Statistical Analysis Plan 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.
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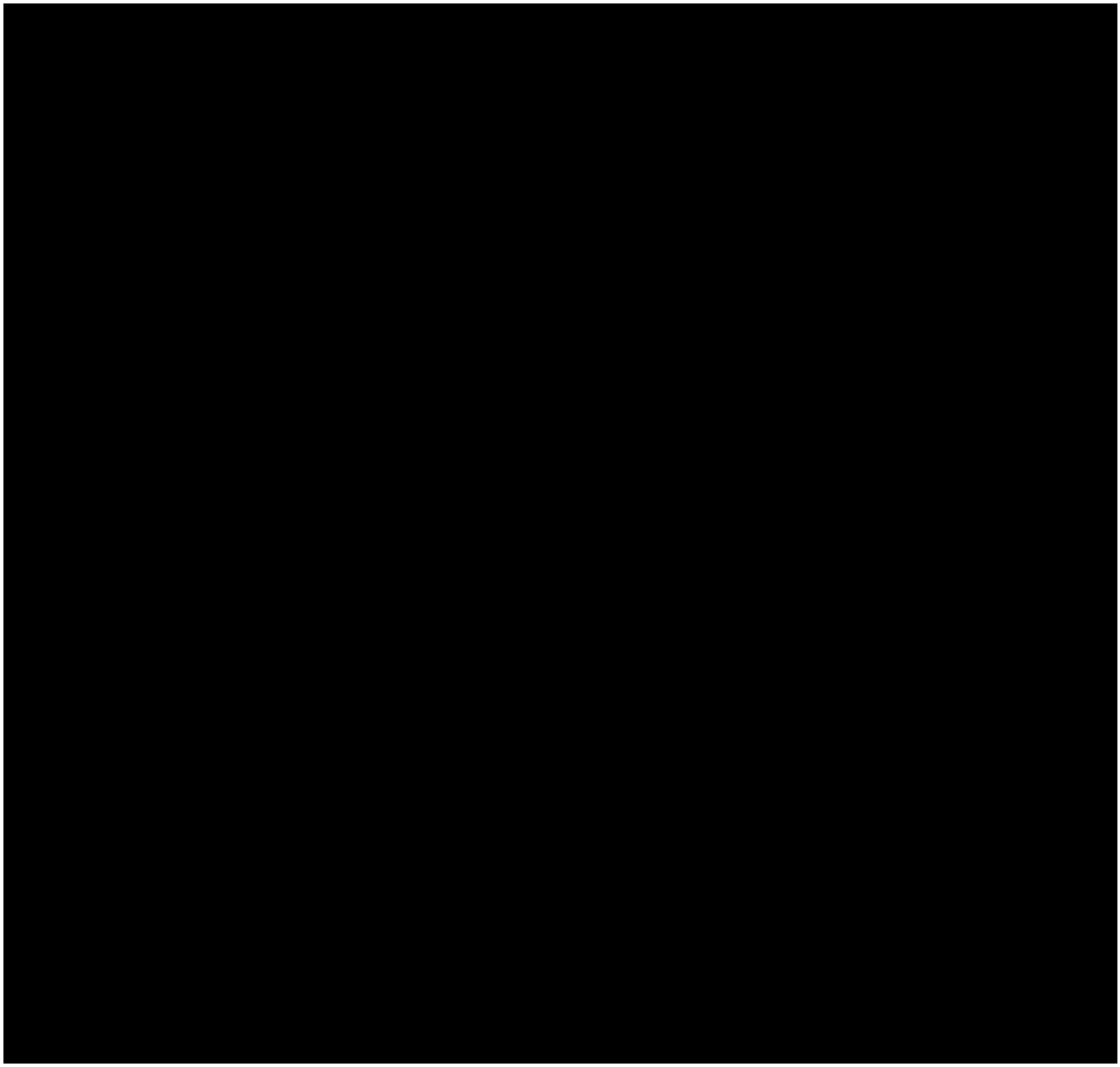
STATISTICAL ANALYSIS PLAN

Protocol Title:	A Phase III, Multinational, Multicenter, Investigator-Masked, Randomized, 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
Product:	DE-130A (latanoprost 50 microg/ml eye drops emulsion, SD)
Protocol Number:	0130A01SA
Sponsor:	Santen Inc. 6401 Hollis Street, Suite 125 Emeryville, CA 94608 U.S.A.
Date:	March 11th, 2022
Status:	Version 1.0

CONFIDENTIAL



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ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
AT	Artificial Tears
BCDVA	Best Corrected Distance Visual Acuity
CSI	Case of Special Interest
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CSR	Clinical Study Report
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GQL-15	Glaucoma Quality of Life-15 Questionnaire
IOP	Intraocular pressure
IOP-L drug	Intraocular Pressure Lowering drug
IWRS	Interactive Web Response System
LOCF	last-observation-carried-forward
MedDRA	Medical Dictionary for Regulatory Activities
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
OSD	Ocular Surface Disease
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SOC	System Organ Classification
TFBUT	Tear Film Breakup Time
TEAE	Treatment Emergent Adverse Event
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from DE-130A within the scope of Santen's Protocol 0130A01SA , "A Phase III, Multinational, Multicenter, Investigator-Masked, Randomized, Active-Controlled Trial, comparing the efficacy and safety of DE-130A with Xalatan® in Subjects 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 ". It applies to the study protocol dated 26 February 2021 and provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

2. OBJECTIVES, ENDPOINTS AND ESTIMANDS

2.1. Objectives

The primary objective is 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 BAK-preserved eye drops solution), in subjects with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT) at Week 12 without using any rescue medication(s).

The secondary objectives are:

- 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 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 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).

2.2. Estimands

Primary estimands of the primary objective is;

- The difference between the mean change from baseline IOP (peak and trough) after Week 12 in subjects with OAG or OHT treated with DE-130A versus Xalatan. For subjects who had received IOP rescue medication before Week 12 or who discontinued due to any reason during double masked period, the data of IOP will be censored (treated as missing value), then primary model will be applied.

Supplementally, estimand for key-secondary endpoint are also described. This will be used when statistical testing strategy (step down approach) is applied (See Section 8.2 and 8.3).

- The difference between the mean change from baseline CFS score after Week 12 in subjects with OAG or OHT and with baseline CFS score ≥ 1 treated with DE-130A versus Xalatan. For subjects who had received rescue medication before Week 12 or who discontinued due to any reason during double masked period, the data will be censored (treated as missing value), then primary model will be applied.
- The difference between the mean change from baseline OSD symptom score after Week 12 in subjects with OAG or OHT and with baseline OSD symptom average score>0 treated with DE-130A versus Xalatan. For subjects who had received rescue medication

before Week 12 or who discontinued due to any reason during double masked period, the data will be censored (treated as missing value), then primary model will be applied.

2.3. Endpoints

2.3.1. Primary 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.

2.3.2. Secondary Endpoints

2.2.2.1. 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 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.

