Statistical Analysis Plan Cover Page

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

PEONY Study

Protocol Title:	**A Phase III, Randomized, Observer-Masked, Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Compared with Latanoprost Ophthalmic Solution 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension- PEONY Study**
Product:	DE-117
Protocol Number:	01171505
Sponsor:	Santen Pharmaceutical Co., Ltd. Grand Front Osaka Tower A 4-20, Ofukacyo, Kita-ku Osaka 530-8552, Japan.
Date:	Feb 12, 2019
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CONFIDENTIAL

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ABBREVIATIONS

AE	Adverse Event
Al-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AR(1)	First-order autoregressive (covariance structure)
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BUN	Blood urea nitrogen
CAI	Carbonic Anhydrase Inhibitor
Cl	Chloride
CS	Compound Symmetry
CSR	Clinical Study Report
eCRF	electronic Case Report Form
CSR	Clinical Study Report
FAS	Full Analysis Set
IOP	Intraocular Pressure
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
K	Potassium
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
MAR	Missing At Random
MCAR	Missing Completely At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model for Repeated Measures
MNAR	Missing Not At Random
Na	Sodium
OAG	Open Angle Glaucoma
OD	Oculus Dexter (right eye)
OHT	Ocular Hypertension

OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
POAG	Primary Open-Angle Glaucoma
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SAS	Statistical Analysis System
SOC	System Organ Classification
UN	Unstructured (covariance structure)
VC	Variance Components (covariance structure)
WHO-DDE	World Health Organization Drug Dictionary Enhanced
γ-GT	Gamma Glutamyl Transferase

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from PEONY study within the scope of Santen's Protocol 01171505, "A Phase III, Randomized, Observer-Masked, Active-Controlled, Parallel-Group, Multinational and Multicenter Study Assessing the Safety and Efficacy of DE-117 Ophthalmic Solution 0.002% Compared with Latanoprost Ophthalmic Solution 0.005% in Subjects with Open-Angle Glaucoma or Ocular Hypertension". It applies to the study protocol dated 28 JUN 2016 and 20 JAN 2017 (for India), 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 specified inferential analyses must be substantiated by sound statistical reasoning and documented in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary objectives

To determine if the mean IOP reduction with DE-117 ophthalmic solution 0.002% is non-inferior to Latanoprost ophthalmic solution 0.005% at each post baseline time point after 3 months of treatment in subjects with OAG or OHT. This secondary objective will be used to meet the FDA non-inferiority requirement.

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

2.1.3. Safety objective

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

2.2. Endpoints

2.2.1. Primary Endpoint

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

2.2.2. Key Secondary Endpoints

The key secondary endpoints are

- Mean IOP in the study eye at the specified timepoints: 9:00, 13:00, and 17:00 at Week 1, Week 6 and Month 3.
- Mean diurnal IOP in the study eye at Week 1. This endpoint is set to confirm the early onset of DE-117 in the IOP lowering effect.

2.2.3. Other Secondary Endpoints

The following secondary endpoints will be assessed:

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

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

2.2.4. Safety Endpoints

The following safety endpoints will be assessed:

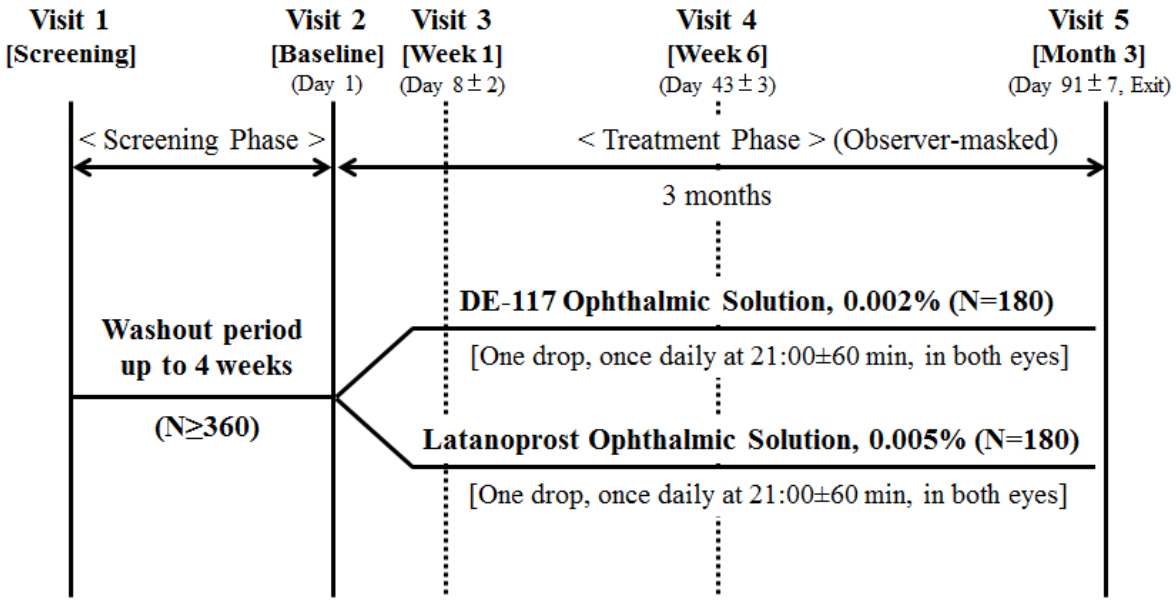
- Incidence of ocular and systemic adverse events (AEs)
- Corrected visual acuity
- Slit-lamp biomicroscopy
- Ophthalmoscopy
- Visual Field (India only)
- Central corneal thickness
- Iris color/eyelash/eyelid

