Study Protocol Cover Page

Official Study Title:	A Randomized, Double-Masked, Parallel-Group, Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Once Daily and Twice Daily in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension-SPECTRUM 6 Study
NCT Number:	NCT03858894
Date of the document:	13 Nov 2018

DE-117

Protocol 011712IN

TITLE: **A Randomized, Double-Masked, Parallel-Group, Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Once Daily and Twice Daily in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension-SPECTRUM 6 Study**

PROTOCOL NUMBER: 011712IN

COMPOUND NUMBER: DE-117

STUDY PHASE: Phase II

SPONSOR: SANTEN INCORPORATED

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

REGULATORY AGENCY IDENTIFIER NUMBER(S): IND Number: 111,518

APPROVAL DATE: V1.0 13NOV2018

I have read the 011712IN protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and have complied with all financial and administrative requirements of the governing body of the clinical institution and Santen as the Sponsor. I will obtain written informed consent from each study subject prior to performing any study-specific procedures. I understand that my electronic signature on an electronic case report form (eCRF) indicates that the data therein has been reviewed and accepted by me as the Investigator.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

Address: _____

_____

Phone: _____

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

COMPANY/SPONSOR APPROVER

Company/Sponsor Address

Santen Incorporated

6401 Hollis Street, Suite 125, Emeryville, CA 94608

Table 1: Contact Information

Emergency Contact Information:		
Role in Study	**Name**	**Address/Phone/Fax/Email**
[redacted]		

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Randomized, Double-Masked, Parallel-Group, Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Once Daily and Twice Daily in Subjects with Primary Open-Angle Glaucoma or Ocular Hypertension- SPECTRUM 6 Study

Rationale:

This dose frequency study 011712IN (SPECTRUM 6) will assess the safety and efficacy of 0.002% DE-117 ophthalmic solution once daily (QD) and twice daily (BID) in subjects with Primary Open-Angle glaucoma (POAG) or ocular hypertension (OHT).

Table 2: Study Objectives and Endpoints

Study Objectives	Corresponding Study Endpoints
Primary objective: To determine whether DE-117 Ophthalmic Solution 0.002% given BID is superior to QD in reducing the intraocular pressure (IOP) after 6 weeks of treatment in subjects with POAG or OHT.	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 12:00 and 16:00 at Week 2 (Visit 3) and Week 6 (Visit 4).
	Secondary Efficacy Endpoints: • Mean diurnal IOP in the study eye at Week 6 (Visit 4) • Absolute change and percent change from baseline in IOP • Absolute change and percent change from baseline in mean diurnal IOP • Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2) at each post-baseline visit • Having a mean diurnal IOP ≤ 18 mmHg at each post-baseline visit
Safety objective: To determine the safety of DE-117 ophthalmic solution 0.002% given BID as compared to QD in subjects with POAG or OHT.	**Safety Endpoints:** Safety will be evaluated by the following parameters: • Incidence of ocular and systemic adverse events (AEs) • Best-corrected visual acuity (BCVA) • Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, abnormal lens findings, anterior synechiae of iris, posterior synechiae of iris • Ophthalmoscopy

Overall Design:

This is a randomized, double-masked, parallel-group, multi-center study. Subjects diagnosed with POAG or OHT who meet eligibility criteria at Visit 1 (Screening) will wash out 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 Visit 2 (Baseline, Day 1) will be randomized to receive study medication for up to 6 weeks.

Approximately 100 subjects with POAG or OHT will be randomized in a 1:1 ratio to either:

- DE-117 ophthalmic solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- DE-117 ophthalmic solution 0.002% BID (20:00 & 08:00)

This study will consist of a screening period of up to 35 days including a washout period of up to 28 days (+ 7 days window), and a 6-week double-masked treatment period.

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

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

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

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

At Visit 2, baseline IOP will be measured for both eyes at 8:00 (±60 min), 12:00 (±60 min) and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet the eligibility criteria, the eye with the higher diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP at Visit 2, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study even if only one eye is eligible per IOP inclusion criteria.

Treatment Period (6 weeks):

Approximately 100 eligible subjects will be randomized to either DE-117 0.002% QD in the evening and vehicle QD in the morning or DE-117 0.002% BID in a 1:1 ratio. Subjects will be treated for 6 weeks with scheduled Visits 2, 3 and 4 (Baseline, Week 2 and Week 6).

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

IOP will be measured at 08:00, 12:00 and 16:00 (±60 minutes). At these scheduled visits, BCVA and slit-lamp biomicroscopy will be performed just prior to the 08:00 IOP measurement. Ophthalmoscopy (fundus examination) will be performed after 16:00 IOP measurement.

Pharmacogenomics/Genomics:

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

Number of Subjects (Planned):

Approximately 100 subjects (50 subjects in each treatment arm) with POAG or OHT in the United States will be enrolled in this study.

Intervention Groups and Duration:

Approximately 100 subjects with POAG or OHT will be randomized in a 1:1 ratio to either:

- DE-117 ophthalmic solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- DE-117 ophthalmic solution 0.002% BID (20:00 & 08:00).

The study duration for each individual subject includes up to a 5-week screening period and up to a 6-week double-masked treatment period.

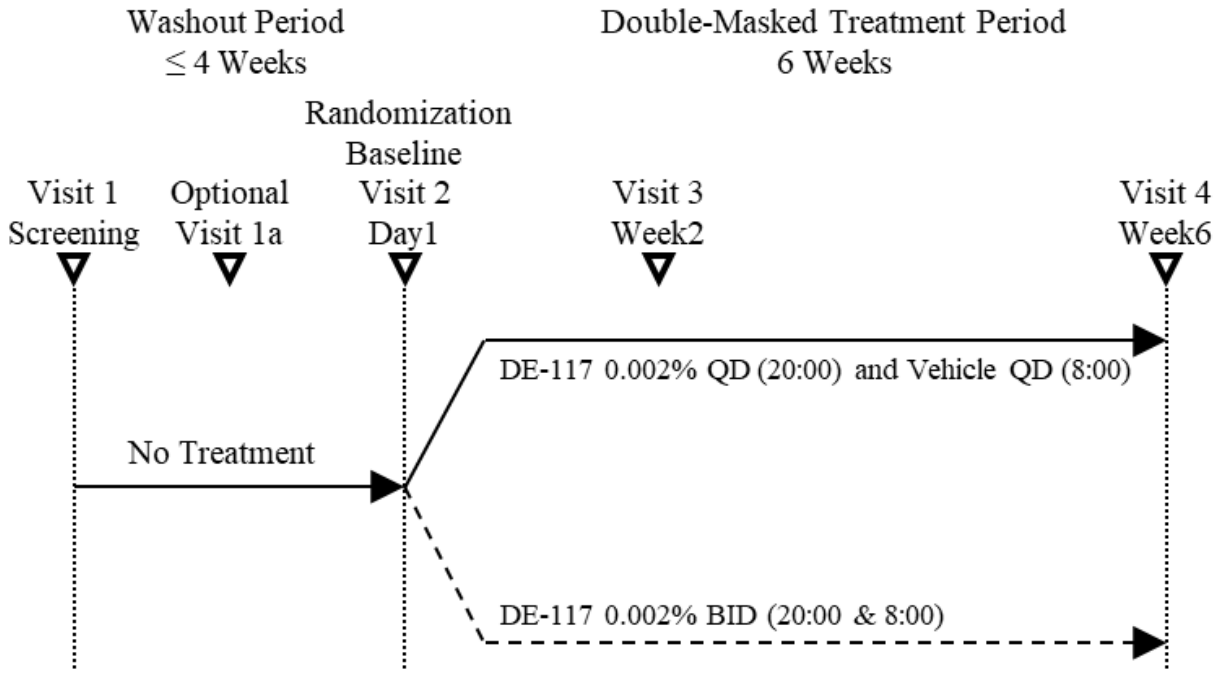
Data Monitoring Committee:

An independent data monitoring committee (DMC) will not be used in this study.

1.2. Schema

Figure 1 provides an overview of the study design.

Figure 1: Study Schema



1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) is provided in Table 3.

