Study Protocol Cover Page

Official Study Title:	A Phase III, Multinational, Multicenter, Investigator-Masked, Randomized, ActiveControlled Trial, comparing the efficacy and safety of DE-130A with Xalatan® in Patients with Open-Angle Glaucoma or Ocular Hypertension over a 3-Month period, followed by a 12-Month Follow-Up with Open-Label DE-130A Treatment.
NCT Number:	NCT04133311
Date of the document:	26 February 2021

PROTOCOL 0130A01SA

A PHASE III, MULTINATIONAL, MULTICENTER, INVESTIGATOR-MASKED, RANDOMISED, ACTIVE-CONTROLLED TRIAL, COMPARING THE EFFICACY AND SAFETY OF DE-130A WITH XALATAN® IN PATIENTS WITH OPEN-ANGLE GLAUCOMA OR OCULAR HYPERTENSION OVER A 3-MONTH PERIOD, FOLLOWED BY A 12-MONTH FOLLOW-UP WITH OPEN-LABEL DE-130A TREATMENT.

Sponsor:	SANTEN SAS Genavenir IV, 1 rue Pierre Fontaine F-91058 Evry, France		
Study Number:	0130A01SA		
IND Number:	N/A	**EudraCT Number:**	2017-004262-95
Compound:	DE-130A (latanoprost 50 microg/ml eye drops emulsion, SD)		
Date:	Original Protocol Version 4.0 17 October 2018 Amendment 1 Version 5.0 26 February 2021		

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Summary of Product characteristics, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also protect the rights, safety, privacy, and well-being of study patients in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 12.2.4.3 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.

I confirm my responsibilities noted on Appendix B of this Protocol.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

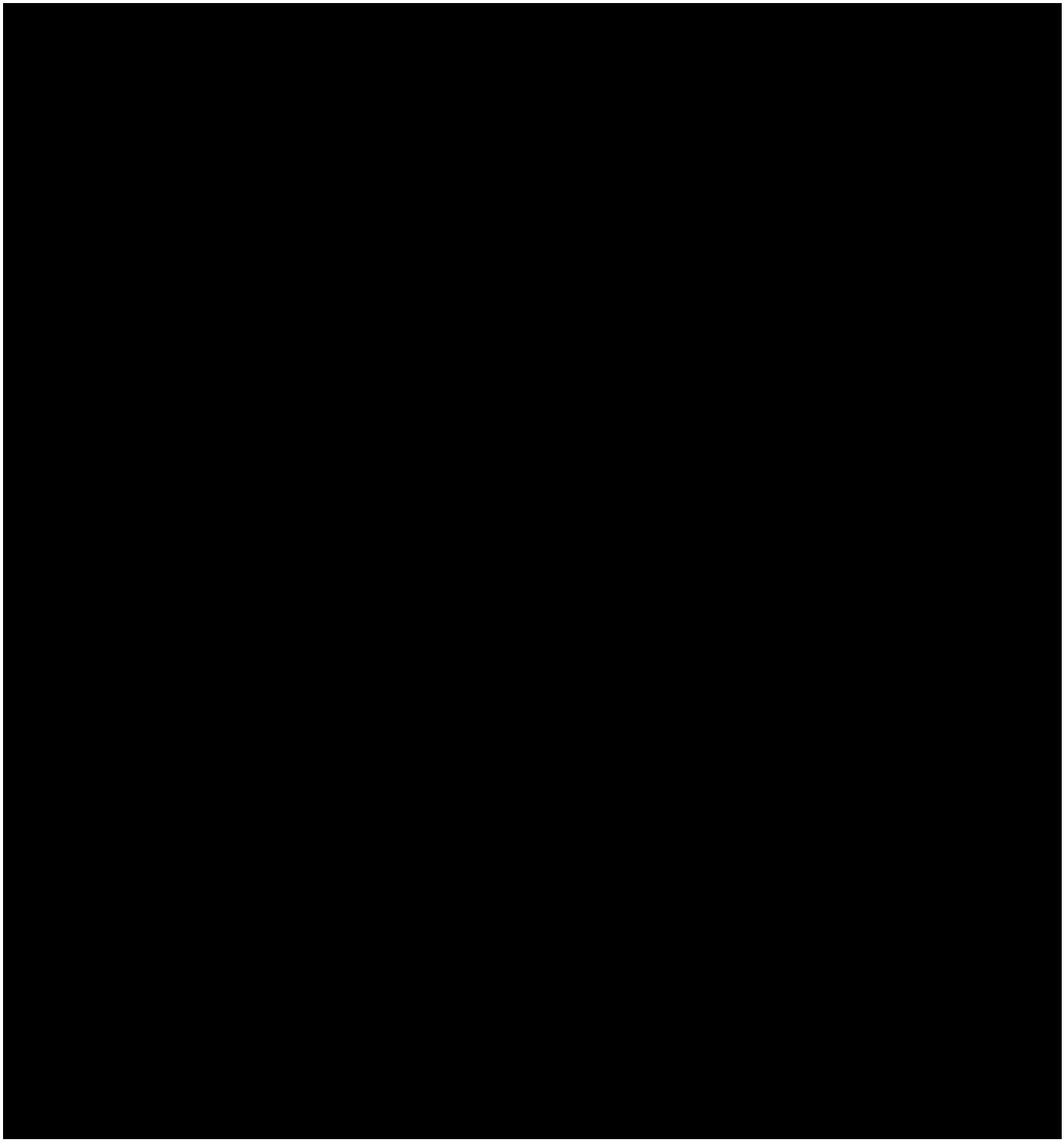
Location of Facility (City, State)

_____

Location of Facility (Country)

_____

Signature of Investigator Date



1. SYNOPSIS

Name of Sponsor/Company: SANTEN SAS	
Name of Active Ingredient: Latanoprost	
Title of Study: A Phase III, Multinational, Multicenter, Investigator-Masked, Randomised, Active-Controlled Trial, comparing the efficacy and safety of DE-130A with Xalatan® in Patients with Open-Angle Glaucoma or Ocular Hypertension over a 3-Month period, followed by a 12-Month Follow-Up with Open-Label DE-130A Treatment	
Coordinating Investigators: [redacted]	
Studied period (years): Estimated date first patient enrolled: February 2019 Estimated date last patient completed: Nov2022	**Phase of development:** III

Objectives:

Primary:

- To demonstrate that the intraocular pressure (IOP) reducing effect of DE-130A (latanoprost 50 microg/ml preservative-free eye drops emulsion) is non-inferior to that of Xalatan® [latanoprost 50 microg/ml Benzalkonium Chloride (BAK)-preserved eye drops solution], in patients with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT) at Week 12 without using any rescue medication(s).

Secondary:

- To compare the effect on improving Ocular Surface Disease (OSD) signs and symptoms between treatment groups over 3 months (Period 1).
- To estimate the effect of DE-130A on OSD signs and symptoms improvement up to 15 months (Periods 1 & 2).
- To compare the efficacy on IOP reduction between treatment group over 3 months (Period 1).
- To estimate the effect of DE-130A on IOP upto 15 months (Periods 1 & 2).
- To estimate the local ocular tolerance and systemic safety of the two treatments over 3 months (Period 1).
- To evaluate the local ocular tolerance and systemic safety of DE-130A up to 15 months (Periods 1 & 2).

Methodology:

Phase III, prospective, interventional, multinational, multicentre, investigator-masked, randomised, active-controlled trial

Study duration:

- 5 days to 6-week washout period
- 15 months for the first 130 patients
- 12 weeks for the next 250 patients

Patients will attend 6 visits following the wash-out phase (up to 6 weeks):

- Period 1 (3-month investigator-masked treatment period, DE-130A *vs* Xalatan®): Randomisation/Baseline visit (Day 1), Week 4 (±3 days) and Week 12 (±3 days)
- Period 2 (12-month follow-up from Week 12, open-label DE-130A treatment for the first 130 patients who complete their week 12 visit and agree to participate in the open-label period of the study): Month 6 (± 7days), Month 9 (±7 days) and Month 15 (± 1 week) visits.

Number of patients (planned):

Approximately 380 patients with Open-Angle Glaucoma (OAG), or ocular hypertension (OHT) (190 in DE-130A group and 190 in Xalatan® group) will be randomised in this study to obtain 173 evaluable patients per treatment group at Week 12 (assumed dropout rate of 10%).

A safety follow up of 12 months is planned for the first 130 patients who will attend the Week 12 visit and agree to participate in the open-label period of the study. They will then be treated with DE-130A in an open-label fashion.

Criteria for inclusion:

Patient eligibility is determined according to the following inclusion criteria:

1. Male or female, 18 years of age or older
2. The patient has signed and dated a written informed consent form and any required privacy authorization prior to the conduct of any study procedures.
3. Diagnosis of OAG (primary open angle glaucoma, pseudo exfoliative glaucoma, or pigmentary glaucoma), or OHT in eligible eye(s) currently on monotherapy.
4. Unilateral OAG, or OHT are permissible as long as the physician does not anticipate significant IOP changes to the fellow eye that would require treatment during the duration of the study.
5. Current treatment with monotherapy for OAG or OHT with a controlled IOP ≤ 18 mmHg in each eye (pre-washout).
6. Stable visual field (based on at least two visual fields available within the last 18 months prior to screening, including one in the last 6 months; A visual field test will be performed at screening if not already performed within the last 6 months prior to screening) in each eye. If historical visual fields are not available within the last 18 months prior to screening, but at least two OCTs (optical coherence tomography) are available, including one in the last 6 months and are stable, the patient can be enrolled in the study if a visual field test is also performed at

screening and shows no defect or only an early visual field loss in either eye (mean deviation lesser than -6 dB).

7. Post-washout IOP ≥ 22 mmHg in at least one eye (defined as baseline visit [Day 1] by IOP measurement at both 9:00 am ±1 hour and 4:00 pm ±1 hour). If IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.
8. Post-washout IOP ≤ 32 mmHg (defined as baseline visit [Day 1] by IOP measurement at both 9:00 am ±1 hour and 4:00 pm ±1 hour) in both eyes.
9. Ability to discontinue their current topical IOP-lowering medication for the required washout period. Washout periods should be as follows;
    - Prostaglandin analogs = 4 weeks
    - Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
    - Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks
    - All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks
10. Snellen best corrected visual acuity score of 20/100 or better in each eye.
11. Patient must be willing to discontinue wearing contact lenses during the study.
12. Adequate health for study participation as determined by the investigator.
13. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements.
14. Patient must be willing and able to undergo and return for scheduled study-related examinations.

Exclusion criteria:

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Any form of glaucoma other than primary open angle glaucoma, pseudo exfoliative glaucoma, and pigmentary glaucoma in either eye.
2. IOP at any time point during the Screening or Baseline visits (Visits 1 or 2) of > 32 mmHg in either eye.
3. Current treatment for glaucoma with a fixed-combination therapy or more than one drug in either eye or with an oral drug within 6 months prior to screening.
4. Corneal abnormalities that would interfere with accurate IOP readings with an applanation tonometer in either eye.

5. Central corneal thickness ≤ 480 µm or ≥ 600 µm in either eye (historical value or at the screening visit)
6. Significant visual field loss (absolute defect in the 10° central point or mean deviation worse than -12 dB) or progressive field loss during the year before screening in either eye.
7. Significant optic nerve abnormality, other than glaucomatous abnormalities in the opinion of the investigator as determined by ophthalmoscopy in either eye.
8. Significant changes of the optic neuropathy (e.g. increase cupping since the last examination, optic nerve hemorrhage) in either eye.
9. Inability to visualize the patient's optic nerve in either eye.
10. Gonioscopy consistent with potential angle closure glaucoma in either eye.
11. Patients with severe blepharitis and/or Meibomian Gland Disease (MGD). Patients enrolled with mild to moderate blepharitis and/or MGD should be treated as appropriate during the study in either eye.
12. Use of oral or topical ophthalmic steroid within the past 14 days from screening date, or anticipated need for ocular steroid treatment during the study in either eye.
13. Use of intravitreal or peribulbar injection of depot steroid or placement of an intravitreal steroid implant within the past 3 months from screening date in either eye.
14. Known allergy or sensitivity to the study medications.
15. Known hypersensitivity to sulfonamides, severe renal impairment or hyperchloraemic acidosis.
16. Active or expected ocular allergy during the period 1.
17. Any active ocular disease (e.g. uveitis, ocular infection, severe dry eye with CFS grade 4 or more on the modified Oxford scale) in either eye. Patients may have mild cataracts, age-related maculopathy or background diabetic retinopathy if, in the opinion of the Investigator, it would not interfere with the conduct of the study.
18. Intraocular surgery within 6 months prior to screening in either eye.
19. Past history of any filtering surgery for glaucoma in either eye.
20. Refractive surgery of any type within 1 year prior to screening in either eye.
21. Uncontrolled systemic disease of any type.
22. Anticipated alteration in chronic therapy with or introduction of agents known to have a substantial effect on IOP (e.g., alpha-adrenergic agonists, beta-adrenergic antagonists, calcium channel blockers, ACE inhibitors and/or angiotensin II receptor blockers), unless the subject and the medication dosage have been stable

for three months prior to the screening visit and the dosage is not expected to change during the study.

23. Anticipated change in dosage of or introduction of new medications for chronic cardiac, pulmonary or hypertensive conditions.
24. Females who are pregnant or lactating and females of child-bearing potential who are not using a medically acceptable, highly effective method of birth control.
25. Current enrolment in an investigational drug or device study or participation in such a study within 30 days prior to screening.
26. History of drug or alcohol abuse.
27. Patient has any condition or situation that, in the Investigator's opinion, might confound the results of the study, may put the patient at significant risk or might interfere with the patient's ability to participate in the study.

Study drug, dosage, mode and duration of administration:

Study drug: DE-130A (latanoprost 50 microg/ml eye drops emulsion, SD) eye drops emulsion in single-dose containers.

Regimen: Instillation of one drop, once daily in the evening (9 pm ±1 hour) in the conjunctival sac of the affected eye(s). Both eyes will be treated unless the patient suffers from unilateral OAG/OHT.

Duration of treatment: 3 months during Period 1 (randomised, investigator-masked treatment) and up to 12 months during Period 2 (open-label DE-130A 12-month extension for the first 130 patients who complete their Week 12 visit and agree to participate in the open-label period of the study).

The period 2 will be open in some countries only.

Comparator, dosage, mode and duration of administration:

Investigational product: Xalatan® (latanoprost 50 microg/ml eye drops solution) eye drops in 2.5 ml dropper containers.

Regimen: Instillation of one drop, once daily in the evening (9 pm ± 1 hour) in the conjunctival sac of the affected eye(s). Both eyes will be treated unless the patient suffers from unilateral OAG/OHT .

Duration of treatment: 3 months during Period 1 (randomised, investigator-masked treatment)

Wash-out phase therapy:

At screening visit, prior therapies for OAG or OHT must be discontinued during a wash-out phase of at least 5 days and up to 6 weeks (according to the IOP lowering medications currently used at screening visit). Washout periods should be as follows:

- Prostaglandin analogs = 4 weeks
- Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
- Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks

- All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks

During this wash-out period, topical IOP-lowering medication will be replaced by brinzolamide* (Azopt®) one drop twice daily. Then brinzolamide will be stopped 5 days before randomisation (6 to 7 days if over the weekend). At baseline, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

*Patients already receiving brinzolamide prior to screening visit will have to stop their treatment for a 5-day washout before randomisation (without any need to receive again the brinzolamide provided by the Sponsor).

Criteria for evaluation:

Efficacy:

The **primary efficacy endpoint** is the change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the two treatment groups in the study eye.

The **key secondary endpoints** are:

- Change from baseline in CFS score in the study eye at Week 12 in patients with baseline CFS ≥ 1.
- Change from baseline in OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score>0.

Other **secondary efficacy endpoints** are:

- Ocular surface disease related endpoints:
  - CFS in the study eye at Week 4 in subjects with baseline CFS ≥ 1
  - Tear film break-up time (TFBUT) in the study eye at Week 4 and Week 12 in subjects with baseline TFBUT ≤ 10
  - Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Week 4, Week 12
  - Conjunctival fluorescein staining in the study eye at Week 4 and Week 12 in subjects with baseline conjunctival fluorescein staining ≥ 1
  - Dry eye sensation symptom in the study eye at Week 4 and Week 12 in subjects with baseline dry eye sensation symptom in mild, moderate, or severe
  - Blurred/poor vision symptom in the study eye at Week 4 and Week 12 in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe

- Burning/stinging/itching symptom in the study eye at Week 4 and Week 12 in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe
- Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris) in the study eye at Week 4 and Week 12
- CFS in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline CFS ≥ 1
- Tear film break-up time (TFBUT) in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline TFBUT ≤ 10
- Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Month 6, Month 9 and Month 15/early termination
- Conjunctival fluorescein staining in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline conjunctival fluorescein staining ≥ 1
- Dry eye sensation symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline dry eye sensation symptom in mild, moderate, or severe
- Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe
- Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe
- Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris) in the study eye at Month 6, Month 9 and Month 15/early termination

- IOP related endpoints:
  - Change from baseline in mean diurnal IOP in the study eye at Week 12
  - Change from baseline in peak, trough, and mean diurnal IOP in the study eye at Week 4
  - Peak, trough, and mean diurnal IOP response in the study eye at Week 4 and Week 12:
    - IOP 20% response (reduction in mean IOP of ≥ 20% from Baseline at the specified follow-up visit)
    - IOP 25% response (reduction in mean IOP of ≥ 25% from Baseline at the specified follow-up visit)
    - IOP 30% response (reduction in mean IOP of ≥ 30% from Baseline at the specified follow-up visit)

- IOP < 18 mmHg response (mean IOP < 18 mmHg at the specified follow-up visit)

- Morning (9:00 am ± 1 hour) IOP in the study eye of patients treated with DE-130A at Month 6, Month 9, Month 15/early termination (Period 2) and change from baseline at each Period 2 visit

- Subject global rating of treatment at Month 15/early terminationand Week 12.
- Quality of life (Glaucoma Quality of Life-15) scores at Baseline visit, Week 12, and Month 15/early termination visits.

Safety:

In the Safety population, at all visits and for each treatment (Period 1) and for the Open-Label population for DE-130A at all visits (Period 2 and Periods 1 & 2 combined), safety and tolerability endpoints are:

- The incidence and severity of ocular and systemic adverse events
- Best-corrected distance visual acuity (BCDVA)
- Slit lamp examination (lashes, anterior chamber and lens).
- Dilated and undilated (for cup-to-disc ratio) fundoscopy.

Statistical methods:

Sample size

Sample size was calculated assuming a mean difference in IOP change from baseline of 0 mmHg and a common standard deviation of 4.26 mmHg in the peak or trough IOPs, respectively, for the comparison between the DE-130A and the Xalatan® (control) groups. A total sample size of approximately 380 subjects (190 per treatment arm) will provide 90% power to demonstrate the non-inferiority of the DE-130A group to the control group (one-sided $\alpha = 0.025$) for non-inferiority margin of 1.5 mmHg, assuming 10% dropout rate.

Randomisation

Patients will be randomly assigned in a 1:1 ratio to receive either DE-130A (experimental) or Xalatan® (comparator) for 3 months. To minimize the effect of baseline OSD severity, randomisation will be stratified according to the CFS score at Baseline visit (CFS ≤ 1 and ≥ 2, modified Oxford scale).

Study eye

Data collection will be done on both eyes, however, efficacy analyses will only be performed on the study eye, which is defined as the eye that qualifies per inclusion/ exclusion criteria at the Baseline Visit. If both eyes are eligible, the eye with the higher IOP at the Baseline Visit will be chosen. If both eyes have the same IOP value, the eye with the higher CFS at the Baseline Visit will be chosen. If both eyes have the same IOP and CFS values, then the right eye will be designated as the study eye.

Analysis Populations

The following analysis populations are considered:

- The **Full Analysis Set (FAS)** population consists of all randomised subjects who received at least one dose of the study medication and provided at least one post-baseline IOP measurement at peak and trough timepoints, separately. The FAS population will be the analysis population for all efficacy endpoints in Period 1 and will use treatment as randomised.
- The **Safety population** consists of all subjects randomized in the study who received at least one dose of the study medication. The Safety population will be the analysis population for all safety analyses in Period 1 and will use treatment as actually received.
- The Glaucoma/OHT **Per-Protocol (PP)** population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the primary efficacy endpoint. The PP population will be used for sensitivity analyses of the primary efficacy endpoints in Period 1 and will use treatment as randomised.
- The **Ocular Surface Disease Per-Protocol (PP)** population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the key secondary endpoints. This population will be used for sensitivity analyses of the key secondary endpoints in Period 1 and will use treatment as randomised.
- The **Open-Label Population** will be a subset of the FAS subjects who complete their Week 12 Visit and agree to participate in the open-label period of the study, and received at least one dose of the study medication during the open-label period and provided at least one morning IOP measurement after the Week 12 Visit.This population will be the analysis population for the analyses of efficacy endpoints in Period 2 and for Periods 1 & 2 combined data and will use treatment as randomised.

Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, race, ethnicity, female patients' menopausal status) and baseline characteristics variables (including time since diagnosis, past surgery or laser treatment in the study eye, and smoking status). They will be summarized by treatment groups for the overall FAS population, Safety population, Open-label population, separately.

In addition, medical history (ocular and systemic), and prior and concomitant medication use will be summarized by treatment group for the overall FAS population.

Analysis of Primary and Key Secondary Efficacy Endpoints

The primary efficacy endpoint is the change from baseline in peak and trough IOP, respectively, between the DE-130A group and the Xalatan® group in the study eye at Week 12. Statistical analysis will be performed using a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Week 12 based on FAS population. A separate MMRM model will be performed for IOP at peak and trough, respectively. The model will include treatment, visit, treatment-by-visit interaction and country as fixed effects, baseline IOP at the respective timepoint (peak or trough) as covariates. Non-inferiority will be

established if the upper limit of the one-sided 97.5% confidence intervalis less than or equal to the non-inferiority margin of 1.5 mmHg at both the peak and trough timepoints at Week 12. Superiority is achieved with respect to this endpoint if the upper limit of the one-sided 97.5% confidence interval is < 0 mmHg for both timepoints at Week 12.