3. STUDY DESIGN

3.1. General Study Design

This is a randomized, observer-masked, active-controlled, parallel-group, multinational, multicenter study assessing the safety and efficacy of DE-117 ophthalmic solution 0.002% compared with Latanoprost ophthalmic solution 0.005% in subjects with OAG or OHT. As shown in the study design diagram (Figure 1), this study consists of up to 4-Week washout period and a 3-Month treatment period. Approximately 360 subjects are planned to be randomized.

Figure 1: Study Design



3.2. Randomization and Masking

Subjects will be randomized on a 1:1 basis to two treatment groups. A blocked randomization will be stratified by 1) the mean diurnal IOP in the study eye at Baseline (< 25 mmHg and ≥ 25 mmHg) and 2) diagnosis of disease in the study eye at Baseline (OAG or OHT). Randomization schedule with a fixed block size will be generated. Each eligible subject will receive a study medication kit numbered using IWRS system.

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

To maintain masking of the Investigator, examiner, and Santen (or designee) during this study, an authorized study staff, other than the Investigator or examiner, will dispense and collect study

medications. The subjects will be instructed not to show the eye drop bottles to either the Investigator, examiner, or the other study subject(s). When collecting the study medications, the kit containing the used and unused four eye drop bottles will be sealed.

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

3.3. Sample Size Planning

The primary endpoint is the mean diurnal IOP in the study eye at Month 3. Assuming a difference of 0 mmHg and a standard deviation of 4.0 mmHg for the comparison between the DE-117 group and the Latanoprost group, a total of 151 subjects per group will provide at least 90% power to demonstrate the non-inferiority of the DE-117 group to the Latanoprost group (one-sided $\alpha = 0.025$ and non-inferiority margin of 1.5 mmHg). The standard deviation of 4.0 mmHg was assumed from a previous DE-117 study conducted in the United States, in which the standard deviation of mean diurnal IOP in the Latanoprost 0.005% group and DE-117 0.002% group ranged from 2.59 mmHg to 4.40 mmHg.

Assuming that 16% subjects will prematurely discontinue the study, a total of 360 subjects (180 subjects per group) are to be randomized to have 302 completers (151 per group) at Month 3.

3.4. Visits and Assessments

There are five scheduled visits for each subject. Assessments at each visit and the time/visit window for each post-baseline assessment are specified in the Assessment Schedule (Table 1). For subjects whose study participation is terminated prior to Visit 5 (Month 3), to the extent possible, all assessments scheduled for Visit 5 (Month 3) will be performed at the Exit Visit.

Table 1. Assessment Schedule

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

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

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

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

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

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

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

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

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

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

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

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

[m] Visual field measurement at Visit 5 (Month 3)/Early Termination will be performed only in Indian sites.

4. DEFINTIONS

4.1. Time-Related Terms

4.1.1. Baseline Visit

In this study, Visit 2 is the *baseline visit* when the subject was randomized.

4.1.2. Treatment Start Date

Treatment start date is the date at which a randomized subject took the first dose of the study medication. In this study, the treatment start date is usually the Visit 2 (Baseline) date.

4.1.3. Treatment End Date

Treatment end date is the date at which a randomized subject took the last dose of the study medication. If the date of the last dose is missing, then

- The day before the Visit 5 (Month 3) date will be considered the treatment end date for subjects who completed the study, and
- The day before the Exit Visit date will be used for subjects who prematurely discontinued the study. 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.

4.1.4. Study Day

The study day describes the relative day of an observation starting with the reference date designated as Study Day 1. In this study, Visit 2 (Baseline) date of the Treatment Period is the reference day and the study day will be calculated as:

- For days prior to the Visit 2 (Baseline) date, Study Day = Date – Visit 2 (Baseline) Date
- For days on/after the Visit 2 (Baseline) date, Study Day = Date – Visit 2 (Baseline) Date + 1

Note that there is no Study Day 0.

For adverse events, prior and concomitant medications, the study day will be calculated from the date of First Exposure to treatment.

4.1.5. Out-of-Window Measurements, Analysis Visit, and Analysis Window

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 a measurement should be mapped to (Table 2).