2.2.2.2. Other Secondary Endpoints

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
    - Blurred/poor vision symptom in the study eye at Week 4 and Week 12
    - Burning/stinging/itching symptom in the study eye at Week 4 and Week 12
    - 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
- Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/early termination
- Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination
- 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

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

2.3.3. Safety and Tolerability Endpoints

For 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

3. STUDY DESIGN

3.1. General Study Design

The proposed 3-month phase III study is a prospective, interventional, multinational, multicenter investigator-masked, randomized, 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 subjects with OAG or OHT. In addition, after Week 12, a 12-month follow-up with open-label DE-130A in a subgroup of subjects (n=130 and some Belgium subjects) will estimate the long-term safety and tolerance and explore the long-term efficacy of DE-130A (Period 2). Period 2 will be open in some countries only.

After a wash-out phase (5 days to 5 weeks) depending on previous IOP lowering medications, approximately 380 subjects are randomized in a 1:1 ratio to receive either:

- **Test regimen** - DE-130A (latanoprost 50 microg/ml preservative-free eye drops emulsion) once daily (QD) at 9 PM for 12-week duration of the double-masked treatment period.

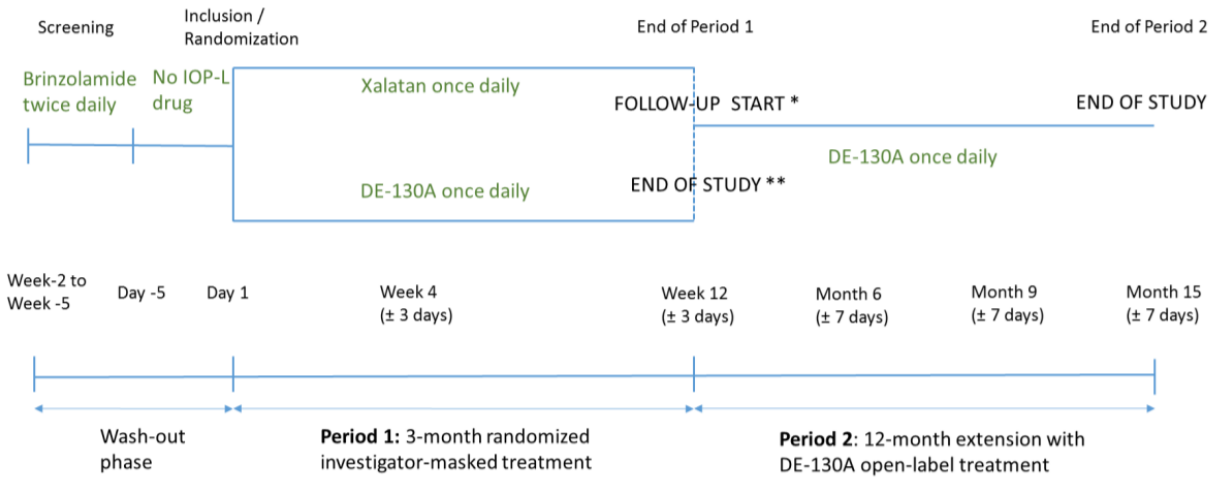
- **Control regimen** - Xalatan® groups (latanoprost 50 microg/ml BAK-preserved eye drops emulsion) QD at 9 PM for 12-week duration of the double-masked treatment period.

At the end of the double-masked period, the first 130 subjects and some Belgium subjects who complete the Week 12 visit and agree to participate in the safety follow-up will enter the open-label period and receive DE-130A QD for additional 12 months (Figure 1).

The study duration (including the wash-out period) will be up to 16 months, and subjects will attend up to 6 scheduled visits after Screening visit (Table 1).

The study design is illustrated by Figure 1.

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 subjects and some Belgium who complete their Week 12 visit and agree to participate in the open-label period of the study.
** End of study for subjects who do not participate in the open-label period of the study.

3.2. Randomization and Masking

At the 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. The randomization will be stratified according to the CFS score of the study eye at the Baseline Visit (CFS $\leq$ 1 vs. CFS $\geq$ 2, modified Oxford scale).

This study is investigator-masked because the appearance of the two eye drops are totally different and it would be impossible to mask the subjects. But subjects shall not be explicitly 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.

3.3. Sample Size Planning

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.

3.4. Visits and Assessments

The schedule for all study-related procedures and evaluations are shown in Table 1: Study Design and Schedule of Assessments. Assessments should be completed at the designated visit/time point(s) and should be performed in both eyes.

Table 1: Study Design and Schedule of Assessments

	Screening	Baseline	Period 1	Period 2		End of Study Visit	
	-5 days to Week -5 [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†	
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						
Randomise qualified subjects to treatment		X					
Dispensation of Washout 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 subjects 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 will only be collected at Week 12 visit.

4. TIME-RELATED TERMS

4.1.1. Baseline Visit (Day 1)

The *Baseline Visit* is Day 1 when the subject is randomized.

NOTE: If an endpoint is not measured at Day 1 Baseline visit, the nearest data prior to first dosing day will be defined as the baseline.

4.1.2. Treatment Start Date and Treatment End Date

Treatment start date and *treatment end date* for each treatment period are defined as follows in Table 2.

Table 2: Definitions for Treatment Start and End Dates by Treatment Period

Treatment Period	***Treatment Start Date***	***Treatment End Date***
Double-Masked (DM) Treatment Period	The date at which a randomized subject takes the first dose of the DM study drug	The date at which a randomized subject takes the last dose of the DM study drug. If the date of the last dose is missing and the subject does not receive any OL study drug: • The day before the Week 12 date will be considered the treatment end date for subjects who completed the Week 12 Visit • The day before the Exit Visit date will be used for subjects who prematurely discontinued from the study before Week 12 visit. If the Exit Visit date of a non-completer is not available, then the day before the last available visit date will be considered the treatment end date
Open-Label (OL) Treatment Period	The date at which a randomized subject takes the first dose of the OL study drug	The date at which a randomized subject takes the last dose of the OL study drug. If the date of the last dose is missing: • The day before the Month 15 date will be considered the treatment end date for subjects who completed the Month 15 Visit • The day before the Exit Visit date will be used for subjects who prematurely discontinued from the study during OL period. If the Exit Visit date of a non-completer is not available,

		then the day before the last available visit date will be considered the treatment end date
Entire Study	The date at which a randomized subject takes the first dose of the DM study drug	The date at which a randomized subject takes the last dose of the study drug. Missing last dose date will be handled the same way as mentioned above.

Notes:
1) For each treatment period, the treatment end date will be set to missing if the treatment start date is missing.
2) OL Treatment Period and Entire Period only apply to the first 130 subjects and some Belgium subjects who complete their week 12 visit and agree to participate in the OL period.

4.1.3. Study Day

The *study day* variable describes the relative day of the observation starting with the reference date. For this study, the treatment start date is the reference date, which is the Baseline Visit (Day 1) date. The study day will be calculated as:

- For days prior to the Baseline Visit, Study Day = Date – Treatment Start Date
- For days on/after the Baseline Visit, Study Day = Date – Treatment Start Date + 1

Note that there is no Day 0 and the Baseline Visit date is Day 1.