If non-inferiority in the primary endpoint is achieved, the two key secondary endpoints will be tested for superiority, sequentially according to hierarchical fixed procedure. MMRM models will be fitted for each key secondary endpoint using a similar model setting as described for the analysis of the primary efficacy endpoint. Fixed sequence procedure will be applied to control the overall Type I error rate across all hypotheses in the primary and key secondary endpoints at the 0.05 level.

Analysis of Other Secondary Efficacy Endpoints

Ocular surface disease Assessments

Change from baseline in Conjunctival fluorescein staining, TFBUT and each individual symptom score in the study eye at each analysis visit in Period 1 will be compared between treatment groups using MMRM on observed cases. More details on the model specifications will be provided in the SAP.

Percentage of patients with conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale (1 to 6))in the study eye at each analysis visit in Period 1 will be compared between treatment groups using a *Chi-squared test* or *Fisher's Exact test* wherever appropriate for the FAS population.

Artificial tears use during Period 1will be summarised by treatment group as a continuous variable as well as by percentage of patients who use artificial tears at each analysis visit..

CSF, corneal and conjunctival fluorescein staining, TFBUT, symptom scores [3-symptom average and individual symptom score], and slit lamp examination and their change from baseline at each visit will be summarized descriptively by treatment group.

Quality of Life Assessments

Mean scores of quality of life (Glaucoma Quality of Life-15), and their change from baseline (Period 1 and Periods 1 & 2) and change from Week 12 (Period 2) will be summarized by study period, analysis visit and by treatment group (Period 1), for the FAS population (Period 1), for the Open-Label Population (Period 2, Periods 1 & 2 combined).

Subjects Global Rating of Treatment

Subjects global rating of treatment at Week 12/early termination will be summarized by treatment groups for the FAS population. Also, it will be summarized at Month 15/early termination for the Open-Label Population.

IOP Assessments

Changes in peak, trough, and mean diurnal IOPs at each analysis will be summarized on the study eye by treatment group.

Peak, trough, and mean diurnal IOP responses in the study eye (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response) at each analysis visit will be summarized by treatment group.

For patients participating in the safety follow-up, change from baseline and change from Week 12, respectively, in mean morning (9:00 am ± 1 hour) IOP will be summarized for the Open-Label population and for CFS subgroups at Month 6, Month 9 and Month 15/early termination.

Analysis of Safety and Tolerability Endpoints

Safety and tolerability endpoints will be summarized for the following three time periods:

- Period 1 (Day 1 to Week 12 Visit): for whole Safety population by treatment group
- Period 2 (Week 12 Visit to Month 15 Visit/early termination): for all subjects who entered into the open-label period (Open-Label Safety population)
- Entire study period (Day 1 to Month 15/early termination): for all subjects who entered into the open-label period (Open-Label Safety population).

Adverse Events

An adverse event is treatment-emergent (TEAE) if it occurs or worsens after the first dose of study treatment. A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the study drug or study procedure caused the adverse event.

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages will be given as follows: 1) Overall summary; 2) by system organ class and preferred term, 3) by system organ class, preferred term and maximal severity, 4) by system organ class, preferred term and relationship to study medication and study procedure, respectively, and 5) by system organ class, preferred term, maximal severity, and relationship to study medication and study procedure, respectively.

Separate analyses will be performed for AEs, SARs, SAEs, serious SARs, and for ocular and non-ocular events. Ocular events will be summarized for the study eye and the fellow eye separately.

Other Safety Assessments

Other safety assessment parameters (e.g. slit lamp examination, dilated fundoscopy, BCDVA, and visual field) will be summarized by analysis visit. They will be summarized for the study eye and the fellow eye separately. Pregnancy test results will be provided in a listing.

Interim Analysis

There is no planned interim analysis for this study.

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURE(S)

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	**Explanation**
AE	Adverse event
API	Active Pharmaceutical Ingredient
AR	Adverse Reaction
AT	Artificial Tears
BAK	Benzalkonium Chloride
BCDVA	Best Corrected Distance Visual Acuity
C/D	Cup-to-Disc ratio
CKC	Cetalkonium Chloride
CFS	Corneal Fluorescein Staining
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
CSI	Case of Special Interest
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FP	Prostaglandin F
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
IOP	Intraocular Pressure
IOP-L drug	Intraocular Pressure Lowering drug
IWRS	Interactive Web Response System
LASEK	Laser Epithelial Keratomileusis
LASIK	Laser in Situ Keratomileusis

Abbreviation or Specialist Term	Explanation
LogMAR	Logarithm of the Minimum Angle of Resolution
MCT	Medium Chain Triglycerides
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	Mixed Model of Repeated Measures
OHT	Ocular Hypertension
OSD	Ocular Surface Disease
OSDI	Ocular Surface Disease Index
PI	Principal Investigator The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
POAG	Primary open-angle glaucoma
PRK	Photorefractive Keratectomy
QD	Quaque Die
QOL	Quality of Life
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SV	Safety Vigilance
TFBUT	Tear Film Breakup Time
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
TFLL	Tear Film Lipid Layer
WHO-DRUG	World Health Organization Drug

4. INTRODUCTION

Glaucoma and IOP

Glaucoma is a chronic degenerative optic neuropathy that can be distinguished from most other forms of acquired optic neuropathy by the characteristic appearance of the optic nerve. Glaucoma is the second leading cause of blindness in Europe (EGS, 2017 (1)). In most Western countries, glaucoma diagnosis is often made late (Martus, 2005 (2)); approximately half of patients with manifest glaucoma are undiagnosed (Tielsch, 1991; Mitchell, 1996; Quigley, 2003 (3-5)).

In glaucoma, the neuroretinal rim of the optic nerve becomes progressively thinner, thereby enlarging the optic-nerve cup. Glaucoma encompasses a group of diseases and is classified by the appearance of the iridocorneal angle (anterior-segment variations) that can elevate intraocular pressure (Kwon, 2009 (6)). There are open-angle, closed-angle, and developmental categories which are further divided into primary and secondary types. Primary open-angle glaucoma (POAG) is the most common type in western countries. POAG is a chronic optic neuropathy which occurs with an open angle in the absence of any explanatory causes. While there is no standard definition, current criteria require the presence of visual field and optic disc damage. OAG can occur at any level of intraocular pressure (IOP); with or without elevated IOP; the latter is sometimes called normal-tension glaucoma (Leske, 2007; Kwon, 2009 (6, 7)). However elevated IOP is the main risk factor for OAG development and reduction of IOP has been demonstrated to protect against further damage to the optic nerve, even in patients with normal tension glaucoma. Other risk factors of POAG than older age are black race, elevated IOP, family history of POAG, myopia or vascular factors (Kwon, 2009 (6)).

Up to 10% of people over 40 years of age have IOPs above 21 mmHg (normal range 10 to 21 mmHg); those who have such high pressures but no optic-nerve damage are considered to have ocular hypertension. In medical practice, patients who have ocular hypertension should be periodically examined (optic nerve, visual fields) to determine whether there is evidence of a progressive damage which would indicate the need to start with treatment. However, a high IOP without optic-nerve damage, in some cases (e.g. additional risk factors for glaucoma) may be treated.

Glaucoma and ocular surface disease

Glaucoma and ocular surface disease (OSD) signs and symptoms commonly occur together, and this overlap suggests an association between the two diseases. It is estimated that 50% to 60% of glaucoma patients have symptoms of OSD, eg. keratitis, conjunctivitis and lid disease (Leung, 2008; Fechtner, 2010 (8, 9)). Abnormal tear film break-up time (TFBUT) with elevated Ocular Surface Disease Index (OSDI) and lissamine green scores were frequent in glaucoma patients when compared with controls (Saade, 2015 (10)). OSD has been found to be aggravated by the use of preserved topical intraocular pressure (IOP) lowering drugs (Pisella et al, 2002; Baudouin, 2010 (11, 12)), and to play an important role in patient satisfaction and compliance (Lemij, 2015 (13)). In addition, Batra and collaborators recently demonstrated that OSD management resulted in

improved IOP control, suggesting that improving the ocular surface condition may help in the control of IOP (Batra, 2014 (14)).

Management of Glaucoma

The current therapeutic approach in open angle glaucoma is lowering IOP by pharmacological means, surgery, micro-invasive surgery, or with laser therapy to preserve visual function (Conlon et al, 2016; The glaucoma laser trial (GLT), 1995 (15, 16)). It is generally accepted that pharmacological treatments should be the first step, and the initial target IOP for each patient should be chosen individually according to the current amount of optic damage and the pressure at which the damage occurred, and that the target IOP will be further adjusted according to the disease progression in subsequent examinations of visual field. Although different clinical aspects will guide the choice of the target initial pressure, it is common to pursue a decrease in the IOP between 20% and 40% depending on the degree of associated damage. Once the patient has achieved a "safe" IOP at which the disease does not progress, additional lowering of the IOP would provide marginal benefit entailing a higher risk of adverse reactions.

The common goal among the various therapies is to lower the IOP to prevent loss of visual fields from excessive pressure on the optic nerve. The IOP level remains the only major glaucoma risk factor known to be modifiable. For that reason, there has been long-standing interest in the potential of IOP-lowering treatment to decrease OAG risk. Several clinical trials have demonstrated the effectiveness of lowering IOP to reduce visual field loss, at the various stages of the disease whether of the 'high pressure' or ''normal pressure' variety as well as reducing the conversion of OHT to POAG (EGS, 2017b (17)).

Several major classes of therapeutic agents are used in the treatment of glaucoma (EGS, 2017b (17)). IOP-L drugs may act in four ways: increasing outflow through the trabecular meshwork; increasing uveoscleral outflow; decreasing episcleral venous pressure; and decreasing aqueous humor production. Until today, the mechanism of action of IOP-L drugs consists of either decreasing aqueous fluid production in the ciliary epithelium, improving aqueous outflow via the trabecular meshwork (responsible for 80% of normal outflow) or increasing the uveoscleral route (20%), or a combination of both (Parikh, 2008 (18)). Recently, a new therapeutic class, the rho kinase and norepinephrine transporter inhibitor (netarsudil), has been developed. It increases the outflow from the trabecular meshwork, and may also lower episcleral venous pressure (Lin, 2018 (19)). In 2018, netarsudil ophthalmic solution was approved by the FDA (Choy, 2018 (20)).

There are thus five classes of topical antiglaucoma drugs administered as first therapy:

- Prostaglandin analogues (including prostamins) that increase uveoscleral outflow
- Beta-receptors agonists (non-selective beta-blockers or selective beta-1-blockers) that decrease aqueous production
- Carbonic anhydrase inhibitors (topical or systemic) that decrease aqueous production
- Alpha-2 selective adrenergic agonists that decrease aqueous production, and are associated with an increase in uveoscleral outflow for brimonidine

- Rho kinase and norepinephrine transporter inhibitors which exhibit additive effects with latanoprost.

Prostaglandin treatment has been shown to provide patients with the highest reduction of IOP followed by non-selective b-blockers, alpha-adrenergic agonists, selective b-blockers and at last topical carbonic anhydrase inhibitors (van der Valk, 2005 (22)). A recent study showed longer visual field preservation in patients with POAG treated with latanoprost compared to those treated with placebo (Garway-Health, 2015(21)). Medical treatment is initiated with a topical ophthalmic drug (eye drops) and if necessary, a second topical drug is added (EGS, 2017b (17)).

4.1. Background on DE-130A

Santen is currently developing the product DE-130A (formerly NOVA21027 of Novagali Pharma today part of SANTEN) which is a preservative-free, sterile ophthalmic emulsion containing latanoprost 50 microg/ml intended for topical use for the treatment of elevated intraocular pressure in patients with open angle glaucoma and/or ocular hypertension. It is a new formulation of the reference IOP lowering medication, Xalatan® (latanoprost 50 microg/ml eye drops solution – Pfizer), which was registered in Europe first in December 1996. These two medicinal products mainly differ by their pharmaceutical form, Xalatan® being a BAK-preserved eye drops solution in a 2.5 ml dropper container while DE-130A is an unpreserved emulsion in a single-dose container.

4.1.1. Background information on the product

Latanoprost (INN) is a well-known substance, a prostaglandin-analogue isopropyl ester prodrug which per se is inactive, but after hydrolysis to the acid of latanoprost becomes biologically active. This prostanoid selective prostaglandin F (FP) receptor agonist is believed to reduce the intraocular pressure (IOP) by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow.

The cationic emulsions in general (Lallemand, 2012; Daull, 2014; Amrane, 2014; Robert, 2016; Leonardi, 2016; Baudouin, 2017 (23-28)), and of latanoprost in particular (Liang, 2009; Daull, 2012; Daull, 2014; Daull, 2017 (24, 29-31)) were demonstrated to be safe and well tolerated by the ocular surface in animal models and patients.

4.1.2. Non-clinical development

Regarding the active pharmaceutical ingredient (API) used in DE-130A, the ocular as well as systemic toxicity of latanoprost has been investigated in several animal species. In animal studies, latanoprost has not been found to have sensitising properties.

In chronic ocular toxicity studies, increased palpebral fissure has been reported at latanoprost 6 µg/eye/day, this reversible effect has not been seen in humans. Latanoprost was found negative in reverse mutation tests in bacteria, gene mutation in mouse lymphoma and mouse micronucleus test. Chromosome aberrations were observed in vitro with human lymphocytes, and this indicates

that it is a class effect. Latanoprost has not been found to have any effect on male or female fertility in animal studies. No teratogenic potential has been detected with latanoprost.

Regarding the vehicle used for the drug product DE-130A, latanoprost is formulated in a cationic emulsion based on the Novasorb® technology (Lallemand, 2012 (23)).

The cationic emulsion vehicles possess protective properties for tear film stabilization via its interactions with the tear film lipid layer (TFLL) (meibum films) of the tear (Georgiev, 2016; Georgiev, 2017 (32, 33)), and help in the prevention of tear film break-up via the interaction of cetalkonium chloride (CKC) with the polar lipids of the TFLL (Cwiklik, 2017 (34)). In addition to these mechanical actions, the cationic emulsion also harbour intrinsic anti-inflammatory properties (Daull, 2016a ; Daull, 2016b (35, 36)) that help in the management of ocular surface inflammation, often present on the ocular surface of glaucoma patients, and wound healing properties (Liang, 2009 (29)). Indeed, latanoprost formulated in cationic emulsion is safe (Daull, 2012 (30)) and appears a promising formulation for the management of ocular hypertension and ocular surface dryness and subclinical inflammation (Daull, 2017 (31)).

Furthermore, when compared to either saline or anionic emulsions, submicron cationic emulsions have been shown to optimize ophthalmic topical drug delivery after instillation of one single drop (Tamilvanan, 2004; Calvo, 1996; Sahin, 2008; Tunc, 2006 (37-40)).

The non-clinical data generated by Santen during DE-130A development (pharmacodynamics, pharmacokinetic and local tolerance) are detailed in the Investigator's brochure. DE-130A and Xalatan® share a similar pharmacodynamic profile (Study PCS09B001 – non-GLP). Both products have efficiently reduced high IOP in monkey glaucomatous eyes.

The pharmacokinetic and toxicokinetic profiles of DE-130A (local biodistribution and systemic exposition) were characterized and compared to the one obtained with Xalatan®. DE-130A has a PK profile slightly inferior at short time points when compared to Xalatan®, as reflected by its lower exposition (AUC). However, the concentrations observed at 4h and 6h were similar for both formulations, suggesting that over a 24h period following a single instillation, DE-130A and Xalatan® have the same PK profile from the time point 4h until 24h. Thus, except for some short time points DE-130A and Xalatan® are comparable. DE-130A has a slower absorption rate, which is compensated by a longer exposition of the emulsion onto the eye surface. The latter being responsible for DE-130A concentrations observed at time points 4h and after.

The local tolerance of DE-130A was assessed on ocular surface and in the nasal mucosa, and compared to that of Xalatan® in rabbits (Study To458 – GLP). DE-130A was well tolerated in the eye and did not induce any significant changes in the nasal mucosa. The UV-LLNA study (41506 TSS – GLP) demonstrated that cationic emulsion vehicle containing 0.005% CKC did not show any phototoxic or photosensitizing (photoallergic) potential.

Taking into account the legal basis of the DE-130A dossier, Article 10(3) of Directive 2001/83/EC, Santen is not anticipating performing any additional non-clinical studies.

4.1.3. Clinical development

Patients with mean baseline IOP of 24-25 mmHg who were treated for 6 months with latanoprost one drop once daily demonstrated 6-8 mmHg reductions in intraocular pressure (Patel,1996; Baudouin, 2006 (41, 42)). Long-term trials (up to 5 years) have shown that latanoprost monotherapy provides clinically significant and sustained IOP reduction (Alm, 2004 (43)).This drug is probably one of the most potent IOP-lowering medications currently available and has become one of the most useful antiglaucoma agents.

The cationic emulsion of latanoprost 50 microg/ml eye drops emulsion, SD (DE-130A) has been evaluated in two phase II clinical trials conducted by Santen.

DE-130A was compared to Travatan Z® in subjects with glaucoma or OHT and OSD over a 3-month treatment period, in the USA (NVG10E118). The 95% confidence interval of the difference between treatment groups suggests at least the non-inferiority of DE-130A versus Travatan Z® in lowering IOP in patients suffering from OAG or OHT. The analysis of signs and symptoms of OSD in these subjects also suffering from OSD showed a statistically significant treatment group effect for corneal fluorescein staining (CFS) in favor of DE-130A associated with greater decrease in artificial tears usage in the DE-130A group compared with the Travatan Z® group. The safety analysis demonstrated the good safety profile of DE-130A, comparable to that of Travatan Z®. No safety concerns were raised as a result of this study.

The second study (NVG09E115) assessed the efficacy and safety of a 3-month DE-130A treatment period after a switch from Xalatan®, in IOP-controlled patients with OAG or OHT (IOP ≤22mmHg) (BAK-preserved latanoprost treatment either in monotherapy or in non-fixed combination with BAK-free anti-hypertensive treatment(s) for at least one month) and OSD, in France. The mean IOP improvement after the switch to DE-130A , with a mean change from baseline of-0.6mmHg at D28 and -0.8mmHg at D84 (Study NVG09E115 – CSR). An improvement in the preexisting mild to moderate signs and symptoms of OSD was observed with during the study. DE-130A was very well tolerated and local tolerance after instillation improved, in particular for Burning/Stinging which was the most impairing symptom after instillation of Xalatan®.

DE-130A effectively and safely lowered IOP and significantly reduced the signs and symptoms of these patients with OSD, demonstrating the benefits of the cationic emulsion on the mechanisms underlying OSD beyond it being preservative-free. These benefits may represent an important improvement in overall quality of life and convenience for OHT or glaucoma patients with OSD.

4.2. Rationale for the Proposed Study

The current pharmacological therapeutic approach in open angle glaucoma or ocular hypertension is lowering IOP. Otherwise, ocular surface disease (OSD) signs and symptoms are commonly associated with glaucoma, as 50% to 60% of glaucoma patients present with symptoms of OSD. A therapy which results in both lowering IOP and improving OSD signs and symptoms may thus positively impact patients' quality of life and compliance with treatment.

At this stage of the development of DE-130A, a comparison to the reference IOP lowering agent (latanoprost) in a different formulation needs to be conducted. In line with the overall development program and with the "Guideline on the choice of the non-inferiority margin" (Doc. Ref. EMEA/CPMP/EWP/2158/99), the non-inferiority study design seems appropriate to compare DE-130A with a different latanoprost eye drop solution. Latanoprost is available as Xalatan® in multidose containers or as Monoprost® in single dose containers (packaging similar to DE-130A). Monoprost® has only showed a non-inferiority to Xalatan®, and as mentioned in the CHMP advise (EMA/CHMP/SAWP/797001/2017), the comparison to preservative-free Monoprost® in single dose containers would have led to a questionable double bridging exercise from a scientific perspective; even though the comparison between DE-130A and Xalatan® prevents a double-masked study. In fact, a double-masked study comparing DE-130A with Xalatan® would have required a double instillation of the active product and the placebo of the other study treatment (which may have led to bias by modifying the contact time of the study treatment). The formulations of DE-130A (preservative-free ophthalmic oily emulsion of latanoprost) and of Xalatan® (BAK-preserved eye drops solution) are most likely to exibit significantly different physicochemical properties, such as viscosity or surface-tension. Furthermore the high viscosity of DE-130A may impact the contact time of the active compound with the ocular surface.

In the proposed non-inferiority study, to approximate the peak and trough times, the IOP will be measured at 9:00 (±1 hour) am and 4:00 (±1 hour) pm, and will be used to assess the primary efficacy endpoint and secondary endpoints during a 3-month period with randomised investigator-masked medication. The chosen non-inferiority margin of 1.5 mmHg is well below (Musch, 2006 (44)) the effect of the active control (−8.6±2.6 mmHg, Rouland, 2013 (45)). In addition to the comparison of peak, trough, and mean diurnal IOP, the rates of different responders (defined by a reduction in mean IOP of ≥ 20%, ≥ 25%, and ≥ 30%, and a mean IOP < 18mm Hg) will be compared between treatment groups.

Regarding the OSD, the potential positive impact of the cationic formulation of DE-130A on OSD signs (using TFBUT, slit lamp examination, corneal, and conjunctival fluorescein staining with modified Oxford scale) and symptoms (using 3-symptom assessment) will be compared with the effect on OSD of the BAK-preserved Xalatan®. Furthermore the quality of life impact will also be compared between treatment groups.

In this context, to ascertain the efficacy and safety according to patients severity, the randomisation will be stratified in order to prevent to high heterogeneity between treatment groups, with two OSD classes (baseline CFS≤1 and ≥2, modified Oxford scale).

Regarding the trial duration, the previous trials with DE-130A had a duration of 3 months, in particular DE-130A ophthalmic emulsion has demonstrated its efficacy in controlling IOP over a 3-month treatment period after a switch from Xalatan®. Three-month treatment duration is thus consistent to assess the IOP reducing effect. However in order to provide long-term additional data on the safety and tolerability of DE-130A, a 12-month follow-up with open-label DE-130A is to be offered to 130 patients (whatever their randomised treatment is) who complete their Week 12

Visit and agree to participate in the open-label period of the study. During this safety follow-up, only the peak IOP will be measured in order to minimize patients' burden.