The analysis visit of a measurement will be determined based on the study day of the measurement and specified analysis windows, and is not necessarily the same with the study visit where the measurement was collected. For example, an out-of-window measurement collected at the Week 1 study visit will be mapped to the Week 6 analysis visit, if the study day of the measurement falls into the analysis window of Week 6.

Table 2. Analysis Visit and Analysis Window

Analysis Visit (Target Assessment Date)	***Visit Window***	***Analysis Window***	
		Ophthalmoscopy and Visual Field	***Other Parameters***
Baseline (Day 1)	[1, 1]	- 1]	- 1]
Week 1 (Day 8)	[6, 10]	NA	[2, 22]
Week 6 (Day 43)	[40, 46]	NA	[23, 61]
Month 3 (Day 91)	[64, 98]	[2 -	[62 -

NA: Not Applicable.

In case that there are two or more measurements at an analysis visit, the measurement closest to the target assessment day will be selected for that visit. In the case that two measurements are closest and equidistant 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.

For analyses of IOP involving post-baseline visits, if there are two or more measurements that fall into the same analysis window of a post-baseline visit, then a visit in which IOP are measured at all the scheduled timepoints (9:00, 13:00 and 17:00) will be selected for that analysis visit. The IOP data measured at 3 days or more after the last treatment will not be used for the efficacy analysis regardless of the analysis window.

4.1.6. Out-of-Time-Window Measurements, Analysis Timepoint and Analysis Timepoint Window

Analysis timepoint is a timing variable to be used for analyses involving timepoints. The IOP will be measured two or three times for each timepoint, and the last recorded time will be used for determining its timepoint. For each analysis timepoint, an *analysis timepoint window* is set up to determine the allowance range (Table 3).

Table 3. Analysis Timepoint and Analysis Timepoint Window

Analysis Timepoint	***Timepoint Window***	***Analysis Timepoint Window***
9:00	[8:00, 10:00]	- 10:59]
13:00	[12:00, 14:00]	[11:00, 14:59]
17:00	[16:00, 18:00]	[15:00 -

If there are two or more measurements that fall into the same analysis timepoint window, the measurement closest to the target assessment time will be selected for that timepoint. In the case that two measurements are closest and equidistant to the target assessment time, i.e., one is before and one is after the target assessment time, the later one will be selected for that timepoint.

4.1.7. Extent of Exposure

The *extent of exposure* to study medication will be assessed by duration of treatment exposure, derived as:

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

4.2. Efficacy and Safety-Related Definitions

4.2.1. Study Eye and Non-Study Eye

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

4.2.2. Baseline Score

The *baseline score* is the observed measurement at Visit 2 (Baseline). If a baseline score is missing, the last observed measurement or derived score prior to the first dose of study medication visit will be used to impute the baseline score.

4.2.3. Change (and Percent Change) from Baseline

The change and the percent change from Baseline in a measure at a post-baseline visit will be derived as:

- Change = (Score at the Post-Baseline Visit) – (Baseline Score)
- Percent Change from Baseline = 100 × Change / (Baseline Score)

4.3. Efficacy-Related Definitions

4.3.1. Intraocular Pressure

For the IOP at each timepoint of measurement, a mean of two consecutive measurements using the Goldmann applanation tonometer will be used as the IOP score at that timepoint. If a ≥3 mmHg difference is shown between the two consecutive measurements, a third measurement will be obtained and the median value of the three measurements will be used.

The mean diurnal IOP is derived as the mean of the IOP scores at the three scheduled timepoints (9:00, 13:00 and 17:00).

4.3.2. Response Endpoint and Response Rate

Four types of response endpoints (Table 4) will be evaluated at each post-Baseline visit (Week 1, Week 6, or Month 3) in this study:

Table 4. Response Endpoints

Response Endpoint	***Response criteria in mean diurnal IOP***
IOP 20% response	Percent Reduction from Baseline ≥ 20%

IOP 25% response	Percent Reduction from Baseline ≥ 25%
IOP 30% response	Percent Reduction from Baseline ≥ 30%
IOP < 18 mmHg response	Mean diurnal IOP < 18 mmHg

For a response endpoint, the response rate at a post-Baseline visit is calculated as the proportion of subjects who met the response criterion at the post-baseline visit.

4.4. Safety-Related Definitions

4.4.1. Adverse Event

Under this study, an AE is any untoward medical occurrence in a subject participated in the study; it does not necessarily have a causal relationship with study treatment. Regardless of relationship to the investigational medicinal product, an AE can be an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product. An on-study AE can occur any time after the date of informed consent through the last study visit. An AE will be considered as treatment-emergent if the AE occurred on or after the treatment start date up to the last study visit. Treatment-emergent AEs are a subset of on-study AEs. Both on-study and treatment-emergent AEs will be reported.

Each AE will be classified into a system organ classification (SOC) and coded to a preferred term using Medical Dictionary for Regulatory Activities (MedDRA 19.0, 2016).