Table 3: Schedule of Activities

	Washout Period		Double-Masked Treatment Period		
	Visit 1 (Screening)	**Washout Period (up to 4 weeks) Optional Visit 1a[k]**	**Visit 2 Eligibility/ Baseline (Day 1)**	**Visit 3 Week 2 (Day 15±2)**	**Visit 4 Week 6 (Day 43±3) Exit or Early Termination[l]**
Informed Consent(s) including the consent for pharmacogenomics/ genomics laboratory research study[a]	X				
Inclusion/Exclusion Criteria	X		X		
Demographics and Medical History	X				
Concomitant Medications / Therapies	X	X	X	X	X

Table 3: Schedule of Activities (Continued)

	Washout Period		Double-Masked Treatment Period		
	Visit 1 (Screening)	**Washout Period (up to 4 weeks) Optional Visit 1a[k]**	**Visit 2 Eligibility/ Baseline (Day 1)**	**Visit 3 Week 2 (Day 15±2)**	**Visit 4 Week 6 (Day 43±3) Exit or Early Termination[l]**
Dosing Compliance				X	X
Adverse Events		X	X	X	X
Pregnancy Test[b]	X		X		X
Refraction[c]	X				
BCVA[c]	X	X	X (prior to 8:00 IOP meas.)	X (prior to 8:00 IOP meas.)	X (prior to 8:00 IOP meas.)
Biomicroscopy[d]	X	X	X (prior to 8:00 IOP meas.)	X (prior to 8:00 IOP meas.)	X (prior to 8:00 IOP meas.)
IOP[e]	X (any time)	X (any time)	08:00 12:00 16:00	08:00 12:00 16:00	08:00 12:00 16:00
Pachymetry[f]	X				
Instill study eye drop after 08:00 IOP measurement				X (after 8:00 IOP meas.)	X (after 8:00 IOP meas.)
Gonioscopy[g]	X				
Visual Field[h]	X				
Ophthalmoscopy[i]	X (pupil dilation)		X (after 16:00 IOP meas.)		X (after 16:00 IOP meas., pupil dilation)
Blood Sampling for Pharmacogenomics/genomics[j]				X	
Dispense Study Medication			X		
Collect Study Medication					X
Phone call to remind subjects to take morning and evening dose on the day before each visit				X	X

a. **Informed Consent(s) including the consent for pharmacogenomics/ genomics laboratory research study**
Informed consent form (ICF) must be signed and dated before study procedures are performed. Informed consent for the optional pharmacogenomics/genomics laboratory research study may be obtained at any visit prior to study exit.

b. **Pregnancy Test**
A urine pregnancy test will be conducted for all female subjects of childbearing potential.

c. **Refraction and BCVA**
Refraction will be performed at the screening visit. If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again. BCVA examination will be completed before IOP is measured at 08:00 (±60 min).

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

e. **IOP**
IOP measurements will be performed at 08:00, 12:00 and 16:00 (±60 min) at all visits except for Visit 1 and optional Visit 1a (screening and mid-washout).

f. **Pachymetry**
Pachymetry will be performed after IOP measurement at Visit 1 (Screening).

g. **Gonioscopy**
If gonioscopy was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary.

h. **Visual Field**
If visual field test was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening visual field test is necessary.

i. **Ophthalmoscopy**
Ophthalmoscopy will be performed at Visits 1, 2 and 4 (i.e. Screening, Baseline and Week 6) after the very last IOP measurement. Ophthalmoscopy will be performed with pupil dilation at Visit 1 and Visit 4/ Study Exit or Early Termination. Dilation of the pupil will be performed after the very last IOP measurement at Visit 1 and Visit 4/ Study Exit or Early Termination.

j. **Blood Sampling for Pharmacogenomics/genomics**
Blood sampling for the pharmacogenomics/genomics laboratory research study may be performed at any visit after pharmacogenomics/genomics informed consent is obtained, subject is randomized and study drug, DE-117 ophthalmic solution 0.002%, dosing has begun.

k. **Optional Visit 1a**
An interim safety visit may be performed during the washout period Visit 1a (optional, mid-washout visit), if in the Investigator's opinion a subject's IOP may be of concern. If subjects are treated with a topical CAI during the washout period. Visit 1a (optional, mid-washout visit) is recommended to be performed.

l. **Exit or Early Termination**
All listed procedures are required for early terminated subjects.

2. INTRODUCTION

DE-117 is an ophthalmic topical formulation of omidenepag isopropyl for the reduction of elevated IOP in patients with Glaucoma and OHT. DE-117 is a pro-drug of its pharmacologically active acid metabolite, UR-7276, omidenepag, a selective EP2 receptor agonist with non-prostaglandin structure.

2.1. Study Rationale

This dose frequency study (011712IN, SPECTRUM 6) will assess the safety and efficacy of 0.002% DE-117 ophthalmic solution QD and BID in subjects with POAG or OHT.

2.2. Background

Glaucoma represents a group of related diseases frequently associated with elevated IOP. When left untreated, glaucoma can lead to retinal ganglion cell death and optic nerve damage, resulting in progressive and irreversible loss of vision. Glaucoma is the second leading cause of blindness worldwide. In 2013, the global prevalence of glaucoma for population aged 40 to 80 years was 3.54%. The number of people (aged 40 to 80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76.0 million in 2020 and 111.8 million in 2040 (Tham et al., 2014). It affects one in two hundred people aged fifty or younger and one in ten over the age of eighty (Resnikoff et al., 2004).

Although currently there is no cure for open-angle glaucoma (OAG), results from multiple studies, including the Advanced Glaucoma Intervention Study (AGIS) (AGIS_Investigators, 2000), the Ocular Hypertension Treatment Study (OHTS) (Kass et al., 2002), and the Early Manifest Glaucoma Trial (EMGT) (Leske et al., 2003), and United Kingdom Glaucoma Treatment Study (UKGTS) (Garway-Heath et al., 2015) have demonstrated that treating elevated IOP with topical ocular hypotensive agents is effective in delaying or preventing disease progression. The lowering of IOP is currently the only method for reducing the risk of glaucomatous visual field loss and remains the primary goal of therapy.

Several classes of ocular hypotensive medications exist today and are differentiated by their mechanism of action at the cellular/molecular level. These include miotics, β-adrenergic receptor antagonists (β-blockers), CAIs, α-adrenergic receptor agonists (α-agonists), prostaglandin analogues (PGAs) and rho kinase (ROCK) inhibitors. 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, ROCK inhibitors, and α-agonists). In general, PGAs are recommended as the first choice agent for most eyes with OHT and OAG. However, as disease progresses and maintaining target IOP becomes difficult, more than one drug is needed to achieve optimum benefit and reach target IOP. Surgical interventions, including laser surgery, shunting of aqueous humor to an appropriate locale, and filtering surgery, are available options for treating insufficiently controlled IOP. In such instances pharmacotherapy may be continued as well.

While adequate IOP-lowering can be achieved by currently available pharmacotherapies in some patients, not all patients are adequately treated and additional IOP-lowering may provide for further slowing of disease progression. In some patients, treatment with a single IOP-lowering compound is not sufficient to obtain optimal IOP control. Adjunctive or combination therapy

using different classes of drugs is often employed in order to achieve additional IOP-lowering effects. Moreover, consistent lowering of IOP over a 24-hour period has not yet been fully realized. If achieved, this could also contribute to slowing of disease progression. Therefore, new pharmacologic agents with new mechanism of action are needed.

Santen has developed an ophthalmic topical formulation of omidenepag isopropyl (UR-7385) for the reduction of elevated IOP in patients with OHT or OAG. DE-117 is a pro-drug of the pharmacologically active acid metabolite, UR-7276, a synthetic non-prostanoid agonist of prostaglandin E2 (PGE_2) receptor, subtype 2 (EP2). PGE_2 has been shown to markedly reduce IOP when applied topically to human and animal eyes (Bito, 2001). PGE_2, its analogues and receptor agonists are thought to mediate the IOP-lowering effect by relaxing the ciliary muscle and increasing outflow of aqueous humor through the uveo-scleral pathway (Yamaji et al., 2005). Very recently, Fuwa et al., demonstrated that DE-117 lowers the IOP through a novel mechanism of action: that is, through both conventional and uveoscleral outflows (Fuwa et al., 2017).Currently approved IOP- lowering medications such as latanoprost (latanoprost ophthalmic solution, 0.005%; NDA 20-597) lower IOP by enhancing uveoscleral outflow only, but do so through effects on a receptor for $PGF_2\alpha$. Unlike latanoprost and other approved prostaglandin F receptor (FP) agonists that are synthetic prostanoid analogues, DE-117 is a non-prostanoid chemical compound.

To date, Santen has completed seven clinical studies including three clinical studies (33-001, 33-002, 33-003) in the U.S. and four clinical studies (01171502, 01171503, 01171504, 01171506) in Japan with DE-117 in healthy adult subjects, or subjects with OAG or OHT to evaluate the safety and efficacy of DE-117. DE-117 ophthalmic solution 0.002% once a day (QD) appeared to be well tolerated and efficacious in IOP lowering. However, it is unclear whether DE-117 ophthalmic solution 0.002% twice a day (BID) will improve the efficacy of IOP lowering without compromising the safety. This study is being performed to complete the dose exploration via assessing the safety and efficacy of DE-117 ophthalmic solution QD and BID in subjects with POAG or OHT.