4.1.4. Out-of-Window Measurements and Analysis Window

For this study, a measurement collected at a visit is an *out-of-window* measurement if the study day of the visit falls outside of a visit window specified in the protocol (Table 1), or it is a *within-window* measurement otherwise.

Analysis visit is a timing variable to be used for analyses involving visits. For each analysis visit, an analysis window is set up to determine the analysis visit to which a measurement should be mapped. The *analysis window*, which is wider than the visit window, will be employed to minimize the impact of missing data due to out-of-window measurements for analysis. The analysis windows for all post-baseline visits will be specified in the ADaM specifications document. The table below shows the analysis windows for post-baseline visits up to Month 15.

Analysis Visit Name (Target Assessment Date)	**Protocol-defined Visit Window**	**Analysis Window**	**Analysis Window** (QOL ONLY)
Week 4 (Day 29)	[26, 32]	[2, 57]	
Week 12 (Day 85)	[82, 88]	[58, 133]	[2, 268]
Month 6 (Day 181)	[174, 188]	[134, 226]	
Month 9 (Day 271)	[264, 278]	[227, 361]	
Month 15 (Day 451)	[444, 458]	[362 -	[269 -

For analyses involving post-baseline visits, if there are two or more measurements that fall into the same analysis window of a post-baseline visit, then the measurement closest to the target assessment day will be selected for that visit for analysis while the other measurement will be excluded from analysis. In the case when the two closest measurements are of the same distance to the target assessment day, i.e., one is before and one is after the target assessment day, the later one will be selected for that visit and used for analysis while the other measurement will be excluded from analysis.

For analyses of IOP involving post-baseline visits in Period 1, if there are two or more visits that fall into the same analysis window of a post-baseline visit, then the visit in which IOP are measured at all the scheduled timepoints (peak and trough) will be selected for that analysis visit first, before applying the above rule.

4.1.5. Extent of Exposure

The *extent of exposure* to study medication will be assessed by duration of treatment exposure, which will be derived using the following formula:

Duration of treatment exposure = (Treatment end date – Treatment start date) + 1

Treatment exposure will also be categorized into the following categories:

- For subjects who only enter Period 1:
  - < 31 days
  - 31 – 60 days
  - 61 – 90 days
  - > 90 days
- Additional categories for subjects who enter Period 2:
  - < 151 days
  - 151 – 240 days
  - 241 – 330 days
  - 331 – 420 days
  - 421 – 481 days
  - > 481 days

5. GENERAL CONSIDERATIONS

All measures will be summarized by treatment (planned or actual received) descriptively. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

Unless otherwise specified, the following conventions will be followed in reporting the decimal places.

Variables	**Decimal Places**
Range (low value, high value)	Recorded decimal places
Mean, median	Recorded value + 1 decimal places
Confidence interval, standard deviation, standard error	Recorded value + 2 decimal places
p-Value	4 Decimal places

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

All data manipulations, descriptive summaries, and statistical hypothesis testing will be performed using SAS® Version 9.4 or later.

Additional analyses not specified in this SAP may be conducted if deemed necessary and will be documented in the CSR.

5.1. Handling of Missing Data

5.1.1. Efficacy Measures

If a subject takes any concomitant medications or undergoes any concomitant therapies listed in Section 8.3 of the protocol, IOP and/or CFS and OSD symptom scores after taking the medication/therapy will be censored (treated as missing) for the primary and/or key secondary efficacy endpoints analyses in double-masked period. 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.

Different lists of medications will be applied to IOP and CFS/Symptom endpoints.

- 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.

For OSD symptom score (average of 3 symptoms) calculation:

- If one out of the three individual symptom scores is missing, use the average of two non-missing symptom scores;
- If two out of the three individual symptom scores are missing, use the one non-missing score.

For primary and key secondary endpoints: the below imputation approach are applied.

- No imputation is needed for the analysis on observed cases using the Mixed-effects Model for Repeated Measures (MMRM).
- Pattern mixture model will be applied to evaluate robustness of primary analysis depending on the reasons of discontinuation or rescue medication

For mean diurnal IOP calculation: if there is a missing IOP measurement at a scheduled timepoint, the mean diurnal IOP will not be calculated.

5.1.2. Safety Measures

Descriptive summaries of safety measures will be based on observed data. No imputation of missing scores will be implemented.

5.1.3. Dates for Medical Events and Medications

The completely or partially missing onset and resolution dates of medical events, i.e., medical history events and AEs, will be imputed in a conservative fashion as follows:

Date	***Type of Missing Date***	***Handling of Missing Date***
Event onset date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied. For AE, the event will be considered treatment emergent. For CM, the event will be considered concomitant. For MH, the event will be considered to occur prior to Inform Consent date.
	Only YYYY is available	Use the first day of YYYY to impute the missing month and date parts of the onset date
	YYYY and MM are available but DD is missing	Use the first day of MM to impute the missing date part of the onset date

Date	*Type of Missing Date*	*Handling of Missing Date*
Event resolution date (e.g., YYYY-MM-DD)	Completely missing	No imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the Study Exit date.
	Only YYYY is available	Use the last day of YYYY to impute the missing month and date parts of the resolution date
	YYYY and MM are available but DD is missing	Use the last day of MM to impute the missing date part of the resolution date

Same rules will be followed to impute the completely or partially missing start and end dates of non-study medications.

5.2. Multi-Center Studies

This study is a multinational and multi-center study. Since there are many small investigational sites, site will not be included as a covariate in statistical models. Instead, country will be used as a covariate in statistical models.

5.3. Multiple Comparisons / Multiplicity

To control for the overall Type I error rate associated with the multiple comparisons on the primary and the key secondary endpoints at the 0.05 level (two-sided), the following hierarchical testing strategy will be employed:

1. Conduct the statistical testing for the primary comparison between DE-130A and Xalatan on the primary endpoint. Difference between the two treatment groups in change from baseline in both the peak and trough IOP at Week 12, separately, have to meet the non-inferiority criterion that 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.
2. If non-inferiority in the primary efficacy endpoints is achieved, conduct the statistical testing for the comparison between DE-130A and Xalatan on the following key secondary endpoints sequentially according to hierarchical fixed sequence procedure:
    1) Change from baseline in CFS score at Week 12 in subjects with baseline CFS ≥ 1. If the hypothesis is rejected at the 0.05 significance level (two-sided), then the following key secondary endpoint will be tested.
    2) 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 subjects with baseline symptom average score >0.

5.4. Interim Analysis and Data Monitoring Committee

There is no planned interim analysis and no data monitoring committee for this study.

At the end of Period 1, when all subjects have completed their Week 12 Visit, database will be "soft" locked and be used to analyze all Period 1 endpoints per this SAP. The data cut plan of

this study is prepared as a separate document, and it details how data collected during period 2 will be cut for this “snapshot”.