4.4.1.1. Ocular Adverse Event

An AE will be counted as an *ocular AE* if the Clinical Investigator selected 'OD', 'OS', or 'OU' under 'Eye(s) affected' on the Adverse Event eCRF form.

4.4.1.2. Suspected Adverse Reaction

An AE will be counted as a *suspected adverse reaction* (SAR) if the Clinical Investigator answered 'Related' to the question 'Relationship to Study Drug?' on the Adverse Event eCRF form.

4.4.1.3. Serious Adverse Event

An AE will be counted as a *serious adverse event* (SAE) if the Clinical Investigator selected 'Yes' to the question "Is the Adverse Event Serious?" on the Adverse Event eCRF form.

4.4.1.3.1. Important Adverse Event

The following *Significant Adverse Event* will be identified throughout the study.

- AE leading to drug withdrawn or drug interruption

4.4.2. Safety Measures

Table 5 lists the measures to be evaluated for this study.

Table 5. Safety Assessments

Safety Measures	***Note***
Visual acuity	Corrected visual acuity will be measured for each eye at each visit under normal room illumination using visual acuity chart (e.g., ETDRS chart, Snellen chart) and the logMAR scoring will be recorded in the subject's source document. Increase in logMAR scores means worsening in visual acuity.
Slit-lamp biomicroscopy	Slit-lamp biomicroscopy examinations (anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, corneal endothelial change (i.e. keratic Precipitate), lens, anterior synechiae of iris, posterior synechiae of iris) will be performed and graded right before the 9:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit).
Central corneal thickness	The central corneal thickness (μm) of each eye using any pachymeter including optical pachymeter, ultrasound pachymeter, OCT (optical coherence tomography) etc. will be measured and recorded right after the 9:00 IOP measurement if it is a contact method at Visit 2, Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination. If it is a non-contact method, the CCT measurement can be performed prior to the IOP measurement at 9:00. For Visit 1 (Screening), central corneal thickness measurement should be performed after IOP measurement.
Visual Field	Visual field examinations will be performed using a static or dynamic perimeter without pupil dilation at Visit 1 (Screening) and Visit 5 (Month 3)/Early Termination. The same perimeter will be used for each subject. Glaucomatous visual field loss will be evaluated by the investigator as presence or absence. The visual field exam at Visit 5 will only be performed in Indian sites.
Ophthalmoscopy	The ophthalmoscopy (fundus) examination will be performed for each eye without pupil dilation at Visit 1, Visit 2, and Visit 5 Study Exit/Early Termination, and graded as None (0), Mild (1), Moderate (2) or Severe (3).
Iris color/eyelash/eyelid	The investigator (or his/her designee) will take frontview and sideview photograph of each eye at Visit 2 (Baseline). The photographs must include iris, eye lids and eyelashes of each eye. The photographs taken at Visit 2 (Baseline) will be used to help the Investigator assess any changes ("No changes", "Increased" or "Decreased") from baseline in iris color pigmentation, eyelid pigmentation, eyelid hair growth, eyelash length, eyelash thickness, eyelash pigmentation and eyelash number at Visit 3, Visit 4 and Visit 5 Study Exit/Early Termination.

4.5. Other Definitions

4.5.1. Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, the *prior medication* is defined as any non-study medication taken and ended prior to the treatment start date. The *concomitant medication* is defined as any non-study medication

taken concurrently while on the study medication, i.e., the treatment period of a concomitant medication taken by a subject needs to overlap with his/her treatment period of the study medication.

5. STUDY POPULATION

5.1. Intent-to-Treat Population

The *Intent-to-Treat* (ITT) population will be comprised of all randomized subjects.

5.2. Full Analysis Set

The *Full Analysis Set* (FAS) will include all randomized subjects who received at least one dose of study medication and provided at least one post-baseline IOP measurement.

This will be the population used for efficacy analyses. Unless specified otherwise, subjects in efficacy analyses are classified by planned treatment, irrespective of the actual treatment received.

5.3. Per-Protocol Population

The Per-Protocol (PP) population is a subset of the FAS. It will include all FAS subjects without protocol deviations that could affect the primary efficacy endpoint.

Santen's study team will review all protocol deviations and identify subjects to be excluded from the PP population before the unmasking of treatment assignment.

5.4. Safety Population

The *Safety* population will include all randomized subjects who received at least one dose of the study medication. It will be the analysis population for safety analyses to be performed with subjects as treated. If a subject received both DE-117 and Latanoprost, the subject will be classified to the first treatment.

6. GENERAL CONSIDERATIONS

All measures will be summarized by treatment (planned or actually 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 (%).

The statistical testing will be conducted at a significance level of 0.05 (two-sided) and 95% the 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.

6.1. Adjustments for Covariates

In general, baseline IOP score, diagnosis and country will be adjusted in the inferential analysis of each IOP endpoint. Detailed information on covariate adjustment is provided in Section 8.1.