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

2.3. Benefit/Risk Assessment

DE-117 ophthalmic solution 0.002% demonstrated clinically meaningful IOP reduction in subjects with OAG or OHT in both US and Japanese population. In a phase III study in Japan, DE-117 0.002% was non-inferior to Latanoprost 0.005% in IOP lowering. DE-117 was generally well-tolerated. No serious suspected adverse reaction has been reported. The severity and the frequency of the reported ocular adverse events were not unexpected for a topical ophthalmic medication. Benefit-risk balance continued to be favorable. DE-117 ophthalmic solution 0.002% once a day received the market authorization approval from Japanese Health Authority on 21 September 2018.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DE-117 may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 4: Study Objectives and Endpoints

Study Objectives	Corresponding Study Endpoints
Primary objective: To determine whether DE-117 Ophthalmic Solution 0.002% given BID is superior to QD in reducing the intraocular pressure (IOP) after 6 weeks of treatment in subjects with POAG or OHT.	**Primary Efficacy Endpoint:** The primary efficacy endpoint is the IOP in the study eye measured at the specified time points: 08:00, 12:00 and 16:00 at Week 2 (Visit 3) and Week 6 (Visit 4).
	Secondary Efficacy Endpoints: • Mean diurnal IOP in the study eye at Week 6 (Visit 4) • Absolute change and percent change from baseline in IOP • Absolute change and percent change from baseline in mean diurnal IOP • Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2) at each post-baseline visit • Having a mean diurnal IOP ≤ 18 mmHg at each post-baseline visit
Safety objective: To determine the safety of DE-117 ophthalmic solution 0.002% given BID as compared to QD in subjects with POAG or OHT.	**Safety Endpoints:** • Safety will be evaluated by the following parameters: • Incidence of ocular and systemic AEs • BCVA • Slit-lamp biomicroscopy findings: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, abnormal lens findings, anterior synechiae of iris, posterior synechiae of iris • Ophthalmoscopy

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-masked, parallel-group, multi-center study. Subjects diagnosed with POAG or OHT who meet eligibility criteria at Visit 1 (Screening) will wash out 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 Visit 2 (Baseline, Day 1) will be randomized to receive study medication for up to 6 weeks.

Approximately 100 subjects with POAG or OHT will be randomized in a 1:1 ratio to either:

- DE-117 ophthalmic solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- DE-117 ophthalmic solution 0.002% BID (20:00 & 08:00)

This study will consist of a screening period of up to 35 days including a washout period of up to 28 days (+ 7 days window), and a 6-week double-masked treatment period.

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

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

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

Final eligibility will be determined at Visit 2 (Baseline) after all necessary washout from prior IOP lowering medications have been completed. Subjects who have not used any IOP lowering

medications for the last 28 days, including treatment-naive subjects, must have ≥ 1 day between their screening visit and Visit 2 (Baseline).

At Visit 2, baseline IOP will be measured for both eyes at 8:00 (±60 min), 12:00 (±60 min) and 16:00 (±60 min). The study eye will be the eye that qualifies per eligibility criteria at Visit 2. If both eyes meet the eligibility criteria, the eye with the higher diurnal IOP at Visit 2 will be designated as the study eye. If both eyes meet the eligibility criteria and have the same mean diurnal IOP at Visit 2, the right eye will be designated as the study eye. Both eyes should be treated with the study medication for the duration of the study even if only one eye is eligible per IOP inclusion criteria.

Treatment Period (6 weeks):

Approximately 100 eligible subjects will be randomized to either DE-117 0.002% QD in the evening and vehicle QD in the morning or DE-117 0.002% BID in a 1:1 ratio. Subjects will be treated for 6 weeks with scheduled Visits 2, 3 and 4 (Baseline, Week 2 and Week 6).

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

IOP will be measured at 08:00, 12:00 and 16:00 (±60 minutes). At these scheduled visits, BCVA and slit-lamp biomicroscopy will be performed just prior to the 08:00 IOP measurement. Ophthalmoscopy (fundus examination) will be performed after 16:00 IOP measurement.

Pharmacogenomics/Genomics:

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

4.2. Scientific Rationale for Study Design

This is a dose frequency comparison study, where QD and BID will be compared.

Although currently there is no cure for open-angle glaucoma, many well controlled studies (AGIS_Investigators, 2000; Garway-Heath et al., 2015; Kass et al., 2002; Leske et al., 2003) have demonstrated that treating elevated IOP with topical ocular hypotensive agents are 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.

The primary endpoint is the IOP measured at the specified time points: 08:00, 12:00 and 16:00 at Visits 3 and 4 (i.e., Week 2, and Week 6 visits). Lowering IOP is the only approach to slow down the glaucoma progression. The IOP is a surrogate endpoint in glaucoma trials, and this surrogate endpoint is well established and accepted by agencies.

A 6-week treatment duration was designed with two considerations: 1) the DE-117 IOP lowering effect will be stabilized within 4 weeks, and 2) any potential carry-over effect of the previous

ocular hypotensive medications after up to 4 weeks of washout will be further eliminated. Therefore, 6 weeks treatment for this study is appropriate.

4.3. Justification for Dose

DE-117 concentrations ranging from 0.0003% to 0.03% were tested in four (4) dose-finding studies (33-001, 33-002, 33-003 in US and 01171503 Stage 1 in Japan). DE-117 ophthalmic solution 0.002% QD appeared to be well tolerated and efficacious in IOP lowering. The higher concentrations (0.0025% and 0.003%) did not reveal significantly better efficacy. As a result, DE-117 0.002% was chosen as the optimal dose for further development.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all visits of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities. The end of the study is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

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

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

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

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

8. Completed the required wait/washout period.

9. At all time points of IOP measurements (8:00, 12:00 and 16:00) at Visit 2 (Baseline, Day 1), have IOP of ≥ 22 mmHg in at least one eye (the same eye), and ≤ 34 mmHg in both eyes.

5.2. Exclusion Criteria

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

General

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

Medications / Therapies

5. Intended or current use of the following prohibited medications/therapies during the study:
    - All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamin), over-the-counter dry eye artificial tears/drops, and study medications.
    - All systemic medications for ocular hypotensive (e.g., oral or intravenous CAI, oral glycerol).
    - Any ocular, periocular, inhaled, nasal or systemic corticosteroids including the joint injection, etc.
    - Lacrimal/punctal occlusion via plug(s) or cautery, dry eye treatments or devices that require a prescription, such as TrueTear®.
6. Subjects who cannot safely discontinue use of ocular hypotensive medications during the wait/washout period.
7. Subjects who will be required to initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, angiotensin-converting enzyme [ACE] inhibitors, and angiotensin II receptor blockers [ARB]). Subjects use the above medication must be on a stable dose use for at least 30 days prior to Visit 1 (Screening) and during the study duration.
8. Use of contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers).
9. Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.

10. History of ocular surgery specifically intended to lower IOP (e.g. laser trabeculoplasty, filtering surgery, tube shunt, Minimally Invasive Glaucoma Surgery [MIGS], or trabeculotomy) in either eye.
11. History of keratorefractive surgery (e.g., RK, PRK or LASIK) in either eye.
12. Allergy, hypersensitivity or contraindications to EP2 receptor agonists, benzalkonium chloride (BAK) or any other components of the study medications, or other study related procedures/medications.

Diseases

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

5.3. Lifestyle Considerations

5.3.1. Contraception Requirements

There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential and male subjects able to father children abstain from intercourse or agree to practice acceptable methods of contraception throughout the course of the study.

If a subject is female of childbearing potential (i.e., not post-menopausal [within 12 months since the last menses] or not surgically sterile [less than 6 months from date of surgery]), subject must

use at least one of the following acceptable contraceptive methods during the study (as well as for 4 weeks following last dose in study).

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

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

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not qualified per inclusion or exclusion criteria and will therefore not be randomized or receive study medication. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

6. STUDY INTERVENTION

Study intervention is a general term that refers to any investigational intervention(s), marketed product(s), placebo, sham, or medical device(s) intended to be administered to a study subject according to a study protocol. In this protocol, the term Investigational Product (IP) is generally used to refer to the study interventions.

6.1. Investigational Product Administered, Formulation, Packaging, and Labelling

Study Drug descriptions are provided in Table 5, including formulation, packaging and labelling.

Table 5: Study Drug Descriptions

Arm Name	**DE-117 QD and Vehicle QD**	**DE-117 BID**
Intervention Name	DE-117 and Vehicle	DE-117
Type	Drug	Drug
Use	Experimental	Experimental
Dose Formulation	Ophthalmic solution	Ophthalmic solution
Unit Dose Strength	DE-117: 0.002% Vehicle: N/A, does not contain the active ingredient, DE-117	0.002%
Dosage Level	DE-117: One drop in each eye, Once daily Vehicle: One drop in each eye, Once daily	One drop in each eye, Twice daily
Route of Administration	Topical, ophthalmic solution	Topical, ophthalmic solution
Sourcing	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee
Packaging and Labeling	DE-117: 2.5 mL fill in a 5 mL white low-density polyethylene bottle, with a tip and cap, placed in a carton. Bottle and carton with “evening” label. Vehicle: 2.5 mL fill in a 5 mL white low-density polyethylene bottle, with a tip and cap, placed in a carton. Bottle and carton with “morning” label. Two DE-117 (“evening”) bottles/cartons and two Vehicle (“morning”) bottles/cartons will be placed in a kit carton. Labeling will include study number, kit number, and other country requirement.	2.5 mL fill in a 5 mL white low-density polyethylene bottle, with a tip and cap, placed in a carton. Bottle and carton with “evening” or “morning” label. Four DE-117 (two “morning” and two “evening”) bottles/cartons will be placed in a kit carton. Labeling will include study number, kit number, and other country requirement.