In order to compare patients with the most homogenous IOP baseline, the study treatment period will be preceded by a wash-out period of previous glaucoma medications. Regarding OSD, the use of artificial tears (AT) will be protocolized (i.e. ATs with main impact on OSD will be excluded and the use of authorized AT will be in agreement with the SmPCs) to allow a comparison between treatment groups.

As a result, the planned multinational, multicenter, investigator-masked, randomised, active-controlled phase III clinical trial (0130A01SA) aims to demonstrate the non-inferiority of DE-130A ophthalmic emulsion (cationic emulsion of latanoprost 50 microg/ml eye drops) compared to BAK-preserved latanoprost 50 microg/ml eye drops ophthalmic solution (Xalatan®) instilled once daily to patients suffering from OAG or OHT. Secondary objectives will include the comparison of the efficacy between treatment groups regarding IOP and OSD, and their safety/tolerability over the 3-month treatment period. In a subgroup of patients eligible for 12-month follow-up with open-label DE-130A administration, the same objectives will be assessed over a 15-month study period.

4.3. Benefit Risk Assessment

The patients participating in the study will benefit either from the reference product (Xalatan®) to treat their OAG or OHT, or from DE-130A a novel BAK-free formulation of latanoprost with potential impact on OSD frequently observed in patients with OAG, in addition to the expected IOP-lowering effect.

After the 3-month treatment period, a 12-month safety follow-up with open-label DE-130A is to be offered to the first 130 patients (whatever their randomised treatment is), who complete their Week 12 Visit and agree to participate in the open-label period of the study, in order to provide them the opportunity to continue their treatment with open-label DE-130A. The supernumerary patients will exit the study at Week 12.

After the study end, patients will receive the best available treatment in the investigator's opinion for OAG or OHT.

Furthermore, patients will benefit from a close follow-up by the investigators (at Week 4 and Week 12) which is not the case in the usual clinical setting during the first 3 months of a new treatment regime, and those patients entering the 12-month study extension will benefit from biannual visits. The risks related to the participation in the study are the adverse events listed in the investigator's brochure, the potential risk of allergy to fluorescein, and anaesthetic eye drops or artificial tears.

In light of the points listed above the benefit risk profile is considered to be favourable.

5. TRIAL OBJECTIVES AND ENDPOINTS

5.1. Primary Objective

The primary objective of the study is to demonstrate that the IOP reducing effect of DE-130A (latanoprost 50 microg/ml preservative-free eye drops emulsion) is non-inferior to that of Xalatan® (latanoprost 50 microg/ml BAK-preserved eye drops solution), in patients with OAG or OHT at Week 12 without using any rescue medication(s).

5.2. Secondary Objectives

The secondary objectives are:

- To compare the effect on improving OSD signs and symptoms between treatment groupsover 3 months (Period 1).
- To estimate the effect of DE-130A on OSD signs and symptoms improvement up to 15 months (Periods 1 & 2).
- To compare the efficacy on IOP reduction between treatment groups over 3 months (Period 1).
- To estimate the effect of DE-130A on IOP up to 15 months (Periods 1 & 2).
- To estimate the local ocular tolerance and systemic safety of the two treatments over 3 months (Period 1).
- To estimate the local ocular tolerance and systemic safety of DE-130A up to 15 months (Periods 1 & 2).

5.3. Endpoints

5.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the two treatment groups in the study eye.

5.3.2. Key Secondary Endpoints

The key secondary endpoints are:

- Change from baseline in CFS score in the study eye at Week 12 in patients with baseline CFS $\geq$ 1.
- Change from baseline in OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score >0.

5.3.3. Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- Ocular surface disease related endpoints:
    - CFS in the study eye at Week 4 in subjects with baseline CFS ≥ 1
    - Tear film break-up time (TFBUT) in the study eye at Week 4 and Week 12 in subjects with baseline TFBUT ≤ 10.
    - Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Week 4, Week 12.
    - Conjunctival fluorescein staining in the study eye at Week 4 and Week 12 in subjects with baseline conjunctival fluorescein staining ≥ 1.
    - Dry eye sensation symptom in the study eye at Week 4 and Week 12 in subjects with baseline dry eye sensation symptom in mild, moderate, or severe.
    - Blurred/poor vision symptom in the study eye at Week 4 and Week 12 in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe.
    - Burning/stinging/itching symptom in the study eye at Week 4 and Week 12 in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe.
    - Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris) in the study eye at Week 4 and Week 12.
    - CFS in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline CFS ≥ 1.
    - Tear film break-up time (TFBUT) in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline TFBUT ≤ 10.
    - Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Month 6, Month 9 and Month 15/early termination.
    - Conjunctival fluorescein staining in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline conjunctival fluorescein staining ≥ 1.
    - Dry eye sensation symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline dry eye sensation symptom in mild, moderate, or severe.
    - Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe.
    - Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe.
    - Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris) in the study eye at Month 6, Month 9 and Month 15/early termination.
- IOP related endpoints:
    - Change from baseline in mean diurnal IOP in the study eye at Week 12

- Change from baseline in peak, trough, and mean diurnal IOPs in the study eye at Week 4
- Peak, trough and mean diurnal IOP response in the study eye at Week 4 and Week 12:
    - IOP 20% response (reduction in mean IOP of ≥ 20% from Baseline at the specified follow-up visit)
    - IOP 25% response (reduction in mean IOP of ≥ 25% from Baseline at the specified follow-up visit)
    - IOP 30% response (reduction in mean IOP of ≥ 30% from Baseline at the specified follow-up visit)
    - IOP < 18 mmHg response (mean IOP < 18 mmHg at the specified follow-up visit)
- Morning (9:00 am ± 1 hour) IOP in the study eye of patients treated with DE-130A enrolled in Period 2 at Month 6, Month 9, Month 15/early termination (Period 2) and change from baseline at each Period 2 visit.

- Subject global rating of treatment at Month 15/early termination and Week 12.
- Quality of life (Glaucoma Quality of Life-15) scores at Baseline visit, Week 12, and Month 15/early termination visits.

5.3.4. Safety and Tolerability Endpoints

In the Safety population, at all visits and for each treatment (Period 1) and for the Open-Label population for DE-130A at all visits (Period 2 and Periods 1 & 2 combined), safety and tolerability endpoints are:

- The incidence and severity of ocular and systemic adverse events
- Best-corrected distance visual acuity (BCDVA)
- Slit lamp examination (lashes,anterior chamber and lens)
- Dilated and undilated (cup-to-disc ratio) fundoscopy

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

The proposed 3-month phase III study is a prospective, interventional, multinational, multicentre investigator-masked, randomised, active-controlled trial to demonstrate the non-inferior IOP reducing effect of DE-130A (latanoprost 50 microg/ml preservative-free eye drops emulsion) compared to Xalatan® (latanoprost 50 microg/ml BAK-preserved eye drops emulsion) over a 12 weeks treatment period (Period 1) in patients with OAG or OHT. In addition, after Week 12, a 12-month follow-up with open-label DE-130A in a subgroup of patients (n=130) will estimate the long-term safety and tolerance and explore the long-term efficacy of DE-130A (Period 2). This Period 2 will be open in some countries only.

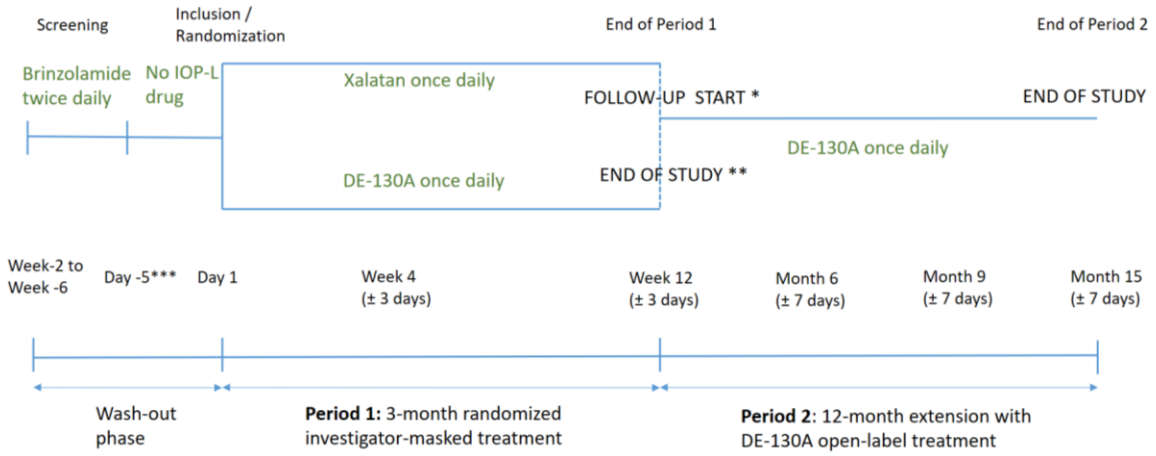
After a wash-out phase (5 days to 6 weeks) depending on previous IOP lowering medications patients will enter:

- A investigator-masked randomised 12-week treatment period (Period 1, DE-130A and Xalatan® groups randomised in 1:1 ratio),
- Followed by a 12-month open-label follow-up treatment period (Period 2, open-label DE-130A once daily) only for the first 130 patients who complete the Week 12 visit and agree to participate in the open-label period of the study

The study duration (including the wash-out period) will be up to 17 months, and patients will attend up to 6 scheduled visits after Screening visit (Table 3).

In order to assess the primary endpoint, patients will be randomly (1:1) allocated to either DE-130A or Xalatan® once daily in the evening for Period 1 (Figure 1). Furthermore, in order to minimize the effect of baseline ocular surface disease severity, the randomisation will be stratified by baseline CFS scores (CFS $\leq$ 1 vs. CFS $\geq$ 2, modified Oxford scale).

Figure 1: Study Design and Schedule of Assessments



IOP-L drug: intraocular pressure lowering drug

Notes:

* Start of the open-label DE-130A 12-month safety follow-up for the first 130 patients who complete their Week 12 visit and agree to participate in the open-label period of the study.

** End of study for patients who do not participate in the open-label period of the study.

*** Brinzolamide will be stopped 5 days before randomisation (6 to 7 days if over the weekend). At Day 1, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

Study visit schedule and assessments are summarized in Table 3.

- **Wash-out Phase**

After the signing of the informed consent and upon completion of the Screening Visit, all eligible study participants will undergo a wash-out phase.

Prior therapies for OAG or IOP must be discontinued during a wash-out phase of at least 5 days and up to 6 weeks (according to the IOP lowering medications currently used at the Screening Visit). Washout periods should be as follows:

- Prostaglandin analogs = 4 weeks
- Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
- Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks
- All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks

During this wash-out period, topical IOP-lowering medication will be replaced by brinzolamide* (Azopt®) one drop twice daily. Then brinzolamide will be stopped 5 days (6 to 7 days if over the weekend) before randomisation.

*Patients already receiving brinzolamide prior to the Screening Visit will have to stop their treatment for a 5-day washout phase before randomisation (without needing to receive again the brinzolamide provided by the Sponsor).

Five days before the Baseline Visit, brinzolamide will end (5-day period without IOP lowering medication) as the purpose of the wash-out phase is to select patients for study inclusion with a post-washout peak IOP ≥ 22 mmHg and ≤ 32 mmHg (defined as the Baseline Visit [Day 1] mean IOP at 9:00 am [±1 hour], see Appendix A-IV) in at least one eye. At baseline, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

Brinzolamide will be provided by the Sponsor. During the wash-out phase protocol-authorised artificial tears (AT, see Section 8.2) are allowed but within the SmPC recommendations.

After the 5 days (6 to 7 days if over the weekend) without any IOP-lowering medication at the end of the wash-out phase, patients will undergo the Baseline Visit (Day 1). Patients who meet the inclusion criteria for IOP ≥ 22 mmHg and ≤ 32 mmHg [defined by a mean IOP at 9:00 am (±1 hour)] in at least one eye will be randomised in 1:1 ratio to either DE-130A or Xalatan® (one drop once daily in the evening) for Period 1 of the study. Patients not fulfilling the inclusion criteria following the wash-out phase will be withdrawn from the study without having received the study medication, and they will start the best treatment for their condition according to their ophthalmologist's opinion.

Eligible patients will thus enter the Study Treatment Periods.

- **Study Treatment Period 1**

During Baseline Visit (Day 1), patients will be instructed to instil one drop of the investigator-masked study treatment once daily in the affected eye(s) (unilateral or bilateral OAG/OHT), and they will be scheduled for 2 additional study visits [Week 4 (± 3 days), Week 12 (± 3 days)] to assess the peak and trough IOPs [at 9:00 am (±1 hour) and 4:00 pm (±1 hour), respectively].

The following other assessments will be performed prior to the morning (9:00 am ±1 hour) IOP measurement:

- Evaluation of OSD signs [corneal and conjunctival fluorescein staining (scored with modified Oxford Scale), tear film break-up time (TFBUT)],
- Completion of quality of life questionnaires (Glaucoma Quality of Life-15),
- Evaluation of ocular tolerance [including slit lamp biomicroscopy and best corrected visual acuity (BCVA)] and systemic safety (medical/medication update).
- Assessement of the Subject Global Rating of Treatment, at Week 12 visit.

At Week 12, after the trough IOP (4:00 pm), a dilated fundoscopy will be carried out.

At Week 12 and early termination visit, a urine pregnancy test will be performed on all females of childbearing potential.

At Week 12, the 130 first patients who complete Period 1 and agree to the open-label follow-up will enter Study Treatment Period 2, while the supernumerary patients will exit the study.

- **Study Treatment Period 2**

At Week 12 visit, the eligible patients for Period 2 will start the 12-month open-label treatment Period 2 study:

During Period 2, 3 additional study visits [Month 6 (±7days), Month 9 (± 7 days), and Month 15 (± 7 days)] will be scheduled to assess the safety and tolerability of DE-130A. The morning IOP [at 9:00 am (±1 hour)] will be measured.

The following other assessments will be performed prior to the IOP measurement:

- Evaluation of OSD signs [corneal and conjunctival fluorescein staining (scored with modified Oxford Scale), tear film break-up time (TFBUT)],
- Completion of quality of life questionnaires (Glaucoma Quality of Life-15),
- Evaluation of ocular tolerance [including slit lamp biomicroscopy and best corrected visual acuity (BCVA)] and systemic safety (medical/medication update).
- Assessement of the Subject Global Rating of Treatment, only at Month 15 visit.

At Month 15 Or early termination visit, women of childbearing potential will performed a urine pregnancy test.

At Month 15 visit, after the morning IOP, a dilated fundoscopy will be carried out.

In addition to the study medication, during the whole study, patients will also be allowed to use, if needed, unpreserved artificial tears to improve their dry eye symptoms. Patients must be instructed not to use artificial tears within 30 minutes before or after use of the study medication and within two hours before a scheduled study visit. All other concomitant medications will be recorded on the electronic case report form (eCRF). A change in the use of the study treatments or any use of topical eye drops other than the study medication, or topical medications allowed during the study will be considered a protocol violation. In this clinical trial, the emergence of complications and the safety of study treatment will be assessed at each visit up to the exit visit (Month 15 for the first 130 patients who completed their Week 12 Visit and willing to participate in the 12-month open-label period of the study and Week 12 for the supernumerative patients).

6.2. Number of Subjects

Approximately 380 patients with Open-Angle Glaucoma (OAG), or ocular hypertension (OHT) (190 in DE-130A group and 190 in Xalatan® group) will be randomised in this study to obtain 173 evaluable patients per treatment group at Week 12 (assuming a dropout rate of 10%).

A safety follow up of 12 months is planned for the first 130 patients who will attend the Week 12 visit and and agree to participate in the open-label period of the study. They will then be treated with DE-130A in an open label fashion.

6.3. Dose Adjustment Criteria

6.3.1. Efficacy Criteria for Adjustment or Stopping Doses

Not applicable.

6.3.2. Safety Criteria for Adjustment or Stopping Doses

Not applicable.

6.3.3. Pharmacokinetic Criteria for Adjustment or Stopping Doses

Not applicable.

6.4. Criteria for Study Termination

The sponsor reserves the right to discontinue the study conduct for any safety, ethical or administrative (force majeure) reason at any time.

If the trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IECs should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

6.5. End of Trial

End of Trial is defined as the last visit of the last subject.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Demographic, Baseline Characteristics, and Medical History

At Screening visit, the information to be obtained will include demographic (age, sex, contraceptive status, race, ethnicity, smoking status) and baseline disease characteristics (OAG, OHT, and OSD history and characteristics).

Medical history to be obtained will include whether the patient has any significant conditions or diseases relevant to the condition/disease under study that stopped at or prior to the signing of the informed consent. Ongoing conditions are considered concurrent medical conditions.

Medication history information to be obtained includes any ophthalmic medication within 1 year prior to signing of the informed consent and any other medication stopped at or within 3 months prior to signing of the informed consent.

7.2. Subject Inclusion Criteria

Patient eligibility is determined according to the following inclusion criteria:

1. Male or female, 18 years of age or older
2. The patient has signed and dated a written informed consent form and any required privacy authorization prior to the conduct of any study procedures.
3. Diagnosis of OAG (primary open angle glaucoma, pseudo exfoliative glaucoma, or pigmentary glaucoma), or OHT in eligible eye(s) currently on monotherapy.
4. Unilateral OAG, or OHT are permissible as long as the physician does not anticipate significant IOP changes to the fellow eye that would require treatment during the duration of the study.
5. Current treatment with monotherapy for OAG or OHT with a controlled IOP ≤ 18 mmHg in each eye (pre-washout).
6. Stable visual field (based on at least two visual fields available within the last 18 months prior to screening, including one in the last 6 months; A visual field test will be performed at screening if not already performed within the last 6 months prior to screening) in each eye. If historical visual fields are not available within the last 18 months prior to screening, but at least two OCTs (optical coherence tomography) are available, including one in the last 6 months and are stable, the patient can be enrolled in the study if a visual field test is also performed at screening and shows no defect or only an early visual field loss in either eye (mean deviation lesser than -6 dB).
7. Post-washout IOP ≥ 22 mmHg in at least one eye (defined at baseline visit [Day 1] by IOP measurement at both 9:00 am ± 1 hour and 4:00 pm ±1 hour). If IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the

second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

8. Post-washout IOP ≤ 32 mmHg (defined at baseline visit [Day 1] by IOP measurement at both 9:00 am ±1 hour and 4:00 pm ±1 hour) in both eyes.
9. Ability to discontinue their current topical IOP-lowering medication for the required washout period. Washout periods should be as follows;
    - Prostaglandin analogs = 4 weeks
    - Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
    - Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks
    - All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks
10. Snellen best corrected visual acuity score of 20/100 or better in each eye
11. Patient must be willing to discontinue wearing contact lenses during the study.
12. Adequate health for study participation as determined by the investigator
13. In the opinion of the investigator, the patient is capable of understanding and complying with protocol requirements
14. Patient must be willing and able to undergo and return for scheduled study-related examinations.

7.3. Subject Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Any form of glaucoma other than primary open angle glaucoma, pseudo exfoliative glaucoma, and pigmentary glaucoma in either eye.
2. IOP at any time point during the Screening or Baseline visits (Visits 1 or 2) of > 32 mmHg in either eye.
3. Current treatment for glaucoma with a fixed-combination therapy or more than one drug in either eye or with an oral drug within 6 months prior to screening.
4. Corneal abnormalities that would interfere with accurate IOP readings with an applanation tonometer in either eye.
5. Central corneal thickness ≤ 480 μm or ≥ 600 μm in either eye (historical data or at the screening visit).
6. Significant visual field loss (absolute defect in the 10° central point or mean deviation worse than -12 dB) or progressive field loss during the year before screening in either.
7. Significant optic nerve abnormality, other than glaucomatous abnormalities in the opinion of the investigator as determined by ophthalmoscopy in either eye.

8. Significant changes of the optic neuropathy (e.g. increase cupping since the last examination, optic nerve hemorrhage) in either eye.
9. Inability to visualize the patient's optic nerve in either eye.
10. Gonioscopy consistent with potential angle closure glaucoma in either eye.
11. Patients with severe blepharitis and/or Meibomian Gland Disease (MGD). Patients enrolled with mild to moderate blepharitis and/or MGD should be treated as appropriate during the study in either eye.
12. Use of oral or topical ophthalmic steroid within the past 14 days from screening date, or anticipated need for ocular steroid treatment during the study in either eye.
13. Use of intravitreal or peribulbar injection of depot steroid or placement of an intravitreal steroid implant within the past 3 months from screening date in either eye.
14. Known allergy or sensitivity to the study medications.
15. Known hypersensitivity to sulfonamides, severe renal impairment or hyperchloraemic acidosis.
16. Active or expected ocular allergy during period 1.
17. Any active ocular disease (e.g. uveitis, ocular infection, severe dry eye with CFS grade 4 or more on the modified Oxford scale) in either eye. Patients may have mild cataracts, age-related maculopathy or background diabetic retinopathy if, in the opinion of the Investigator, it would not interfere with the conduct of the study.
18. Intraocular surgery within 6 months prior to screening in either eye.
19. Past history of any filtering surgery for glaucoma in either eye.
20. Refractive surgery of any type within 1 year prior to screening in either eye.
21. Uncontrolled systemic disease of any type.
22. Anticipated alteration in chronic therapy with or introduction of agents known to have a substantial effect on IOP (e.g., alpha-adrenergic agonists, beta-adrenergic antagonists, calcium channel blockers, ACE inhibitors and/or angiotensin II receptor blockers), unless the subject and the medication dosage have been stable for three months prior to the screening visit and the dosage is not expected to change during the study.
23. Anticipated change in dosage of or introduction of new medications for chronic cardiac, pulmonary or hypertensive conditions.
24. Females who are pregnant or lactating and females of child-bearing potential who are not using a medically acceptable, highly effective method of birth control.
25. Current enrolment in an investigational drug or device study or participation in such a study within 30 days prior to screening.
26. History of drug or alcohol abuse.

27. Patient has any condition or situation that, in the Investigator's opinion, might confound the results of the study, may put the patient at significant risk or might interfere with the patient's ability to participate in the study.