6.2. Handling of Missing Data

6.2.1. General

For each post-baseline IOP endpoint, no imputation is needed for the analysis on observed cases using the mixed-effects model for repeated measures (MMRM). The Last Observation Carried Forward (LOCF) imputation will be implemented in the sensitivity analysis (Section 8.1.2).

Descriptive summaries of safety measures will be based on observed data only. No imputation of missing scores will be implemented except for Baseline (Section 4.1.1).

Completely or partially missing onset and resolution dates for AEs will be imputed in a conservative fashion as follows:

Date	***Type of Missing Date***	***Handling of Missing Date***
Event start date (e.g., YYYY-MM-DD)	Completely missing	Use the treatment start date to impute the missing date
	Only YYYY is available	If YYYY is the same as the year part of the treatment start date, then use the treatment start date to impute the partially missing date; otherwise 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	If YYYY and MM are the same as the year and month parts of the treatment start date, then use the treatment start date to impute the partially missing date; otherwise use the first day of MM to impute the missing date part of the onset date.
Event end date	Completely missing	No imputation will be applied. The event will be

(e.g., YYYY-MM-DD)		considered ongoing (i.e., not resolved) at the last visit date.
	Only YYYY is available	Use the last day of YYYY to impute the missing month and date parts of the resolution date If the date above is a future date, no imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the last visit 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. If the date above is a future date, no imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the last visit date.

Same rules will be followed to impute the completely or partially missing start and end dates of concomitant medications. If a medication was started prior to the washout period, the start dates of the concomitant medications will not be imputed.

6.2.2. Intraocular Pressure

In general, the assessment of IOP will be conducted for two or three times at a scheduled timepoint depending on the difference between the first two IOP measurements. If the first two measurements differ by 2 mmHg or less, then the average of the two measurements becomes the recorded IOP. 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 mean diurnal IOP will be derived as the mean of the IOP measurements at three scheduled timepoints (9:00, 13:00 and 17:00). If there is a missing IOP measurement at a scheduled timepoint, the mean diurnal IOP will not be calculated.

6.3. Multi-Center Studies

This is a multi-center study enrolling subjects from approximately 30 sites in Asian countries including Singapore, India, Taiwan and Korea. Due to the large number of sites and the small numbers of subjects per center and treatment group, the sites may be pooled by country for analysis purposes.

Unless specified otherwise, country will be included as a factor in the statistical models for the analyses of the primary and the secondary efficacy endpoints.

6.4. Multiple Comparisons / Multiplicity

To control the overall Type I error rate associated with the three comparisons on the primary endpoint (non-inferiority in the mean diurnal IOP at Month 3) and the two key secondary endpoints (non-inferiority in the IOP at each timepoint at Week 1, Week 6 and Month 3 and superiority in the mean diurnal IOP at Week 1) at the 0.05 level (two-sided), a fixed sequence procedure will be implemented. The three sets of hypothesis testing will be prioritized as follows:

1) Non-inferiority of 0.002% DE-117 to 0.005% Latanoprost in the mean diurnal IOP at Month 3
2) Non-inferiority of 0.002% DE-117 to 0.005% Latanoprost in the IOP at all timepoints (9:00, 13:00 and 17:00) at Week 1, Week 6 and Month 3
3) Superiority of 0.002% DE-117 to 0.005% Latanoprost in the mean diurnal IOP at Week 1

The second hypothesis testing will be claimed only if the first one is confirmed. The third hypothesis testing will be claimed only if the first and the second ones are confirmed.

6.5. Interim Analysis

No formal interim analysis is planned for this study.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The number of subjects with informed consent will be shown. The disposition of the ITT population (i.e., all randomized subjects) will be summarized by treatment and overall. The summary will include the number and percentage of ITT subjects in the Safety population, FAS, and the PP Population. The disposition summary will also include the number and percentage of completers and non-completers at Visit 5 (Month 3), as well as the number and percentage of non-completers at Visit 5 (Month 3) by the primary discontinuation reason.

7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for FAS and Safety population by planned (or actual) treatment and overall. Specifically for subject demographics, the following variables will be summarized:

- Age at randomization (continuous and categorical: < 65 years or ≥ 65 years)
- Sex (categorical: Male or Female)
- Race (categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other/Multiracial)
- Ethnicity (categorical: Hispanic or Latino or Not Hispanic or Latino)
- Country (categorical: India, Korea, Singapore, or Taiwan)

For baseline characteristics, the following variables will be summarized for study eye:

- Iris Color (categorical: Blue/Gray, Blue/Gray with Slightly Brown, Blue/Gray – Brown, Green, Green with Slightly Brown, Green – Brown, Yellow – Brown, or Brown)
- Diagnosis (categorical: OAG [subcategories: POAG, Pseudoexfoliative Glaucoma, Pigmentary Glaucoma], or OHT)
- Prior use of IOP-lowering medication(s) (categorical: ß-adrenergic antagonist, prostamide or prostaglandin analogue, α-adrenergic agonist, carbonic anhydrase inhibitors, miotic agent, other, or none)
- Baseline mean diurnal IOP score and baseline IOP score at each scheduled timepoint (09:00, 13:00, or 17:00)
- Baseline central corneal thickness
- Baseline degree of angle closure in Shaffer scale (ordinal: Grade 2, Grade 3, or Grade 4)
- Baseline glaucoma visual field loss (categorical: No or Yes)
- Baseline glaucomatous findings in fundus (categorical: None, Mild, Moderate, or Severe)

7.3. Concurrent Disease

For this study, concurrent disease will be coded using MedDRA 19.0, 2016. Each concurrent disease will be classified into a system organ class (SOC) and mapped to a preferred term (PT).

The concurrent disease will be summarized for the FAS population. Subjects reporting any concurrent disease at baseline will be tabulated by SOC and preferred term for each planned treatment and overall.

7.4. Protocol Deviations

In this study, important protocol deviations are categorized as follows: Protocol deviations related to:

- Informed consent
- Study conduct/procedure
- Investigational product
- Other

ITT subjects with any protocol deviation(s) above will be summarized and listed.

7.5. Prior and Concomitant Medications

For this study, non-study medications, including prior and concomitant medications, will be coded using WHO-DDE (MAR 2016). Each non-study medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO-DDE preferred drug name.

Non-study medications will be summarized for the Safety population. Subjects taking any prior medications will be tabulated by ATC level 3, level 4 and preferred drug name for each actual treatment received and overall. A subject will be counted at most once for each prior medication, even if the subject took the same prior medication on multiple occasions. Subjects taking any concomitant medications will be tabulated similarly. In addition, prior medications and concomitant medications will also be listed, separately.

7.6. Treatment Compliance

The compliance rate for a subject will be calculated as follows:

- Compliance Rate (%) = (Duration – ∑Miss) / Duration × 100

Where

Duration: The number of days subject should have administered study medication, calculated as last visit date - Visit 2 date. The last visit date is the Visit 5 date for completers and the study Exit Visit date for subjects who prematurely discontinued the study. If the Exit Visit date of a non-completer is not available, then the last available visit date will be considered the Exit date.

Miss: Total number of days that subject did not follow the proper dosing procedures and dosing schedule since the last visit day(s)

For subject in FAS, the compliance rate will be summarized by post-baseline analysis visit for each planned treatment and overall.

7.7. Exposure to Study Medication

The duration of exposure to a study medication is measured by days on treatment as derived in Section 4.1.7. For subjects in the Safety Population, the duration of exposure will be summarized using descriptive statistics, and frequency and percentage of subjects will be tabulated by duration category (1-30 days, 31-60 days or ≥ 61 days) for each actual treatment received.

8. EFFICACY ANALYSES

Unless specified otherwise, all efficacy analyses will be performed on the FAS, where subjects are classified by planned treatment, irrespective of the actual treatment received. Unless specified otherwise, all efficacy analyses will be performed on the study eye, and the data on non-study eye will be excluded.

8.1. Analyses of Primary and Key Secondary Endpoint

8.1.1. Primary Analysis

8.1.1.1. Primary Analysis of Primary Endpoint

The primary efficacy endpoint is the mean diurnal intraocular pressure at Month 3.

For the primary endpoint, the comparison between the 0.002% DE-117 group (*T*) and the 0.005% Latanoprost group (*C*) will be performed with the following pair of testing hypotheses:

$$H_0: \mu_C + \Delta \leq \mu_T$$

Versus

$$H_1: \mu_C + \Delta > \mu_T$$

where μ_T and μ_C denote the mean values of the primary endpoint in the 0.002% DE-117 group and the 0.005% Latanoprost group, respectively, and Δ denotes the non-inferiority margin of 1.5 mmHg.

The primary analysis will be performed using MMRM on the FAS. The model will include treatment, visit, diagnosis (OAG or OHT), country and treatment-by-visit interaction as fixed effects, baseline IOP as a covariate, and subject as a random effect. Within-subject errors will be modeled using an unstructured covariance matrix. Least squares means of the treatment response within each treatment group and treatment differences between the 0.002% DE-117 group and the 0.005% Latanoprost group will be reported along with 95% confidence intervals. Non-inferiority is established if the upper limit of the 95% confidence interval for the difference between DE-117 and Latanoprost in the mean diurnal IOP at Month 3 is less than or equal to 1.5 mmHg.

8.1.1.2. Primary Analysis of Key Secondary Endpoints

This study has two key secondary endpoints.