6.2. Investigational Product Preparation, Handling, Storage and Accountability

6.2.1. Study Medication Preparation

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

6.2.2. Study Medication Administration

Subjects will instill one drop of study medication in each eye at approximately 20:00 (±60 min) and 8:00 (±60 min) daily for a total of 6 weeks.

Each subject will be instructed to instill one drop of study medication from bottle labeled "evening" in each eye at 20:00 and one drop of study medication from bottle labeled "morning" in each eye at 08:00, starting the evening of Visit 2 (Baseline, Day 1) through the morning before Visit 4 (Week 6).

6.2.3. Study Medication Handling and Disposal

The used study medication kits returned by the subject 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.

6.2.4. Study Medication Storage

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

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

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

6.2.5. Study Medication Accountability

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

(or designee). The receipt of clinical supplies form should be completed, signed, dated, and returned as directed. A copy must be maintained at the site for the Investigator's records.

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

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

6.3. Measures to Minimize Bias: Randomization and Masking

A permuted-block randomization will be employed to randomize eligible subjects in a 1:1 ratio to either DE-117 QD/Vehicle QD arm or DE-117 BID arm.

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

This study is a double-masked study. The subjects, investigators, examiners and Santen personnel involved in the conduct of the study will be masked to the study treatment. A study staff member at the investigative site will dispense and collect study medication(s) and query about dosing compliance. The appearance of the bottles of DE-117 ophthalmic solution 0.002% and the vehicle will be identical. All subjects will receive bottles labeled "morning" for the morning dose and bottles labeled "evening" for the evening dose. Each eligible subject will be assigned to receive a numbered study medication kit as assigned by central randomization via Interactive Response Technology at Visit 2 (Baseline).

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

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

6.4. Study Intervention Compliance

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

- Subjects will receive verbal and written instructions for proper instillation of the study medication, the dosing regimen, and the conditions of the study medication storage.
- Subjects will be reminded at study visits to consistently dose in each eye at the same time of the day.

  - Twice daily at 20:00 and 8:00 [±60 min] through Visit 2 to 4.

- Subjects will be reminded of the morning and evening instillation of the study drug on the day prior to Visit 3 (Week 2) and Visit 4 (Week 6)/Early Termination respectably.
- Subjects will be reminded that the morning instillation of the study drug at Visit 3 (Week 2) and Visit 4 (Week 6)/Early Termination will be done at the clinic.
- Since subjects must have a diagnosis of POAG or OHT in both eyes, both eyes should be treated for the duration of the study, even if only one eye is eligible per IOP inclusion criteria.
- Subjects will be queried regarding compliance with the protocol's dosing regimen at Visit 3 (Week 2) and Visit 4 (Week 6)/Early Termination.
- Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%. If a subject deviates from the prescribed dosage regimen, the specific dates of the missed doses should be recorded.
- A subject's dosing compliance for a specific period is determined by the total number of days that subject followed the proper dosing procedures and dosing schedule. Stoppage of study medication use, overdosing of study medication, incorrect time (outside of protocol-specified time point ±60 min) of study medication administration, will be noted as non-compliance. The subject's dosing compliance will be recorded in the subject's source documents and on the eCRF at Visit 3 (Week 2) and Visit 4 (Week 6)/Early Termination.
- Subjects may be discontinued from the study at the discretion of the Investigator if the subject cannot be brought into compliance.

6.5. Discontinue Use of All IOP-lowering Medications

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

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

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

6.6. Concomitant Medication/Therapy

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

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

6.6.1. Prohibited Medications or Therapies

- All ocular medications other than sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents (e.g., glutathione, pirenoxine), Vitamin B_{12} formulation (e.g., cyanocobalamin), over-the-counter dry eye artificial tears/drops, and study medications during the study duration.
  - If artificial sodium chloride/potassium chloride ophthalmic solution, cataract treatment agents, Vitamin B_{12} formulation, over-the-counter dry eye artificial tears/drops are concomitantly used, there must be an interval of **at least 5 minutes** between use of these ocular medications and use of the study medication.
- All systemic medications that are ocular hypotensive agents (e.g., oral or intravenous CAI, oral glycerol) during the study duration.
- Any ocular, periocular, inhaled, nasal or systemic corticosteroids including joint injection, etc. during the study duration.
- Lacrimal/punctal occlusion via plug (s) or cautery, dry eye treatments or devices that require a prescription such as, TrueTear®, during the study duration.
- Initiate or modify any systemic or topical medication known to affect IOP (e.g., β-adrenergic antagonists, α-adrenergic agonists, calcium channel blockers, ACE inhibitors, and ARB) within the first 30 days prior to Visit 1 (Screening) and during the study duration.

- Contact lenses within 2-3 weeks prior to Visit 2 (Baseline, Day 1) until end of treatment in either eye.
- Any ocular surgery or ocular laser treatment within 180 days prior to Visit 1 (Screening) and throughout the study in either eye.
- Participation in any other clinical trial involving an investigational product or device within 4 weeks prior to Visit 1 (Screening) and during the study.

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

6.7. Dose Modification

In this study, the study drug dose (DE-117 ophthalmic solution 0.002%) regimen (QD vs. BID) is assigned by randomization. Dose modification is not allowed.

6.8. Intervention after the End of the Study

No subsequent intervention is currently planned for subjects after completing 6-week treatment period.

7. DISCONTINUATION OF STUDY INTERVENTION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Subjects may be discontinued from study drug administration for adverse events, non-compliance with study treatment, protocol deviation, lack of efficacy, withdrawal by subject, lost to follow-up, study termination, or other reasons. The investigator or Santen medical monitor may discontinue a subject from further study drug administration for reasons related to the best interest of the subject.

Subjects should be encouraged to continue participating in all remaining follow-up study visits/procedures on an observational basis when study drug administration is discontinued prior to the last scheduled visit (Visit 4).

If subjects agree to continue the study participation, then to the extent possible, all procedures for Early Termination will be performed on the day of early drug discontinuation or at the earliest opportunity.

7.2. Subject Discontinuation/Withdrawal from the Study

Subjects may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, an early termination visit will be conducted to collect the data as shown in the SoA (Table 3); the subject will be permanently discontinued both from the study intervention and from the study at that time.

If the subject withdraws consent for disclosure of future information, Santen may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Subject Withdrawal Criteria

An early termination occurs when a subject who provides written informed consent ceases participation in the study after enrollment (Visit 2 Baseline [Day 1]), regardless of circumstances, and before the completion of the study. Subjects may be voluntarily discontinued from study medication or withdrawn from the study at any time for any reason. In addition, the Principal Investigator or Medical Monitor may discontinue the study drug administration or terminate a subject's study participation due to any of the following reasons:

- AE (e.g., not compatible with study continuation)
- Non-compliance with study drug
- Lack of efficacy (e.g., IOP exceeds 34 mmHg in either eye after enrollment)
- Progressive disease
- Protocol deviation (e.g., not fulfilling eligibility criteria)

- Pregnancy
- Voluntary withdrawal by subject at any time for any reason
- Lost to follow-up (e.g., no contact is possible)
- Death
- Other

Subjects who are terminated from the study early will not be replaced.

7.3. Lost to Follow up

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

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or discontinuation of the study is handled as indicated in Section 10.1.11.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Santen immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 3) and Procedures of Assessments (Section 8.2).

The amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required around is 10 mL for subjects who consent to the optional pharmacogenomics/genomics laboratory study. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Visit Details

8.1.1. Visit 1 (Screening)

- Explain the purpose and conduct of the study to the subject and obtain written individual informed consent. Informed consent for the optional pharmacogenomics/genomics laboratory research study may be obtained at any visit prior to blood sampling. Ensure the subject understands that if he/she does not wish to provide a blood sample for the pharmacogenomics/genomics laboratory research study that their decision will have no influence on their participation in the main study.
- Prepare the list of screening/registration of subjects.
- Obtain demographics.
- Obtain medications, procedures/therapies and medical history including all lifetime ocular medical history to the extent possible, non-ocular medical history within 5 years, diagnosis, ocular surgical history, current ocular and systemic conditions.
- Obtain urine and perform urine pregnancy test, if the subject is a female of child-bearing potential.
- As per the SoA (Table 3) and Procedures of Assessments (Section 8.2), perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):

  - Refraction
  - BCVA (prior to IOP measurement)
  - Gonioscopy
  - Visual field
  - Biomicroscopy (prior to IOP measurement)
  - IOP
  - Pachymetry (after IOP measurement)
  - Ophthalmoscopy **with pupil dilation** (after IOP measurement)
- Determine if the subject meets eligibility criteria.
- Eligible subjects will be instructed to discontinue use of all IOP-lowering medications, if any, as follows (up to +7 days is allowed):
  - Miotics: 7 days
  - Oral/topical CAIs: 7 days
  - Alpha agonists: 14 days
  - Alpha/beta agonists: 14 days
  - Alpha antagonists (α1 blocker): 28 days
  - Beta antagonists (β blocker, including αβ blockers): 28 days
  - Prostaglandins Analogs (PGA): 28 days
  - Rho kinase (ROCK) inhibitor: 28 days
  - Combination drugs: The longest washout period of the individual component will be used.
- During the required washout period, subjects who discontinue their current treatment may, if the Investigator deems necessary for safety, be treated with a short-acting IOP lowing agent, topical CAI, e.g., brinzolamide or dorzolamide eye drops, one drop twice daily. Topical CAI treatment must be stopped 1 week before the randomization at Visit 2 (Baseline, Day 1).
- An interim safety visit during the washout period (mid-washout visit: Visit 1a) may be performed if, in the investigator's opinion, a subject's IOP may be of concern during the washout period. If subjects are treated with a topical CAI during the washout period, a mid-washout visit (Visit 1a) is recommended.
- The eligibility visit (Visit 2) will be scheduled at the end of the washout period for those subjects on prior IOP-lowering medications.
- Subjects who have not used an IOP-lowering medication for the last 28 days, including treatment-naive subjects, will need a wait period of ≥ 1 day before their Visit 2 (Baseline, Day 1).

  - If a subject does not require washout from an IOP-lowering medication, but they use contact lenses in either eye, they will need a wait period of ≥ 2-3 weeks (2 weeks for soft contact lens wearers, and 3 weeks for rigid contact lens wearers) with no contact use before their Visit 2 (Baseline, Day 1).
- Schedule the eligible subject to return for Visit 2 (Baseline, Day 1) after the required wait/washout period.
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.

8.1.2. Visit 1a (Optional, Washout Period)

- Visit 1a is an interim safety visit (referred to as mid-washout visit) that may be performed during the washout period if, in the Investigator's opinion, a subject's IOP causes any safety concern during washout period.
- Update concomitant medications and procedures/therapies.
- Query the subject regarding AEs.
- As per the SoA (Table 3) and Procedures of Assessments (Section 8.2), perform the following procedures or assessments (all ophthalmic procedures to be performed in both eyes):
  - BCVA (prior to IOP measurement)
  - Biomicroscopy (prior to IOP measurement)
  - IOP

8.1.3. Visit 2 (Baseline, Day 1)

- Update concomitant medications and procedures/therapies.
- Confirm the subject has complied with the required wait/washout period for ocular hypotensive medication(s), or contact lenses use, if required.
- Query the subject regarding AEs.
- Obtain urine and perform urine pregnancy test, if the subject is a female of child-bearing potential.
- As per the SoA (Table 3) and Procedures of Assessments (Section 8.2), perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (prior to the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (prior to the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).

  - If subject meets the 08:00 IOP eligibility requirements, schedule additional IOP measurements at 12:00.
- Perform IOP measurement at 12:00 (±60 min).
  - If subject meets the 08:00 and 12:00 IOP eligibility requirements, schedule additional IOP measurements at 16:00
- Perform IOP measurement at 16:00 (±60 min).
- Perform ophthalmoscopy in both eyes after the 16:00 IOP measurement.
- Perform final review of eligibility criteria after the 16:00 IOP measurement and ophthalmoscopy. The subject will then be randomized, via Interactive Response Technology (Medidata Balance/RTSM).
- A subject who does not meet eligibility criteria or will not otherwise continue in the study is considered a screen failure.
- After the subject has been randomized to a treatment arm, and assigned a treatment kit by Balance/RTSM, a study staff member must:
  - Dispense the assigned kit to the subject which will contain the following;
    - Two (2) bottle of study drug labeled "morning"
    - Two (2) bottle of study drug labeled "evening"
  - Give the subject verbal and written instructions for proper instillation of the study medication, the dosing schedule and regimen, and study medication storage.
- Instruct the subject to instill the study medicine daily, starting from this evening ("evening" dose) (20:00).
- Schedule the subject to return on Day 15 ± 2 for Visit 3 (Week 2).
- Inform the subjects they will be reminded of the morning and evening instillation of the study medication by phone call a few days before Visit 3.
- Remind the subjects that the morning dose of Visit 3 will be done at the clinic.
- Remind the subject to bring all used and unused study medication at Visit 3.

8.1.4. Visit 3 (Week 2, Day 15 ± 2)

- Update concomitant medications and procedures/therapies.
- A study staff member should query the subject regarding dosing compliance and ensure subject has sufficient study medication to complete dosing through Visit 4.
  - Subjects will be counseled on proper dosing procedures and dosing schedule if the subject's compliance is not 100%. If a subject deviates from the prescribed dosage regimen, the specific dates of the missed doses should be recorded.
- Query the subject regarding AEs.

- As per the SoA (Table 3) and Procedures of Assessments (Section 8.2), perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (prior to the 08:00 IOP measurement)
    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (prior to the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes. A study staff should make sure the instillation is performed.
- Perform IOP measurement at 12:00 and 16:00 (±60 min).
- If the subject provided written consent to provide a blood sample for a future pharmacogenomics/genomics laboratory research study, collect the sample at this visit or subsequent visit prior to exit from the study.
  - Note: If a blood sample cannot be collected at this visit, it may be collected at Visit 4 or unscheduled or early termination visit.
- Schedule the subject to return on Day 43±3 for Visit 4 (Week 6).
- Remind the subject to continue dosing according to the written instructions.
- Inform the subjects they will be reminded of the morning and evening instillation of the study medication by phone call a few days before Visit 4.
- Remind the subjects that the morning dose of Visit 4 will be done at the clinic.
- Remind the subject to bring all used and unused study medication at Visit 4.

8.1.5. Visit 4 (Week 6, Day 43 ± 3) Study Exit/Early Termination

- Update concomitant medications and procedures/therapies.
- A study staff member should query the subject regarding dosing compliance.
  - If a subject deviates from the prescribed dosage regimen, the specific dates of the missed doses should be recorded.
- A study staff member **must** collect all used bottles of study medication.
- Query the subject regarding AEs.
- Obtain urine and perform urine pregnancy test, if the subject is a female of child-bearing potential.
- As per the SoA (Table 3) and Procedures of Assessments (Section 8.2), perform the following procedures or assessments immediately before the 08:00 IOP measurement (all ophthalmic procedures to be performed in both eyes):
  - BCVA (prior to the 08:00 IOP measurement)

    - If more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.
  - Biomicroscopy (prior to the 08:00 IOP measurement)
- Perform IOP measurement at 08:00 (±60 min).
- Instill study medication/eye drop after the 08:00 IOP measurement in both eyes. A study staff should make sure the instillation is performed.
- Perform IOP measurement at 12:00, and 16:00 (±60 min).
- Perform pupil dilation in both eyes after the 16:00 IOP measurement.
- Perform ophthalmoscopy with pupil dilation in both eyes after the 16:00 IOP measurement.
- If the subject provided written consent to provide a blood sample for a future pharmacogenomics/genomics laboratory research study, the sample must be collected at this visit, if not collected at the previous visits.
- Exit the subject from the study.

Note: If a subject's study participation is terminated prior to Visit 4, then, to the extent possible, all scheduled Visit 4 procedures will be performed at the earliest visit or on the day of early termination.

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

8.2. Procedures of Assessments

8.2.1. Efficacy Assessments

8.2.1.1. Intraocular Pressure

IOP will be performed at each visit. At Visit 1 (Screening) and Visit 1a (optional, mid-washout visit), IOP can be measured at any time. For Visit 2 to Visit 4 Study Exit/Early Termination, IOP measurements will be scheduled for 08:00 (±60 min), 12:00 (±60 min) and 16:00 (±60 min).

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

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

A single measurement is made as follows:

- The Investigator adjusts the force on the tonometer dial to an initial setting corresponding to 10 mmHg. The slit-lamp magnification is set at 10X. The light

source is positioned at an angle of approximately 45º, and the aperture is maximally opened. A cobalt blue filter is employed.

- After instillation of a topical anesthetic, a fluorescein paper strip is placed near the lateral canthus in the lower conjunctival sac. Once the lacrimal fluid is sufficiently colored, the paper strip is removed. Alternatively, one drop of premixed fluorescein and anesthetic (Fluress, Barnes Hind) may be instilled. The Investigator should use the same technique each time, be it a paper strip or a pre-mixed eye drop.
- The subject and slit-lamp are adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The subject is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the Investigator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The subject is cautioned not to hold his breath.
- The Investigator looks through the slit-lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.
- The Investigator adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.
- The Investigator removes the tip from the cornea, and the authorized study staff (recorder) records the reading on the dial, rounded to the next highest integer. For example, if the measurement indicated is between 16 and 17, then 17 is recorded as the measurement in the subject's source document.
  - The Investigator may also be the recorder instead of an authorized study staff member, if a study staff member was not assigned.
- If corneal astigmatism is greater than 3.0 D, the prism is rotated so that the red line corresponds to the orientation of the longer axis of the elliptical applanated area.

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

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

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

8.2.1.1.1. Goldmann Applanation Tonometer Calibration

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

8.2.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 3).

8.2.2.1. Demographics, Medication/Therapy and Medical History

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

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

Medical and Surgical History
Followings must be confirmed.

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

Following details must be recorded in the source documents.

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

Medications
Following must be confirmed.

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

Following details must be recorded in the source documents.

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

Therapies

Following must be confirmed.

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

Following details must be recorded in the source documents.

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

Surgical procedures occurring during the study

Following details must be recorded in the source documents.

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

8.2.2.2. 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 4 Study Exit/Early Termination for all females of childbearing potential. A female is considered of childbearing potential unless she is post-menopausal (at least 12 months since last menses occurred), is without a uterus or without both ovaries, or has had a bilateral tubal ligation. To perform the pregnancy test, follow instructions provided by the manufacturer of the urine pregnancy test kit.

8.2.2.3. Refraction

Refraction will be performed for each eye at Visit 1 (Screening). At Visits 2 to 4, if more than 10 letters in BCVA were lost compared to the screening visit, then refraction should be performed again.

8.2.2.4. Best-Corrected Visual Acuity

Best-Corrected Visual Acuity (BCVA) will be measured for each eye prior to the 08:00 (±60 min) IOP measurement at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit). For Visit 1 (Screening) and Visit 1a (optional, mid-washout visit), BCVA will be performed prior to IOP measurement. BCVA will be measured under normal room illumination using visual acuity chart (ETDRS chart) and the logMAR scoring will be recorded in the subject's source document. The following procedure should be followed using ETDRS chart for BCVA testing.

8.2.2.4.1. 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.

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

Example:

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

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

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

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

Table 6: 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

8.2.2.5. Slit-lamp Biomicroscopy

As described below, slit-lamp biomicroscopy examinations will be performed and graded immediately prior to the 08:00 (±60 min) IOP measurement at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit). For Visit 1 (Screening) and Visit1a (optional, mid-washout visit), the biomicroscopy examinations should be performed prior to IOP measurement. Some exception can be applied, if pupil dilation is required for evaluation. For example, the possible tear(s) in the posterior lens capsule. The slit-lamp exam for posterior lens capsule can be performed after the pupil dilation, that is at 16:00 after 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 punctate staining

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

Keratic Precipitate

None (0) = Normal

Mild (1) = Slight pigmentation or keratic precipitate

Moderate (2) = Moderate pigmentation or keratic precipitate

Severe (3) = Dense pigmentation or keratic precipitate

Lens

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

None (0) = No lens discoloration nor opacification

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

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

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

Anterior Synechiae of Iris

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

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

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

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

Posterior Synechiae of Iris

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

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

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

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

8.2.2.6. Pachymetry (Central Corneal Thickness)

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

8.2.2.7. Gonioscopy

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

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

(1) = approximately 10 degrees

(2) = approximately 20 degrees

(3) = approximately 30 degrees

(4) = approximately 40 degrees or more

8.2.2.8. Visual Field

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

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

8.2.2.9. Ophthalmoscopy (Fundus) Examination

The ophthalmoscopy (fundus) examination will be performed for each eye at Visit 1 (Screening), Visit 2 (Baseline, Day 1), and Visit 4 Study Exit/Early Termination, and graded as described

below. Ophthalmoscopy will be performed under dilation at Visit 1 (Screening) and Visit 4 Study Exit/Early Termination. Pupil dilation must be performed after all other ocular procedures have been completed. Cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will also be evaluated.

Glaucomatous Optic Nerve Findings

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

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

8.2.2.10. Events of Special Interest (ESIs)

Events of Special Interest (ESIs) are medical events both anticipated and unanticipated that may have particular impact on the benefit/risk profile of DE-117 and therefore may require more detailed characterization. The DE-117 ESIs are as follows:

- Pregnancy:
  - There are no controlled data with the investigational product in human pregnancy. It is required that females of childbearing potential use effective contraception during the study and recommended for 4 weeks for female subjects of childbearing potential and 12 weeks for male subjects capable of fathering children after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject will be discontinued from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.
- Medication administration errors
  - Study medication administration errors determined to be **significant** by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: incorrect dose of study medication and administration of study medication from an incorrect kit. An AE does not necessarily need to have occurred to count as a study medication administration error. A medication administration error is an unintended failure in the process of treatment with a medicinal product that leads to, or has the potential to lead to harm of the subject.
- Macular edema (including cystoid macular edema):
  - Macular edema has been reported in some patients during the DE-117 clinical trials. Any cases of macular edema (including cystoid macular edema) should be reported in the ESI form in eCRF, or in case the Electronic Data Capture (EDC) system is down, in the manual ESI form. Any cases of macular edema (including

cystoid macular edema) will need to be followed until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained as per Section 8.3.3.

Most ESIs are AEs, some ESIs may also be SAEs, and some ESIs may not be AEs (e.g., an IP administration error may not be an AE; pregnancies are not AEs). However, all ESIs should be reported within 24 hours of knowledge of the event using applicable eCRFs and recording as much information as available. ESIs should be followed by the investigator to the same extent as SAEs, that is, until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained. Monitoring for pregnancy and follow-up of pregnancy is described in Section 8.3.5.

8.2.3. Other Assessments

8.2.3.1. Blood Sample for Pharmacogenomics/genomics Study

For sites which elect to participate and for subjects who agree to provide a blood sample, an exploratory biomarker laboratory research study will be performed to evaluate the association of possible genetic biomarkers with the study drug(s) and/or ophthalmologic conditions. Approximately 10 mL of blood will be collected for genetic analysis from the subject and stored until shipment. Please refer to the separate procedure manual for sample handling, storage, and shipment. The samples will be coded to protect the subjects' private information. Nucleic acids will be extracted from blood sample and stored in the repository for future pharmacogenomics/genomics studies performed by appropriate assay platforms such as PCR (Polymerase Chain Reaction), hybridization, and sequencing on the genes involved in the study drug(s) and/or ophthalmologic conditions. Individual subjects' results from the research testing on their samples will not be communicated to them.

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

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

8.2.3.2. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.2.3.3. Biomarkers

Biomarkers are not evaluated in this study.

8.2.3.4. Pharmacokinetics

PK parameters are not evaluated in this study.

8.2.4. Study Supplies

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

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.2.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, SAE or ESI and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study intervention (see Section 7).

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

All SAEs will be collected from the signing of the ICF until the subject withdrawals or completes the scheduled exit visit.

All AEs will be collected from the signing of the ICF until the subject withdrawals or completes the scheduled exit visit.

All SAEs and ESIs will be recorded and reported to Santen or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.2. The investigator will submit any updated SAE or ESI data to Santen within 24 hours of it being available.

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

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE, SAE and ESI and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

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

8.3.3. Follow-up of AEs and SAEs

All reported AEs should be followed by the investigator until resolution or until the subject's participation in the study ends.

More extensive follow-up is required for (1) SAEs, (2) ESIs and (3) IP related AEs that lead to or cause early withdrawal of a subject from the study. All of these types of events should be followed by the investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained. In

addition to the above, Santen (or designee) may request, on a case-by-case basis, follow up of events/subjects beyond the scheduled exit visit.

Prior to database lock, follow-up information on an individual SAE or AE (or ESI) will be entered into the eCRF. When database lock has already been completed, or if information requested by Santen is not part of the eCRF, the site's response to follow-up requests should be emailed or documented on paper and faxed to Santen Global Pharmacovigilance (see Table 1).

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from Santen will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

8.3.5.1. Female subjects who become pregnant

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded in eCRF and on the appropriate manual form and submitted to Santen within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy.

The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to Santen. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an Event of Special Interest (ESI). Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to Santen. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous

reporting. Any female subject who becomes pregnant while participating in the study will discontinue IP and be withdrawn from the study.

8.3.5.2. Male subjects with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Santen within 24 hours of learning of the partner's pregnancy.

8.4. Treatment of Overdose

Overdose is unlikely to occur after ocular administration. If overdose occurs, treatment should be symptomatic.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.5. Health Economics/Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

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

Unless specified otherwise, efficacy measures will be summarized by planned (i.e., randomized) treatment and based on the FAS population, and safety measures will be summarized by actual treatment received and based on the Safety population. All AEs will be analyzed at the subject level. Other safety assessments that pertain to the eye may be analyzed by the study eye and fellow eye separately.

Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, medium, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

All data manipulations, descriptive summaries, and statistical hypothesis testing will be performed using Statistical Analysis System (SAS) Version 9.4 or later. Food and Drug Administration (FDA) guidance regarding case report tabulations (annotated eCRFs, SAS datasets, metadata, and SAS programs) in electronic submissions will be followed. Data definition tables will be created for Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets separately.

9.1. Statistical Hypotheses

The primary efficacy endpoint is the IOP at each scheduled time point (08:00, 12:00 and 16:00) in the study eye at Week 2 and 6 (Visit 3 and 4). The comparison between DE-117 BID arm and QD arm will be performed with the following hypotheses:

$$H_{0i}: \mu_{Bi} = \mu_{Qi}$$

versus

$$H_{1i}: \mu_{Bi} \neq \mu_{Qi}$$

where μ_B and μ_Q denote the mean values of the primary endpoint in DE-117 BID arm and QD arm at i =1,2, …6 timepoints, with i = 1, 2, 3 represent 08:00, 12:00 and 16:00 at Week 2 and i = 4, 5, 6 represent 08:00, 12:00 and 16:00 at Week 6, respectively.

9.2. Sample Size Determination

The sample size calculation does not take into account of multiplicity from multiple time points. Assuming a two-sided type I error rate of 5% and a standard deviation of 3.5 mmHg, 50 patients per treatment arm (100 in total) will have 80% power to detect a 2.0 mmHg between-treatment difference.

9.3. Populations for Analyses

The following analysis populations for study analyses are defined: Safety, Full Analysis and Per-Protocol (PP).

9.3.1. 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 and will use actual treatment received.

9.3.2. Full Analysis Set

The Full Analysis Set (FAS) will consist of 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 and will use treatment as randomized.

9.3.3. Per-Protocol Population

The Per-Protocol (PP) Population is a subset of the FAS. It will be the analysis population for sensitivity analyses and will use treatment as randomized. Any subject affected by a significant protocol deviation will be excluded from the PP population. PP Population will be identified before the unmasking of treatment assignments.

9.3.4. Statistical Analyses

Details of statistical analyses will be described in the SAP, which will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.5. Handling of Missing Values

In the analysis of IOP, subjects with missing IOP value at any timepoint at Week2 or Week6 may be imputed using the last-observation-carried-forward (LOCF) approach for sensitivity analyses.

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

Unless otherwise specified, descriptive summaries will be based on observed cases. Additional details on handling of missing data will be provided in the SAP.

9.3.6. Efficacy Analyses

Unless specified otherwise, the efficacy analyses will be performed on the FAS, where subjects are classified by planned treatment, irrespective of the actual treatment received.

9.3.6.1. Analysis of Primary Endpoint

The primary efficacy endpoint is IOP in the study eye at each specified timepoint (08:00, 12:00 and 16:00) at Week 2 (Visit 3) and Week 6 (Visit 4). For the primary analysis, a mixed-effect model for repeated measures (MMRM) will be carried out and least squares mean of the endpoint will be reported. The model will include treatment, visit, and treatment-by-visit interaction as fixed effects, baseline IOP as a covariate, and subject as a random effect. Treatment differences between the DE-117 BID arm and QD arm will be reported for each time point along with p-values and 95% confidence intervals.

Analysis of covariance (ANCOVA) with missing data imputed by an LOCF approach will be used as sensitivity analyses.

In addition, plots of IOP measures versus analysis time/analysis visit will be provided.

9.3.6.2. Analysis of Secondary Efficacy Endpoints:

- Mean diurnal IOP in the study eye at Week 6 (Visit 4)
- Absolute change and percent change from baseline in IOP
- Absolute change and percent change from baseline in mean diurnal IOP
- Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2) at each post-baseline visit
- Having a mean diurnal IOP ≤ 18 mmHg at each post-baseline visit

Continuous secondary efficacy endpoints will be analyzed by a mixed-effects model for repeated measures (MMRM) using observed cases or analysis of covariance (ANCOVA) with missing data imputed by an LOCF approach. Binary secondary efficacy endpoints will be analyzed using Pearson's Chi-square test.

9.3.7. Safety Analyses

All safety analyses will be performed on the Safety Population by each actual treatment received.

Safety of DE-117 will be primarily assessed by AEs, BCVA and evaluation with slit-lamp biomicroscopy and indirect ophthalmoscopy.

Besides the overall summary of AEs, subjects with any AE(s) will be tabulated by system organ class (SOC) and preferred term specified in MedDRA dictionary. They will also be tabulated by SOC, preferred term, and maximum severity. For AE tables, a subject who experienced multiple AEs within a SOC or preferred term will be counted only once at the maximum severity for that SOC or preferred term. SAEs will be tabulated similarly. Separate summaries for ocular AEs and non-ocular AEs will also be performed.

AEs leading to death, SAEs, and AEs leading to discontinuation, if any, will be listed separately. Events of special interest will be listed by type of event. For other safety assessments, descriptive summaries of observed score, change from baseline, whichever applicable, will be performed.

9.4. Interim Analyses

There is no planned interim analysis for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH-GCP Guidelines
- Applicable laws and regulations

10.1.2. Obligations of Investigators

In summary, the clinical investigator has agreed to the following obligations:

- Obtaining signed and dated informed consent from every subject prior to the subject's participation in any study related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and ensuring a copy of the letter indicating IRB/IEC approval is available at the investigational site before involving any subject in any study related activity; submitting verification of the approval to Santen. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Submitting the final report to IRB/IEC and to Santen.
- 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/IEC of all protocol amendments/modifications and obtaining approval for the amendment/modification from the IRB/IEC in accordance with local requirements before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects; sending Santen a copy of the letter from the IRB/IEC approving the amendment/modification.
- Reporting to Santen and the IRB/IEC any SAEs or other significant safety findings that occur in the course of the investigation.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.
- 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/IEC including the subject

consent form and recruitment materials; maintaining records of all actions by the IRB/IEC regarding the study.

- Making study records available for inspection by the Sponsor (Santen) and representatives of the FDA and other regulatory agencies; keeping records until notified by the Sponsor that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to the Sponsor:

I. Prior to the Beginning of the Study

- A signed Form FDA-1572, Statement of Investigator.
- A current curriculum vitae (CV) if not submitted to Santen previously or if updated.
- CVs for all sub-investigators listed on the FDA-1572.
- A letter from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) indicating that the protocol was approved, including the name and address of the IRB/IEC.
- A copy of the consent form approved by IRB/IEC.
- A list of current members of the IRB/IEC.
- Financial disclosure (Section 10.1.3).

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.
- Original Case Report Forms for each subject enrolled in the study.
- Information regarding all deviations from the protocol.
- Information regarding all adverse events occurring to a subject while enrolled in the study.
- Annual progress report (if study is ongoing for more than one year). Letter from the IRB/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.
- A final study report.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide Santen with sufficient, accurate financial information as requested to allow Santen to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible

for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.4. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study. Each subject should be allowed time to consider the information provided.
- Subjects must be informed that their participation is voluntary and that they are free to discontinue from the study at any time. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The Informed Consent Form must be approved by the governing IRB or IEC.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The subject's signed and dated informed consent must be obtained before any protocol-directed procedures are performed.
- The subjects signature must be witnessed by the authorized person obtaining the informed consent. If the investigator obtains informed consent, then the subjects signature must be witnessed by another individual (e.g., member of the site staff).
- The investigator or authorized person obtaining the informed consent must also sign and date the IRB-approved Informed Consent Form where designated.
- Subjects must be re-consented to the most current version of the IRB-approved ICF(s) during their participation in the study.
- The Principal Investigator(s) must maintain the original, signed Informed Consent Form with the study records. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- The ICF will contain a separate section that addresses blood samples collected and stored for subsequent pharmacogenomics/genomics analysis by Santen. The investigator or authorized designee will explain to each subject the objectives of this exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's consent to participate in the pharmacogenomics/genomics blood sampling and allow collected sample to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

See Section 10.1.4.1 for further details on the content of informed consent.

10.1.4.1. Elements of Informed Consent

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written Informed Consent Form.

1. State that the study involves RESEARCH.
   A. Explain the PURPOSE of the research.
   B. State the expected DURATION of the subject's participation.
   C. Describe the PROCEDURES to be followed.
   D. Identify any EXPERIMENTAL procedures.
2. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
3. Describe any BENEFITS to the subject or to others that may reasonably be expected from the research.
4. Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
5. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained. Note that regulatory agencies MAY INSPECT the records.
6. For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain what they consist of, OR where further information may be obtained.
7. Tell whom to contact for ANSWERS to pertinent questions about the research, and research subjects' rights and whom to contact in the event of a research-related INJURY to the subject.
8. State that participation is VOLUNTARY, refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled, and the subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

II. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in this protocol are not intended to preempt any applicable Federal, State, or 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 Federal, State, or local law.

REFERENCE: 21 CFR Part 50.25 – PROTECTION OF HUMAN SUBJECTS, Elements of Informed Consent.

10.1.5. Data Protection

- Subjects will be assigned a unique identifier by Santen. Any subject records or datasets that are transferred to Santen will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by Santen in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Santen, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to Santen or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.

- Santen or designee is responsible for the data management of this study including quality checking of the data.
- Santen assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for until notified by Santen that the records may be destroyed. No records may be destroyed during the retention period without the written approval of Santen. No records may be transferred to another location or party without written notification to Santen.

10.1.7. Source Data

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

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

The investigator must maintain detailed source documents on all study subjects who are enrolled in the study or who undergo screening. Definition of what constitutes source data can be found in the Source Data Agreement. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., visual field test printouts). Data for enrolled subjects will be transcribed on to eCRFs provided by Santen. All data should be transcribed completely, promptly, and legibly on the eCRFs. Data transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Exit forms are to be completed for all enrolled subjects, regardless if they did or did not complete the study (e.g., subject discontinuation, study termination).

The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. 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
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of study drug accountability
- Occurrence and status of any AEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation

10.1.9. Data Collection

The Principal Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened subjects will be entered into eCRFs. eCRFs should be completed within 3 business days of each subject visit as much as possible. Review of the eCRFs will be completed remotely by Santen (or designee). At designated intervals, a study monitor will perform Source Data Verification on site. During those visits, Santen (or designee) will monitor the subject data recorded in the eCRF against source documents at the study site. Santen (or designee) will review and evaluate eCRF data and use standard system edits, and may use centralized monitoring evaluations, to detect errors in data collection. At the end of the study, a copy of the completed eCRFs will be sent to the site to be maintained as study records.

10.1.10. Sponsor's Direct Access to Source Data/Documents and IRB/IEC Materials for Monitoring and Audit

10.1.10.1. Study Monitoring

Santen or Santen's designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Before an investigational site can enter a patient into the study, a representative of Santen will visit the investigational study site to:

- Determine the adequacy of the facilities, and

- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Santen or its representatives. This will be documented in a Clinical Study Agreement between Santen or its designee and the investigator.

During the study, a monitor from Santen or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol and ICH-GCP, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, 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 non-serious AEs and SAEs have been properly documented on eCRFs and confirm any safety information requiring expedited reporting to Santen global PV (including SAEs, ESIs and Pregnancies) have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff need information or advice.

10.1.10.2. Audits and Inspections

Authorized representatives of Santen, a regulatory authority (national or foreign), an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements. The investigator should contact Santen immediately if contacted by a regulatory agency about an inspection.

10.1.11. Study and Site Closure

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

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

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

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

10.1.12. 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.

This study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

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

10.2. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Table 7: Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study intervention, whether or not it is considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Table 7: Definition of AE (Continued)

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

Table 8: Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Sight threatening event: A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event. • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Table 9: Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is not acceptable for the investigator to send photocopies of the subject's medical records to Santen in lieu of completion of the Santen AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Santen. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to Santen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. • Death and hospitalization are outcomes of events. The event leading to death or hospitalization should be recorded as the SAE. Death or hospitalization should only be recorded as the primary event if all reasonable attempts to arrive at a diagnosis are unsuccessful. • Indicate the outcome of the AE and provide resolution date or date of death. <u>For intermittent events</u> (e.g., intermittent headache), the date should reflect when the last occurrence resolved or stopped. For example, if a subject has an intermittent headache from 12/14/2010 until 12/21/2010 and each individual headache lasts 3 hours a day, then the date of resolution is 12/21/2010 (NOT 12/14/2010). If treatment was initiated, then include the treatment and duration in the comments section (e.g., subject took acetaminophen for headache on 12/14/2010, 12/17/2010 and 12/20/2010).
Assessment of Severity
The investigator will assess severity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the severity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe. <u>For intermittent events</u>, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate. Record that the severity of the headaches ranged from mild to moderate in the comment section of the form.

Table 9: Recording and Follow-Up of AE and/or SAE (Continued)

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The following criteria can be used to make a causality judgment: • Related (possibly or probably) o There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or o There is a biologically plausible mechanism for study drug causing or contributing to the AE; and o The AE may or may not be attributed to concurrent/underlying illness, other drugs, or protocol procedures. • Not Related o A clinically plausible temporal sequence is inconsistent with the onset of the AE and study drug administration/protocol procedure; and/or o A causal relationship is considered biologically implausible. The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Santen. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to Santen.** • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 9: Recording and Follow-Up of AE and/or SAE (Continued)

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

Table 10: Reporting of SAEs and ESIs

SAE/ESI Reporting to Santen via an Electronic Data Collection Tool
• The primary mechanism for reporting SAEs to Santen will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Santen Global Pharmacovigilance (Table 1). • Contacts for SAE reporting can be found in Table 1. • For SAE supporting information (i.e. X-ray reports, hospital summaries, etc.) that are not included in the EDC format, follow a procedure analogous to the manual SAE reporting process (see next section). • All ESIs should be reported within 24 hours of knowledge of the event using applicable eCRFs and recording as much information as available. Pregnancy information will be recorded in eCRF and on the appropriate manual paper form and submitted to Santen within 24 hours of learning of a subject's pregnancy. • ESIs should be followed by the investigator to the same extent as SAEs, that is, until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained.

Table 10: Reporting of SAEs and ESIs (Continued)

SAE/ESI Reporting to Santen via Paper CRF (If Electronic Data Collection Tool is Unavailable)
• Complete the paper AE, SAE, or ESI Forms as applicable (located in your site regulatory binder) • Attach a Fax Cover Sheet with your contact information and fax to Santen Global Pharmacovigilance (Table 1). • In the rare circumstance of the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper AE, SAE or ESI forms sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE or ESI CRF pages within the designated reporting time frames. • Contacts for SAE/ESI reporting can be found in Table 1.

10.3. List of Abbreviations and Specialist Terms

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

Table 11: List of Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACE	Angiotensin-Converting Enzyme
ADaM	Analysis Data Model
AE	Adverse Event
AGIS	The Advanced Glaucoma Intervention Study
ANCOVA	Analysis of Covariance
ARB	Angiotensin II Receptor Blockers
BAK	Benzalkonium Chloride
BCVA	Best-corrected Visual Acuity
BID	Twice Daily
CAI	Carbonic Anhydrase Inhibitors
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	the Consolidated Standards of Reporting Trials
CV	Curriculum Vitae
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMGT	the Early Manifest Glaucoma Trial
EP2	Prostaglandin E Receptor Subtype 2

Table 11: List of Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ESI	Events of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Prostaglandin F receptor
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IUD	Intrauterine Device
LASIK	Laser-Assisted-in-Situ Keratomileusis
LOCF	Last-observation-carried-forward
MIGS	Minimally Invasive Glaucoma Surgery
MMRM	Mixed-effect Model for Repeated Measures
NDA	New Drug Application
OAG	Open-angle Glaucoma
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
OHTS	the Ocular Hypertension Treatment Study
PCR	Polymerase Chain Reaction
PGA	Prostaglandins Analogs
PGE_2	Prostaglandin E2
POAG	Primary Open-Angle glaucoma
PP	Per-Protocol
PRK	Photo-Refractive Keratectomy
QD	Once Daily

Table 11: List of Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
RK	Radial Keratotomy
ROCK	Rho Kinase
RTSM	Randomization and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SoA	Schedule of Activities
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
UKGTS	United Kingdom Glaucoma Treatment Study

11. REFERENCES

11.1. Literature

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11.2. Study Data

1. Data on File: Santen Study 33-001. A Phase I/II, Randomized, Observer-masked, Placebo-and-active-controlled, Parallel-group, Multi-center Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension
2. Data on File: Santen Study 33-002. A Phase II, Randomized, Observer-masked, Placebo-and Active-controlled, Parallel-group, Multi-center Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution Compared with Latanoprost and Placebo in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension
3. Data on File: Santen Study 33-003. A Phase IIb, Randomized, Observer-masked, Active-controlled, Parallel-group, Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution Compared with Latanoprost Ophthalmic Solution, 0.005% in Subjects with Primary Open-angle Glaucoma or Ocular Hypertension – SEE Study
4. Data on File: Santen Study 01171502. A Pharmacokinetic Study of DE-117 Ophthalmic Solution in Healthy Adult Male Subjects - Phase I Study -
5. Data on File: Santen Study 01171503. A Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution in Subjects With Primary Open Angle Glaucoma or Ocular Hypertension -AYAME Study-
6. Data on File: Santen Study 01171504. A Long-term Study of DE-117 Ophthalmic Solution Monotherapy and Concomitant Use of DE-117 Ophthalmic Solution With Timolol Ophthalmic Solution in Patients With OAG or OH: RENGE Study
7. Data on File: Santen Study 01171506. A Study Assessing the Safety and Efficacy of DE-117 in Subjects With POAG or OH Who Are Non-/Low-responders to Latanoprost: FUJI Study

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