7.4. Screen Failure

Investigators must account for all patients who sign informed consent. If the patient is found to be not eligible at screening or baseline visit, the investigator should complete the eCRF for all assessments they performed.

The primary reason for screen failure should be recorded in the eCRF using the following categories:

- Did not meet inclusion criteria or did meet exclusion criteria.
- Adverse events

Patient numbers assigned to patients who fail screening should not be reused. Re-screening is possible.

7.5. Subject Withdrawal Criteria

The primary reason for discontinuation or withdrawal of the patient from the study should be recorded in the electronic case report form (eCRF) using the following categories.

1. Adverse event (AE). The patient has experienced a AE that requires early termination because continued participation imposes an unacceptable risk to the patient's health or the patient is unwilling to continue because of a AE. Patients discontinued for drug – related AE(s) will be followed-up after patient's discontinuation until the event is resolved, stabilized or a final assessment can otherwise be done by the investigator.
2. Protocol deviation. The discovery after administration of the first dose of study drug that the patient failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the patient's health.
3. Lost to follow-up. The patient did not return to the clinic and attempts to contact the patient were unsuccessful. In case of a patient lost-to-follow-up, the investigator must do his/her best to contact the patient initially by phone, then by letter, and finally by certified mail. If no response is obtained from the patient, the investigator is encouraged to contact one of the patient's relatives or his/her general physician. These attempts must be documented and associated documentation filed in the patient medical chart.
4. Voluntary withdrawal. The patient (or patient's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Study termination. The Sponsor, IEC, or regulatory agency terminates the study.
6. Lack of efficacy. the patient or the physician does not feel that the study medication has adequately relieved his/her symptoms.
7. Pregnancy. The patient is found to be pregnant.

   Note: If the patient is found to be pregnant, the patient must be withdrawn immediately.
8. Investigator decision due to non-compliance (to IMP, study visits or study related procedure).
9. Other reason, specify.

   Note: All attempts should be made to determine the reason if Other is chosen (e.g. moving) and specific primary reason should be recorded in the "specify" field of the eCRF.

7.6. Procedures for Discontinuation or Withdrawal of a Patient

The investigator may terminate a patient's study participation at any time during the study when the patient meets the study withdrawal criteria described in Section 7.5. Efforts should be made to perform all procedures scheduled for the Week 12/Month 15/Early Termination (ET) visit. Discontinued patients will not be replaced.

7.7. Completed Enrolment

The study enrolment will be considered as completed when the desired number of at least 380 patients is randomised. Patients between the screening visit and the baseline visit at the time the desired number of 380 randomised patients is achieved, are eligible for inclusion if they fulfil the inclusion/exclusion criteria at the Baseline Visit (Day 1).

8. TREATMENT OF SUBJECTS

8.1. Description of Study Drug

8.1.1. DE-130A

DE-130A 50 microg/ml eye drops emulsion, SD is formulated as sterile, preservative free, positively charged (cationic) oil-in-water ophthalmic emulsion using well-known excipients. It contains 50 micrograms of latanoprost per ml of emulsion. DE-130A is an oil-in-water emulsion, in which the oil droplets, containing latanoprost, are dispersed in the aqueous phase (see the Investigator's Brochure).

DE-130A contains the following excipients:

- Medium Chain Triglycerides (MCT; w/w: 1.0%): the emulsion's oily agent that constitutes the main droplet core component and solubilizes the drug.
- Cetalkonium chloride (CKC; w/w: 0.005%): a cationic (positively charged) surfactant that ensures the emulsion stability by providing a positive charge to the oil droplets and consequently an electrostatic repulsion between droplets.
- Polysorbate 80 (w/w: 0.050%) is a non-ionic surfactant and it is used to obtain stable emulsion.
- Glycerol (w/w: 2.400%) is used to make the emulsion isotonic. Glycerol was selected as osmotic agent because it does not destabilize the emulsion.
- Water for injections is added as a solvent

Batch number and expiration dates of the investigational drug will be provided in the certificate of analysis.

8.1.2. Xalatan®

Xalatan® composition is described in its SmPC. Its active substance is latanoprost (50 microg/ml) and excipients include sodium chloride, benzalkonium chloride (BAK, 0.02%), sodium dihydrogen phosphate monohydrate, anhydrous disodium phosphate, water for injections.

8.2. Azopt®

Azopt® will be provided to the patients for the wash out prior to the Day 1 visit.

Patients already receiving brinzolamide prior to screening visit will have to stop their treatment for a 5-day washout before randomisation (6 to 7 days if over the weekend) without any need to receive again the brinzolamide provided by the Sponsor. At baseline, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment

should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

Azopt® composition is described in its SmPC. Its active substance is brinzolamide (10mg/ml).

8.3. Concomitant Medications/Therapies

Concomitant therapies consist of any treatment or medication given concurrently with the study medication. The following concomitant medication(s)/treatment(s) are prohibited during study participation:

- Use of any preserved artificial tears
- Use of preservative free artificial tears over the SmPC recommended regimen
- Use of Cationorm®
- Use of any topical ocular treatments other than the study medication except preservative free artificial tears used according to the SmPC recommended regimen (but these artificial tears usage should remain stable during the course of the study).
- Any refractive surgery (LASIK, LASEK, PRK, etc.) during the course of the study.

The initiation or use during the course of the study of any treatments or procedures described above will be considered as a protocol deviation.

8.4. Treatment Compliance

Patient compliance will be assessed at each visit by pharmacist or person in charge of study delivery by questioning the patient and comparison to drug accountablity. All reported incidents of the lack of compliance will be recorded on the eCRF with the reasons. If a patient is persistently noncompliant with the study medication, the patient should be withdrawn from the study. All patients should be reinstructed about the dosing requirement during study visits. The authorized study personnel conducting the re-education must document the process in the patient source records.

8.5. Randomisation and Masking

At Baseline visit (Day 1), subjects who are eligible for the study will be randomly assigned (by the IWRS) in a 1:1 ratio to receive either DE-130A or Xalatan® for 12 weeks in a investigator-masked fashion. The randomisation will be stratified according to the CFS score of the study eye at Baseline visit (CFS $\leq$ 1 vs. CFS $\geq$ 2, modified Oxford scale). A computer algorithm for random number generation will be used to generate the treatment assignments.

Treatment assignments will be masked to Investigators. The investigator should try to avoid knowing the masked treatment. However, **IN CASE OF EMERGENCY ONLY, (i.e. SERIOUS ADVERSE EVENT AND ONLY WHEN THIS INFORMATION INFLUENCES THE PATIENT'S MANAGEMENT)**, the investigator may unmask the patient by using IWRS, in order to obtain the study medication information (i.e. DE-130A or Xalatan®) to immediately start

the appropriate treatment [to be recorded in the source data and eCRF (electronic Case Report Form)]. A record will be made for the date, time and reason for breaking the code. The investigator should inform the Sponsor immediately after unmasking. The details of this unmasking procedure will be described in a separate document. Patients unmasked for the management of a SAE will be discontinued from the study.

Treatment masking to the patients would be impossible due to the difference in the appearance of the DE-130A and Xalantan eye drops. But the patients shall not be explicitely told about the name of the study drug by the drug dispensing staff. Every effort will be made to keep all study team members involved in the study masked during the whole Period 1 study period, this shall include Santen personnel (except for drug supply personnel), CRO personnel (including CRAs except the ones in charge of accountability), and staffs at all clinical centers (except the drug dispensing person), etc.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Refer to section 8.1.

9.2. Study Drug Packaging and Labeling

9.2.1. Investigator-masked study treatment sequence of Period 1

The investigational medical products will be supplied in investigator-masked sealed cardboard box for the 3-month Period 1:

- DE-130A: polyethylene single-dose containers presented in sealed laminate aluminum pouch package (1 pouch contains 5 single-dose containers). 22 aluminum pouches (i.e. 110 single-dose containers) will be placed together in a sealed cardboard box. Each single dose container is sufficient to treat both eyes.
- Xalatan®: Three 2.5 ml dropper containers will be placed together in a sealed cardboard box.

Investigational medicinal products are labelled in accordance with GMP Annex 13 requirements.

Investigational medicinal products should not be labelled by site staff or by pharmacy with any additional label without written permission from the Sponsor and IEC.

9.2.2. Open-label DE-130A of Period 2

For the 130 patients entering for the 12-month safety follow-up (Period 2), DE-130A will be provided at Week 12, Month 6 and Month 9 visits.

At Week 12 and Month 6 Visits, DE-130A will be supplied in polyethylene single-dose containers presented in sealed laminate aluminum pouch package (1 pouch contains 5 single-dose containers:

- 22 aluminum pouches (i.e. 110 single-dose containers) will be placed together in a sealed cardboard box (called one kit).

At Month 9, DE-130A will also be supplied in polyethylene single-dose containers presented in sealed laminate aluminum pouch package (1 pouch contains 5 single-dose containers):

- 44 aluminum pouches (i.e. 220 single-dose containers) of DE-130A will be dispensed to the patient i.e. two kits.

Investigational medicinal products are labelled in accordance with GMP Annex 13 requirements.

9.3. Study Drug Storage

All clinical trial material must be kept in an appropriate, limited-access, secure location until it is used or returned to the sponsor or designee for destruction. All study medication must be stored under the conditions specified on the label, and remain in the original container until dispensed. **A daily temperature log of the drug storage area must be maintained every working day**. Any temperature excursion of study drug should be notified to the sponsor and the supplies placed in quarantine before further instruction is received from the sponsor. The study medication will be delivered to the study centres by the clinical supplies distributor.

The study medication, DE-130A must be stored below 30°C and it must not be frozen. After opening of the aluminium pouch, the single dose container should be kept in the original pouch in order to avoid evaporation. The single dose container is to be used immediately after opening and the contents of one single dose container is sufficient for both eyes. The remaining content of the single dose container sould be discarded immediately after administration.

The study medication Xalatan® must not be stored above 25°C and after opening of container used within four weeks. Keep the container in the outer carton box in order to protect from light.

Initially each centre will receive adequate supplies of study medication to cover the study treatment period for a pre-defined number of patients. Additional supplies will be dispatched after taking into account the recruitment rate of each study centre. The investigator or his/her designee will be responsible for correct handling and storage of the study medication during the course of the study.

9.4. Study Drug Preparation

Not applicable.

9.5. Administration

The investigational product of both Study Treatment Periods (investigator-masked study medication and open-label DE-130A) will be instilled one drop, once daily in the evening (9 pm ±1 hour) in the conjunctival sac of the affected eye(s)

The study medication is to be dispensed only by the investigator designee, and will be used in accordance with this protocol. Under no circumstances will the investigator allow the study products to be used other than directed by the protocol. All dispensations and returns of study medication have to be documented in the investigator's file provided by the Sponsor.

In order to ensure patient anonymity, patients will be identified by codes or other means of record identification.

9.6. Study Drug Accountability and Destruction

The Principal Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The receipt of clinical supplies should be completed, signed and returned

as directed by Santen (or designee). A copy must be maintained at the site for the Investigator's records. The Principal Investigator will keep a current record of the inventory and dispensing of all study drugs. This record will be made available to CRO or Santen Monitor (or designee) for the purpose of accounting for all clinical supplies. Any discrepancy and/or deficiency must be recorded with an explanation. All supplies sent to investigator must be accounted for and in no case will study drugs be used in any unauthorized situation.

It is a responsibility of the Principal Investigator to return any unused supplies to Santen monitor (or designee) at the conclusion of the study.

Subjects are instructed to return all unused Single Dose containers, pouches and cardboard box of DE-130A and all used and unused IMP bottles and cardboard box of Xalatan® at the next visit. The used SD containers should be discarded by the subject after daily drop(s) have been instilled. Subjects are instructed to return wash-out medication including outer cardboard box back to the site at Baseline visit (Day 1).

Upon completion or earlier termination of the study the investigator will, unless otherwise agreed, return to the clinical supplies distributor any surplus quantities, unused single dose containers and used and unused bottles, of study medication. The investigator will record each quantity of study medication that has been damaged or is missing.

Drug supplies will be counted and reconciled at the site before being returned to Santen or designee or being destroyed by the site after Sponsor written approval.

10. SCHEDULE OF OBSERVATIONS AND PROCEDURES

The schedule for all study-related procedures and evaluations is shown in Table 3. Assessments should be completed at the designated visit/time point(s), and should be performed in both eyes.

Table 3: Study Design and Schedule of Assessments

	Screening	**Baseline**	**Period 1**	**Period 2**		**End of Study Visit**	
	-5 days to Week -6 [a]	Day 1	Week 4 (Day 29 ± 3 days)	Month 6 [b] (Day181 ±7days)	Month 9 [b] (Day 271 ±7days)	**Period 1**: Week 12 (Day 85 ± 3 days) **Period 2**: Month 15 [b] (Day451± 7 days) **Early Termination**	Unscheduled visit
Signed Informed consent	X						
Demographic information	X						
Review of Inclusion/Exclusion Criteria	X	X					
Ocular and systemic medical history	X						
Previous and concomitant ocular and systemic medications (including ATs)	X	X†	X†	X†	X†	X†	X†
Urine pregnancy test (women of childbearing potential only)	X					X	
Unpreserved artificial tears use[c]	X	X†	X†	X†	X†	X†	X†
OSD symptoms [d]	X	X†	X†	X†	X†	X†	X†
Quality of life questionnaire (Glaucoma Quality of Life-15) [e]		X†				X†	

	Screening	**Baseline**	**Period 1**	**Period 2**		**End of Study Visit**	
	-5 days to Week -6 [a]	Day 1	Week 4 (Day 29 ± 3 days)	Month 6 [b] (Day181 ±7days)	Month 9 [b] (Day 271 ±7days)	**Period 1**: Week 12 (Day 85 ± 3 days) **Period 2**: Month 15 [b] (Day451± 7 days) **Early Termination**	Unscheduled visit
Subject Global Rating of Treatment						X†	X
Best corrected distance visual acuity (BCDVA)	X	X†	X†	X†	X†	X†	X†
Slit lamp examination	X	X†	X†	X†	X†	X†	X†
Ocular Surface Disease Evaluations (TFBUT, corneal and conjunctival fluorescein staining with modified Oxford scale)	X	X†	X†	X†	X†	X†	X†
Morning IOP [f]	X			X	X	X (*only Period 2*)	X (only if during Period 2)
Diurnal IOP (Peak and trough times) [g]		X	X			X (*only Period 1*)	X (only if during Period 1)
Cup to disc ratio (undilated fundoscopy)		X	X	X	X		X
Dilated fundoscopy	X					X#	
Visual Field*	X	X			X		
Adverse events (AEs) [i]		X	X	X	X	X	X
Discontinuation of current IOP lowering medication	X						

	Screening	**Baseline**	**Period 1**	**Period 2**		**End of Study Visit**	
	-5 days to Week -6 [a]	Day 1	Week 4 (Day 29 ± 3 days)	Month 6 [b] (Day181 ±7days)	Month 9 [b] (Day 271 ±7days)	**Period 1**: Week 12 (Day 85 ± 3 days) **Period 2**: Month 15 [b] (Day451± 7 days) **Early Termination**	Unscheduled visit
Randomise qualified subjects to treatment		X					
Dispensation of Wash-out IOP lowering medication [j]	X						
Collection of Wash-out IOP lowering medication [j]		X					
Dispensation of **investigator-masked study medication** [k]		X					
Dispensation of **open-label study medication** [l]				X	X	X	
Collection of unused study medication [m]				X	X	X	

† To be performed/completed before the morning IOP time point (9:00 am ± 1 hour)

‡ To be performed/completed after the afternoon IOP time point (4:00 pm ± 1 hour)

Period 1: To be performed/completed after the afternoon IOP time point (4:00 pm ± 1 hour
Period 2: To be performed/completed after the morning IOP time point (9:00 am ± 1 hour)

[a] *in agreement with the following conditions:*

- *Prostaglandin analogs: = 4 weeks*
- *Topical beta blockers: ≥ 3 weeks and ≤ 4 weeks*
- *Topical carbonic anhydrase inhibitors: ≥ 5 days and ≤ 4 weeks*
- *All other IOP lowering medication: ≥ 2 weeks and ≤ 4 weeks*

***** *At screening if not already performed within the last 6 months prior to screening. At baseline and Month 9 for the first 130 patients who will be part on the period 2.*

[b] *Months are of 30 days length.*

[c] *Unpreserved artificial tears (AT) use : average daily use of AT will be asked by the investigator.*

[d] *3-symptom will be completed at the investigational site.*
[e] *QoL questionnaires to be completed at the investigational site.*
[f] *Must be performed at 9:00 am (all IOP measurements must be conducted within +/- 1 hour of the required time), using Goldmann applanation tonometry.*
[g] *Must be performed at 9:00 am and 4:00 pm time points (all IOP measurements must be conducted within +/- 1 hour of the required time), using Goldmann applanation tonometry.*
[i] *Record AEs if the unscheduled visit is after the first study drug administration.*
[j] *Over the wash-out period: brinzolamide one drop twice daily.*
[k] *EITHER one drop of **DE-130A** (latanoprost 50 microg/ml) OR one drop of **Xalatan®**(latanoprost 50 microg/ml) once daily in the evening (9 pm ± 1 hour), in the conjunctival sac of the affected eye(s).*
[l] *one drop of **DE-130A** once daily (latanoprost 50 microg/ml) for 12 months.*
[m] *In order to keep the investigator masked to the study medication, **the unused study medication of Period 1 wil only be collected at Week 12 visit.***

10.1. Screening

Patients will be screened for the study from 6 weeks to 5 days prior to the first dose of study medication, depending on the previous IOP lowering medication. Patients will be screened in accordance with predefined inclusion and exclusion criteria.

Screening Visit: Day -5 to Week -6

Procedures to be completed at Screening Visit include:

- Sign Informed consent.
- Inclusion/exclusion criteria review.
- Demographic information.
- Ocular and systemic medical history.
- Urine pregnancy test (women of childbearing potential only).
- Previous and concomitant ocular and systemic medications [including artificial tears (AT) usage].
- Unpreserved artificial tears (AT) average use over the previous week will be asked by the investigator.
- Assess the severity of each of 3 OSD symptoms during the previous week (Appendix A-I).
- BCDVA (in Snellen).
- Slit lamp examination (Appendix A-II).
- Tear break up time (TFBUT).
- Corneal and conjunctival fluorescein staining (modified Oxford scale, Appendix A-III).
- Intraocular Pressure measurement using the Goldmann applanation tonometry (Appendix A-IV).
- Dilated fundoscopy, after the peak IOP (9:00 am) (Appendix A-VI).
- Eligible patients will discontinue their IOP lowering medication and any prohibited ocular treatments.
- Use of AT will be explained to patients.
- Patients will be scheduled to return to the clinic in the delay established according to their previous IO lowering medication for the Baseline visit.

Of note: A visual Field test will be performed at screening visit for patients who have not performed a visual field test in the past six months prior to this visit.

10.2. Investigator-masked treatment Phase (Period 1)

The visit time is to be established according to the IOP morning measurement (9:00 am $\pm$1 hour). All assessments should be done in the mentioned order to ensure that additional producedure doesn't interfere with the results of other examinations.

10.2.1. Baseline: Day 1

- Inclusion/exclusion criteria review.

- Record of concomitant ocular and systemic medications.
- Daily average of unpreserved AT use
- Assess the severity of each of 3 OSD symptoms during the previous week
- Quality of life questionnaires (Glaucoma Quality of Life-15, Appendix A-V).
- Visual field for the first 130 patients who will be part of the period 2
- BCDVA (in Snellen).
- Slit lamp examination.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am $\pm$1 hour).
- Afternoon IOP (4:00 pm $\pm$1 hour).
- Cup to disc ratio (undilated fundoscopy)
- Record adverse event
- Collection of the brinzolamide container.
- Verify inclusion and exclusion criteria based on evaluations just performed:
  - Patients **fulfilling** the inclusion / exclusion criteria will receive the study treatment for the next 3 months.
  - Patients **not fulfilling** the inclusion / exclusion criteria will be discontinued from the study and the patient becomes a screen failure.
- The site will contact IWRS system - Medidata Balance, to obtain the investigator-masked treatment number.
- Dispensation of investigator-masked study medication for the 3-month period.

10.2.2. Week 4 (±3 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage].
- Record adverse events (AEs).
- Daily average of unpreserved AT use
- Assess the severity of each of 3 OSD symptoms during the previous week
- BCDVA (in Snellen).
- Slit lamp examination.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am $\pm$1 hour).
- Afternoon IOP (4:00 pm $\pm$1 hour).
- Cup to disc ratio (undilated fundoscopy, after the trough IOP (4:00 pm)).

10.2.3. Week 12 (±3 days) - End of study visit of the other patients than the 130 first completers

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage].
- Urine pregnancy test (women of childbearing potential only).
- Record adverse events (AEs).
- Daily average of unpreserved AT use
- Assess the severity of each of 3 OSD symptoms during the previous week
- Quality of life questionnaires (Glaucoma Quality of Life-15).
- Subject Global Rating of Treatment
- BCDVA (in Snellen).
- Slit lamp examination.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am ±1 hour).
- Afternoon IOP (4:00 pm ±1 hour).
- Dilated fundoscopy, after the trough IOP (4:00 pm)
- Cup to disc ratio.
- Collection of the study medication containers (not by investigator performing examinations) (unused).
- Assessment of compliance to study medication.

First 130 Period 1 completer patients - Patients will enter the 12-month safety follow-up

- Dispensation of open-label DE-130A for the 3-month period.

Period 1 supernumerative patients - Patients will exit the study

- The investigator will prescribe the most appropriate therapy to the patients.

10.3. Open-label DE-130A treatment Phase (Period 2)

The visit time is to be established according to the IOP morning measurement (9:00 am ±1 hour). All assessments should be done in the mentioned order to ensure that additional producedure doesn't interfere with the results of other examinations.