One of the key secondary efficacy endpoint is the mean intraocular pressure at 9:00, 13:00 and 17:00 at Week 1, Week 6 and Month 3. The same MMRM for the primary efficacy endpoint will be applied. A separate model will be fitted for each scheduled timepoint using baseline IOP at the corresponding timepoint as a covariate. Non-inferiority is achieved if the upper limit of the 95% confidence interval for the difference between DE-117 and Latanoprost is less than or equal to 1.5 mmHg at all timepoints and less than or equal to 1.0 mmHg at the majority of the timepoints.

The other key secondary efficacy endpoint is the mean diurnal intraocular pressure at Week 1. If non-inferiority in the primary and key secondary endpoints is achieved, then superiority will be tested for this key secondary endpoint as follows:

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

The primary analysis of the key secondary endpoint will be performed using the same MMRM for the primary efficacy endpoint simultaneously (Section 8.1.1.1). Superiority is claimed if the upper limit of the 95% confidence interval for the difference between DE-117 and Latanoprost in the mean diurnal IOP at Week 1 is less than 0 mmHg.

8.1.2. Sensitivity Analyses

For the primary endpoint and the key secondary endpoint, to assess the robustness of the results from the primary analysis, the following sensitivity analyses will be performed:

Statistical Method	Analysis Population	Assumption of Missing Mechanism	Handling of Missing Data
MMRM	PP population	MAR	Observed cases
MMRM including treatment-by-country interaction	FAS	MAR	Observed cases
ANCOVA (factor: treatment, diagnosis and country; covariate: baseline IOP)	FAS	-	Last observation carried forward (LOCF)
	PP population	-	LOCF
	Completers at Month 3	MCAR	not applicable

All the primary and sensitivity analyses will be implemented using SAS PROC MIXED. The main part of the SAS code for the specified MMRM analysis and ANCOVA are provided in Appendix 12.1.1 and 12.1.2, respectively.

8.2. Analyses of Secondary Endpoints

The following secondary endpoints will be analyzed using the same MMRM for the primary and the first key secondary efficacy endpoints simultaneously (Section 8.1.1).

- The mean diurnal IOP in the study eye at Week 6
- The overall (grand) mean diurnal IOP in the study eye, defined as the average of the mean diurnal IOP in the study eye at 3 post-baseline visits (Week 1, Week 6, and Month 3)

The following secondary endpoints will be analyzed using the same MMRM for the primary efficacy endpoint. A separate model will be fitted for each scheduled timepoint using baseline IOP at the corresponding timepoint as a covariate.

- The percent change from baseline (CFB) in mean diurnal IOP in the study eye at a post-baseline visit (Week 1, Week 6, Month 3, or Overall)
- The percent change in IOP in the study eye at a specified timepoint (9:00, 13:00, or 17:00) at a post-baseline visits (Week 1, Week 6, Month 3, or Overall)

The following secondary endpoints will be presented descriptively by treatment group.

- The CFB in mean diurnal IOP in the study eye at a post-baseline visit (Week 1, Week 6, or Month 3)
- The CFB in IOP in the study eye at a specified timepoint (9:00, 13:00, or 17:00) at a post-baseline visit (Week 1, Week 6, or Month 3)

The following response rates will be summarized by treatment group and visit.

- IOP 20% response (having a percent reduction in mean diurnal IOP in the study eye of ≥ 20% from Baseline) at a post-Baseline visit (Week 1, Week 6, or Month 3)
- IOP 25% response (having a percent reduction in mean diurnal IOP in the study eye of ≥ 25% from Baseline) at a post-Baseline visit (Week 1, Week 6, or Month 3)
- IOP 30% response (having a percent reduction in mean diurnal IOP in the study eye of ≥ 30% from Baseline) at a post-Baseline visit (Week 1, Week 6, or Month 3)
- IOP < 18 mmHg response (having a mean diurnal IOP < 18 mmHg in the study eye) at a post-Baseline visit (Week 1, Week 6, or Month 3)

A logistic model for repeated measures will be fitted to response (response/non response). The model will include treatment, visit, diagnosis, country and treatment-by-visit interaction as fixed effects, baseline IOP as a covariate, and subject as a random effect. Within-subject errors will be modeled using an unstructured (UN) covariance matrix. If the model is not converged, covariance matrices will be applied with the following order: first-order autoregressive [AR(1)], compound symmetry (CS) or variance components (VC). Odds ratios will be calculated along with 95% confidence intervals. The main part of the SAS code is provided in Appendix 12.1.3.

8.3. Subgroup Analyses

To assess the homogeneity of treatment effects among subgroups, descriptive summaries by age group (< 65 or ≥ 65 years), sex (Male or Female) , country (India, Korea , Singapore or Taiwan), diagnosis (Open Angle Glaucoma or Ocular Hypertension), prior use of IOP lowering medication (ß-adrenergic antagonist, prostamide or prostaglandin analogue, α-adrenergic agonist, carbonic anhydrase inhibitors, miotic agent, other, or none), mean diurnal IOP at baseline (< 25 or ≥ 25 mmHg) and IOP (9:00) at baseline (< 25 or ≥ 25 mmHg) will be reported for mean diurnal IOP and its change from baseline.