6. ANALYSIS POPULATION

6.1. Randomized Subject Population

This population consists of all subjects who randomized in the study.

6.2. Full Analysis Set (FAS) Population

The FAS population consists of all randomized subjects who received at least one dose of study medication and provided at least one post-baseline IOP measurement at peak and trough timepoints, separately. Unless specified otherwise, the FAS population will be the analysis population for efficacy endpoints analyses in Period 1 and will use treatment as randomized.

6.3. Safety Population

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.

6.4. Per-Protocol Population

Per-Protocol (PP) population is a subset of the FAS and is defined as two separate definitions depending on endpoints, primary efficacy (Glaucoma PP population) and key secondary endpoints (Ocular Surface PP population).

Before the unmasking of treatment assignment, Santen's study team will review all protocol deviations, identify subjects with any protocol deviation that could affect the efficacy outcome, and determine whether or not to exclude the subject from these PP population.

6.4.1. Glaucoma Per-Protocol Population

The Glaucoma 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 Glaucoma PP population will be used for sensitivity analyses of the primary efficacy endpoints in Period 1 and will use treatment as randomized.

6.4.2. Ocular Surface Disease Per-Protocol Population

The Ocular Surface Disease Per-Protocol (OSD-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 efficacy endpoint. The OSD - PP population will be used for sensitivity analyses of the key secondary efficacy endpoints in Period 1 and will use treatment as randomized.

6.5. Enrolled Population to Open-Label Period

The enrolled population to open-label period will be the first 130 and some Belgium subjects who had informed consent to enroll in period 2.

6.6. Open-Label Population

The Open-Label population will be subjects who are the first 130 subjects and some Belgium 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 randomized.

6.7. Open-Label Safety Population

The Open-Label Safety population will be subjects who are the first 130 subjects and some Belgium 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.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The subject disposition will be summarized based on all screened subjects for Period 1 (double masked period) and based on all enrolled subjects to Period 2 (enrolled population to open label period) for Period 2 separately.

For the period 1, it will be summarized by planned treatment group (and overall) and include the number of screened subjects, the number (n) and percentage (%) of Safety, FAS and PP subjects (on randomized subjects). This disposition summary will also include the n and % of subjects who completed or discontinued. For discontinued subjects, the summary (n and %) will also be summarized by each reason.

For the period 2, it will be summarized by planned treatment group (and overall) and include the number of enrolled subjects in period 2, the number (n) and percentage (%) of open-label safety population and open label population subjects (on all enrolled subject in period 2 (signed informed consent for this period)). This disposition summary will also include the n and % of subjects who completed, subjects who are still on the study at the time of data cut (interim data only), or subjects who discontinued during period 2. For discontinued subjects, the summary (n and %) will also be summarized by each reason.

In addition, the subject enrollment will be summarized by region (EU, and non-EU), country and primary investigator name.

7.2. Demographics and Baseline Characteristics

Subject demographic characteristics and baseline characteristics will be summarized by planned treatment group on FAS and Open-label population, separately.

7.2.1. Demographics

The following subject demographics variables will be summarized:

- Age on consent date (continuous and categorical: < 65 years and ≥ 65 years)
- Sex (categorical: male and female)
- Race (categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, and Unknown)

7.2.2. Baseline Characteristics

The following baseline characteristics variables will be summarized for study eye and fellow eye separately. In addition, this table will be summarized by planned treatment group and by CFS subgroups on FAS:

- Primary diagnosis (categorical):
    - Primary open angle glaucoma

    - Pseudo exfoliative glaucoma
    - Pigmentary glaucoma
    - Ocular hypertension
- Time since diagnosis (continuous)
- Baseline IOP-lowering medication(s) (categorical: prostaglandin analogues, beta blocking agents, carbonic anhydrase inhibitors, each combination of medications, other)
  - *For "each combination of medications", all combinations of this study will be included in the table.*
- Baseline peak (9 am), trough (4 pm), and mean diurnal IOP (continuous)
- Baseline CFS score (continuous and categorical)
  - Categorical (Grade): 0.5, 1, 2, 3, 4, 5
  - *This is not included for CFS subgroup tables because CFS is considered as subgroup factor.*

In addition, the following variables at baseline will be summarized.

- Alcohol use [yes or no; if yes, ≤ 30 g per day (women) or ≤ 40 g per day (men), > 30 g per day (women) or > 40 g per day (men)]
- Illicit or recreational drug use (yes or no)
- Tobacco use
    - Yes
        - Ex-smoker (number of packets per year and duration of smoking)
        - Current smoker (number of packets per year and duration of smoking)
    - No
        - Passive tobacco use (yes, no)

7.3. Medical and Surgical History

The medical history events will be coded using the MedDRA Version 23.1 and summarized based on FAS for period 1 and based on open-label population for period 2.

Subjects reporting any medical history events will be tabulated by SOC and preferred term. In addition, subjects reporting any medical history events ongoing at baseline will also be tabulated. Any subject with more than one medical and/or surgical term within the same SOC (or mapped to the same preferred term) will be counted only once for that SOC (or preferred term).

This study also collects data on the surgical procedures/therapies that are performed during the study. Those data will be listed.

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Consent Issues
- Enrollment Issues
- Protocol Implementation Issues
- Safety Issues
- Investigational and Non-Investigational Product
- Others

A protocol deviation is considered major if it may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Santen's study team will review all protocol deviations and determine the major protocol deviations prior to database lock.

FAS subjects or open label population to open label period subjects with any major protocol deviations will be tabulated by deviation category for period 1and 2. In addition, two types protocol deviation list will be prepared, all significant (major) protocol deviation and subjects who excluded from per protocol population (Period 1 only).

7.5. Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, *prior medications* are non-study medications started and ended prior to the treatment start date (Day 1). *Concomitant medications* are defined as any non-study medications taken concurrently while on the study medication.

All prior and concomitant medications will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system, mapped to a World Health Organization Drug Dictionary, Version Enhanced (WHO-DDE, September 2018) format B3 preferred drug name, and summarized on the FAS subjects for Period 1, and open label population for Period 2, separately. A subject will be counted at most once for each prior or concomitant medication, separately, even if the subject might take the same prior or concomitant medication on multiple occasions.

7.6. Treatment Compliance

Treatment compliance will be summarized (continuously and categorically) on the FAS population for Period 1, and on open-label population for Period 2 and the entire study period separately.

Treatment compliance will be assessed at each scheduled visit and unscheduled visit. Dose(s) missed since the previous visit will be asked. For the purpose of treatment compliance calculation, there will be five study intervals:

- Baseline Visit (Day 1) to Week 4 Visit
- Week 4 Visit to Week 12 Visit

- Week 12 Visit to Month 6 Visit
- Month 6 Visit to Month 9 Visit
- Month 9 Visit to Month 15 Visit

For a given study interval, compliance rate will be calculated using the following formula:

$$\text{Compliance} = \frac{\text{Number of days of the followup interval} - \text{Number of missed doses}}{\text{Number of days of the followup interval}} \text{ x } 100$$

Compliance rate of ≥ 80% will be treated as compliant.

7.7. Treatment Exposure

The duration of exposure to a study medication is measured by days on treatment as derived in Section 4.1.5. The duration of exposure will be summarized using descriptive statistics, and frequency and percentage of subjects will be tabulated by actual treatment received for period 1 (Safety population), period 2 (Open-label safety population), and the entire study (Safety population) separately. For the entire study period, the duration of exposure to overall DE-130A treatment will also be provided, which will combine exposure to DE-130A from both period 1 arms. For subjects who were in the Xalatan arm during period 1, their duration of exposure to DE-130A will be the total duration on the study minus the number of days they were exposed to Xalatan treatment.

8. EFFICACY ANALYSES

All efficacy analyses will use treatment as randomized, and, unless specified otherwise:

8.1. Endpoint-Related Definitions

8.1.1. Study Eye and Fellow Eye

The *study eye* is defined as the eye that qualifies based on protocol-defined inclusion/exclusion criteria at the Baseline Visit. If both eyes are eligible, the eye with the higher morning IOP at the Baseline Visit will be chosen. If both eyes have the same morning 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. The *fellow eye* is the non study eye.

NOTE: If there is any reason by a investigator site to identify study eye, the team will discuss it to define the eye.

Study eyes and fellow eyes that are designated by this definition will be used for all efficacy endpoints analyses. All safety endpoints and baseline characteristics summaries will be based on study eyes and fellow eyes.

8.1.2. Baseline Score

For any measure, the *baseline score* is the last observed measurement prior to instillation of the first drop of the study drug. If any variable is missing a value on Day 1, values from the Screening Visit will be used to impute the baseline score, i.e., the last observation carried forward (LOCF) approach will be used to impute the baseline score and used for the purpose of calculating change from baseline scores.

8.1.3. Change from Baseline

For any measure, the *change from baseline* at a post-baseline visit will be derived as:

Change from baseline at a post-baseline visit =

(Score at the post-baseline visit) – (Baseline score).

8.1.4. Efficacy Measures

8.1.4.1. Intraocular Pressure

IOP will be measured using Goldman applanation tonometry. Morning IOP (9:00 am ± 1 hour) as well as afternoon IOP (4:00 pm ± 1 hour) will be measured at the Baseline (Day 1) Visit, Week 4 Visit, Week 12 Visit, and unscheduled visits during Period 1. IOP will be measured only in the morning (9:00 am ± 1 hour) at the Screening Visit, Month 6, Month 9 Visit, Month 15 Visit, and unscheduled visits during Period 2.

At each time point, IOP will be measured twice on each eye. If the two measurements differ by less than 3 mmHg, then the average of the two measurements becomes the 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.

A decrease in IOP at follow-up visits will indicate improvement.

8.1.4.2. Corneal and Conjunctival Fluorescein Staining

Corneal and conjunctival fluorescein staining will be performed at each scheduled and unscheduled visit and will be graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5) for cornea and conjunctiva (nasal and temporal conjunctiva) separately on each eye.

A CFS grade of 0 represents complete corneal clearing. A decrease in CFS and/or conjunctival fluorescein staining score at follow-up visits will indicate improvement.

8.1.4.3. Ocular Surface Disease (OSD) Symptom Scores

Three OSD symptoms regarding ocular discomfort unrelated to instillation of the study drug will be assessed at each scheduled visit and unscheduled visit:

- Dry eye sensation
- Blurred/poor vision
- Burning/stinging/itching

The subject will grade each ocular symptom for the week before each visit by its level of severity on a 5-point scale (0 = Absent, 1 = Mild, 2 = Moderate, 3 = Severe, and 4 = Very severe).

A decrease in OSD symptom scores at follow-up visits will indicate improvement.

8.1.4.4. Tear Film Break-Up Time

Tear film break-up time (TFBUT) will be measured by determining the time to tear break-up. At each visit, the TFBUT will be measured twice on each eye separately. 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.

An increase in TFBUT at follow-up visits will indicate improvement.

8.1.4.5. Use of Concomitant Artificial Tears (AT)

The use of protocol-authorized, unpreserved artificial tears will be monitored over the course of the study for each subject. Subjects 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 at each scheduled and unscheduled visit. Artificial tear usage in the past 7 days will be derived using the following equation:

AT usage = Average number of times per day used AT × (7 – number of days without AT use)

A decrease in AT usage at follow-up visits will indicate improvement.

8.1.4.6. Slit Lamp Examination

External ocular examination and undilated biomicroscopy will be performed using a slit lamp at each scheduled visit and unscheduled visit. Grading of the Meibomian glands, conjunctival erythema/ hyperaemia, anterior chamber inflammation, and lens will be on a 0 to 3 scale; 0

indicates normal and 3 indicates the most severe state. Lid erythema, lid swelling, conjunctival chemosis, and tear film debris will be graded on a 0 to 4 scale; 0 indicates normal and 4 indicates the most severe state. Lashes will be graded as normal or abnormal.

A decrease in slit lamp grading at follow-up visits will indicate an improvement.

8.1.4.7. Subjects Global Rating of Treatment

At Week 12 Visit and Month 15 Visit (open-label population only) or early termination visit, subjects will be asked to rate their overall assessment of the effect of the glaucoma study medication:

1 = Unsatisfactory

2 = Not very satisfactory

3 = Satisfactory

4 = Very satisfactory.

Higher score indicates higher satisfaction from the subjects.

8.1.4.8. Glaucoma Quality of Life-15 (GQL-15) Questionnaire

The Glaucoma Quality of Life-15 (GQL-15) is a questionnaire developed to assess visual disability resulting from glaucoma. Subjects will be asked to complete the questionnaire at the Baseline Visit, Week 12 Visit, and Month 15 Visit (open-label population only).

Subjects will be asked to rate the level of difficulty in terms of their vision (with glasses on) on 15 activities:

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**

Sum of individual scores, other than those 0s, will be calculated. For questions that are answered as 0s, they will be set as missing and not be used in the analysis.

Decrease in the sum score at the follow-up visits will indicate improvement.

8.2. Analysis of Primary Efficacy Endpoints

The primary efficacy endpoints are 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 DE-130A and Xalatan® groups in the study eye.

Several endpoint definitions were updated from protocol version 5.0, and only subjects who meet the criterion are included in each endpoint analysis. The below is the lists of criteria. Please refer to each endpoint definition for the detail.

- Subjects with baseline CFS ≥ 1
- Subjects with baseline OSD symptom average score >0.
- Subjects with baseline TFBUT ≤ 10
- Subjects with baseline conjunctival fluorescein staining ≥ 1

8.2.1. Primary Analysis of the Primary Efficacy Endpoints

For the primary efficacy endpoint, the following hypotheses will be tested:

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

vs.

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

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. Noninferiority 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 rough timepoints. 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.