10.3.1. Month 6 (± 7 days) and Month 9 (±7 days)

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage].
- Record adverse events (AEs).
- Daily average of unpreserved AT use

- Assess the severity of each of 3 OSD symptoms during the previous week
- Only at month 9: Visual field
- BCDVA (in Snellen).
- Slit lamp examination.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am $\pm$1 hour).
- Cup to disc ratio (undilated fundoscopy, after the peak IOP (9:00 am)).
- Collection of the study medication containers (unused).
- Dispensation of open-label DE-130A for the 3-month period at M6 and 6-month period at M9.
- Compliance with study medication

10.3.2. Month 15 (±7 days) - End of study visit of the 130 first completers of Period 1

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage].
- Urine pregnancy test (women of childbearing potential only).
- Record adverse events (AEs).
- Daily average of unpreserved AT use
- Assess the severity of each of 3 OSD symptoms during the previous week.
- Quality of life questionnaires (Glaucoma Quality of Life-15).
- Subject Global Rating of Treatment .
- BCDVA (in Snellen).
- Slit lamp examination.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am $\pm$1 hour).
- Dilated fundoscopy, after the peak IOP (9:00 am)
- Collection of the study medication containers (unused).
- Assessment of compliance to study medication.
- The investigator will prescribe the most appropriate therapy to the patients.

10.3.3. Unscheduled Visit

An Unscheduled visit will be performed if required between two scheduled visits (e.g: patient's request, to check of medical events as needed, but not for routine care that is not related to the protocol) and the reason for such a visit will be recorded in the CRF. In this case, the investigator

may perform any of the following applicable study procedures and examinations as long as the chronological order defined below is followed.

- Record of concomitant ocular and systemic medications [other than artificial tear (AT) usage].
- Record adverse events (AEs).
- Daily average of unpreserved AT use
- OSD symptom assessments
- Subject Global Rating of Treatment
- BCDVA (in Snellen)
- Slit lamp examination.
- Cup to disc ratio (undilated fundoscopy) , after the trough IOP (4:00 pm) if during Period 1.
- Cup to disc ratio (undilated fundoscopy) , after the IOP (9:00 am) if during Period 2.
- TFBUT.
- Corneal and conjunctival fluorescein staining (modified Oxford scale).
- Morning IOP (9:00 am $\pm$1 hour).
- Afternoon IOP (4:00 pm $\pm$1 hour), ONLY if during Period 1.
- Assessment of compliance to study medication.

If necessary (e.g. to follow up an AE) the investigator may schedule further visits at his discretion.

In case of patient's premature study discontinuation:

- the investigator will be asked to perform all the examinations and assessments scheduled for the End of Study Visit (Week 12/Month 15/Early Termination) .
- the investigator will ensure that unused (SD container) and used and unused (IMP bottles) study medication for the study period has been collected from the patient by the appointed person at the study site (the used SD containers should be discarded by the patient after daily drop(s) have been instilled).

11. ASSESSMENT OF EFFICACY

11.1. Tonometry for measurement of Intraocular Pressure (IOP) (mmHg)

IOP will be measured using Goldman applanation tonometry (one measurement), after instillation of one drop of oxybuprocaine 0.4% and fluorescein 2% solutions (both solutions provided by the Sponsor) (Appendix A-IV) . IOP will be assessed after completion of all other slit lamp examinations and dry eye assessments to avoid oxybuprocaine interference with the other examinations.

Morning IOP must be performed at 9:00 am and afternoon IOP at 4:00 pm. all IOP measurements must be conducted within +/- 1 hour of the required time points.

The patient and slit lamp should be adjusted so that the patient's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Both eyes will be tested, with the right eye preceding the left eye. The same equipment must be used throughout the course of the study.

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

11.2. Corneal and Conjunctival Fluorescein Staining

Corneal and conjunctival fluorescein staining will be assessed immediately following the TFBUT. Reading will be performed between 1 and 4 minutes after fluorescein instillation for the TFBUT, to ensure that the dye does not diffuse into stroma blurring the discrete margin of any staining defects. The eye will then be examined at the slit lamp (16X magnification) using a yellow barrier filter and cobalt blue illumination to enhance visibility of staining.

Staining using fluorescein (provided by the Sponsor) will be graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5 per area [cornea + nasal and temporal conjunctiva]) for cornea and conjunctiva separately, see Appendix A-III. On this modified scale, the score 0 corresponds to no staining dots and the score 0.5 corresponds to one staining dot per area.

A CFS grade of 0 represents complete corneal clearing.

A negative change score from baseline (Period 1) and/or from Week 12 (Period 2) will indicate improvement.

11.3. Tear Film Break-Up Time

Tear film break-up time (TFBUT) will be measured by determining the time to tear break-up.

The tear film break-up time (TFBUT) measurement is performed in conjunction with corneal/conjunctival fluorescein staining. 2 µl of non-preserved 2% sodium fluorescein is instilled onto the bulbar conjunctiva of each eye without inducing reflex tearing by using a micro-pipette.

To thoroughly mix the fluorescein with the tear film, the patient will be instructed to blink several times. In order to achieve maximum fluorescence, the examiner should wait approximately 30 seconds after instillation before evaluating TFBUT. With the aid of a slit lamp at 10X magnification using cobalt blue illumination, the examiner will monitor the integrity of the tear film, noting the time it takes to form lacunae (clear spaces in the tear film) from the time that the eye is opened after the last blink. The TFBUT will be measured twice during the first minute after the instillation of the fluorescein, by using a stop watch. If the 2 readings differ by more than 2 seconds, then a third reading will be taken.

The TFBUT value will be the average of the 2 or 3 measurements.

A positive change from baseline (Period 1) and/or from Week 12 (Period 2) will indicate improvement.

11.4. Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The subject will be seated while being examined; grading of the Meibomian glands, lids, lashes, conjunctiva, tear film debris, anterior chamber and lens will be done according the scales in AppendixA-II.

Slit lamp examination will also be used as a safety assessment (see 12.1.2).

11.5. Dilated and undilated fundoscopy

After the dilatation of the pupil with mydriatic eye drops, the fundus examination will be performed to assess the retina, optic nerve head, blood vessels. Cup-to-disc (C/D) ratio will be evaluated to assess the progression of glaucoma (Appendix A-VI). At Baseline, Week 4, Month 6, and Month 9 the fundoscopy will be done without dilatation.

11.6. Use of Concomitant Artificial Tears

The use of unpreserved artificial tears will be monitored over the course of the study for each patient. Patients will be asked about the average number of times per day artificial tears was used over the last week, and number of days they were not used during the week preceding the visits.

11.7. Symptom Assessment

Symptoms of ocular discomfort (unrelated to instillation of the study medication), including burning/stinging/itching, dry eye sensation, and blurred/poor vision will be done according to the scales in Appendix A-I.

11.8. Subject global rating of treatment

At Week 12 Visit (for subjects not participating in the open-label extension study) or at Month 15 Visit (for subjects who participate in the open-label extension study), or at early termination visit, a staff member will ask the subject the following question during the office visit: “Please select one of the following 4 choices to rate your overall assessment of the effect of the glaucoma study medication you have been using once a day in the evening:”

1. Unsatisfactory;
2. Not very satisfactory;
3. Satisfactory;
4. Very satisfactory.

11.9. Quality of Life Questionnaires

11.9.1. Glaucoma Quality of Life-15

The Glaucoma Quality of Life-15 is a questionnaire developed to assess visual disability resulting from glaucoma. This questionnaire quantifies different psychophysical aspects of visual function and assess the relationship between objective measures of visual function and patients' perception of their vision-related quality of life (Nelson 2003).

The Glaucoma Quality of Life-15 is self-administered and should be completed by the patient (see AppendixA-V).

11.10. Exploratory investigations

- Not applicable.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

12.1.1. Best Corrected Distance Visual Acuity (BCDVA)

Best corrected distance VA will be measured with the patient's best correction and recorded in Snellen.

12.1.2. Slit lamp examination

Slit lamp examination will be performed at each visit. Any clinically significant change in that occurred during the study will be reported as AEs.

12.1.3. Adverse Events (AEs)

Adverse events, including ocular AEs, ocular complications, and systemic AEs will be recorded in the eCRFs. Any clinically significant change in concomitant disease or new concomitant conditions that occurred between the Screening Visit and the Baseline Visit will be reported as AEs.

12.1.4. Pregnancy Screen

Women of childbearing potential cannot be included in the study if they are not using a medically acceptable, highly effective method of birth control (such as hormonal implants, injectable or oral contraceptives, intrauterine devices, sexual abstinence or vasectomized partner) from the Screening Visit throughout the conduct of the study treatment periods and up to 2 weeks after the study end. Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and should be in line with the preferred and usual lifestyle of the subject. Post-menopausal women (two years without menstruation) do not need to use any method of birth control. For women of childbearing potential only, urine hCG pregnancy tests provided by the sponsor will be performed during the course of the study, and they will receive continued guidance with respect to the avoidance of pregnancy, as part of the Schedule of Study Procedures

Patients must have a negative urine pregnancy test at Baseline and throughout the study.

12.2. Adverse Events and Other Safety Information

12.2.1. Definitions

12.2.1.1. Adverse Event (AE)

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a study drug. An AE does not necessarily have a causal relationship with the study drug. For this study, the study drugs are DE-130A (latanoprost 50 microg/ml eye drops emulsion) and Xalatan® (latanoprost 50 microg/ml eye dropssolution). An AE can be any unfavourable unintended sign (including for example an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug which does not necessarily have to have a causal relationship with the study treatment.

In general, changes in clinical safety variables will be recorded as AEs if clinically significant changes as judged by the investigator occur during the study. These may include, but are not limited

to, cases where a patient spontaneously reports a new symptom or when a change from baseline of clinical importance as judged by the investigator occurs. A clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE.

Worsening of findings e.g. in biomicroscopy from no findings to finding graded as moderate/severe, or change in grading from mild to severe, may be an indication of an AE. By investigator's judgment, also milder changes can be recorded as AEs.

An elective surgical procedure scheduled or planned prior to study entry is not considered an AE, and the underlying diagnosis for the procedure should be captured in the medical history as a pre-existing condition.

The lack of efficacy of the study treatment for the condition being investigated is not considered an AE unless a clinically significant change in the patient's condition is assessed by the investigator.

Patients' answers given to study questionnaires (or changes in these) are not reviewed as a basis for occurrence of AEs. However, the investigators will collect information on AEs at each subject contact by asking an open question on the subject's general health.

12.2.1.2. Serious Adverse Event (SAE)

A serious AE may occur during any study phase (ie, screening, baseline, treatment, washout, or follow-up) at any dose of the study drug, comparator or artificial tears. Serious AEs are abbreviated as 'SAEs' in the protocol. SAE must fulfil one or more of the following criteria:

- Results in death
- It is immediately life-threatening*
- It requires in-patient hospitalization or prolongation of existing hospitalization
- It results in persistent or significant disability or incapacity
- Results in a congenital abnormality or birth defect
- It is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above (including sight-threatening** events and cancer or neoplasm of any type).

*Herein 'Life-threatening' refers to an event in which the patient was at immediate risk of death at the time of event; it does not refer to an event which hypothetically might have caused death.

**Similarly 'Sight-threatening' refers to an event in which the patient was at immediate risk of losing sight; it does not refer to an event which hypothetically might have caused losing of sight.

Serious ocular adverse events include, but are not limited to the following adverse events which are considered to be sight-threatening and are to be reported as SAEs (medically important criteria):

- Adverse Events that caused a decrease in visual acuity of >6 lines (compared with the last assessment of visual acuity at the last visit)
- Adverse Events that caused a decrease in visual acuity to the level of Light Perception or worse
- Adverse Events that required surgical intervention or laser to prevent permanent loss of sight
- Adverse Events associated with severe intraocular inflammation (i.e., 3+ anterior chamber cell/flare or 3+ vitritis)

- Corneal perforation
- Adverse Events that, in the opinion of the investigator, may require medical intervention to prevent permanent loss of sight

12.2.1.3. Case of Special Interest (CSI)

The following cases are considered to be of special interest by the Sponsor:

- Non-serious AEs requiring (24 h) reporting to the sponsor:
    - Corneal ulceration
    - Decrease in visual acuity of 3-6 lines (compared with the last assessment of visual acuity at the last visit)
- Overdose of study drug
    - Administration of a quantity of a medicinal product exceeding the dose defined in the study protocol.
- Misuse of study drug
    - Situations where the medicinal product is intentionally and inappropriately used not in accordance with the study protocol.
- Medication error
    - Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or patient.
- Abuse of study drug
    - Persistent or sporadic, intentional excessive use of medicinal product which is accompanied by harmful physical or psychological effects.

12.2.1.4. Pregnancy Reports

It is required that women of childbearing potential are using a medically acceptable, highly effective method of birth control during the study and up to 2 weeks after the study end. Any pregnancy occurring during the study or within 14 days of completing the study should be reported to Santen EMEA Safety Vigilance (SV) and the subject will be removed from the study.

Pregnancies in partners of study subjects with paternal drug exposure must also be reported to Santen EMEA SV.

12.2.2. Assessment of Adverse Events

All AEs (non-serious and serious) spontaneously reported by the subject and/or in response to an open question from the study personnel or revealed by observation will be recorded and assessed during the study at the investigational site.

Information about AEs will be collected from the signing of consent form until the end of the study. Even after completion of the study, the investigator shall notify Santen EMEA SV of any new SAEs that may be associated with the study drug.

All non-serious AEs will be evaluated until recovery or until the last post-study visit/contact. The investigator must follow up subjects with a SAE with causal relationship to study treatment until it

has resolved, stabilized or a final assessment can otherwise be made. The same principle applies to all study drug -related AEs which can lead to early termination and AEs which are under special interest.

The investigator will take appropriate and necessary therapeutic measures required for resolution of the AE. Any medication necessary for the treatment of a AE must be recorded. During the investigator-masked treatment period, the investigator should only unmask the treatment allocation if this is relevant to the safety of the subject.

During the study, patients will also be allowed to use unpreserved artificial tears with the same dose regimen and frequency as before baseline. The events reported during the washout period with artificial tears are considered as AEs. After the first administration of the study drug, the events with causal relationship to the artificial tears are considered as AEs. The AEs with causal relationship to the artificial tears are also assessed, recorded and reported as described in the further section.

12.2.2.1. Seriousness

The seriousness of each AE must be assessed by the investigator according to the criteria set for SAEs in section 12.2.1.2. If the event does not meet the criteria of a SAE, it is assessed as non-serious.

12.2.2.2. Causality to Study Drug or Artificial Tears

An investigator who is qualified in medicine must make the determination of causality to artificial tears for each AE during the washout period, and the causality assessment to the study drug and artificial tears, respectively, for AEs occurred during the treatment periods. The following categories shall be used:

Related: There is a reasonable possibility that the AE may have been caused by the study drug or AT.

Not related: There is no reasonable possibility that the AE may have been caused by the study drug or AT.

The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study drug or artificial tears. If no valid reason exists for suggesting a relationship, then the AE should be classified as “unrelated.” If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the study drug (or artificial tears) and the occurrence of the AE, then the AE should be considered “related”.

The Sponsor should report serious adverse reactions with causal relationship to non-investigational medicinal product (artificial tears) to the MAH of the product (if not the Sponsor) or to the relevant competent authorities.

12.2.3. Relationship to Study Procedures

The relationship to study procedures (e.g., wash-out period) should be determined for AE using the following categories:

Related: There is a reasonable possibility that an event may have been caused by a study procedure.

Not Related: There is no reasonable possibility that an event may have been caused by a study procedure.

12.2.3.1. Severity

Severity will be assessed according to the following scale:

- Mild: awareness of sign or symptom, but easily tolerated
- Moderate: discomfort sufficient to cause interference with normal activities
- Severe: incapacitating, with inability to perform normal activities

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria under Section 12.2.1.2. An AE of severe intensity may not be considered serious.

12.2.4. Expectedness

AEs will be evaluated as to whether they are expected or unexpected. The assessment is performed by the Sponsor and in this study it is based on reference safety information (Investigator's Brochure)

- Expected: An AE is expected when the nature or severity of which is consistent with the applicable product information.
- Unexpected: An AE is unexpected when the nature or severity of which is not consistent with the applicable product information.

12.2.5. Reporting of Safety Information

12.2.5.1. Reporting of Adverse Events

All serious and non-serious AEs including non-serious AEs considered to be of special interest (CSIs) by sponsor (in Section 12.2.1.3), must be reported on the adverse event electronic case report form (AE eCRF). In addition, SAEs and non-serious AEs, which have been considered to be CSI, must be reported expeditedly to the sponsor (Section 12.2.4.3).

For each AE, the investigator will evaluate and report

- the event term (verbatim),
- the onset date,
- severity,
- location (e.g. right/left eye, both eyes, or not applicable if non ocular event),
- causality to study drug (for AEs only) and artificial tears,
- relationship to study procedures,
- action taken for study drug (for AEs only),
- seriousness,
- outcome of event
- the end date, and
- whether or not it caused the patient to discontinue the study.

The AE term should be reported in standard medical terminology when possible.

If known, the diagnosis (i.e., disease or syndrome) must be recorded rather than component signs and symptoms (e.g., record as "worsening of cataract" rather than "drop in vision"). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if worsening of macular edema and worsening of panuveitis are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).

12.2.5.2. Reporting of Case of Special Interest and Pregnancy

Other CSIs (non-serious AEs covered in the Section 12.2.1.3) or spontaneously reported pregnancy (Section 12.2.1.4) in a patient or in a partner to the patient must be recorded in the source documents at the investigation site and reported expeditedly to Santen EMEA SV (Section 12.2.4.3).

Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The pregnancy which occurs during the study or within 14 days of completing the study must be reported.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study presuming that the informed consent is obtained for this from the patient. The outcome (health of infant) must also be reported to the Santen EMEA SV.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.2.5.3. Expedited reporting

All SAE, CSI and Pregnancy reports must be reported to Santen EMEA SV immediately but no later than within 24 hours of the first awareness of the event. The investigator must complete, sign and date the SAE (or CSI/Pregnancy) pages, verify the accuracy of the information recorded on the SAE (or CSI/Pregnancy) pages, and send a copy by e-mail or fax to Santen EMEA SV:

Santen EMEA, Safety Vigilance (SV)

Email to safetyEU@santen.com **or**

Phone +358 3 284 8625

The Sponsor records all SAE, CSI and Pregnancy reports in the safety database of Santen.

Additional follow-up information, if required or available, should all be sent by e-mail or faxed to Santen EMEA SV immediately but no later than within 24 hours of receipt and this should be completed on a follow-up SAE (or CSI/Pregnancy) form and placed with the original information and kept with the appropriate section of the eCRF and/or study file.

The Sponsor is responsible for ongoing safety evaluation of the study drug. If there is at least a reasonable possibility that the event is related to the study drug and it is both serious and unexpected (SUSAR), the sponsor shall initiate expedited reporting according to applicable reporting requirements to all relevant parties, including regulatory authorities, ethics committees and investigators. Reporting responsibilities are described in the study specific safety management plan.

12.2.5.4. Follow-up of Adverse Events

All reported AEs should be followed until resolution or until the scheduled exit visit. A Subject with the following types of events should be followed by the Investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained.

- On-going SAEs
- On-going CSIs (excluding medication errors or <other special situations(e.g. overdose)> not resulting in AEs)
- Early termination and withdrawal from the study due to study drug related AEs

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

The follow-up information on an individual SAE, AE or CSI will be entered into the eCRF prior to database lock. If the information requested by Santen is not part of the eCRF, or when database lock has already been completed, the site's response to follow-up requests should be emailed, faxed or reported in writting to the appropriate Email/fax numbers or personnel identified in section 12.2.4.3.

12.2.6. Documentation of Safety Information

All AEs will be recorded during the study in the subject's medicinal records and on the appropriate AE eCRF at the investigational site. CSIs and Pregnancies will be recorded in the source documents. The Sponsor records all SAEs, CSIs and Pregnancy reports in the safety database of Santen.

13. STATISTICS

13.1. General Considerations

Unless specified otherwise, for Period 1 analyses, efficacy measures will be summarized by planned treatment on the FAS population, and safety measures will be summarized by actual treatment received on the Safety population. For Period 2, and Periods 1 & 2 combined analyses, both efficacy and safety measures will be summarized for DE-130A group on the Open-Label population.

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 (%). For the variables recorded for both eyes, the descriptions will be given separately for the study eye and for the fellow eye for all ocular safety measures. All efficacy analyses will only be performed on the study eye.

All data manipulations and descriptive summaries will be performed using SAS Version 9.4 or later. The ICH guideline on case report tabulations will be followed. A Statistical Analysis Plan (SAP) will be written and finalized before the start of the analysis of the study data, which will present the details of how all the analyses will be performed.

Unless otherwise specified, all statistical testing will be done with Type I error rate of 0.05 (2-sided).

13.1.1. Sample Size

For the primary efficacy endpoint of change from baseline in peak IOP and trough IOP, separately, at Week 12 visit, sample size calculation was based on data obtained from the phase II study (NVG10E118).

Sample size was thus calculated assuming a mean difference in IOP change from baseline of 0 mmHg and a common standard deviation of 4.26 mmHg in the peak or trough IOPs, respectively, for the comparison between the DE-130A and the control (Xalatan®) groups. A total sample size of approximately 380 subjects (190 per treatment arm) will provide 90% power to demonstrate the non-inferiority of the DE-130A group to the control group (one-sided $\alpha = 0.025$) for non-inferiority margin of 1.5 mmHg, assuming 10% dropout rate.

13.1.2. Study Eye

Data collection will be done on both eyes, however, efficacy analyses will only be performed on the study eye.

The study eye is defined as the eye that qualifies per inclusion / exclusion criteria at the Baseline Visit. If both eyes are eligible, the eye with the higher IOP at the Baseline Visit will be chosen. If both eyes have the same IOP value at Baseline, the eye with the higher CFS score at the Baseline Visit will be chosen. If both eyes have the same IOP and CFS values, then the right eye will be designated as the study eye.

13.1.3. Multiple Comparisons/Multiplicity

To control the overall type I error rate at 0.05 level, the three hypotheses testing in the primary and key sencondary endpoints will be performed sequentially according to hierarchical fixed sequence procedure below:

1. Hypothesis testing of non-inferiority of DE-130A to Xalatan® for the primary endpoint: change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12.
2. Hypothesis testing of superiority of DE-130A to Xalatan® for the first key secondary endpoint: change from baseline in CFS score at Week 12 in subjects with baseline CFS ≥ 1.
3. Hypothesis testing of superiority of DE-130A to Xalatan® for the second key secondary endpoint: change from baseline in symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) at Week 12 in subjects with baseline symptom average score >0.

13.2. Analysis Populations

The following analysis populations are considered:

- The **Full Analysis Set (FAS)** population consists of all randomised subjects who received at least one dose of the study medication and provided at least one post-baseline IOP measurement at peak and trough timepoints, separately. The FAS population will be the analysis population for all efficacy endpoints in Period 1 and will use treatment as randomised.
- The **Safety population** consists of all subjects randomised in the study who received at least one dose of the study medication. The Safety population will be the analysis population for all safety analyses in Period 1 and will use treatment as actually received.
- The Glaucoma/OHT **Per-Protocol (PP)** population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the primary efficacy endpoint. The PP population will be used for sensitivity analyses of the primary efficacy endpoints in Period 1 and will use treatment as randomised.
- The **Ocular Surface Disease Per-Protocol (PP)** population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the key secondary endpoints. This population will be used for sensitivity analyses of the key secondary endpoints in Period 1 and will use treatment as randomised.
- The **Open-Label Population** will be a subset of the FAS subjects whocomplete their Week 12 Visit and agree to participate in the open-label period of the study, and received at least one dose of the study medication during the open-label period and provided at least one morning IOP measurement after the Week 12 Visit. This population will be the analysis population for the analyses of efficacy endpoints in Period 2 and for Periods 1 & 2 combined data and will use treatment as randomised.
- The **Open-Label Safety** population will be a subset of the FAS subjects who complete their Week 12 Visit and agree to participate in the open-label period of the study, and received at least one dose of the study medication during the open-label period. The Open-Label Safety population will be the analysis population for all safety analyses in Period 2 and for Periods 1 & 2 combined data and will use treatment as actually received.

13.3. Analysis of Demographics and Baseline Characteristics

Descriptive summaries will be performed for demographic (including age, gender, race, ethnicity, female patients' menopausal status) and baseline characteristics variables (including time since diagnosis and past surgery or laser treatment in the study eye, and smoking status).

In addition, medical history (ocular and systemic), and prior and concomitant medication uses will be summarized by treatment groups for the overall FAS population, Safety population, Open-label population, separately. In addition, medical history (ocular and systemic) and prior and concomitant medication use will be summarized by treatment group for the overall FAS population. Prior medication is defined as any medication that was used by the patients that is discontinued before the Baseline Visit (Day 1).

13.4. Efficacy analyses

During period 1, if a patient takes any concomitant medications or undergoes any concomitant therapies listed in Section 8.2 of this protocol, IOP and/or CFS and OSD symptom scores after taking the medication/therapy will be censored for the primary and/or key secondary efficacy endpoints analyses. The endpoint(s) that will be censored depends on the medications or therapies taken, which will be determined by the Sponsor team during the masked data review before database lock.

- IOP data will be censored after any IOP-lowering medication/therapy is taken.
- CFS and symptom scores will be censored after any medication (including artificial tears change)/therapy that might have any effect on the OSD signs and symptoms.

If it is determined that a medication or therapy could have an effect on both IOP and OSD endpoints, IOP, CFS and symptom scores will all be censored.

13.4.1. Analysis of Primary Efficacy Endpoint

The analysis of primary efficacy endpoint will be performed on the FAS population.

The difference in change from baseline in peak and trough IOP between the DE-130A group and the Xalatan® group at the Week 12 Visit in the IOP study eye will be compared using a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Week 12 based on FAS population. A separate MMRM model will be used for IOP at peak and trough, respectively. The model will include treatment, visit, treatment-by-visit interaction and country as fixed effects, baseline IOP at the respective timepoint (peak or trough) as covariates. The 95% confidence intervals intervals and p-values will be reported.
For the primary efficacy endpoint, the following hypotheses will be tested:

$$H_0: \mu_T - \mu_C > \Delta \text{ for at least one timepoint}$$

versus

$$H_A: \mu_T - \mu_C \leq \Delta \text{ for both timepoints}$$

where μ_T and μ_C denote the mean change from baseline in peak or trough IOP in DE-130A and Xalatan® groups, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg. Non-inferiority will be established if the upper limit of the one-sided 97.5% confidence interval is less

than or equal to the non-inferiority margin of 1.5 mmHg at both the peak and trough timepoints at Week 12.

Sensitivity analysis of the primary efficacy endpoints will be done with the Glaucoma/OHT PP population.

Because both the peak and trough IOP endpoints have to meet the non-inferiority criterion in order to claim non-inferiority of DE-130A as compared to Xalatan®, no multiplicity adjustment is needed for the primary efficacy endpoint.

13.4.2. Analysis of Secondary Efficacy Endpoints

13.4.2.1. Analysis of the Key Secondary Endpoints

The key secondary endpoints are:

- Change from baseline in CFS score in the study eye at Week 12 in patients with baseline CFS ≥ 1
- Change from baseline in OSD symptom score (average of 3-symptom: dry eye sensation, blurred/poor vision and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score >0

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

1) Change from baseline in CFS score at Week 12 in subjects with baseline CFS ≥ 1

The MMRM model with a similar model setting described for the analysis of the primary efficacy endpoint will be used to test the following hypotheses:

$$H_{0S_1}: \mu_{Ts_1} - \mu_{Cs_1} = 0$$
versus
$$H_{AS_1}: \mu_{Ts_1} - \mu_{Cs_1} \neq 0$$

where μ_{Ts_1} and μ_{Cs_1} denote the mean change from baseline in CFS in DE-130A and Xalatan® groups, respectively.

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

2) Change from baseline in symptom score (3-symptom average) at Week 12 in subjects with baseline symptom score >0

The MMRM model with a similar model setting described for the analysis of the primary efficacy endpoint will be used to test the following hypotheses:

$$H_{0S_2}: \mu_{Ts_2} - \mu_{Cs_2} = 0$$
versus
$$H_{AS_2}: \mu_{Ts_2} - \mu_{Cs_2} \neq 0$$

where μ_{Ts_2} and μ_{Cs_2} denote the mean change from baseline in symptom score (3-symptom average) in DE-130A and Xalatan® groups, respectively.

The Ocular Surface Disease PP population will be used for the sensitivity analysis of the two key secondary efficacy endpoints.

13.4.2.2. Analysis of the Other Secondary Endpoints

Ocular Surface Disease Assessments

Change from baseline in conjunctival fluorescein staining, TFBUT, and each individual symptom score in the study eye at each analysis visit in Period 1 will be compared between treatment groups using MMRM on observed cases. More details on the model specifications will be provided in the SAP.

Percentage of patients with conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6)) in the study eye at each analysis visit in Period 1 will be compared between treatment groups using a *Chi-squared test* or *Fisher's Exact test* wherever appropriate for the FAS population.

CFS, corneal and conjunctival fluorescein staining, TFBUT, 3-symptom average and individual symptom score, and slit lamp examination in the study eye at each analysis visit will be summarized descriptively by treatment group.

Artificial tears use during Period 1 will be summarised by treatment group as a continuous variable as well as by percentage of patients who use artificial tears at each analysis visit.

Descriptive statistics will also be provided for ocular surface disease endpoints (corneal and conjunctival fluorescein staining, TFBUT, symptom scores [3-symptom average and individual symptom score]) and their change from baseline at each visit by analysis visit and treatment group in Period 1 only.

For the patients participating to the safety follow-up, OSD endpoints and their change from baseline will be summarized for subjects within the Open-Label population by analysis visit for the whole study period (Periods 1 & 2) and change from Week 12 for Period 2.

IOP Assessments

Changes in peak, trough, and mean diurnal IOPs on the study eye will be summarized by treatment group at Week 4 and Week 12.

Peak, trough, and mean diurnal IOP responses on the study eye (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response, defined in Section 5.3.3) will be summarized by treatment group at Week 4 and Week 12.

Quality of life Assessements

Mean scores of quality of life (Glaucoma Quality of Life-15), and their change from baseline (Period 1 and Periods 1 & 2) and change from Week 12 (Period 2) will be summarized by study period, analysis visit and by treatment group (Period 1), for the FAS population (Period 1), for the Open-Label Population (Period 2, Periods 1 & 2).

Subjects Global Rating of Treatment

Subjects global rating of treatment at Week 12/early termination will be summarized by treatment groups for the FAS population. Also, it will be summarized at Month 15/early termination for the Open-Label Population.

13.5. Analysis of Safety and Tolerability Endpoints

Safety and tolerability endpoints will be summarized for the following three time periods:

- Period 1 (Day 1 to Week 12 Visit): for whole Safety population by treatment group
- Period 2 (Week 12 Visit to Month 15 Visit/early termination): for all subjects who entered into the open-label period (Open-Label Safety population)
- Entire study period (Day 1 to Month 15/early termination): for all subjects who entered into the open-label period (Open-Label Safety population).

13.5.1. Adverse Events

An adverse event is treatment-emergent (TEAE) if it occurs or worsens after the first dose of study treatment. A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the study drug, study procedure or artificial tears caused the adverse event.

Adverse events will be coded using the MedDRA dictionary. Frequencies and percentages will be given as follows: 1) Overall summary; 2) by system organ class and preferred term, 3) by system organ class, preferred term and maximal severity, 4) by system organ class, preferred term and relationship to study medication and study procedure, respectively, and 5) by system organ class, preferred term, maximal severity, and relationship to study medication and study procedure, respectively.

Separate analyses will be performed for AEs, SARs, SAEs, serious SARs, and for ocular and non-ocular events. Ocular events will be summarized for the study eye and the fellow eye separately.

13.5.2. Other Safety Assessments

Other safety assessment parameters (e.g. slit lamp examination, dilated fundoscopy, BCDVA, and visual field) will be summarized by study period, analysis visit and treatment group (Period 1 only). They will be summarized for the study eye and the fellow eye separately. Pregnancy test results will be provided in a listing.

13.6. Interim Analysis

There is no planned interim analysis for this study.

13.7. Handling of Missing Values

Missing data will be handled within the MMRM model for all efficacy assessment analysed using this statistical model.

No missing data on safety endpoints will be imputed.

For medical events including AEs, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the Statistical Analysis Plan (SAP). Likewise, rules will be applied to impute the completely or partially missing start and end dates of non-study medications.

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

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

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

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

- Determine the adequacy of the facilities.
- 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, 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 patient'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 patient (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 EMEA SV (including SAEs, CSIs 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 needs information or advice.

14.2. 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, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should contact Santen immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

A written favourable opinion of IRB or IEC (as appropriate) must be obtain prior starting the study. Initial IRB/IEC approval, and all materials approved by the IRB/IEC for this study including the patient consent form and recruitment materials must be maintained by the Investigator in the Investigational Site File and made available for inspection.

15. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Santen may conduct a quality assurance audit. Please see Section 14.2 for more details regarding the audit process.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. A copy of the letter indicating IRB/IEC approval or a favorable opinion must be available at the investigational site before the site can enroll any patient/subject into the study.

Any amendment to the protocol must be reviewed by IRB/IEC in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit patients for the study.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements. Please see Appendix B- "Responsibilities of the Investigator" and Appendix E- Declaration of Helsinki.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's signed and dated informed consent must be obtained before any protocol-directed procedures are performed.

The Principal Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the patient.

17. DATA HANDLING AND RECORD KEEPING

17.1. Inspection of Records

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.

17.2. Retention of Records

The Principal Investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the test article for investigation. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and Sponsor. If it becomes necessary for Santen or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

17.3. Source Documents

The patient source documentation should include hospital reports, doctor's/nurse's notes, laboratory results, reports of special examinations, the signed consent forms, consultants letters. The Investigator is asked to report the following information in the patient's medical file (source documents) according to Sources Data Agreement signed by the Principal Investigator of each Investigational site:

- Mention of patient's participation in the study, patient code and treatment number, date and process of signature of informed consent form
- Demographic data
- Past medical and surgery history
- Past and recent treatments
- Concomitant treatments at inclusion
- Change in concomitant treatments throughout the study
- Date of each study visit
- Date of the final visit
- Date and reason of premature withdrawal
- All data related to study procedures
- Any non-serious AEs, SAEs, and CSIs occurred during the time course of the study and study drug-associated SAEs which occurred after the completion of the study
- Any pregnancy occurring during the study or within 14 days of completing the study
- Any data that could be judged by the Investigator as relevant

This list is not exhaustive.

17.4. Data Collection

The Principal Investigator must maintain detailed records on all subjects who provided informed consent. Data for screened and enrolled subjects will be entered into eCRFs, designed according to the protocol. 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.

18. PUBLICATION POLICY

The investigator is obliged to provide the Sponsor with complete test results and all data derived by the investigator from the study. During the study, only the Sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

The Sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Master Services Agreement or equivalent agreement. In the event of any discrepancy between the protocol and the Master Services Agreement or equivalent agreement, the Master Services Agreement or equivalent agreement will prevail.

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20. APPENDICES

Appendix A-I Symptom Assessments

The patient will be asked to assess 3 OSD symptoms regarding ocular discomfort unrelated to instillation : dry eye sensation, blurred/poor vision and burning/stinging/itching. The patient will grade each ocular symptom by its level of severity during the week before each visit :

0 = Absent

1 = Mild

2 = Moderate

3 = Severe

4 = Very severe

Appendix A-II Slit lamp examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp. The subject will be seated while being examined; grading of the Meibomian glands, lashes, lids, conjunctiva, tear film debris, anterior chamber and lens will be done according to the following scales:

Meibomian Glands:

0 = None (none are plugged).

1 = Mild (1 to 2 glands are plugged).

2 = Moderate (3 to 4 glands are plugged).

3 = Severe (All glands are plugged).

Lid and Lid Margin:

- Erythema:

0 = None (normal).

1 = Mild (redness localized to a small region of the lid(s) margin OR skin).

2 = Moderate (redness of most or all lid margin OR skin).

3 = Severe (redness of most or all lid margin AND skin).

4 = Very severe (marketed diffuse redness of both lid margin AND skin).

- Swelling:

0 = None (normal).

1 = Mild (localized to a small region of the lid).

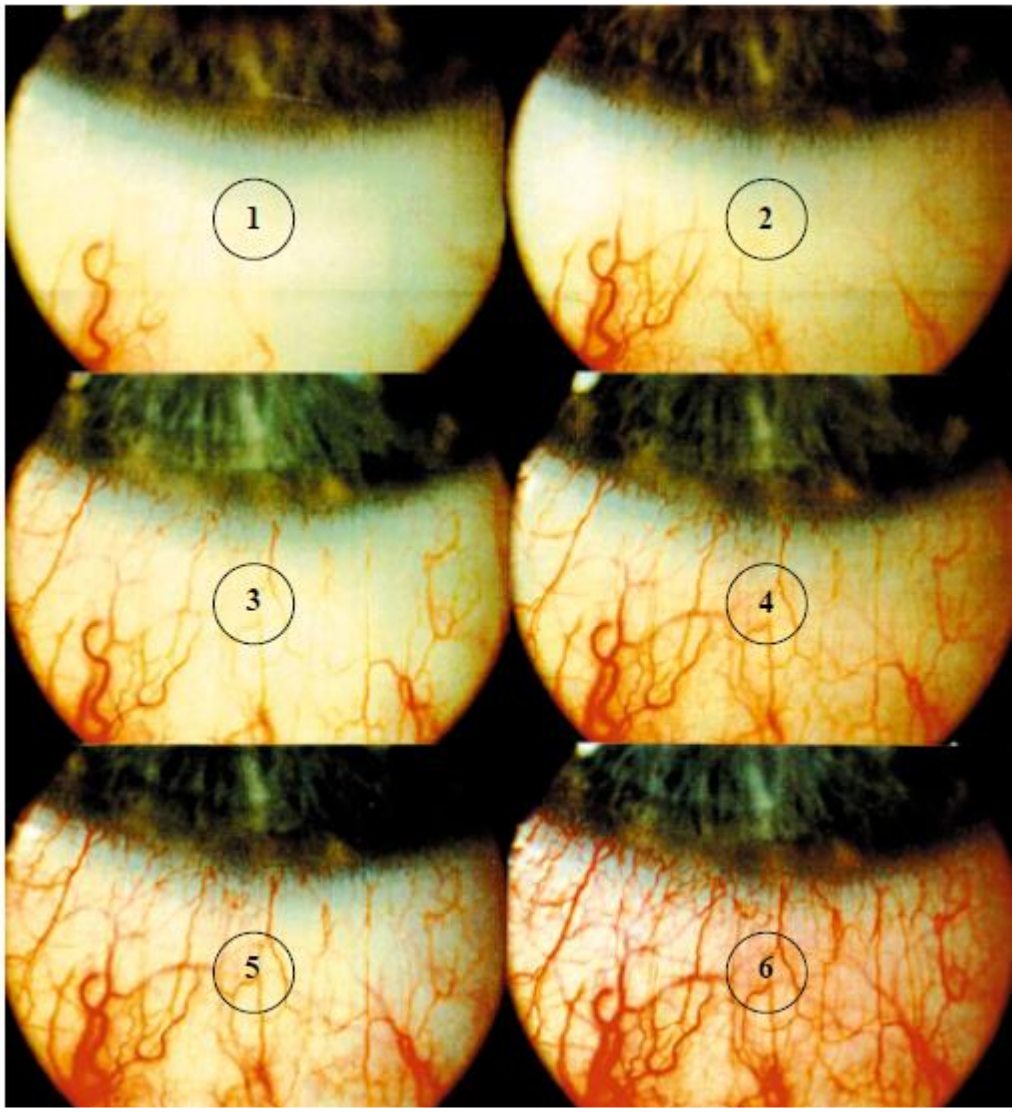
2 = Moderate (diffuse, most or all lid but not prominent/protruding).

3 = Severe (diffuse, most or all lid AND prominent/protruding).

4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).

Conjunctiva:

- Erythema/hyperaemia will be scored using the photographic scale derived from Mac Monnies scale (1 to 6) :



- Chemosis:

0 = None (normal).

1 = Mild (slight localized swelling).

2 = Moderate (pink moderate/medium localized swelling or mild diffuse swelling).

3 = Severe (severe diffuse swelling).

4 = Very severe (very prominent/protruding diffuse swelling).

Lashes

0 = Normal

1 = Abnormal (specify)

Tear Film Debris:

0 = None (absence of debris).

1 = Mild (presence of debris in inferior tear meniscus).

2 = Moderate (presence of debris in inferior tear meniscus and in tear film overlying cornea).

3 = Severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of mucus strands in inferior fornix of on bulbar conjunctiva).

4 = Very severe (presence of debris in inferior tear meniscus and in tear film overlying cornea. Presence of numerous AND/OR adherent mucus strands in inferior fornix and on bulbar conjunctiva or filamentary keratitis).

Anterior Chamber Inflammation (Tyndall Effect) / (Slit beam= 0.3 mm wide, 1.0 mm long):

0 = None (no Tyndall effect).

1 = Mild (Tyndall effect barely discernible).

2 = Moderate (Tyndall beam in the anterior chamber is moderately intense).

3 = Severe (Tyndall beam in the anterior chamber is severely intense).

Lens:

0 = No opacification (normal lens).

1 = Mild lens opacification.

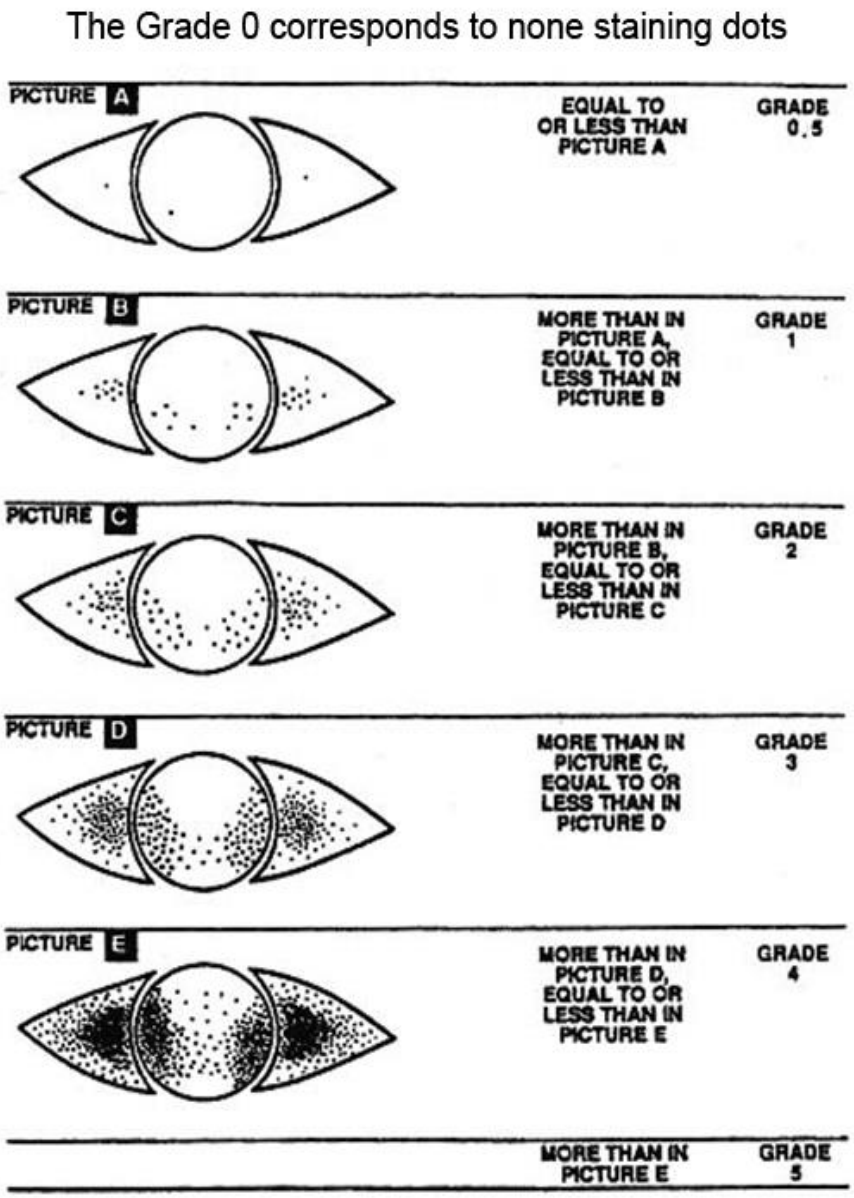
2 = Moderate lens opacification.

3 = Severe lens opacification.

Appendix A-III Corneal and Conjunctival Fluorescein Staining

Modified Oxford scale

(Grading of corneal and conjunctival fluorescein staining)



Appendix A-IV Intraocular Pressure measurement

Using the Goldmann applanation tonometry

IOP will be performed at each visit.

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

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 (oxybuprocaine 0.4%) one drop of fluorescein 2% may be instilled.
- The subject and slit-lamp are adjusted so that the subject's head is firmly positioned on the chin rest and against the forehead rest without leaning forward or straining. Tight-fitting neckwear is loosened. The subject is asked to look straight ahead at a distant object or fixation target. If it is necessary to hold the eyelids open, the Investigator holds the eyelids against the orbit rim, taking care not to apply any pressure to the globe. The subject is cautioned not to hold his breath.
- The Investigator looks through the slit-lamp and gently brings the tip of the prism into contact with the center of the cornea. The mires are well-focused, centered horizontally, and positioned vertically so that they are of equal circumference above and below the horizontal dividing line. If the mires are narrower than approximately 1/10 their diameter, additional fluorescein is instilled.
- The Investigator adjusts the measuring drum until the inner borders of the two mires just touch each other or, if pulsation is present, until the mires separate a given distance during systole and overlap the same distance during diastole.
- The Investigator removes the tip from the cornea, and the authorized study staff (recorder) records the reading on the dial, rounded to the next highest integer. For example, if the measurement indicated is between 16 and 17, then 17 is recorded as the measurement in the subject's source document.
  - The Investigator may be recorder instead of the authorized study staff, if he/she is not assigned.

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

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

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

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

Appendix A-V Glaucoma Quality of Life-15

The Glaucoma Quality of Life-15 is self-administered and should be completed by the patient.

Patient instruction: Please, circle the correct answer on the scale ranging from 1 to 5 where [1] stands for no difficulty, [2] for a little bit of difficulty, [3] for some difficulty, [4] for quite a lot of difficulty, and [5] for severe difficulty. If you do not perform any of the activities for other than visual reasons, please circle [0].

Does your vision give you any difficulty, even with glasses, with the following activities?

	None	A little bit	Some	Quite a lot	Severe	Do not perform for nonvisual reasons
Reading newspapers	**1**	**2**	**3**	**4**	**5**	**0**
Walking after dark	**1**	**2**	**3**	**4**	**5**	**0**
Seeing at night	**1**	**2**	**3**	**4**	**5**	**0**
Walking on uneven ground	**1**	**2**	**3**	**4**	**5**	**0**
Adjusting to bright lights	**1**	**2**	**3**	**4**	**5**	**0**
Adjusting to dim lights	**1**	**2**	**3**	**4**	**5**	**0**
Going from light to dark room or vice versa	**1**	**2**	**3**	**4**	**5**	**0**
Tripping over objects	**1**	**2**	**3**	**4**	**5**	**0**
Seeing objects coming from the side	**1**	**2**	**3**	**4**	**5**	**0**
Crossing the road	**1**	**2**	**3**	**4**	**5**	**0**
Walking on steps/stairs	**1**	**2**	**3**	**4**	**5**	**0**
Bumping into objects	**1**	**2**	**3**	**4**	**5**	**0**
Judging distance of foot to step/curb	**1**	**2**	**3**	**4**	**5**	**0**
Finding dropped objects	**1**	**2**	**3**	**4**	**5**	**0**
Recognizing faces	**1**	**2**	**3**	**4**	**5**	**0**

Appendix A-VI Dilated fundoscopy

The ophthalmoscopy (fundus) examination will be performed for each eye and graded as described below. The examination will be performed with pupil dilated at screening, Week 12 and Month 15 visits. Please dilate pupil and perform after all other ocular procedures have been completed. Cup to disc ratio and abnormality in retina, macula, choroid, and vitreous will 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

Appendix BResponsibilities of the Investigator

Clinical research studies sponsored by the Sponsor are patient to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures; including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential patients, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are adequately informed of these obligations and that they are qualified to their roles.
5. The Principal investigator is responsible for supervising any individual or party to whom the investigator delegates study-related duties and functions conducted at the site
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to patients. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in, ICH and local regulations, are met.
9. Obtain valid informed consent from each patient who participates in the study, and document the date of consent in the patient's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a patient authorization section that describes the uses and disclosures of a patient's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a patient authorization, then the investigator must obtain a separate patient authorization form from each patient or the patient's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the Sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs and return all unused sponsor-supplied drugs to the Sponsor.
13. IMP destruction at site requires prior written approval from the Sponsor.
14. Report adverse reactions to the Sponsor promptly. In the event of an SAE, notify the Sponsor within 24 hours.

Appendix CElements of the Patient Informed Consent

In seeking informed consent, the following information shall be provided to each patient:

- A statement that the study involves research.
- An explanation of the purposes of the research.
- The expected duration of the patient's participation.
- A description of the procedures to be followed, including invasive procedures.
- The identification of any procedures that are experimental.
- The estimated number of patients involved in the study.
- A description of the patient's responsibilities.
- A description of the conduct of the study.
- A statement describing the treatment(s) and the probability for random assignment to each treatment.
- A description of the possible side effects of the treatment that the patient may receive.
- A description of any reasonably foreseeable risks or discomforts to the patient and, when applicable, to an embryo, fetus, or nursing infant.
- A description of any benefits to the patient or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
- Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient and their important potential risks and benefits.
- A statement describing the extent to which confidentiality of records identifying the patient will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.
- For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
- The anticipated prorated payment(s), if any, to the patient for participating in the study.
- The anticipated expenses, if any, to the patient for participating in the study.
- An explanation of whom to contact for answers to pertinent questions about the research (investigator), patient's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the patient.

- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient otherwise is entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled.
- The consequences of a patient's decision to withdraw from the research and procedures for orderly termination of participation by the patient.
- A statement that the patient or the patient's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the patient's willingness to continue participation in the study.
- The foreseeable circumstances or reasons under which the patient's participation in the study may be terminated.
- 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.
- A written patient authorization (either contained within the informed consent form or provided as a separate document) describing to the patient the contemplated and permissible uses and disclosures of the patient's personal information (including personal health information) for purposes of conducting the study. The patient authorization must contain the following statements regarding the uses and disclosures of the patient's personal information:

a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Santen, its affiliates, and licensing partners; (2) business partners assisting Santen, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;

b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer patients the same level of protection as the data protection laws within this country; however, Santen will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;

c) that personal information (including personal health information) may be added to Santen's research databases for purposes of developing a better understanding of the safety and effectiveness of the study medication(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;

d) that patients agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and

e) that the patient's identity will remain confidential in the event that study results are published.

Appendix DInvestigator Consent to Use of Personal Information

Santen will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., the United Kingdom, United States, Japan), including the following:

- Santen, its affiliates, and licensing partners.
- Business partners assisting Santen, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Santen and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Santen, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Santen and other parties for the purposes described above.

Appendix EDeclaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix F - Protocol Amendment 01 Modification Summary

Protocol 0130A01SA has been amended (Amendment 01) in order to optimize the statistical analyses and to harmonize the exclusion criteria throughout the study.
A listing of protocol modifications are listed below.
A red-lined version of Protocol 0130A01SA, Amendment 01 is on file with the Sponsor.
Amended text is highlighted in bold italics.
Deleted text is highlighted in bold italics and crossed out

Table 4: Protocol 0130A01SA, Amendment 01 Modifications

Page	Section Number	Section Title	Description of Change
Numerous	Numerous	Numerous	Administrative changes in abbreviations, capitalization and formatting were made in the document. These individual changes are not listed in this table.
3	Table 1:	Emergency Contact Information	Update of Santen internal information regarding Safety Vigilance in the protocol synopsis, Table 1 and in the protocol sections 3, 12 and Sponsor signatory personal on the last page of the protocol.
4	1.	SYNOPSIS Studied period (years):	Update of the estimated date last patient completed: Nov2022
15-21	2.	Table of Contents	Administrative changes.
22-23	3.	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS	Removal and addition of several abbreviations due to statistical analysis change.
4 31	1. 5.2.	SYNOPSIS Objectives: Secondary Protocol: Secondary	The following wording has been deleted in order to optimize the statistical analyses: • To compare the effect on improving Ocular Surface Disease (OSD) signs and symptoms between treatment groups ~~[***for the FAS population and by corneal fluorescein staining***~~

		Objectives	~~***CFS subgroups, baseline study eye CFS≤1 vs.CFS ≥2, modified oxford scale]***~~ over 3 months (Period 1). • To estimate the effect of DE-130A on OSD signs and symptoms ***improvement*** ~~***for the Open-Label population and by OSD sub-groups***~~ up to 15 months (Periods 1 & 2). • To compare the efficacy on IOP reduction between treatment group~~***s for the FAS population and OSD subgroups***~~ over 3 months (Period 1). • To estimate the effect of DE-130A on IOP ~~***for the Open-Label population and by OSD subgroups***~~ up to 15 months (Periods 1 & 2). • To ~~estimate~~ ***evalutate*** the local ocular tolerance and systemic safety of the two treatments over 3 months (Period 1, ~~***Safety population)***~~**.** To estimate the local ocular tolerance and systemic safety of DE-130A up to 15 months (Periods 1 & 2, ~~***Open-Label population***~~).
5 34 55	1. 6.1 10.1.	SYNOPSIS Methodology: Study duration: Protocol Wash Out Phase Study Design and Schedule of Assessments Table 3 Screening	Wash out period has been updated to 6-weeks to reflect the added wording to Criteria for inclusion 7.
	1.	SYNOPSIS Protocol	The term “enrolled” has been replaced by “randomized” throughout the synopsis and main protocol to clearly define the number of planned patients.
5	1.	SYNOPSIS Criteria for inclusion 6.: Patient eligibility is determined according to	The following wording was added do define that the imaging technique such as optical coherence tomography (OCT) is useful in particular for the follow-up of glaucoma patients. In the early stage glaucoma, OCT is considered as an efficient tool to monitor the progression of the disease. Therefore several glaucoma physicians use OCT instead of

39	7.2	the following inclusion criteria: Protocol : Subject Inclusion Criteria 6.	visual field to monitor early stage glaucoma patients. Consequently we propose to add the OCT as an acceptable tool to assess the inclusion criteria #6 for the enrolment of patients in the study: ***If historical visual fields are not available within the last 18 months prior to screening, but at least two OCTs (optical coherence tomography) are available, including one in the last 6 months and are stable, the patient can be enrolled in the study if a visual field test is also performed at screening and shows no defect or only an early visual field loss in either eye (mean deviation lesser than -6 dB).***
6 39	1. 7.2	SYNOPSIS Criteria for inclusion 7.: Protocol : Subject Inclusion Criteria	The following wording was added do define that the washout period after discontinuation of a treatment may vary between individuals. The protocol specifies that Post-washout IOP should be measured 5 to 7 days after stopping Brinzolamide as this timeframe is considered in many clinical trials. However it is possible that for some patients, some additional days may be necessary before the drug is considered washed out. In addition the patient is not at risk when receiving no treatment for a few more days given the IOP is in the normal range (ie. <22 mmHg) and the patient is closely monitored. Therefore, the time for IOP measurement after Brinzolamide discontinuation can be extended up to 6 additional days: ***If IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.***

7 40	1. 7.3.	SYNOPSIS Exclusion criteria 15.: Protocol: Subject Exclusion Criteria 15.	New exclusion criterion added to harmonize the exclusion criteria with the German AM1, to ensure the patients' safety: ***Known hypersensitivity to sulfonamides, severe renal impairment or hyperchloraemic acidosis.***
8-9 34 44	1. 6.1 8.2.	SYNOPSIS Wash-out phase therapy: Protocol Overall Study Design Wash-out Phase Protocol Azopt®	The following wording was added to reflect the updates made in terms of Criteria for inclusion 7.: ***At baseline, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.***
9 31	1. 5.3.2.	SYNOPSIS Efficacy: The key secondary endpoints are: Protocol: Key Secondary Endpoints	The following wording was added to optimize the statistical analysis part: - Change from baseline in CFS score ***in the study eye*** at Week 12 ***in patients with baseline CFS ≥ 1.*** -Change from baseline in OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) ***in the study eye*** at Week 12 ***in patients with baseline symptom average score>0.***
9	1.	SYNOPSIS Efficacy: The key secondary endpoints are:	The following wording was deleted to optimize the statistical analysis part: Other secondary efficacy endpoints are: ~~***over the 3-month (Period 1), and for DE-130A up to 15 months (Periods 1 & 2),***~~ are:

9	1.	SYNOPSIS Other secondary efficacy endpoints are:	Added wording due to statistical analyses optimization. Deletion of the use of artificial tears as secondary endpoint since per protocol this use should remain stable: ***-IOP related endpoints:*** -Change from baseline in mean diurnal IOP ***in the study eye*** at Week 12 -Change from baseline in peak, trough, and mean diurnal IOP ***in the study eye*** at Week 4 Morning (9:00 am ± 1 hour) IOP ***in the study eye*** of patients treated with DE-130A at Month 6, Month 9, Month 15/early termination (Period 2) and change from baseline at each Period 2 visit
33	5.3.3.	Protocol : The other secondary efficacy endpoints are:	Morning (9:00 am ± 1 hour) IOP ***in the study eye*** of patients treated with DE-130A ***enrolled in Period 2*** at Month 6, Month 9, Month 15/early termination (Period 2) and change from baseline at each Period 2 visit.
11	1.	SYNOPSIS Other secondary efficacy endpoints are:	Deleted wording due to statistical analyses optimization. Deletion of the use of artificial tears as secondary endpoint since per protocol this use should remain stable:
33	5.3.3.	Protocol : The other secondary efficacy endpoints are:	~~***-Ocular surface disease assessment at Week 4, Week 12, Month 6, Month 9 and Month 15/early termination:***~~ ~~***-Corneal and conjunctival fluorescein staining (modified Oxford Scale)***~~ ~~***-OSD symptom assessments***~~ ~~***-TFBUT***~~ ~~***-Use of artificial tears (AT)***~~ ~~***-Slit lamp examination (Meibomian gland dysfunction, conjunctiva, lids and tear film debris)***~~
11	1.	SYNOPSIS Other secondary efficacy endpoints are:	Added and deleted wording due to statistical analyses optimization. Deletion of the use of artificial tears as secondary endpoint since per protocol this use should remain stable: -Subject global rating of treatment at Month 15/early termination ~~***(Open-Label Population)***~~

33	5.3.3.	Protocol : The other secondary efficacy endpoints are:	~~***or and***~~ Week 12 ~~***(subjects not entering Period 2)***~~ -Quality of life (Glaucoma Quality of Life-15) scores at Baseline visit, Week 12, and Month 15***/early termination*** visits.
11 33	1. 5.3.4	SYNOPSIS Safety Protocol: Safety and Tolerability Endpoints	Added wording to clarify that undilated fundoscopy is performed as safety endpoint (already planned but not mentioned in this section of the protocol): - Best-corrected distance visual acuity ***(BCDVA)*** -Dilated ***and undilated (for cup-to-disc ratio)*** fundoscopy
11 72	1. 13.2.	SYNOPSIS Statistical methods: Analysis Populations Protocol Analysis Populations	The following wording has been deleted or added in order to optimize the statistical analyses part: -The Full Analysis Set (FAS) population consists of all ~~***enrolled***~~ ***randomized*** subjects who received at least one dose of the study medication ***and provided at least one post-baseline IOP measurement at peak and trough timepoints, separately.*** The FAS population will be the analysis population for all efficacy ***endpoints*** ~~***analyses***~~ in Period 1 and will use treatment as randomised. -The **Safety population** consists of all ~~***patients***~~ ***subjects*** ~~***enrolled***~~ ***randomized*** in the study who received at least one dose of the study medication ~~***and for whom any follow-up information is available.***~~ The Safety population will be the analysis population for all safety analyses in Period 1 and will use treatment as actually received. -The ***Glaucoma/OHT*** Per-Protocol (PP) population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the primary efficacy endpoint. The PP population will be ***used*** ~~***the analysis population***~~ for sensitivity analyses of the ***primary*** efficacy endpoints in Period 1 and will use treatment as randomised. ***-The Ocular Surface Disease Per-Protocol (PP) population will be a subset of the FAS subjects. It includes all FAS subjects without any of the major protocol deviations that could affect the key secondary endpoints. This population will be used for***

			sensitivity analyses of the key secondary endpoints in Period 1 and will use treatment as randomised. -The Open-Label Population will be a subset of the FAS subjects who ~~***are the first 130 subjects who***~~ complete their Week 12 Visit and ~~***enter the Period 2 of the study***~~ ***agree to participate in the open-label period of the study, and received at least one dose of the study medication during the open-label period and provided at least one morning IOP measurement after the Week 12 Visit.*** This population will be the analysis population for the analyses of efficacy ~~***and safety***~~ endpoints in Period 2 and for Periods 1 & 2 combined data ***and will use treatment as randomised.*** ***-The Open-Label Safety population will be a subset of the FAS subjects who complete their Week 12 Visit and agree to participate in the open-label period of the study, and received at least one dose of the study medication during the open-label period. The Open-Label Safety population will be the analysis population for all safety analyses in Period 2 and for Periods 1 & 2 combined data and will use treatment as actually received.*** ~~***-Efficacy analyses will also be done for the following subgroups in both Period 1 and Period 2 as well as for Periods 1 & 2 combined data:***~~ ~~***-CFS subgroups are defined as baseline CFS ≤ 1 vs. CFS ≥ 2 (modified Oxford scale) in the study eye.***~~ ~~***The analysis of the OSD endpoints will be performed on FAS and CFS subgroups.***~~
12 73	1. 13.3.	SYNOPSIS Analysis of Demographics and Baseline Characteristics Protocol Analysis of Demographics and Baseline Characteristics	The following wording has been deleted or added in order to optimize the statistical analyses part: They will be summarized ***by treatment groups*** ~~***and***~~ for the overall FAS population ***Safety population, Open-label population, separately.*** ~~***for the OSD subgroups, respectively.***~~
12-13	1.	SYNOPSIS	The following wording has been deleted or added in order to optimize the statistical analyses:

		Analysis of Primary and Key Secondary Efficacy Endpoints	The primary efficacy endpoint is the change from baseline in peak and trough ***IOP***, respectively, between the DE-130A group and the Xalatan® group in the study eye at Week 12. ***Statistical analysis will be performed using a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Week 12 based on FAS population. A separate MMRM model will be performed for IOP at peak and trough, respectively. The model will include treatment, visit, treatment-by-visit interaction and country as fixed effects, baseline IOP at the respective timepoint (peak or trough) as covariates.*** Non-inferiority will be established if the upper limit of the one-sided 97.5% confidence interval ***~~from the independent-sample Student's t-test for the difference between DE-130A and Xalatan® in change from baseline peak and trough IOP, respectively, at Week 12~~*** is less than or equal to the non-inferiority margin of 1.5 mmHg ***at both the peak and trough timepoints at Week 12. Superiority is achieved with respect to this endpoint if the upper limit of the one-sided 97.5% confidence interval is < 0 mmHg for both timepoints at Week 12.*** If non-inferiority in the primary endpoint is achieved, the two key secondary endpoints will be tested ***for superiority***, sequentially according to hierarchical fixed ***~~sequence~~*** procedure. ***MMRM models will be fitted for each key secondary endpoint using a similar model setting as described for the analysis of the primary efficacy endpoint Fixed sequence procedure will be applied to control the overall Type I error rate across all hypotheses in the primary and key secondary endpoints at the 0.05 level.*** ***~~-Change from baseline in CFS score at Week 12~~*** ***~~-Change from baseline in symptom score (3-symptom average) at Week 12~~***
13 74	1. 13.4.2.	SYNOPSIS Analysis of Secondary Efficacy Endpoints Protocol	The following wording has been deleted or added in order to optimize the statistical analyses part: Analysis of ***Other*** Secondary Efficacy Endpoints

		Analysis of Secondary Efficacy Endpoints SYNOPSIS	***~~The analysis of secondary efficacy endpoints will be performed on the FAS population and CFS subgroups (CFS ≤ 1 vs. CFS ≥ 2, modified Oxford scale). All efficacy analyses will be performed on the study eye.~~*** Analysis of ***Other*** Secondary Efficacy Endpoints ***~~IOP Assessments~~*** ***~~Changes in peak, trough, and mean diurnal IOPs will be summarized by treatment groups at Week 4 and Week 12, respectively, for the FAS population and CFS subgroups.~~*** ***~~Peak, trough, and mean diurnal IOP responses (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response) will be summarized by treatment groups at Week 4 and Week 12, respectively, for the FAS population and CFS subgroups.~~*** ***~~For patients participating in the safety follow-up, change from baseline and change from Week 12, respectively, in mean morning (9:00 am ± 1 hour) IOP will be summarized for the Open-Label population and for CFS subgroups at Month 6, Month 9 and Month 15/early termination.~~*** *Ocular surface disease Assessments* -Change from baseline in ***Conjunctival fluorescein staining, TFBUT and*** each individual symptom score, ***and ~~TFBUT~~*** at ***each analysis visit in Period 1 ~~Week 12~~*** will be compared between treatment groups using ***MMRM on observed cases. More details on the model specifications will be provided in the SAP. ~~an independent-sample Student's t-test for the FAS population and for CFS subgroups, respectively.~~*** Percentage of patients with ***~~moderate and severe~~*** conjunctival hyperemia (***~~grade ≥ 3~~*** measured by slit lamp scored using the photographic scale derived from McMonnies scale (1 to 6)) ***in the study eye at each analysis visit in Period 1 ~~at Week 12~~*** will be compared between treatment groups ***using a Chi-squared test or Fisher's***

