Statistical Analysis Plan Cover Page

Official Study Title:	An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension - Spectrum 5 Study
NCT Number:	NCT03697811
Date of the document:	08 Feb 2022

STATISTICAL ANALYSIS PLAN

DE-117 SPECTRUM 5

Protocol Title:	An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension – Spectrum 5 Study
Product:	DE-117
Protocol Number:	011711IN
Sponsor:	Santen Inc. 6401 Hollis Street, Suite 125 Emeryville, CA 94608 USA
Date:	February 08, 2022
Status:	Version 1.0

CONFIDENTIAL

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[redacted]

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ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
ATC	Anatomical-Therapeutic-Chemical
BCVA	Best-Corrected Visual Acuity
CI	Confidence Interval
CM	Concomitant Medications
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ESI(s)	Event(s) of Special Interest
ET	Early Termination
FAS	Full Analysis Set
IOP	Intraocular Pressure
LOCF	Last-observation-carried-forward
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
mmHg	Millimeter of Mercury
OHT	Ocular Hypertension
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
POAG	Primary Open-Angle Glaucoma
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
US	United States
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from the SPECTRUM 5 study within the scope of Santen's Protocol 011711IN, "An Open-Label, Multicenter Study Assessing the Efficacy and Safety of DE-117 Ophthalmic Solution 0.002% in Latanoprost Low/Non-Responder Subjects Diagnosed with Primary Open-Angle Glaucoma or Ocular Hypertension – Spectrum 5." It applies to the study protocol version 1.0, dated 18 July 2018, 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 study. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

To evaluate the intraocular pressure (IOP) lowering effect of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with Primary Open-Angle Glaucoma (POAG) or Ocular Hypertension (OHT). Specifically, the primary efficacy endpoint is the change from baseline (Day 1, Visit 4) in mean diurnal IOP at Month 3 (Visit 7).

2.1.2. Secondary Objectives

To evaluate the IOP lowering efficacy (change, percentage change and proportion of responders) of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT at each timepoint.

2.1.3. Safety Objective

To evaluate the safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder diagnosed with POAG or OHT.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline (Visit 4) in mean diurnal IOP at Month 3 (Visit 7).

2.2.2. Secondary Efficacy Endpoints

- Percent change from baseline (Visit 4) in mean diurnal IOP at Month 3 (Visit 7)
- Change and percent change from baseline (Visit 4) in mean diurnal IOP at Week 2 (Visit 5) and Week 6 (Visit 6)
- Change and percent change from baseline (Visit 4) in IOP for each post-baseline timepoint/visit
- Having a mean diurnal IOP reduction ≥ 10%, ≥ 15%, ≥ 20%, ≥ 25%, or ≥ 30% from baseline (Visit 4) at Month 3 (Visit 7)
- Having a mean diurnal IOP ≤ 18 mmHg at Month 3 (Visit 7)

2.2.3. Safety Endpoints

The safety of DE-117 will be evaluated by:

- Incidence of ocular and non-ocular adverse events (AEs)
- Events of special interest (ESIs, which were defined to be macular edema, medication administration errors, and pregnancy)
- Best-corrected visual acuity (BCVA)

- Slit-lamp biomicroscopy; severity scores for the following 12 parameters: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, lens, anterior synechiae of iris, posterior synechiae of iris
- Ophthalmoscopy (cup-to-disc ratio, glaucomatous optic nerve severity score, and assessments of retina, macula, choroid, and vitreous)
- Assessments for deepening of the upper eyelid sulcus (DUES) and other changes in eyelid, eyelash, and iris

3. STUDY DESIGN

3.1. General Study Design

This is an open-label, multicenter study investigating the efficacy and safety of DE-117 ophthalmic solution 0.002% in latanoprost low/non-responder subjects diagnosed with POAG or OHT. As shown in the study design diagram in Figure 1, subjects diagnosed with POAG or OHT who meet the eligibility criteria at Visit 1 (Screening) will enter a Washout Period of up to 35 days (28 days + 7 days window) depending on their current topical IOP-lowering medication(s), if any. After completing the required Washout Period, subjects will return for Visit 2 (Week –8, start of a Run-in Period). Subjects who remain qualified will start a Run-in Period dosing latanoprost ophthalmic solution 0.005% once daily, and then return for Visit 3 (Week –4, mid-point of the Run-in Period) and Visit 4 (Baseline, Day 1), to confirm ongoing eligibility. IOP will be measured at three timepoints (08:00, 12:00, and 16:00) at each scheduled visit. Table 1 lists the IOP-related inclusion criteria at Visit 2, Visit 3 and Visit 4.

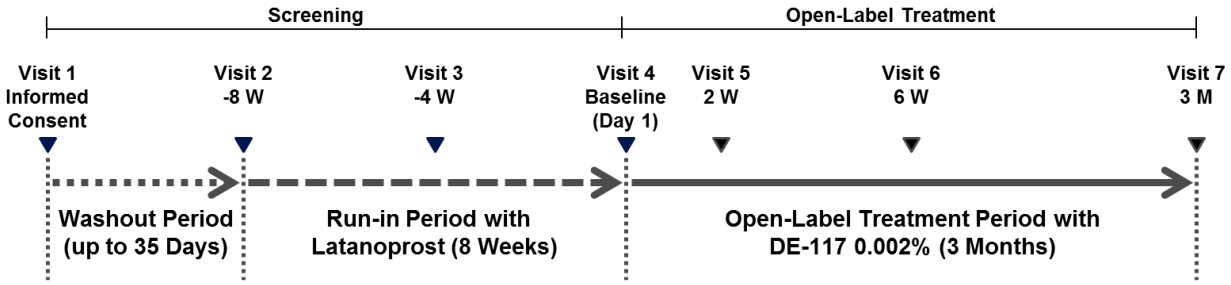
Table 1: IOP-related Inclusion Criteria at the Specified Visits during Screening Phase

Visit	IOP at each scheduled timepoint (08:00, 12:00, and 16:00)	Change in IOP at each scheduled timepoint (08:00, 12:00, and 16:00) from Visit 2 (Start of Run-in Period)
Visit 2 (Start of Run-in Period)	IOP in at least one eye ≥ 22 mmHg IOP in both eyes ≤ 34 mmHg	
Visit 3	IOP in both eyes ≤ 34 mmHg	Percent decrease of ≤ 25%
Visit 4 (End of Run-in Period)	IOP in both eyes ≤ 34 mmHg	Percent decrease of ≤ 15%

Subjects who meet all eligibility criteria at Visit 4 (Baseline, Day 1), will enter the Treatment Period and will be treated with DE-117 ophthalmic solution 0.002% for 3 months.

Approximately 100 subjects with POAG or OHT who meet all eligible criteria are planned to enter the Treatment Period and be treated with DE-117 0.002% ophthalmic solution.

Figure 1: Study Design Diagram



3.2. Randomization and Masking

This is an open-label study; masking will not be applied. There will be no randomization for this study.

3.3. Sample Size Planning

Using one sample t-test with a significant level of 5%, a sample size of 100 will have 75% power to detect a mean diurnal IOP reduction of 1.0 mmHg from baseline with a standard deviation 3.5 mmHg, after taking into account of up to 12% dropouts.

3.4. Visits and Assessments

There are 7 scheduled visits for each enrolled subject. Assessments at each visit and the time/visit window for each post-baseline assessment are specified in the Assessment Schedule (Table 2). For subjects whose study participation is terminated prior to Visit 7 (Month 3), to the extent possible, all assessments scheduled for Visit 7 (Month 3) will be performed at the Exit Visit.

Table 2: Assessment Schedule

	Washout Period		**Run-in Period**		**Treatment Period**			
	Visit 1 Screening	**Washout Period (up to 4 weeks) Optional Visit 1a[b]**	**Visit 2 Week -8 (Day-56±3)**	**Visit 3 Week -4 (Day-28±3)**	**Visit 4 Baseline (Day 1)**	**Visit 5 Week 2 (Day 15±3)**	**Visit 6 Week 6 (Day 43 ±5)**	**Visit 7 Month 3 (Day 91±7) Exit or Early Termination**
Informed Consent(s) including the optional consent for pharmacogenomics/ genomics laboratory research study [a]	X							
Inclusion/Exclusion Criteria	X		X	X	X			
Demographics and Medical History, including prior PGA [c]	X							
Concomitant Medications/ Therapies	X	X	X	X	X	X	X	X
Dosing Compliance				X	X	X	X	X
AEs		X	X	X	X	X	X	X
Pregnancy Test [d]	X				X			X
Refraction [e]	X							
BCVA[e]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)
Biomicroscopy [f]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)	X (08:00)
IOP [g]	X (any time)	X (any time)	08:00 12:00 16:00	08:00 12:00 16:00	08:00 12:00 16:00	08:00 12:00 16:00	08:00 12:00 16:00	08:00 12:00 16:00

Table 2: Assessment Schedule (Continued)

	Washout Period		Run-in Period		Treatment Period			
	Visit 1 Screening	Washout Period (up to 4 weeks) Optional Visit 1a[b]	Visit 2 Week -8 (Day-56±3)	Visit 3 Week -4 (Day-28±3)	Visit 4 Baseline (Day 1)	Visit 5 Week 2 (Day 15±3)	Visit 6 Week 6 (Day 43 ±5)	Visit 7 Month 3 (Day 91±7) Exit or Early Termination
Pachymetry [h]	X							
Iris color, eyelash, eyelid [i]					X (photo)			X (photo)
Gonioscopy [j]	X							
Visual Field [k]	X							
Ophthalmoscopy [l]	X (pupil dilation)				X (16:00)			X (16:00, pupil dilation)
Blood Sampling for Pharmacogenomics/genomics [m]						X		
Dispense Study Medication			X	X	X		X	
Collect Study Medication				X	X		X	X
Phone call to remind subject to take evening dose on the day before each visit				X	X	X	X	X

[a] Informed Consent Form must be signed and dated before study procedures are performed. Informed consent for the optional pharmacogenomics/genomics laboratory research study may be obtained at any visit prior to study exit.

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

[c] The previous use of prostaglandin analogs should be confirmed by either subject's medical records or subject history.

[d] A urine pregnancy test will be conducted for all female subjects of childbearing potential.

[e] Refraction will be performed at the screening visit. If more than 10 letters in BCVA are lost compared to the screening visit, then refraction should be performed again. BCVA examination will be completed before IOP measurement at 08:00 (±60 min).

[f] Biomicroscopy examination must be completed before IOP is measured at 08:00 (±60 min). Aqueous flare and cell evaluation will be performed before fluorescein instillation.

[g] IOP measurements will be performed at 08:00, 12:00, and 16:00 (±60 min) at all visits except for Visit 1 (Screening) and Visit 1a (optional, mid-washout visit).

[h] Pachymetry will be performed after IOP measurement at Visit 1 (Screening).

[i] Eye photograph will be taken at Visits 4 (Baseline, Visit 4) and 7 (Month 3).

[j] If gonioscopy was performed within 3 months (90 days) prior to screening and was documented in the subject's records, no additional screening gonioscopy examination is necessary. Gonioscopy will be performed after IOP measurement at Visit 1 (Screening).

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

[l] Ophthalmoscopy will be performed at Visits 1, 4, and 7 (i.e., Screening, Baseline and Month 3) after the 16:00 IOP measurements. Ophthalmoscopy will be performed with pupil dilation at Screening and Visit 7 (Month 3)/Study Exit or Early Termination. Dilation of the pupil will be performed after the 16:00 IOP measurement.

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

4. TIME-RELATED TERMS

4.1. Baseline Visit

The *Baseline Visit* is Visit 4 (Day 1) when the subject is enrolled for treatment with DE-117 0.002% ophthalmic solution.

4.2. Study Periods, Treatment Start Date, and Treatment End Date

This study has two study periods when subjects received treatments provided by the Sponsor: Run-in Period and Treatment Period. The start date and end date for each period are defined as follows in Table 3.

Table 3: Definitions for Period Start and End Dates by Study Period

Study Period	Period Start Date	Period End Date
Run-in Period	The date at which a subject takes the first dose of latanoprost 0.005%	The date at which a subject takes the last dose of latanoprost 0.005%. If the date of the last dose is missing, the day before the Visit 4 (Day 1) date will considered as the end date.
Treatment Period	The date at which a subject takes the first dose of the study medication, DE-117.	The date at which a subject takes the last dose of the study medication, DE-117. If the date of the last dose is missing, then • The day before the Visit 7 (Month 3) date will be considered the end date for subjects who completed the study. • The day before the Exit Visit date will be used for subjects who prematurely discontinued from 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 end date.

Treatment start date and *Treatment end date* are the start date and the end date of the Treatment Period, defined in Table 3.

4.3. 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, the treatment start date is the reference date. Thus, the study day will be calculated as:

- For a pre-baseline date, Study Day = Date – Treatment Start Date
- For a post-baseline date, Study Day = Date – Treatment Start Date + 1

4.4. 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 to which a measurement should be mapped (Table 4). 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 as the study visit at which the measurement was collected. For example, an out-of-window measurement collected at the Week 2 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.

The following *analysis windows* will be applied to minimize the amount of missing data for analysis purposes:

Table 4: Analysis Visit and Analysis Window

Analysis Visit Name (Target Day)	Protocol Visit Window	Analysis Window		
		Ophthalmoscopy	Iris Color, Eyelash, and Eyelid	Other Parameters
Baseline (Day 1)	[1, 1]	[- , 1]	[1, 1]	[1, 1]
Week 2 (Day 15)	[12, 18]	NA*	NA*	[2, 28]
Week 6 (Day 43)	[38, 48]	NA*	NA*	[29, 61]
Month 3 (Day 91)	[84, 98]	[2, -]	[2, -]	[62, -]

*Not collected at this visit.

If there are two or more visits that fall into the same analysis window, then the visit closest to the target assessment day will be selected for that visit window. In the case that two visits are 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 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 (8:00, 12:00, and 16:00) will be selected for that analysis visit first, before applying the above rule.

4.5. Analysis Timepoint and Analysis Timepoint Window

Analysis timepoint is a timing variable to be used for analyses involving timepoints. For each analysis timepoint, an *analysis timepoint window* is set up to determine the allowance range (Table 5).

Table 5: Analysis Timepoint and Analysis Timepoint Window

Analysis Timepoint	Protocol Timepoint Window	Analysis Timepoint Window
8:00	[7:00, 9:00]	[- , 9:59]
12:00	[11:00, 13:00]	[10:00, 13:59]
16:00	[15:00, 17:00]	[14:00, -]

4.6. 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

5. GENERAL CONSIDERATIONS

All measures will be summarized descriptively. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, standard error, 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.

Reporting Statistics	**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 (ex. 0.0021)

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 Statistical Analysis System (SAS) Version 9.4 or later. Individual data, including relevant derived variables, will be listed.

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

5.1. Adjustments for Covariates

The efficacy endpoint will be analyzed using a paired t-test; hence no covariate adjustment will be necessary.

5.2. Handling of Missing Data

5.2.1. Efficacy Measures

The primary analysis of IOP will be based on observed cases. As a sensitive analysis of the primary efficacy endpoint, missing IOP data at Month 3 will be imputed by last observed post-baseline IOP. If none of the post-baseline IOP data is available, baseline IOP can be used to impute the missing IOP data at Month 3.

5.2.2. Safety Measures

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

5.2.3. Dates for Medical Events and Medications

Completely or partially missing onset and resolution dates for AEs, Concomitant Medications (CM), and Medical History (MH) will be imputed in a conservative fashion as follows:

Incomplete Adverse Event Onset Date

1. Year imputation
   - If *year* is missing (or AE onset date is completely missing), then the onset date will not be imputed.
2. Month imputation
   - If *year* is not missing but *month* is missing, then:
     - If *year* = year of first study dose date, then set the *month* and *day* to the day and month of first study dose
     - Else if *year* ≠ year of first study dose: set *month* to January
3. Day imputation
   - If *day* is missing (*month and year* not missing), then:
     - If *year* = year and *month* = *month* of first study dose, then set *day* to day of first study dose
     - Else if *year* ≠ *year* and *month* ≠ *month* of first study dose, then set *day* to first day of the *month* in the year

Incomplete Adverse Event Resolution Date

- Do not impute if any resolution date is missing
- If the duration of AE is needed, the following approach may be considered:
  - If *year* is missing (or AE resolution date is completely missing): do not impute
  - If *year* is not missing but *month* and *day* are missing: impute December 31st for missing *month* and *day*
  - If *year* and *day* are not missing but *month* is missing: impute December for missing *month*
  - If *year* and *month* are not missing but *day* is missing: impute last day of the *month* for missing *day.*

Incomplete CM or MH Onset Date

1. If *year* is missing (or CM/MH onset date is completely missing): do not impute
2. If *year* is not missing but *month* and *day* are missing: impute January 1st for missing *month* and *day*
3. If *year* and *day* are not missing but *month* is missing: impute January for missing *month*
4. If year and month are not missing but day is missing: impute 01 for missing day

Incomplete CM or MH Resolution Date

- Do not impute if any resolution date is missing.

5.3. Multi-Center Studies

This is a multi-center study enrolling subjects from approximately 25 US sites. The number of subjects per site might be small. Therefore, there are no analyses adjusting for sites.

5.4. Multiple Comparisons / Multiplicity

This trial plans to have only one hypothesis testing, which is for the primary efficacy endpoint. Therefore, multiple comparisons do not apply and there is no need to adjust for multiplicity.

5.5. Interim Analysis

No interim analysis is planned for this study.

6. STUDY POPULATION

6.1. Safety Population

The Safety Population will include all subjects who signed informed consent and received at least one dose of the study medication, DE-117. The safety analyses will be performed on the Safety Population.

6.2. Full Analysis Set

The Full Analysis Set (FAS) will include all Safety population who had at least one post-baseline IOP measurement. The efficacy analyses will be performed using the FAS or a subset of the FAS.

6.3. Per-Protocol Set

The Per-Protocol Set (PPS) is a subset of the FAS, restricted to the subjects who fulfill the protocol in the terms of eligibility, interventions, and other assessment. It will be the analysis population for some sensitivity analyses.

Before database lock, Santen's study team will review all protocol deviations, identify subjects with any protocol deviation that could impact the efficacy outcome, and determine whether to exclude the subject from the PPS.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The disposition of all subjects who enrolled for open-label DE-117 treatment will be summarized. The summary will include the number and percentage of subjects in the Safety population, FAS, and PPS. The disposition summary will also include the number and percentage of subjects who completed the study drug, subjects who discontinued the study drug prematurely but continued with study participation and among which who completed or not completed all study visits, as well as the number and percentage of subjects who discontinued from the study or discontinued the study drug prior to Month 3 Visit by the primary discontinuation reason separately.

7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for FAS. Specifically, for subject demographics, the following variables will be summarized:

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

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

- Primary ocular diagnosis (categorical: POAG or OHT)
- Prior use of IOP-lowering medications (categorical: oral/topical carbonic anhydrase inhibitors, alpha agonists, beta-blockers, prostaglandin/prostaglandin analogues, Rho kinase inhibitor, Miotics, other IOP medication, or none)
- Baseline lens status (categorical: phakic or pseudophakic/aphakic)
- Mean diurnal IOP score and IOP score at each scheduled timepoint (08:00, 12:00, and 16:00) at Baseline (Day 1).
- BCVA (logMAR)
- Central corneal thickness (μm)
- Glaucomatous optic nerve findings (categorical: none, mild, moderate, or severe)
- Anterior chamber angle classification (Shaffer scale; categorical: approximately 20 degrees, approximately 30 degrees, or approximately 40 degrees or more)
- Iris Color (categorical: Blue/Gray, Blue/Gray with Slightly Brown, Blue/Gray – Brown, Green, Green with Slightly Brown, Green – Brown, Yellow – Brown, or Brown)

- Visual field (parameters: glaucoma Hemifield test, visual field mean deviation by device, and visual field pattern standard deviation by device)

7.3. Medical and Surgical History

For this study, medical and surgical history and adverse events will be coded using MedDRA 21.1, 2018. Each medical event will be classified into a SOC and mapped to a Preferred Term (PT).

The medical and surgical history will be summarized for the Safety population. Subjects reporting any medical and surgical history at baseline will be tabulated by SOC and PT.

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Informed Consent
- Inclusion/Exclusion Criteria
- Concomitant Treatment
- Investigational Product
- Procedures/Tests/Assessments
- Laboratory
- Time Window
- Other

A protocol deviation is considered significant if it may affect the subject's rights, safety, or well-being, and/or the completeness, accuracy, or reliability of the study data. Santen's study team will review all protocol deviations and determine the list of significant protocol deviations prior to database lock. All enrolled subjects with any significant protocol deviation(s) will be tabulated by deviation category. In addition, two listings will be provided: (1) all significant protocol deviations and (2) subjects excluded from the per protocol population.

7.5. Impact of the COVID-19 Pandemic

The impact of the COVID-19 pandemic is defined as any disruption to the study and subject participation, such as changes in study visits, missed visits, subject discontinuations, etc. All Safety Population subjects who experienced any of such impact will be summarized and listed along with the description of how their participation was altered.

7.6. Prior and Concomitant Medications

Non-study medications will be categorized into prior medications and concomitant medications. Specifically, *prior medication* is defined as any non-study medication taken and ended prior to the study medication (DE-117) start date. The latanoprost ophthalmic solution 0.005%, administered during the Run-in Period, is qualified as one of the prior medications by the above definition. However, it becomes trivial to include the latanoprost in any summaries or listings as

all enrolled subjects must complete the Run-in Period before taking the study medication, DE-117. Hence, the latanoprost medication will be excluded from the prior medication analyses. However, any latanoprost medication used prior to entering the Run-in Period will still be included in the prior medication.

Concomitant medication is defined as any non-study medication taken concurrently while receiving study medication (DE-117), i.e., the period of time from first dose to last dose of a concomitant medication taken by a subject must overlap with the period of time from first dose to last dose of the study medication (DE-117). While latanoprost medication taken during the Run-in Period will be excluded from the prior medication analyses, any latanoprost medication used as a rescue medication during the Treatment Period will be included in the concomitant medication analyses.

For this study, non-study medications, including prior and concomitant medications, will be coded using World Health Organization (WHO) Drug Global, Version September 2018, format B3. Each non-study medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO Drug 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. 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.

7.7. Treatment Compliance

For the purpose of compliance calculation, there will be three study intervals in the Treatment Period:

- Baseline Visit to Week 2
- Week 2 to Week 6
- Week 6 to Month 3

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

$$\text{Compliance Rate (\%)} = (\text{Duration} - \sum\text{Miss}) / \text{Duration} \times 100$$

Where

Duration: The number of days subject should have administered study medication (i.e., DE-117) calculated as:

Study Interval	**Equation for Duration Calculation**
Baseline Visit to Week 2	Week 2 Visit date – Date of first DE-117 drug dispensation
Week 2 to Week 6	Week 6 Visit date – Week 2 Visit date
Week 6 to Month 3	Month 3 Visit date – Week 6 Visit date

Miss: The number of missed doses since the last visit.

The compliance rate of subjects in the FAS will be summarized by study intervals in the Treatment Period.

7.8. Exposure to Study Medication

The duration of exposure to a study medication, DE-117 ophthalmic solution 0.002%, is measured by days on treatment as derived in Section 4.3. 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, 61-70 days, 71-80 days, 81-90 days, or ≥ 91 days).

8. EFFICACY ANALYSES

8.1. Efficacy-Related Definitions

8.1.1. Study Eye and Fellow Eye

The *study eye* of a treated subject will be the eye that received the study medication, the DE-117 ophthalmic solution 0.002%, and met the eligible criteria as study eye at Visit 4 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 4 (Baseline, Day 1) will be designated as the study eye. If both eyes meet the eligibility 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, or *fellow eye*.

8.1.2. Baseline Score

The *baseline score* is the observed measurement at Visit 4 (Baseline). If a baseline score is missing, the last observed measurement or derived score prior to the first dose of study medication will be used to impute the baseline score.

8.1.3. 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)

8.1.4. Response Endpoint and Response Rate

Six IOP response endpoints (Table 6) will be evaluated at Month 3 (Visit 7) in this study:

Table 6: Response Endpoints

Response Endpoint	Response criteria in mean diurnal IOP
IOP 10% response	Percent reduction from Baseline ≥ 10%
IOP 15% response	Percent reduction from Baseline ≥ 15%
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 Month 3 (Visit 7) is calculated as the proportion of subjects who met the response criterion at Month 3 (Visit 7).

8.2. Analyses of Primary Endpoint and Secondary Endpoints

Unless specified otherwise, efficacy analyses will be performed on the study eye, based on the FAS, and data on fellow eye will not be used.

8.2.1. Primary Analyses

The primary efficacy endpoint is the change from Baseline (Day 1) in the mean diurnal intraocular pressure at Month 3 (Visit 7).

For the primary endpoint, the change of mean diurnal IOP will be evaluated in accordance with the following null (versus alternative) hypothesis:

$$H_0: \mu_j - \mu_i = 0$$

versus

$$H_A: \mu_j - \mu_i \neq 0$$

where μ_i is the mean value of mean diurnal IOP at Baseline (Day 1) and μ_j is that value at Month 3 (Visit 7).

The primary analysis of the primary efficacy endpoint will be performed based on the observed cases of the FAS. Paired t-test will be used to determine whether the change from the Baseline (Visit 4) in mean diurnal IOP at Month 3 (Visit 7) is different from zero. The mean value and standard deviation of the change from baseline in mean diurnal IOP will be reported along with a 95% confidence interval and a p-value.

8.2.2. Sensitivity Analyses

The following sensitivity analyses will be performed to assess the robustness of the results from the primary analysis (Table 7).

Table 7: Overview of Primary and Sensitivity Analysis Methods

Primary or Sensitivity Analysis	Statistical Method	Analysis Population	Handling of Missing Data
Primary	Paired t-test	FAS	Observed cases
Sensitivity	Paired t-test	FAS	LOCF
	Paired t-test	PPS	Observed cases

Abbreviations: FAS = full analysis set; PPS = per protocol set; LOCF = Last observation carried forward.

Paired t-tests in primary and sensitive analyses will be implemented using SAS PROC TTEST.

8.2.3. Analyses of Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed:

- Percent change from baseline in mean diurnal IOP at Month 3 (Visit 7)
- Change and percent change from baseline (Visit 4) in mean diurnal IOP at Week 2 (Visit 5) and Week 6 (Visit 6)
- Change and percent change from baseline in IOP at each post-baseline timepoint/visit
- Having a mean diurnal IOP reduction ≥ 10%, ≥ 15%, ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 4) at Month 3 (Visit 7)
- Having a mean diurnal IOP ≤ 18mmHg at Month 3 (Visit 7)

For continuous secondary endpoints (change and percent change from baseline in IOP and in mean diurnal IOP) at Week 2 (Visit 5), Week 6 (Visit 6), and Month 3 (Visit 7), descriptive statistics will be provided including the number of subjects (n), mean, standard deviation, median, minimum and maximum. For binary secondary endpoints, the responder rates will be tabulated using frequencies and percentages.

8.3. Subgroup Analyses

The homogeneity of treatment effects among prospectively defined subgroups will be assessed via descriptive statistics of the mean diurnal IOP and its change from baseline by analysis visit for the following subgroups:

- Age (< 65 or ≥ 65 years)
- Sex (males or females)
- Race (White, Black or African American, Asian)
- Primary ocular diagnosis (POAG or OHT)
- Prior use of IOP-lowering medication (oral/topical carbonic anhydrase inhibitors, alpha agonists, beta-blockers, prostaglandin/prostaglandin analogues, ROCK Rho kinase inhibitor, Miotics, other IOP medications, or none)
- Mean diurnal IOP at baseline (< 25 or ≥ 25 mmHg)
- Baseline lens status (categorical: phakic or pseudophakic/aphakic)

Other subgroup analyses may be performed as deemed necessary.

9. SAFETY ANALYSES

9.1. Safety-Related Definitions

9.1.1. Adverse Event

Under Protocol 011711IN, an AE is defined as any *on*-study untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness) that occurs in a study subject, regardless of the suspected cause and regardless of the timing of the study medication administration. 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 2 days after treatment end date (or the last study visit). For this study, treatment refers to the study treatment of DE-117 ophthalmic solution 0.002%. Treatment-emergent AEs (TEAEs) are a subset of on-study AEs. All on-study AEs will be collected, but only AEs occurring during the Treatment Period (TEAEs) will be tabulated.

The severity of each AE will be graded by the Clinical Investigator as Mild, Moderate, or Severe. AEs will also be rated by the Investigator as to their causality/relationship to the study drug.

Each AE will be classified into a system organ class (SOC) and coded to a preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA), version 21.1 published in 2018.

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" under 'Eye(s) affected' on the AE eCRF.

9.1.1.2. Adverse Drug Reaction

An AE will be counted as an *adverse drug reaction* (ADR) if the Clinical Investigator answered 'Related' to the AE eCRF question "Relationship to Study Drug" for AEs that started during the Treatment Period.

9.1.1.3. 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 AE eCRF. Any AE is considered a SAE if it fulfills one or more of the following criteria:

- Death (i.e., the AE caused or led to death)
- Life threatening (i.e., immediately life-threatening)
- It required or prolonged inpatient hospitalization.
- It resulted in a persistent or significant disability/incapacity (i.e., the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions).
- It resulted in a congenital anomaly/birth defect in the offspring of a study subject who was exposed to study therapy prior to conception or during pregnancy.

- It is a medically significant event(s), which may include "sight-threatening events," that may not meet any of the above serious criteria but may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed above.

9.1.1.4. Events of Special Interest

For this study, *events of special interest* (ESI) are pregnancy, clinically significant study medication administration error, and macular edema/cystoid macular edema.

9.1.2. Safety Measures

Table 8 lists the safety measures to be evaluated for this study.

Table 8: Safety Assessments

Safety Measures	Note
BCVA	Best-corrected visual acuity will be measured for each eye at each visit under normal room illumination using visual acuity chart (e.g., ETDRS 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 (severity scores for 12 parameters: anterior chamber cells, anterior chamber flare, lid hyperemia, lid edema, conjunctival hyperemia, conjunctival chemosis, corneal edema, corneal staining, keratic precipitates, lens, anterior synechiae of iris, posterior synechiae of iris) will be performed and graded right before the 8:00 IOP measurement at all visits except Visit 1/1a (Screening or mid washout visit). Cataract severity will be assessed for subjects with phakic lens.
Ophthalmoscopy	The ophthalmoscopy (fundus) examination will be performed for each eye at Visit 1, Visit 4, and Visit 7 Study Exit/Early Termination. Variables from ophthalmoscopy are cup-to-disc ratio, glaucomatous optic nerve severity, and assessments of vitreous, retina, macula, and choroid.
Eyelid Sulcus, Eyelid, and Iris Color	The investigator (or his/her designee) will take front view and side view photograph of each eye at Visit 4 (Baseline). The photographs must include iris, eye lids and eyelashes of each eye. The photographs taken at Visit 4 (Baseline) will be used to help the Investigator assess any changes ("No changes", "Increased", or "Decreased") from baseline in eyelid, eyelashes, iris color, and DUES ("Yes", "No") at Visit 7 Study Exit/Early Termination.

The safety-related measures collected in this study include AEs, events of special interest (ESIs), best-corrected visual acuity, slit-lamp biomicroscopy (severity scores for 12 parameters), ophthalmoscopy (cup-to-disc ratio, glaucomatous optic nerve severity score, and assessments of retina, macula, choroid, and vitreous), and eyelid sulcus/eyelid/eyelash/iris color. The Safety population will be used for all summaries during the Treatment Period.

All the safety-related measures will be summarized descriptively. Except AEs, the descriptive summary of each ocular safety-related measure and the change from baseline in that measure will be performed for study eyes and fellow eyes separately.

9.2. Adverse Events

AEs, SAEs, ADRs, serious ADRs, and significant AEs (AEs leading to study drug discontinuation and AEs leading to death) will be tabulated by type of AEs for all AEs, ocular AEs, and non-ocular AEs separately.

Besides the overall AE summary, AEs, SAEs, ADRs, serious ADRs will be tabulated by SOC and preferred term for all AEs, ocular AEs, and non-ocular AEs separately. A subject who experienced multiple AEs within a SOC or preferred term will be counted only once for that SOC or preferred term. Non-serious AEs (including number of events) will also be summarized by SOC and preferred term. ESIs will be summarized descriptively.

AEs, SAEs, ADRs, serious ADRs, ocular AEs, AEs leading to death, AEs leading to study drug discontinuation, non-TEAEs, and ESIs, if any, will be listed separately.

9.2.1. Ocular Inflammation

Subjects who developed AEs during the Treatment Period with one of the following preferred terms will be included in the ocular inflammation summary:

- Anterior chamber cell
- Anterior chamber flare
- Anterior chamber inflammation
- Eye inflammation
- Iridocyclitis
- Iritis
- Uveitis

Other preferred terms might be added upon review of the AE data before database lock.

Ocular inflammation leading to study drug discontinuation, requiring steroid treatment, or requiring NSAIDs treatment will be summarized by frequency and percentage separately.

Ocular inflammation start time (in terms of study day) and duration of the AE will be summarized at the eye level using mean, standard deviation, median, minimum, and maximum by study eye and fellow eye separately. To allow for the computation of simple descriptive statistics, only subjects who develop ocular inflammation during the Treatment Period will be used for the ocular inflammation start time summary, and only subjects who develop these AEs during the Treatment Period and later resolved will be used in the duration of AE analysis.

All ocular inflammation AEs will be provided in a listing.

9.2.2. Macular Edema

Subjects who developed AEs during the Treatment Period with one of the following preferred terms will be included in the macular edema summary:

- Macular edema
- Cystoid macular edema

Macular edema start time (in terms of study day) and duration of the AE will be summarized using mean, standard deviation, median, minimum, and maximum by study eye and fellow eye separately. To allow for the computation of simple descriptive statistics, only subjects who develop macular edema during the Treatment Period will be used for the macular edema start time summary, and only subjects who develop these AEs during the Treatment Period and later resolved will be used in the duration of AE analysis.

Change from baseline in BCVA at the onset of macular edema, when macular edema is resolved, and at the last visit will be summarized using mean, standard deviation, median, minimum, and maximum by study eye and fellow eye separately. Subjects with pseudophakic lens or phakic lens at baseline who developed macular edema during the Treatment Period will be summarized by frequencies and percentages separately.

The aforementioned summaries will be performed at the eye level. All macular edema AEs will be provided in a listing.

9.2.3. Cosmetic Change(s)

Subjects who developed AEs during the Treatment Period with one of the following preferred terms will be included in the cosmetic change summary:

- Blepharal pigmentation
- Eyelash changes
- Eyelash hyperpigmentation
- Eyelash thickening
- Growth of eyelashes
- Lid sulcus deepened
- Trichiasis
- Iris hyperpigmentation

Other preferred terms might be added upon review of the AE data before database lock.

Cosmetic change(s) start time (in terms of study day) will be summarized using mean, standard deviation, median, minimum, and maximum by study eye and fellow eye separately. To allow for the computation of simple descriptive statistics, only subjects who develop cosmetic change(s) during the Treatment Period will be used for the cosmetic change start time summary.

The aforementioned summaries will be performed at the eye level. All cosmetic change AEs will be provided in a listing.

9.3. Best-Corrected Visual Acuity

BCVA (logMAR scores) and changes from baseline will be summarized by analysis visit for study eyes and fellow eyes, separately. In addition, any worsening of ≥ 0.2 LogMAR (2 lines) from baseline will be summarized and listed.

9.4. Slit-lamp Biomicroscopy

For each biomicroscopy parameter rated on a 0-3 scale (0=None, 1=Mild, 2=Moderate, 3=Severe), rating scores and changes from baseline will be summarized by analysis visit for study eyes and fellow eyes, separately. In addition, any clinically significant worsening (increase of ≥ 1 unit in rating scale of anterior chamber cell and of anterior chamber flare and increase of ≥ 2 units in other parameters) from baseline in severity will be listed.

9.5. Ophthalmoscopy

Cup-to-disc ratio will be summarized with n, mean, standard deviation, median, minimum, and maximum by analysis visit for study eyes and fellow eyes separately. In addition, subjects with at least 0.2 increase in cup/disc ratio from baseline will be listed.

Glaucomatous optic nerve findings will be assessed as 0 = none, 1 = mild, 2 = moderate, or 3 = severe. Frequency and percentage of rating scores will be summarized by analysis visit for study eyes and fellow eyes, separately. In addition, subjects with any worsening (increase) of ≥ 2 units from baseline at Month 3 will be listed.

Retina/Macula/Choroid and vitreous will be assessed as normal or abnormal. Shift from baseline at Month 3 will be summarized on study eyes and fellow eyes separately. In addition, subjects with change from baseline from normal to abnormal in these parameters will be listed.

9.6. Eyelid Sulcus, Eyelid, Eyelash, and Iris Color

For changes from baseline in eyelid pigmentation, eyelid hair growth, eyelash length, eyelash thickness, eyelash pigmentation, eyelash number, and iris color/pigmentation, frequency and percentage of subjects with No change, Increased, or Decreased will be summarized by analysis visit for study eyes and for fellow eyes. For changes from baseline in eyelid sulcus, count and percentage of changes (Yes) at Month 3 will be summarized for study eyes and for fellow eyes. In addition, any changes from baseline in eyelid sulcus at Month 3 will be listed.

10. EXPLORATORY ANALYSES

In order to enroll the study targeted population, latanoprost low/non-responders, there is an additional Run-in Period in this study. The exploratory analyses, specified below in this section, will be conducted to facilitate the description of this population.

10.1. Definitions

10.1.1. