (Baseline, Day 1), Visit 3 (Day 8 ±2), and Visit 4 (Day 43 ±3) to consistently dose at the same time of the day (once daily at 21:00 [±60min]), and to complete the medication dosing diary. Since subjects must have a

diagnosis of OAG or OHT in both eyes, both eyes will be treated for the duration of the study, even if only one eye is eligible per IOP inclusion criteria. The medication dosing diary will be kept with the subject's source documents.

- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 (Day 8 ±2), Visit 4 (Day 43 ±3), and Visit 5 (Day 91 ±7) Study Exit/Early Termination. Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%.

- A subject's dosing compliance for a specific period is determined by the total number of days that subject did not follow the proper dosing procedures and dosing schedule (e.g., any stoppage of study medication use, overdosing of study medication, incorrect time of study medication administration). The subject's dosing compliance will be recorded in the subject's source documents at Visit 3 (Day 8 ±2), Visit 4 (Day 43 ±3), and Visit 5 (Day 91 ±7) Study Exit/Early Termination. Subjects may be discontinued from the study at the discretion of the Investigator if the subject cannot be brought into compliance.

9.4. Randomization and Masking

Subjects will be equally randomized to two treatment groups. A blocked randomization will be stratified by 1) the mean diurnal IOP in the study eye at Visit 2 (< 25 mmHg and ≥ 25 mmHg) to ensure balanced baseline IOP between treatment groups, 2) diagnosis of OAG and OHT in the study eye at baseline to ensure balanced OAG and OHT allocation between treatment groups. Randomization schedule with a fixed block size will be generated. Each eligible subject will receive a study medication kit numbered using the randomization schedule.

DE-117 ophthalmic solution 0.002% or latanoprost ophthalmic solution 0.005% will be supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle. The shape of the bottle is different between DE-117 ophthalmic solution and latanoprost ophthalmic solution. Therefore, the study will be observer-masked although eye drop bottles of study medication will be placed in a kit which is indistinguishable in appearance.

To maintain masking of the Investigator, examiner, and Santen (or designee) during this study, an authorized study staff, other than the Investigator or examiner, will dispense and collect study medications. The subjects will be instructed not to show the eye drop bottles to either the investigator, examiner, or the other study subject(s). When collecting the study medications, the kit containing the used and unused four eye drop bottles will be sealed.

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

Additionally, the adverse event or serious adverse event for which study treatment was unmasked should be reported to Santen Pharmacovigilance.

10. STUDY MEDICATION MATERIALS AND MANAGEMENT

10.1. Study Medication

10.1.1. Investigational Product

DE-117 ophthalmic solution contains 0.002% DE-117. Each 2.5 mL of DE-117 ophthalmic solution 0.002% contains 50 µg of DE-117. In addition, [redacted]

10.1.2. Active Control

The active control used in this clinical study, Latanoprost ophthalmic solution 0.005%, is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost. Each 2.5 mL of Latanoprost ophthalmic solution 0.005% contains 125 µg of latanoprost. [redacted] The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water for injection.

One drop of Latanoprost ophthalmic solution 0.005% contains approximately 1.5 µg of latanoprost. Assuming a 0.03 mL drop size and a total of up to 180 drops in both eyes, the extent of total exposure of each subject is approximately 270 µg Latanoprost after 90 days of treatment.

10.2. Study Medication Packaging and Labeling

DE-117 ophthalmic solution 0.002% or latanoprost ophthalmic solution 0.005% will be supplied as a 2.5 mL solution in a 5 mL clear low density polyethylene bottle. Four eye drop bottles of study medication will be placed in one kit. The eye drop bottles and the kit will be labeled with the protocol number, kit number, storage conditions, and dosing instructions.

One kit containing four eye drop bottles of study medication will be dispensed at Visit 2 (Day 1, Baseline) and Visit 4 (Day 43 ±3), respectively. An authorized study staff, other than the Investigator or examiner, will dispense and collect study medications. When collecting the study medications, the kit containing the used and unused four eye drop bottles will be sealed.

10.3. Study Medication Storage

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

Study medications should be stored under refrigeration at 2° to 8 °C (36° to 46 °F), protected from light and stored upright. Undispensed kits should be stored under refrigeration at 2° to 8 °C (36° to 46 °F) until dispensed. After the refrigeration storage, the Investigator (or his/her designee) will verify and record that the temperature was maintained at 2° to 8°C (36° to 46°F) using temperature recorder at least once every three business days of the investigational site thereafter, until the last subject has exited the study. In the event of a temperature excursion or any study medications damaged during storage, the Investigator (or his/her designee) will notify Santen (or designee) and will not dispense the study medications until obtaining authorization from Santen (or designee).

Subjects will be reminded to store all dispensed eye drop bottles under refrigeration, protection from light and upright. Study medications should not be frozen.

10.4. Study Medication Preparation

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

10.5. Study Medication Administration

Subjects will instill one drop of study medication in each eye at approximately 21:00 (±60min) for 3 months. Once daily administration at 21:00 (±60min) is selected because the results of the US and Japan clinical studies demonstrated intraocular pressure lowering efficacy by once daily instillation at night time. The treatment duration is set as 3 months because results of the US 33-003 clinical study demonstrated stabilization of intraocular pressure lowering effect from Month 1 to Month 3.

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) 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, temperature recorder and customized saliva sample collection kits for the pharmacogenetic 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 mean diurnal IOP at each post-baseline visit and the observed IOP at each scheduled time point (9:00, 13:00 and 17:00) of each post-baseline visit will be evaluated. Besides observed IOP measurements, change from baseline in IOP, and percent changes from baseline in IOP at each scheduled time point as well as the change from baseline in mean diurnal IOP will also be calculated and evaluated.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events, Serious Adverse Events and Events of Special Interest

12.1.1. Definition of Adverse Events

In clinical studies, an AE can be considered as an undesirable medical condition occurring at any time, including baseline or wash-out periods, even if no study treatment has been administered.

An AE is any untoward medical occurrence in a subject participated in the study; it does not necessarily have a causal relationship with study treatment. Regardless of relationship to the investigational medicinal product, an AE can be an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product.

Any significant change in a subject's condition from baseline, regardless of causality, is to be considered an AE (unless the change is determined to be a continuation of a pre-existing condition documented in the subject's medical history). However, 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 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 lack of efficacy of the study treatment for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Investigator.

12.1.1.1. Assessment of Adverse Events

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

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

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

Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions and reporting of serious adverse events (SAEs) in Section 12.1.2.

An Investigator who is medically qualified must make the determination of relationship (related or not related) to the investigational medicinal product for each AE or SAE. When determining relationship to study medication, the Investigator will consider any investigational medicinal 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 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 medicinal 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, and outcome of the AE.

Regardless of relationship to the clinical study, AEs that occur at any time after the subject has provided written informed consent until the last study procedure is performed, must be recorded.

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

- Whenever possible, use recognized medical terms for capturing AEs (do not use colloquialisms and/or abbreviations).
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms (e.g., record as "worsening of cataract" rather than "drop in vision"). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if worsening of macular edema and worsening of panuveitis are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).
- For intermittent events (e.g., intermittent headache) and events that occur with each instillation (e.g., eyes burn for 5 minutes after every dose).
    - The event start date should be recorded as the date the subject first started to experience the event. The end date should reflect when the last occurrence resolved or stopped. For example, if a subject had an intermittent headache from 04 APR 2014 until 10 APR 2014 and each individual headache lasts 3 hours a day, then the date of resolution is 10APR2014 (not 04APR2014).
    - 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.
- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. For example, if the subject contracted infectious keratitis and subsequently experienced residual corneal edema wherein she experienced decreased vision, the primary AE is infectious keratitis.

12.1.2. Serious Adverse Events

12.1.2.1. Assessment of Serious Adverse Events

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

- It resulted in death (i.e., the AE caused or led to death).
- It was life threatening (i.e., immediately life-threatening versus a hypothetically life-threatening event if it were more severe).
- It required or prolonged inpatient hospitalization (i.e., an overnight hospital admission or prolonged a hospitalization beyond the expected length of stay).

- 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

A SAE eCRF must be completed with as much available information 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 an masked expedited safety report for expedited reporting of SAEs to the IRB or IEC. The Principal Investigator is responsible for receiving and reviewing expedited safety reports, submitting expedited safety reports to the IRB or IEC, and maintaining copies of expedited safety reports in the study records.