The analysis of primary efficacy endpoint will be performed on the FAS population using a mixed-effects model for repeated measures (MMRM) on observed cases collected up to Week 12 (Laird & Ware, 1982; Lindstrom & Bates, 1988). No imputation of missing data will be needed. A separate MMRM model will be used for IOP at each timepoint (peak and trough). The model will include treatment, visit, and treatment-by-visit interaction as fixed effects, baseline IOP at the respective timepoint (peak or trough) and country as covariates. Within-subject errors will be modeled using an unstructured (UN) covariance matrix.

If the UN model fails to converge, then the first-order auto-regression [AR(1)] model and the variance components (VC) model will be fitted sequentially until the convergence criteria are met.

NOTE: The two-visit data, change from baseline to week 4 or 12, will be used as response values to fit a MMRM model, and a two by two matrix will be considered as variance-covariance matrix. Several structures (e.g. TOEPH, TOEP, ARH (1), CS) are same structure as AR(1).

From the MMRM, estimates of treatment effects at Week 12 and the pair wise treatment comparison will be based on least square means (LS mean) and the corresponding 95% confidence intervals (CI) will be provided.

8.2.2. Sensitivity Analyses of the Primary Efficacy Endpoints

To assess the robustness of the primary analysis results, the following sensitivity analyses will be performed on the primary efficacy endpoints:

- The primary analysis will be repeated on the PP population.
- The primary analysis will be repeated with multiple imputation using pattern mixture model. See the below for the detail.

Pattern Mixture Model:

This analysis applies pattern mixture model with two different multiple imputation approach depending on the reason to evaluate the robustness of primary analysis under different missing mechanism of missing not at random (MNAR) (Ratitch et al. (2013)).

Glaucoma is a chronic disease, and this scenario assumes that IOP would return to baseline value in short term (within 3 month) when a subjects stopped to take the treatment due to the reasons (AE and Lack of efficacy) or the censoring after IOP medication, while all other reason of DC is assumed to IOP change as other subjects. The below table shows overall strategy of multiple imputation by different type of missing data.

	Type of Missing Data	**Imputation Method**
#1	- For subjects who discontinued due to AE (Including SAE, Death), or Lack of efficacy, the data after the discontinuation. - For subjects how had any rescue medication, data after rescue medication (This is assumed to be equivalent to lack of efficacy discontinuation).	Baseline value is used as the response value to generate multiple imputed data of post-baseline IOP values based on the below equation (about monotone regression). Baseline IOP* = Age + Sex + Primary Diagnosis (Study Eye) + Time since diagnosis (Study Eye).
#2	- For subjects who discontinued due to all other reasons, the data after the discontinuation.	Treatment and all post-baseline IOP are used to impute post-baseline IOP data based on the "monotone regression" under MAR assumptions.

* For key secondary endpoints, this will be replaced to baseline CFS or baseline OSD score.

PMM depending on the reasons will be applied, as follows:

- Use Markov chain Monte Carlo (MCMC) to create monotone missingness first. The missing data are filled in and 50 complete datasets are created. The seed that will be used in the SAS program is 1234.
- For each IOP value that had been missing because of (1) censoring after having received IOP-lowering rescue therapy; or because of (2) early study discontinuation due to lack of efficacy or AE, regardless of treatment arm, BOCF type multiple imputation will be applied based on the model in the above table (#1). The seed that will be used in the SAS program is 2345.
- For each IOP value that had been missing because of other reasons from the above bullet, monotone regression with treatment and all post-baseline data will be applied to impute to the rest of missing data (#2). The seed that will be used in the SAS program is 3456.
- Each of the complete datasets will be analyzed separately using the same MMRM as used for the primary analysis.

- The estimates obtained from the MMRM analysis of each complete dataset are combined for inference purposes.
- NOTE: Similar analysis will be applied to key-secondary endpoints as well.

8.3. Analysis of Secondary Endpoints

8.3.1. Analysis of the Key Secondary Efficacy Endpoints

8.3.1.1. Primary Analysis of the Key Secondary Efficacy Endpoints

The following key secondary endpoints will be analyzed using the same MMRM model as specified for the primary efficacy endpoint using the observed data:

- Change from baseline in CFS score in the study eye at Week 12 in subjects 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 subjects with baseline symptom average score >0.

The hierarchical testing strategy described in Section 5.3 will be applied to control the overall type I error rate associated with the multiple comparisons on the primary and key secondary endpoints at the 0.05 level (two-sided).

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:

- Change from baseline in CFS score in the study eye at Week 12 in subjects with baseline CFS ≥ 1

The MMRM model (with observed data) will be used to test the following hypotheses:

$$H0S_1: \mu Ts_1 - \mu Cs_1 = 0$$

versus

$$HAS_1: \mu Ts_1 - \mu Cs_1 \neq 0$$

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.

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

The MMRM model (with observed data) 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.

8.2.1.2. Sensitivity Analysis of the Key Secondary Efficacy Endpoints

The following sensitivity analyses will be conducted on the two key secondary endpoints:

- The primary analysis will be repeated on the PP population.
- The primary analysis will be repeated with multiple imputation using pattern mixture model. .

Additionally, for the CFS score (NOT to change from baseline), shift table with n and the proportion (%) will be generated by planned treatment group to evaluate from baseline CFS score to each visit (Week 4 or 12) of period 1. This table includes all available data of subjects who meet FAS criteria regardless of baseline CFS score.

8.3.2. Analysis of Other Secondary Efficacy Endpoints

8.3.2.1 IOP Assessments

For the following IOP secondary endpoints, summary statistics (n, mean, SD, SE, median, min, and max) by treatment group will provided for period 1, period 2 and entire study period. In addition, the mean difference between two groups and the corresponding 95% confidence interval will be also provided.

For continuous endpoint (mean diurnal IOP), a similar MMRM to primary endpoint analysis will be performed for period 1, and the model includes treatment, visit, and treatment-by-visit interaction as fixed effects, baseline diurnal IOP and country as covariates. Estimates of treatment effects will be based on least square means (LS mean). The LS mean, difference of the LS mean between two groups, and the corresponding 95% confidence intervals (CI) will be provided at each visit.

For the binary endpoints, number of subjects who achieved the criteria, response rate (%), risk difference and the corresponding 95% confidence interval, and p-value (Chi-squared test) will be provided.

- Period 1, for FAS Population by treatment group, respectively:
    - Changes from baseline in peak, trough, and mean diurnal IOPs at Week 4 and Week 12, respectively

        - NOTE: Change from baseline in peak and trough IOP a Week 4 is included in the MMRM of primary efficacy endpoint at Week 12.
    - Peak, trough and mean diurnal IOP response, separately, 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)
- Period 2 for Open-Label Population:
    - Change from Week 12, respectively, in mean morning (9:00 am ± 1 hour) IOP at Month 6, Month 9 and Month 15.
- Entire Study period for Open-Label Population:
    - Change from baseline in mean morning (9:00 am ± 1 hour) IOP at Week 4, Week 12, Month 6, Month 9 and Month 15.