Other subgroup analyses may be performed as needed.

9. SAFETY ANALYSES

The safety-related measures collected in this study include AEs, visual acuity, slit-lamp biomicroscopy, central corneal thickness, ophthalmoscopy and iris color/eyelash/eyelid. The Safety population will be used for all safety summaries, where subjects will be classified by actual treatment received. In the event that a subject accidently took both DE-117 and Latanoprost during the study, that subject will be included in the 0.002% DE-117 group.

All the safety-related measures will be summarized descriptively by actual treatment received. Except AEs, the descriptive summary of each safety-related measure and the change from baseline in that measure will be performed.

9.1. Adverse Event

Subjects with any AE(s), SAE(s), SAR(s) serious SAR(s) and significant AE (AE leading to study discontinuation) will be tabulated by type of AE(s) for each actual treatment received.

Besides the overall AE summary, subjects with any AE(s) and any SAR(s) will be tabulated by SOC and preferred term. A subject who experienced multiple AEs within a SOC or preferred term will be counted only once for that SOC or preferred term.

Subjects with any AE(s) and any SAR(s) will be tabulated by SOC, preferred term and maximum severity. A subject who experienced multiple AEs within a SOC or preferred term will be counted only once at the maximum severity for that SOC or preferred term.

The same analysis above will be performed for ocular AEs and non-ocular AEs.

AEs, AEs leading to death, SAEs and AEs leading to discontinuation, if any, will be listed separately.

The following AE summary tables will also be prepared by countries:

- Overall AE summary
- AE(s) by SOC and preferred term
- SAR(s) by SOC and preferred term

9.2. Visual Acuity

The logMAR scores and changes from baseline will be summarized by treatment and analysis visit for study eyes and non-study eyes, separately. In addition, any change (worsening or improvement) of $\geq$ 0.2 LogMAR (2 lines) from baseline will be summarized and listed.

9.3. Slit-lamp Biomicroscopy

For each biomicroscopy parameter, frequency and percentage of rating scores will be summarized by analysis visit for study eyes and non-study eyes, separately. In addition, any worsening (increase) of $\geq$ 2 units from baseline will be summarized and listed.

9.4. Central corneal thickness

Central corneal thickness scores and changes from baseline will be summarized by treatment and analysis visit for study eyes and non-study eyes, separately. In addition, any increase of > 50 µm from baseline will be summarized and listed.

9.5. Ophthalmoscopy

Frequency and percentage of rating scores will be summarized by treatment and analysis visit for study eyes and non-study eyes, separately. In addition, any worsening (increase) of ≥ 2 units from baseline will be summarized and listed.

9.6. Iris Color, Eyelash and Eyelid

For changes from baseline in Iris Color Pigmentation, Eyelid Pigmentation, Eyelid Hair Growth, Eyelash Length, Eyelash Thickness, Eyelash Pigmentation and Eyelash Number, frequency and percentage of changes (No change, Increased or Decreased) will be summarized by treatment and analysis visit for study eyes and non-study eyes, separately. In addition, any changes from baseline will be listed.

9.7. Visual Field

Visual field loss (Yes or No) will be summarized by treatment and analysis visit for study eyes and non-study eyes, separately. In addition, any worsening in status from No at baseline to Yes after screening will also be summarized and listed.

10. ANALYSES OF OTHER MEASURES

[redacted]

11. REFERENCES

None.

12. APPENDICES

12.2. Changes from Protocol

Change 1:

The secondary objective and the key secondary endpoint were modified as follows in order to evaluate the non-inferiority of DE-117 to Latanoprost in IOP lowering effect at each timepoint.

The following secondary objective was added.

"To determine if the mean intraocular pressure (IOP) reduction with DE-117 ophthalmic solution 0.002% is non-inferior to Latanoprost ophthalmic solution 0.005% at each post baseline timepoint after 3 months of treatment in subjects with open-angle glaucoma (OAG) or ocular hypertension (OHT)."

The following key secondary endpoint was added.

- Mean IOP in the study eye at the specified timepoints: 9:00, 13:00, and 17:00 at week1, week6 and Month 3.

Change 2:

Due to incorrect expression in signs of hypothesis, the following change was applied from the protocol:

Original text (Protocol 14.6.1):

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

Revised text (SAP 8.1.1.1):

$H_0: \mu_C + \Delta \leq \mu_T$ versus $H_1: \mu_C + \Delta > \mu_T$

Change 3:

Due to incorrect expression in signs, the following change was applied from the protocol:

Original text (Protocol 14.6.2.2):

- Proportion of subjects with mean diurnal IOP ≤ 18 mmHg in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).

Revised text (SAP 2.2.3):

- Proportion of subjects with mean diurnal IOP < 18 mmHg in the study eye at Visit 3 (Week 1), Visit 4 (Week 6) and Visit 5 (Month 3).