12.1.3. Reporting Pregnancy

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

12.1.4. Follow-up of Adverse Events

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

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

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

12.1.5. Manual Back-Up Reporting Procedures

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

- Complete an AE Form and an SAE Form.
- Attach a cover sheet with your contact information and address to Santen (or its designee).
- Email (preferred) or Fax the cover sheet, AE, and SAE form to Santen (or its designee) at DrugSafety.Sydney@covance.com or +61-2-98888322.

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:

- Corrected visual acuity
- Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, corneal endothelial change, lens, anterior synechiae of iris, posterior synechiae of iris

- Central corneal thickness
- Ophthalmoscopy variables: glaucomatous optic nerve
- Iris color/eyelash/eyelid

13. OTHER ASSESSMENTS

13.1. Demographic, Baseline Characteristics and Other Assessments

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

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

14. STATISTICAL METHODS

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

14.1. Analysis Time Points

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

14.1.1. Interim Analysis

There are no interim analyses planned during this study.

14.1.2. Final Analysis

An unmasked final analysis will be performed to evaluate the safety and efficacy of DE-117 ophthalmic solution 0.002% compared with Latanoprost ophthalmic solution 0.005%.

14.2. General Considerations

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

The study eye will be defined as the eye that qualifies per inclusion criteria at Visit 2. If both eyes qualify, the eye with the higher mean diurnal IOP at baseline (Visit 2) will be the study eye, although both eyes may receive study drug. If both eyes have the same mean diurnal IOP at baseline, then the right eye will be designated as the study eye.

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

14.2.1. Sample Size

The standard deviations of mean diurnal intraocular pressure in the latanoprost 0.005% group and DE-117 0.002% group ranged from 2.59 mmHg to 4.40 mmHg in Study 33-003. Assuming a difference of 0 mmHg and a standard deviation of 4.0 mmHg for the comparison between the DE-117 group and the latanoprost group, a total of 151 subjects per treatment group will provide 90% power to demonstrate the non-inferiority of the DE-117 group to the latanoprost group (two-sided $\alpha = 0.05$ and non-inferiority margin of 1.5 mmHg). Assuming that 16% subjects will prematurely discontinue the study, a total of 360 subjects (180 subjects per group) are to be randomized.

14.2.2. Statistical Hypotheses and Level of Significance

The primary efficacy endpoint is the mean diurnal IOP (average of IOP at three time points: 9:00, 13:00 and 17:00) in the study eye at Visit 5 (Month 3).

For the primary endpoint, the comparison between DE-117 group and Latanoprost group will be performed with the following pair of testing hypotheses:

H_0: $\mu_C - \Delta \geq \mu_T$ versus H_1: $\mu_C - \Delta < \mu_T$

where μ_T and μ_C denote the mean values of the primary endpoint in DE-117 treatment group and Latanoprost group, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg.

Treatment differences between the DE-117 group and the Latanoprost group will be reported along with 95% confidence intervals. Non-inferiority is established if the upper limit of the 95% confidence interval for the difference is less than or equal to 1.5 mmHg for mean diurnal IOP at Month 3

If non-inferiority in the primary endpoint is achieved, then superiority will be tested for the key secondary endpoint as follows:

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

Superiority is shown if the upper limit of the 95% confidence interval for the difference is less than 0 mmHg at Visit 3 (Week 1).

14.3. Study Populations

14.3.1. Safety Population

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

14.3.2. Full Analysis Set

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

14.3.3. Per-Protocol Population

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

14.4. Handling of Missing Values

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

14.5. Demographic and Baseline Characteristics

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

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

Subjects using any prior medications that has been used for OAG or OHT within 4 weeks before the date of Visit 1 will be tabulated by treatment, Anatomical Therapeutic Chemical (ATC) levels, and preferred term specified in the World Health Organization Drug Dictionary Enhanced (WHO-DDE) (World Health Organization Drug Dictionary Enhanced, 2016).

14.6. Efficacy Analyses

14.6.1. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the mean diurnal IOP (average of IOP at three time points: 9:00, 13:00 and 17:00) in the study eye at Visit 5 (Month 3).

A mixed-effect model analysis for repeated measures (MMRM) will be carried out and 95% confidence interval for the difference in means (0.002% DE-117 vs. latanoprost) will be estimated. Non-inferiority is established if the upper limit of the 95% confidence interval for the difference is less than or equal to 1.5mmHg for mean diurnal IOP at Month 3.