			Exact test wherever appropriate for the FAS population. ***~~Proportion of subjects using~~ Artificial tears use during Period 1 ~~at Week 12~~*** will ***~~also~~*** be ***~~compared~~ summarised ~~between~~ by*** treatment group ***as a continuous variable as well as by percentage of patients who use artificial tears at each analysis visit. ~~using a Chi-squared test or Fisher's Exact test wherever appropriate for the FAS population and for CFS subgroups, respectively.~~*** ***~~Ocular surface disease endpoints (~~***Corneal and conjunctival fluorescein staining, ***~~[modified Oxford scale],~~*** TFBUT, symptom scores [3-symptom average and individual symptom score], ***~~use of artificial tears [continuous variable],~~*** and slit lamp examination) and their change from baseline at each visit will be summarized ***~~for the FAS population and for CFS subgroups, respectively~~, descriptively*** by treatment group ***~~(Period 1) and by analysis visit.~~*** ***~~Artificial tears use during Period 1 (Day 1 to Week 12 Visit) will also be analyzed by treatment group on percentage of patients who use artificial tears at each visit.~~*** ***~~For the patients participating in the safety follow-up, OSD endpoints and their change from baseline will be summarized for the Open-Label population and for CFS subgroups by analysis visit for the whole study (Periods 1 & 2) and change from Week 12 for Period 2.~~*** *Quality of Life Assessments* Mean scores of quality of life (Glaucoma Quality of Life-15), and their change from baseline (Period 1 and Periods 1 & 2) and change from Week 12 (Period 2) will be summarized by analysis visit and by treatment group (Period 1), for the FAS population (Period 1), for the Open-Label Population (Period 2, Periods 1 & 2) ***combined~~)., and for CFS subgroups.~~*** *Subjects Global Rating of Treatment* Subjects global rating of treatment at Week 12/early termination will be summarized by treatment groups for the FAS population. ***~~and~~***

			~~for CFS subgroups, respectively.~~ Also, it will be summarized at Month 15/early termination for the Open-Label Population. ***IOP Assessments*** ***Changes in peak, trough, and mean diurnal IOPs at each analysis will be summarized on the study eye by treatment group.*** ***Peak, trough, and mean diurnal IOP responses in the study eye (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response) at each analysis visit will be summarized by treatment group.*** ***For patients participating in the safety follow-up, change from baseline and change from Week 12, respectively, in mean morning (9:00 am ± 1 hour) IOP will be summarized for the Open-Label population and for CFS subgroups at Month 6, Month 9 and Month 15/early termination.***
14 76	1. 13.5	SYNOPSIS Analysis of Safety and Tolerability Endpoints Protocol Analysis of Safety and Tolerability Endpoints	The following wording has been added in order to optimize the statistical analyses part: -Period 2 (Week 12 Visit to Month 15 Visit/early termination): for all subjects who entered into the open-label period (Open-Label ***Safety*** population) Entire study period (Day 1 to Month 15/early termination): for all subjects who entered into the open-label ***Safety*** period (Open-Label population).
28-30	4.2	Protocol: Rationale for the Proposed Study	The following wording has been deleted or added in order to optimize the statistical analyses part: In the proposed non-inferiority study, to approximate the peak and trough times, the IOP will be measured at 9:00 (±1 hour) am and 4:00 (±1 hour) pm, and ***~~the diurnal mean~~*** will be used to assess the primary efficacy endpoint and secondary endpoints during a 3-month period with randomised investigator-masked medication. The chosen non-inferiority margin of 1.5 mmHg is well below (Musch, 2006 the

			effect of the active control (−8.6±2.6 mmHg, Rouland, 2013 (**45**)). In addition to the comparison of ***peak, trough, and*** mean diurnal IOP, the rates of different responders (defined by a reduction in mean IOP of ≥ 20%, ≥ 25%, and ≥ 30%, and a mean IOP < 18mm Hg) will be compared between treatment groups. Regarding the OSD, the potential positive impact of the cationic formulation of DE-130A on OSD signs (using TFBUT, slit lamp examination, corneal, and conjunctival fluorescein staining with modified Oxford scale) and symptoms (using 3-symptom assessment ~~***and artificial tears us***~~e) will be compared with the effect on OSD of the BAK-preserved Xalatan®. Furthermore the quality of life impact will also be compared between treatment groups. However in order to provide long-term additional data on the safety and tolerability of DE-130A, a 12-month follow-up with open-label DE-130A is to be offered ~~***up***~~ to ~~***the first***~~ 130 patients (whatever their randomised treatment is) who complete their Week 12 Visit and agree to participate in the open-label period of the study. During this safety follow-up, only the peak IOP will be measured in order to minimize patients' burden.
31-33	5.3.3	Protocol: The other secondary efficacy endpoints are:	New added wording to optimize the statistical analysis part: -Ocular surface disease related endpoints: **-CFS in the study eye at Week 4 in subjects with baseline CFS ≥ 1** **-Tear film break-up time (TFBUT) in the study eye at Week 4 and Week 12 in subjects with baseline TFBUT ≤ 10** ***-Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Week 4, Week 12*** ***-Conjunctival fluorescein staining in the study eye at Week 4 and Week 12 in subjects with baseline conjunctival fluorescein staining ≥ 1*** ***-Dry eye sensation symptom in the study eye at Week 4 and Week 12 in subjects with baseline***

			dry eye sensation symptom in mild, moderate, or severe ***-Blurred/poor vision symptom in the study eye at Week 4 and Week 12 in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe*** ***-Burning/stinging/itching symptom in the study eye at Week 4 and Week 12 in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe*** ***-Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris) in the study eye at Week 4 and Week 12*** ***-CFS in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline CFS ≥ 1*** ***-Tear film break-up time (TFBUT) in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline TFBUT ≤ 10*** ***-Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Month 6, Month 9 and Month 15/early termination*** ***-Conjunctival fluorescein staining in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline conjunctival fluorescein staining ≥ 1*** ***-Dry eye sensation symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline dry eye sensation symptom in mild, moderate, or severe*** ***-Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline blurred/poor vision symptom in mild, moderate, or severe*** ***-Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination in subjects with baseline burning/stinging/itching symptom in mild, moderate, or severe*** ***-Slit lamp examination (Meibomian gland dysfunction, conjunctiva, lids and tear film***

			debris) in the study eye at Month 6, Month 9 and Month 15/early termination
34	6.1	Protocol : Overall Study Design	The following wording has been deleted in order to optimize the statistical analyses: ***The Sponsor expects to enroll approximately 65% or more subjects with OSD in this study. For eyes to be considered as having an OSD, the eligible eye must satisfy all of the following three criteria at baseline (Day 1):*** ***-CFS score of 1, 2, or 3 (Modified Oxford scale)*** ***-At least one of the symptom scores (burning/stinging/itching, eye dryness, or blurred/poor vision) is of a severity moderate or worse, AND*** ***-TFBUT of 10 seconds or less.***
34	6.1	Protocol : Overall Study Design	The study duration was updated to reflect the updated of the wash out period to 6-weeks. The study duration (including the wash-out period) will be up to ~~***16***~~***17*** months, and patients will attend up to 6 scheduled visits after Screening visit (Table 3).
35		Protocol Figure 1:	The following wording has been added in order to optimize the statistical analyses part: ****** Brinzolamide will be stopped 5 days before randomisation (6 to 7 days if over the weekend). At Day 1, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement. If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.***
36	6.1	Protocol Study Treatment Period 1	The following wording has been deleted in order to optimize the statistical analyses part: Assessement of the Subject Global Rating of Treatment ~~***(on the study eye),***~~ at Week 12 visit.
37	6.1	Protocol Study Treatment Period 2	The following wording has been deleted in order to optimize the statistical analyses part:

			Assessement of the Subject Global Rating of Treatment ~~***(on the study eye),***~~ only at Month 15 visit.
38	6.5	Protocol End of Trial	Added to harmonize with the Latvian AM1: ***End of Trial is defined as the last visit of the last subject***
55 57 57 58 58	10.2. 10.2.3. 10.3. 10.3.2. 10.3.3.	Protocol Investigator-masked treatment Phase Period 1 Week 12 Open-label DE-130A treatment Phase Period 2 Month 15 Unscheduled Visit	The wording ”study eyes” has been deleted in terms of subject global rating of the treatment because it is expected a global rating not a specific one per eye: Subject Global Rating of Treatment ~~***(Study Eye)***~~
61	11.5.	Protocol Dilated fundoscopy	The following wording has been added to clarify that the undilated fundoscopy is performed as safety endpoint (already planned but not mentioned in this section of the protocol): Dilated ***and undilated*** fundoscopy
61	11.6.	Protocol Use of Concomitant Artificial Tears	The following wording has been deleted since per protocol this use should remain stable: ~~***A decrease in artificial tear use from baseline (Period 1) and/or from Week 12 (Period 2) will indicate improvement.***~~
64	12.1.4.	Protocol Pregnancy Screen	The following wording has been added in order to optimize safety measures: ***Sexual abstinence is defined as refraining from heterosexual intercourse during the entire study period and should be in line with the preferred and usual lifestyle of the subject.***
69	12.2.4.3.	Expedited reporting	The following wording has been deleted or andded to clarify the preferred choice of reporting: “email then phone then fax” rather than “email then fax then phone”. Santen EMEA, ***Safety Vigilance*** ~~**Pharmacovigilance Unit (PVU)** ***(SV)***~~

			Email to safetyEU@santen.com **or** ~~***Fax to +358 3 318 1060***~~ **Phone +358 3 284 8625**
71	13.1.3	Protocol Multiple Comparisons/Multiplicity	The following wording has been added in order to optimize the statistical analyses part: ***To control the overall type I error rate at 0.05 level, the three hypotheses testing in the primary and key sencondary endpoints will be performed sequentially according to hierarchical fixed sequence procedure below:*** ***4. Hypothesis testing of non-inferiority of DE-130A to Xalatan® for the primary endpoint: change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12.*** ***5. Hypothesis testing of superiority of DE-130A to Xalatan® for the first key secondary endpoint: change from baseline in CFS score at Week 12 in subjects with baseline CFS ≥ 1.*** ***6. Hypothesis testing of superiority of DE-130A to Xalatan® for the second key secondary endpoint: change from baseline in symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) at Week 12 in subjects with baseline symptom average score >0.***
73	13.4	Protocol Efficacy analyses	The following wording has been added to change the statistical method for the primary analysis of the efficacy endpoints so that (1) will be able to adjust for baseline variables to improve the precision of estimates on treatment effect ; (2) handle missing data with a newer approach: ***During period 1, if a patient takes any concomitant medications or undergoes any concomitant therapies listed in Section 8.2 of this protocol, IOP and/or CFS and OSD symptom scores after taking the medication/therapy will be censored for the***

			primary and/or key secondary efficacy endpoints analyses. The endpoint(s) that will be censored depends on the medications or therapies taken, which will be determined by the Sponsor team during the masked data review before database lock. ***-IOP data will be censored after any IOP-lowering medication/therapy is taken.*** ***-CFS and symptom scores will be censored after any medication (including artificial tears change)/therapy that might have any effect on the OSD signs and symptoms.*** ***If it is determined that a medication or therapy could have an effect on both IOP and OSD endpoints, IOP, CFS and symptom scores will all be censored***.
73	13.4.1.	Protocol Analysis of Primary Efficacy Endpoint	The following wording has been added or deleted to change the statistical method for the primary analysis of the efficacy endpoints so that (1) will be able to adjust for baseline variables to improve the precision of estimates on treatment effect ; (2) handle missing data with a newer approach: The difference in change from baseline in peak and trough IOP between the DE-130A group and the Xalatan® group at the Week 12 Visit in the ***IOP*** study eye will be compared using ***a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Week 12 based on FAS population. A separate MMRM model will be used for IOP at peak and trough, respectively. The model will include treatment, visit, treatment-by-visit interaction and country as fixed effects, baseline IOP at the respective timepoint (peak or trough) as covariates.*** ~~***an independent-sample Student's t-test and reported along with its The***~~ 95% confidence interval***s intervals and p-values will be reported.***~~***, respectively.***~~ For the primary efficacy endpoint, the following hypotheses will be tested:

			H_0: $\mu_T - \mu_C > \Delta$ ***or at least one timepoint*** versus H_A: $\mu_T - \mu_C \leq \Delta$ ***for both timepoints*** where μ_T and μ_C denote the mean change from baseline in peak or trough IOP in DE-130A and Xalatan® groups, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg. Non-inferiority will be established if the upper limit of the one-sided 97.5% confidence interval is less than or equal to the non-inferiority margin of 1.5 mmHg ***at both the peak and trough timepoints at Week 12.*** Sensitivity analysis of the primary efficacy endpoints will be done with the ***Glaucoma/OHT*** PP population ~~***and with the observed cases only.***~~ Because both the peak and trough IOP endpoints have to meet the non-inferiority criterion in order to claim non-inferiority of DE-130A as compared to Xalatan®, no multiplicity adjustment is needed ***for the primary efficacy endpoint.*** ~~***During period 1, if a patient takes any concomitant medications or undergoes any concomitant therapies listed in Section 8.2 of this protocol, IOP and/or CFS and OSD symptom scores after taking the medication/therapy will be censored for the primary and/or key secondary efficacy endpoints analyses. The variable(s) that will be censored depends on the medications or therapies taken, which will be determined by the Sponsor team during the masked data review before database lock. IOP data will censored after any IOP-lowering medication/therapy is taken; CFS and symptom scores will be censored after any medication (including artificial tears)/therapy that might have any effect on the OSD signs and symptoms. If it is determined that a medication or therapy could have an effect on both IOP and OSD endpoints, IOP, CFS and symptom scores will all be censored.***~~

74	13.4.2.1.	Protocol Analysis of Key Secondary Endpoints	The following wording has been added or deleted to change the statistical method for the primary analysis of the efficacy endpoints so that (1) will be able to adjust for baseline variables to improve the precision of estimates on treatment effect ; (2) handle missing data with a newer approach: The key secondary endpoints are: -Change from baseline in CFS score at Week 12 ***in subjects with baseline CFS ≥ 1*** -Change from baseline in symptom score (3-symptom average: ***dry eye sensation, blurred/poor vision and burning/stinging/itching***) at Week 12 ***in subjects with baseline symptom score >0*** If non-inferiority in the primary endpoint is achieved, the above two key secondary endpoints will be tested sequentially according to hierarchical fixed sequence procedure: 3) Change from baseline in CFS score at Week 12 ***in subjects with baseline CFS ≥ 1*** ***The MMRM model with a similar model setting described for the analysis of the primary efficacy endpoint*** ~~***An independent-sample Student's t-test***~~ will be used to test the following hypotheses: $H0S_1: \mu Ts_1 - \mu Cs_1 = 0$ versus $H_{AS_1}: \mu Ts_1 - \mu Cs_1 \neq 0$ where μTs_1 and μCs_1 denote the mean change from baseline in CFS in DE-130A and Xalatan® groups, respectively. If the hypothesis is rejected at 0.05 significance level, then the following key secondary endpoint will be tested. ***4)*** Change from baseline in symptom score (3-symptom average) at Week 12 ***in subjects with baseline symptom score >0***

			The MMRM model with a similar model setting described for the analysis of the primary efficacy endpoint ~~An independent-sample Student's t-test~~ will be used to test the following hypotheses: $H0S_2: \mu Ts_2 - \mu Cs_2 = 0$ versus $HAS_2: \mu Ts_2 - \mu Cs_2 \neq 0$ where μTs_2 and μCs_2 denote the mean change from baseline in symptom score (3-symptom average) in DE-130A and Xalatan® groups, respectively. ***~~As a~~ The Ocular Surface Disease PP population will be used for the sensitivity analysis of the two key secondary efficacy endpoints ~~sensitivity analysis of these key secondary endpoints, a subject will be excluded from these analyses if his/her artificial tears use status has changed prior to the Week 12 visit. The artificial tears use status change is defined as meeting one of the following criteria:~~*** ***~~- For patients who do not use artificial tears before the Screening Visit, if they start to use artificial tears at any time in between Baseline and the Week 12 visits.~~*** ***~~- For patients who already use artificial tears before the Screening Visit, if at any time in between Baseline and the Week 12 visits:~~*** ***~~o The dosing frequency increased ≥ 2 drops/day~~*** ***~~Add a new or change to another artificial tears.~~***
75	13.4.2.2.	Protocol Analysis of Other Secondary Endpoints Ocular Surface Disease Assessments	The following wording has been deleted or added in order to optimize the statistical analyses part: ***~~IOP Assessments~~*** ***Change from baseline in conjunctival fluorescein staining, TFBUT, and each individual symptom score in the study eye at each analysis visit in Period 1 will be compared between treatment groups using***

			MMRM on observed cases. More details on the model specifications will be provided in the SAP. ***Percentage of patients with conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6)) in the study eye at each analysis visit in Period 1 will be compared between treatment groups using a Chi-squared test or Fisher's Exact test wherever appropriate for the FAS population.*** ***CFS, conjunctival fluorescein staining, TFBUT, 3-symptom average and individual symptom score, and slit lamp examination in the study eye at each analysis visit will be summarized descriptively by treatment group.*** ***Artificial tears use during Period 1 will be summarised by treatment group as a continuous variable as well as by percentage of patients who use artificial tears at each analysis visit.*** ***Descriptive statistics will also be provided for ocular surface disease endpoints (corneal and conjunctival fluorescein staining, TFBUT, symptom scores [3-symptom average and individual symptom score]) and their change from baseline at each visit by analysis visit and treatment group in Period 1 only.*** ***For the patients participating to the safety follow-up, OSD endpoints and their change from baseline will be summarized for subjects within the Open-Label population by analysis visit for the whole study period (Periods 1 & 2) and change from Week 12 for Period 2.*** ***IOP Assessments*** ***Changes in peak, trough, and mean diurnal IOPs on the study eye will be summarized by treatment group at Week 4 and Week 12.*** ***Peak, trough, and mean diurnal IOP responses on the study eye (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response, defined in Section 5.3.3) will be summarized by treatment group at Week 4 and Week 12.*** ~~***Changes in peak, trough, and mean diurnal IOPs will be summarized by treatment groups at***~~

			~~***Week 4 and Week 12, respectively, for the FAS population and CFS subgroups.***~~ ~~***Peak, trough, and mean diurnal IOP responses (IOP 20%, 25%, 30% responses, and IOP < 18 mmHg response, defined in Section 5.3.3) will be summarized by treatment groups at Week 4 and Week 12, respectively, for the FAS population and CFS subgroups.***~~ ~~***For patients participating to the safety follow-up, change from baseline and change from Week 12, respectively, in mean morning (9:00 am ± 1 hour) IOP will be summarized for the Open-Label population and for CFS subgroups at Month 6, Month 9 and Month 15/early termination.***~~ ~~***Ocular surface disease Assessments***~~ • ~~***Change from baseline in each individual symptom score, and TFBUT at Week 12 will be compared between treatment groups using an independent-sample Student's t-test for the FAS population and for CFS subgroups, respectively.***~~ • ~~***Percentage of patients with moderate and severe conjunctival hyperemia (grade ≥ 3 measured by slit lamp scored using the photographic scale derived from McMonnies scale (1 to 6)) at Week 12 will be compared between treatment groups.***~~ • ~~***Proportion of subjects using artificial tears at Week 12 will also be compared between treatment group using a Chi-squared test or Fisher's Exact test wherever appropriate for the FAS population and for CFS subgroups, respectively.***~~ ~~***Ocular surface disease endpoints (corneal and conjunctival fluorescein staining [modified Oxford scale], TFBUT, symptom scores [3-symptom average and individual symptom score], use of artificial tears [continuous variable], and slit lamp examination) and their change from baseline at each visit will be summarized for the FAS population and for***~~

			~~***CFS subgroups, respectively, by treatment group (Period 1) and by analysis visit.***~~ ~~***Artificial tears use during Period 1 (Day 1 to Week 12 Visit) will also be analyzed by treatment group on percentage of patients who use artificial tears at each visit.***~~ ~~***For the patients participating to the safety follow-up, OSD endpoints and their change from baseline will be summarized for the Open-Label population and for CFS subgroups by analysis visit for the whole study (Periods 1 & 2) and change from Week 12 for Period 2.***~~ Quality of life Assessments Mean scores of quality of life (Glaucoma Quality of Life-15), and their change from baseline (Period 1 and Periods 1 & 2) and change from Week 12 (Period 2) will be summarized ***by study period***, analysis visit and by treatment group (Period 1), for the FAS population (Period 1), for the Open-Label Population (Period 2, Periods 1 & 2***).***~~***, and for CFS subgroups.***~~ Subjects Global Rating of Treatment Subjects global rating of treatment at Week 12/early termination will be summarized by treatment groups for the FAS population ~~***and for CFS subgroups, respectively.***~~ Also, it will be summarized at Month 15/early termination for the Open-Label Population.
76	13.5.1.	Protocol Adverse Events	The following wording has been deleted or added in order to optimize the statistical analyses part: A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the study drug ~~***or***~~ study procedure ***or artificial tears*** caused the adverse event.
76	13.5.2.	Protocol Other Safety Assessments	The following wording has been added in order to optimize the statistical analyses part: Other safety assessment parameters (e.g. slit lamp examination, dilated fundoscopy, BCDVA, and visual field) will be summarized by ***study period,*** analysis visit ***and treatment group (Period 1 only).***

76	13.7.	Protocol Handling of Missing Values	The following wording has been deleted or added in order to optimize the statistical analyses part: ***Missing data will be handled within the MMRM model for all efficacy assessment analysed using this statistical model.*** ***No missing data on safety endpoints will be imputed.*** ~~***subjects whose IOP, or CFS/symptom score data got censored due to the usage of prohibited medications/therapies, their censored data after being rescued will be imputed using a last-observation-carried-forward approach (LOCF). For missing IOP measures, IOP values taken at the same time point (peak or trough) at the last visit prior to being rescued will be used for the imputation.***~~ ~~***If during Period 1, a subject has missing data but not taking any concomitant medications or therapies that has IOP-lowering or OSD sign and/or symptom improving effect, the LOCF approach will be used to impute the missing data on IOP, CFS, or symptom scores (3-symptom average). For peak or trough IOP, the last observation at peak or trough, respectively, will be carried forward. Missing data will be only imputed for the primary and key secondary efficacy endpoints 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 the Statistical Analysis Plan (SAP). ~~***Same***~~ ***Likewise*** rules will be ***applied*** ~~***followed***~~ to impute the completely or partially missing start and end dates of non-study medications.
	NAP	COMPANY/SPONSOR APPROVERS	Replace the name of the clinical operation leader due to new organisation inside Santen company.