For IOP (Peak, trough, mean diurnal IOP), the score (raw value) will also be summarized as a supportive information.

8.2.2.2 Ocular Surface Disease (OSD) Assessments

The below is the list of OSD endpoints. For continuous endpoint, summary statistics (n, mean, SD, SE, median, min, and max) by planed treatment group will provided for period 1 (FAS), period 2 (Open-Label Population) and entire study period (Open-Label Population) depending on each endpoint. In addition, the mean difference between two groups and the corresponding 95% confidence interval will be also provided. For the binary endpoints, number of subjects who achieved the criteria, response rate (%), risk difference and the corresponding 95% confidence interval will be provided.

- OSD endpoints:
    - Score and change from baseline: Each individual symptom score,
    - Time: Tear film break-up time (TFBUT) in the study eye in subjects with baseline TFBUT $\leqslant$ 10,
    - Score and change from baseline: Conjunctival hyperemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]),
        - In addition, proportion of subjects with moderate and severe conjunctival hyperemia (grade ≥ 3 measured by slit lamp) is considered,

- Score and change from baseline: Conjunctival fluorescein staining in the study eye in subjects with baseline conjunctival fluorescein staining ⩾ 1,
- Score and change from baseline: Dry eye sensation symptom in the study eye,
- Score and change from baseline: Blurred/poor vision symptom in the study eye,
- Score and change from baseline: Burning/stinging/itching symptom in the study eye,
- Score and change from baseline: Slit lamp examination (Meibomian gland dysfunction, conjunctiva chemosis, lids and tear film debris),

8.2.2.3 Quality of Life Assessments

Glaucoma Quality of Life-15 (GQL-15) data will be summarized as follows:

- Period 1, for FAS Population by treatment group, respectively:
  - Score and change from baseline in GQL-15 at Week 12
- Period 2, for Open-Label Population:
  - Score and change from baseline and change from Week 12, respectively, in GQL-15 at Month 15.

Summary statistics (n, mean, SD, SE, median, min, and max) of each individual score and the sum of them will be provided by treatment group at each visit for period 1 (FAS), period 2 (Open-label population). In addition, the number of subjects in each category and the percentage (%) will be provided by treatment group.

8.2.2.4 Subject Global Rating of Treatment

Subject global rating of treatment will be assessed at the Week 12 Visit and Month 15 Visit (for Open-Label Population only), or Study Exit Visit. The number of subjects in each category (Unsatisfactory, Not very satisfactory, Satisfactory, Very satisfactory) and the percentage (%) will be provided by treatment group.

8.4. Subgroup Analyses

To assess the homogeneity of treatment effects among subgroups, the primary efficacy endpoints will be summarized for the following subgroups on the FAS. The primary analysis (MMRM) for primary endpoint will be conducted by each subgroup when total sample size of each subgroup is equal or more than 10:

- Age group (< 65 or ≥ 65 years)
- Sex (male or female)
- Primary ocular diagnosis (open angle glaucoma or ocular hypertension)
- Baseline use of IOP lowering medication (prostaglandin analogues, beta blocking agents, carbonic anhydrase inhibitors, other)
- Baseline lens status (phakic, or pseudophakic/aphakic)

- CFS scores at Baseline (CFS ≤ 1 or CFS ≥2)

In addition to table of these subgroups, forest plots will be prepared.

9. SAFETY ANALYSES

Safety measures collected in this study include AEs, slit-lamp examination, BCDVA, dilated and undilated fundoscopy, and visual field.

All the safety endpoints will be summarized by treatment arm using actual treatment received based on safety population for the following three study periods separately:

- Period 1 (Day 1 to Week 12 Visit): for Safety Population by treatment group
- Period 2 (Week 12 Visit to Month 15 Visit): for Open-Label Safety Population
- Entire Study period (Day 1 to Month 15): for Open-Label Safety Population.

9.1. Safety-Related Definitions

9.1.1. Adverse Event (AE)

An AE can be any unfavorable 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.

Each AE will be graded by the Clinical Investigator as Mild (aware or unaware of event, but easily tolerated), Moderate (discomfort enough to cause interference with usual activity), or Severe (incapacitating; unable to work or perform usual activity). AEs will also be rated by the Investigator as to their causality/relationship to the study medication, to artificial tears, as well as to the study procedures (related vs. not related).

For tabulations of AEs during this study, only the *treatment-emergent* AEs, i.e., AEs that occurred on or after the treatment start date and before or on the treatment end date of the analysis period or worsened relative to pre-treatment state will be included. Note that events that occurred before the first drop of DE-130A or Xalatan are considered medical history and will be tabulated separately.

Each AE will be classified into a System Organ Classification (SOC) and coded to a preferred term and a lowest level term using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1.

9.1.1.1. Ocular Adverse Event

An AE will be counted as an *ocular AE* if the Clinical Investigator selected ‘OD’, ‘OS’, or ‘OU’ for the AE eCRF field “Event Location”.

9.1.1.2. Suspected Adverse Reaction

Suspected adverse reactions are defined as any AEs that are deemed related to study drug, or study procedure, or artificial tears by the Investigators. Any ocular AE that occurred simultaneously to both eyes will be counted once for both the study eye and the fellow eye.

9.1.1.3. Serious Adverse Event (SAE)

A serious AE may occur during any study phase (i.e., screening, washout, treatment) with study drug (Test or Control) or artificial tears. AEs will be classified as SAEs if it meets one or more of the following criteria:

- Results in death
- It is immediately life-threatening*
- It requires in-subject 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 subject 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 subject 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 subject was at immediate risk of losing sight; it does not refer to an event which hypothetically might have caused losing of sight, refer to definitions in Section 9.1.1.4.

9.1.1.4. Sight-Threatening Adverse Event

A *sight-threatening AE* is any SAE that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event. In this study, the following serious ocular AEs will be reported as sight-threatening AEs if it meets one or more of the following 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

9.1.1.5. Adverse Event Leading to Discontinuation

An AE will be counted as an *AE leading to Discontinuation* if the Clinical Investigator selected "Adverse event" in the "Primary reason for discontinuation" checklist under the Study Exit eCRF and checked "Drug withdrawn" in the "Action taken with study drug as related to adverse event" checklist under the AE eCRF.

9.1.1.6. Case of Special Interest

In this study, *cases of special interest* (CSIs) include, but are not limited to,

- 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)
- Medication error: Any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or subject.
  - 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.
  - Abuse of study drug: Persistent or sporadic, intentional excessive use of medicinal product which is accompanied by harmful physical or psychological effects.
  - Other

9.1.2. Other Safety Measures

9.1.2.1. Slit Lamp Examination

Slit lamp examination is described in Section 8.1.4.6. It is an efficacy measure as well as a safety measure.

9.1.2.2. Best-Corrected Distance Visual Acuity (BCDVA)

BCDVA will be measured with the subject's best correction and recorded in Snellen notation.

An increase in BCDVA (i.e., decrease in Snellen denominator) indicates improvement in the best-corrected distance visual acuity.

9.1.2.3. Dilated and Undilated Fundoscopy

At the Screening, Week 12, and Month 15 visits, dilated fundoscopy will be performed. Glaucomatous optic nerve finding will be graded as 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Retina, macula, choroid, and vitreous will be graded as 0 = normal, 1 = abnormal, and 2 = unable to assess.

Cup-to-disc (C/D) ratio will be evaluated to assess the progression of glaucoma. It will be assessed via dilated fundoscopy together with other parameters. Also, it will be assessed using undilated fundoscopy at the Baseline (Day 1), Week 4, Month 6, Month 9, and unscheduled visits.

9.1.2.4. Visual Field

A visual field test is an eye examination that can detect dysfunction in central and peripheral vision which may be caused by medical conditions like glaucoma. A visual field test will be performed in each eye at the Screening Visit if the subject has not performed the test within the 6 months prior to the Screening Visit. For subjects who will be entering Period 2 (the first 130 subjects), visual field will be assessed at the Baseline and Month 6 visits.

9.2. Adverse Event

AEs are defined in Section 9.1. Only TEAEs will be included in the tabulations. All the AEs collected during this study, including those non-TEAEs, will be provided in a listing.

In the overall AE summaries, subjects with any AE(s) will be tabulated by the following types of AEs:

- AEs
- SAEs
- Non-Serious AEs (including number of events)
- Suspected adverse reactions (SARs)
  - AEs related to the study medication
  - AEs related to study procedures
  - AEs related to artificial tears
- Serious SARs (Serious SARs)
- AEs leading to premature discontinuation
- Sight threatening AEs
- Case of special interest

- Death

The above summaries will be repeated for ocular AEs, and non-ocular AEs, respectively.

Besides the overall summary of AEs, subjects with any AE(s) will be tabulated by system organ class (SOC) and preferred term (PT) coded in MedDRA Version 23.1 by study period and treatment. For AE summaries, a subject who experienced multiple AEs within a SOC and/or PT will be counted only once at the maximum severity for that SOC and/or PT.

AEs will be summarized for the following categories by SOC and PT:

- All AEs
- Ocular AEs (for study eye and fellow eye separately)
- Non-ocular AEs
- Suspected adverse reactions (SARs)
    - AEs related to study drug
    - AEs related to study procedure
    - AEs related to artificial tears
    - Please note that SAR will be summarized by each category for ocular AE and will be summarized for non-ocular SAR (AEs related to study drug).

SAEs and serious SARs will be repeated for all of the above AE and SAR summaries. A separate table will be generated that will include number of events for SAEs.

Non-serious AEs, with number of events, will be summarized by SOC and PT.

In addition, AEs will be tabulated by the following categories:

- SOC, PT, and maximal severity
- SOC, PT, and relationship (related to study medication, study procedure, or artificial tears)
- SOC, PT, maximal severity, and relationship (related to study medication, study procedure, or artificial tears)

Sight-threatening AEs and cases of special interest will be summarized by type of events specified in Section 9.1.1.4 and Section 9.1.1.6.

AEs, AEs leading to discontinuation, SAEs, sight-threatening AEs, case of special interest, and death, if any, will be listed separately.

9.3. Slit-lamp Examination

The lashes, anterior chamber, cataract severity, and lens are defined as safety endpoint of slit-lamp examination.

For each slit lamp parameter rated on a 0-3 scale (0=None, 1=Mild, 2=Moderate, or 3=Severe) or 0-4 scale (0=None, 1=Mild, 2=Moderate, 3=Severe, and 4=Very severe), the number of subjects in each scale and the percentage (%) will be provided by treatment group by study period,

treatment, and analysis visit. In addition, any worsening (increase) of ≥ 2 units from baseline will be listed.

For lashes, which are collected as Normal or Abnormal, rating scores and shift from baseline in status will be summarized by study period, treatment, and analysis visit.

For lens, shift from baseline in status will be summarized by study period, treatment, and analysis visit.

9.4. Dilated and Undilated Fundoscopy

Frequency and percentage of ratings on glaucomatous optic nerve findings, retina, macula, choroid, and vitreous will be summarized by treatment (for Period 1 only) and analysis visit and shift from baseline in status will be summarized by study period, treatment (Period 1 only), and analysis visit. In addition, any worsening (increase) of ≥ 2 units from baseline on glaucomatous optic nerve findings, or any change from Normal at baseline to Abnormal on retina, macula, choroid, and vitreous will be listed by ophthalmoscopic parameter.

For cup/disc ratio, score and change-from-baseline score will be summarized by study period, treatment, and analysis visit (combined the dilated and undilated readings). Subjects with any worsening (increase) of 0.2 units or more from baseline in cup/disc ratio will be listed for dilated and undilated readings.

9.5. Best Corrected Distance Visual Acuity (BCDVA)

BCDVA scores and changes from baseline in BCDVA will be summarized by study period, treatment, and analysis visit. This endpoint is converted to log MAR scale, then the data will be summarized.

9.6. Visual Field

Visual field scores and changes from baseline in Visual field score will be summarized device type, treatment, and analysis visit.

10. CHANGES FROM THE PROTOCOL

10.1 Analysis Population

A subject was only measured peak IOP (Not measured trough IOP) during the double mask period, then was entered into the open label period. Original definition of Open-Label Population and Open-Label Safety population were a subset of FAS subjects in Section 6.6 and 6.7. Because no IOP trough measurement is not impacted to efficacy in open label period evaluation, "a subset of FAS subjects" was removed from these definitions.

In this SAP, the below underlines were removed from the definition in the protocol.

Open Label Population

The Open-Label population will be a subset of the FAS subjects who are the first 130 subjects and some Belgium 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 randomized.

Open-Label Safety Population

The Open-Label Safety population will be a subset of the FAS subjects who are the first 130 subjects and some Belgium 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.

10.2 Secondary Efficacy Endpoint

Endpoints of OSD each symptom scores (dry eye sensation symptom, blurred/poor vision symptom, and burning/stinging/itching symptom) is limited for subjects with baseline severity of mild, moderate, or severe in the protocol (ver 5.0). However, clinical science colleagues suggested to summarize regardless of baseline status in the second TFL review meeting in February 8th 2022.

Protocol (Ver 5.0):

- 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
- 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

SAP:

- Dry eye sensation symptom in the study eye at Week 4 and Week 12
- Blurred/poor vision symptom in the study eye at Week 4 and Week 12
- Burning/stinging/itching symptom in the study eye at Week 4 and Week 12
- Dry eye sensation symptom in the study eye at Month 6, Month 9 and Month 15/early termination
- Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/early termination
- Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination

11. REFERENCES

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3. Ratitch, Bohdana, Michael O'Kelly, and Robert Tosiello. "Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models." Pharmaceutical statistics 12.6 (2013): 337-347.

12. APPENDICES