The primary analysis will be based on the FAS and sensitivity analysis will be performed on the PP Population.

14.6.2. Analysis of Secondary Efficacy Endpoints

14.6.2.1. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is the mean diurnal IOP in the study eye at Visit 3 (Week 1).

If non-inferiority in the primary endpoint is achieved, then superiority will be tested for the key secondary endpoint. Accordingly, superiority is shown if the upper limit of the 95% confidence interval for the difference is less than 0 mmHg at Week 1.

14.6.2.2. Other Secondary Efficacy Endpoints

- Mean diurnal IOP in the study eye at Visit 4 (Week 6).

- Proportion of subjects with mean diurnal IOP reduction from baseline ≥ 20%, 25 % and 30% in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).
- Proportion of subjects with mean diurnal IOP ≤ 18 mmHg in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).
- Change and percent change from baseline (CFB) in mean diurnal IOP in the study eye at each post-baseline visit (Visit 3, 4, and 5 [Week 1, Week 6 and Month 3, respectively]).
- IOP in the study eye at the specified time points: 9:00, 13:00, and 17:00 at each post-baseline visit.
- Change and percent change from baseline (CFB) in IOP in the study eye at the specified time points: 9:00, 13:00, and 17:00 at each post-baseline visit.
- Overall (grand) mean diurnal IOP (average of 4 visits) in the study eye.

14.7. Safety Analyses

All safety outcome measures will be summarized descriptively for the Safety Population. The safety outcome measures include AEs, corrected visual acuity, slit-lamp biomicroscopy findings, central corneal thickness, ophthalmoscopy variables, iris color, eyelash, and eyelid.

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

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

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Principal Investigator will allow representatives of Santen's monitoring team (or designee), the governing institutional review board (IRB) 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 GCP.
- Perform investigational product accountability checks and quality control procedures.
- Ensure the on-going implementation of accurate data entry in the eCRF.
- Perform source data verification, including a comparison of the data in the eCRFs with the subject's medical records and other records relevant to the study. This will require direct access to all original records for each subject (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Santen.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

- Confirm sites have a complete record of all study IND Safety Reports and filed them with the IRB.

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 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)

The Principal Investigator must obtain IRB approval for the study. Initial IRB approval, and all materials approved by the IRB for this study including the patient 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 primary study at least, and other study related material, as appropriate, must be approved in writing by an IRB or IEC as appropriate. If an IRB or IEC does not approve the collection of saliva samples for optional future pharmacogenetic research that it will not affect conducting the primary study. The Principal Investigator must submit written approval to Santen (or designee) before study initiation. See 21.1 Appendix A for a list of obligations of Investigators.

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

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

17.2. Ethical Conduct of the Study

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

17.3. Written Informed Consent

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

18.2. Retention of Records

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

18.2.1. Source Documents

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

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

- The date the subject entered the study and the subject number
- The study protocol number and the name of Santen
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study-related subject visits (scheduled and unscheduled)
- Evidence that required procedures and/or evaluations were completed
- Use of any concomitant medications
- Documentation of study medication accountability
- Occurrence and status of any AEs

- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination

- If unmasking at the site occurred, proper documentation and notifications were made.

18.2.2. Source Data

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

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

18.2.3. Data Collection

The Principal Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened and randomized subjects will be entered into eCRFs. eCRFs must be completed within 3 business days of each subject visit. 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

1. Alm, A. (2014). Latanoprost in the treatment of glaucoma. Clin Ophthalmol. 8:1967-1985

2. Bito, L. (2001). A New Approach to the Medical Management of Glaucoma, from the Bench to the Clinic, and Beyond. Investigative Ophthalmology & Visual Science 42(6):1126-33.

3. Kass, M., Heuer, D., Higginbotham, E., Johnson, C., Keltner, J., Miller, J., Parrish, R., Wilson, M., Gordon, M. (2002). The Ocular Hypertension Treatment Study. A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma. Arch Ophthalmol 120:701-13.

4. Leske, M., Heijl, A., Hussein, M., engtsson, B., Hyman, L., Komaroff, E. (2003). Factors for progression and glaucoma treatment: The Early Manifest Glaucoma Trial. Arch Ophthalmol 121(1):48-56.

5. MedDRA. MedDRA MSSO, Medical Dictionary for Regulatory Activities, Version 14.1. Available from http://www.meddramsso.com/

6. Resnikoff, S., Pascolini, D., Etya ale, D., Kocur, I., Pararajasegaram, R., Pokharel, G., Mariotti, S. (2004). Global data on visual impairment in the year 2002. Bulletin of the World Health Organization 82(11):844-52.

7. Tham, Y., Li, X., Wong, T., Quigley, H., Aung, T., Cheng, C. (2014). Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophthalmology 121(11):2081-90.

8. The AGIS Investigators. (2000). The advanced glaucoma intervention study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 130(4):429-40.

9. World Health Organization Drug Dictionary Enhanced. World Health Organization Drug Dictionary Enhanced (WHO-DDE), September 2011 Version. Available from http://www.umc-products.com/DynPage.aspx?id=73588&mn1=1107&mn2=1139

10. Yamaji, K., Yoshitomi, T., Ishikawa, H., Usui, S. (2005). Prostaglandins E_1 and E_2, but not $F_{2\alpha}$ or Latanoprost, Inhibit Monkey Ciliary Muscle Contraction. Current Eye Research 30:661-5.

20.2. Santen 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 01171503. A Phase II/III randomized, double-masked, controlled, parallel group, multicenter study assessing the efficacy and safety of DE-117 ophthalmic solution in subjects with primary open angle glaucoma or ocular hypertension

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 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.

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

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

E. The subject's responsibilities.

F. Those aspects of the trial that are experimental.

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

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

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

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

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

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

M. 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.

N. 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.

O. 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.

P. 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.

Q. 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.

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

S. The expected duration of the subject's participation in the trial.

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

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

II. Additional Elements of Informed Consent for Optional Future Pharmacogenetic Laboratory Research Study

The following information must be provided to each subject in obtaining informed consent for the future pharmacogenetic 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, and ethnicity will be obtained through subject interviews at Visit 1 (Screening).

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

Following details of prior medication that has been used for OAG or OHT within 4 weeks before the date of Visit 1, or any concomitant medication, must be recorded in the subject's source documents.

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

Following details of prior therapy that has been received for OAG or OHT within 4 weeks before the date of Visit 1, or any concomitant therapy, must be recorded in the subject's source documents.

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

Medical history will be confirmed through subject interviews at Visit 1 (Screening) to determine if the subject meets eligibility criteria. Primary diagnosis, OAG (Primary Open Angle Glaucoma [POAG], Pigmentary Glaucoma, or Pseudoexfoliative Glaucoma) or OHT, and the affected eye must be recorded in the subject's source documents.

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

21.3.2. Pregnancy Test

A urine pregnancy test will be conducted using a commercially available test kit at Visit 1 (Screening), Visit 2 (Baseline, Day 1) and Visit 5 (Day 91 ±7) Study Exit/Early Termination for all women of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 12 months since last menses occurred), is without a uterus and/or 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, Eyelash, Eyelid

The investigator (or his/her designee) will take frontview and sideview photograph of each eye at Visit 2 (Baseline, Day 1). The photographs must include iris, eye lids and eyelashes of each eye. The photographs taken at Visit 2 (Baseline) will be used to help the Investigator assess iris color (e.g., brown, yellow-brown, green-brown, green with slightly brown, green, blue/gray-brown, blue/gray with slightly brown, blue/gray) and any changes from baseline in iris color, eyelash and eyelid at Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination.

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

21.3.3.1. Iris Color

The investigator will assess the iris color change (e.g., pigmentation) at Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination using the photographs obtained at Visit 2 (Baseline).

21.3.3.2. Eyelash

The investigator will assess eyelash change at Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination (e.g., length, thickness, pigmentation and number) using the photographs obtained at Visit 2 (Baseline).

21.3.3.3. Eyelid

The investigator will assess eyelid at Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination (e.g., pigmentation and hair growth) using the photographs obtained at Visit 2 (Baseline).

21.3.4. Corrected Visual Acuity

Corrected visual acuity will be measured for each eye at each visit under normal room illumination using visual acuity chart (e.g., ETDRS chart, Snellen chart) and the logMAR scoring will be recorded in the subject's source document. Corrected visual acuity will be collected with the up to date prescription (within 12 months) if applicable. Refraction can be performed at the principal investigator's discretion. If so, refraction should be documented in the subject's source document. If ETDRS chart is used, the following procedure should be followed.

21.3.4.1. 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.

Total the 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

21.3.5. Slit-lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded right before the 9:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). For Visit 1/1a, the biomicroscopy examinations should be performed before IOP measurement.

Anterior chamber cells and flare will be observed and graded using the Standardization of Uveitis Nomenclature (SUN) scale, before fluorescein instillation.

Anterior Chamber Cells

(0) = No cells

(0.5) = 1-5 cells

(1) = 6-15 cells

(2) = 16-25 cells

(3) = 26-50 cells

(4) = >50 cells

Anterior Chamber Flare

(0) = None

(1) = Faint

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

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

(4) = Intense (fibrin/plastic aqueous)

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

Lid Hyperemia

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

Lid Edema

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

Conjunctival (Palpebral and Bulbar) Hyperemia

None	(0) =	Normal
Mild	(1) =	Slight localized injection
Moderate	(2) =	Pink color, confined to palpebral OR bulbar conjunctiva
Severe	(3) =	Red color of the palpebral AND/OR bulbar conjunctiva

Conjunctival Chemosis

None	(0) =	Normal
Mild	(1) =	Slight localized swelling

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

Severe (3) = Moderate diffuse swelling

Corneal Edema

None (0) = Normal

Mild (1) = Mild, diffuse stromal haze

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

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

Corneal Staining (with fluorescein)

None (0) = Normal

Mild (1) = Localized, occasional punctate staining

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

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

Corneal Endothelial Change

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

21.3.6. Intraocular Pressure

IOP will be performed at each visit. At visit 1/1a, IOP can be measured at any time. For Visit 2, Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination, IOP measurements will be scheduled for 9:00 (±60min), 13:00 (±60min) and 17:00 (±60min).

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

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

A single measurement is made as follows:

- The Investigator adjusts the force on the tonometer dial to an initial setting corresponding to 10 mmHg. The slit lamp magnification is set at 10X. The light source is positioned at an angle of approximately 45º, and the aperture is maximally opened. A cobalt blue filter is employed.

- After instillation of a topical anesthetic, a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic (Fluress, Barnes Hind) may be instilled. The Investigator should use the same technique each time, be it a paper strip or a pre-mixed eye drop.

- The subject and slit lamp are adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting

neckwear is loosened. The subject is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the Investigator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The subject is cautioned not to hold his breath.

- The investigator looks through the slit lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.

- The Investigator adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.

- The Investigator removes the tip from the cornea, and the authorized study staff (recorder) records the reading on the dial, rounded to the next highest integer. For example, if the measurement indicated is between 16 and 17, then 17 is recorded as the measurement in the subject's source document.

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

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

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

- If the two measurements differ by 2 mmHg or less, 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 arraying 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.

21.3.6.1. Tonometer Calibration

The tonometer must be calibrated for accuracy before the first subject undergoes screening, and at least once every 4 weeks thereafter, until the last subject has exited the study. For checking calibration, follow the manufacturer's instructions. If the variation is within ±2 mmHg, the tonometer is considered adequately calibrated. However, if the variation exceeds this amount, the

tonometer should be sent for repair and a different, adequately calibrated instrument should be used for IOP measurement. The date of each calibration, along with the name and signature (or initials) of the person who performed the calibration, will be documented. The tonometer calibration record will be retained as a part of the study record.

21.3.7. 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 right after the 9:00 IOP measurement at Visit 2, Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination. For Visit 1 (Screening), central corneal thickness measurement should be performed after IOP measurement.

21.3.8. Gonioscopy

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

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

(1) = approximately 10 degrees

(2) = approximately 20 degrees

(3) = approximately 30 degrees

(4) = approximately 40 degrees or more

21.3.9. Visual Field

Visual field examinations will be performed using a static or dynamic perimeter without pupil dilation at Visit 1 (Screening), if it has not been performed within 3 months or the previous visual field test(s) indicates low subject reliability (e.g., due to fixation losses, false positive errors, or false negative errors). Glaucomatous visual field loss will be evaluated by the investigator as presence or absence.

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.

21.3.10. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination will be performed for each eye without pupil dilation at Visit 1, Visit 2, and Visit 5 Study Exit/Early Termination, and graded as described below.

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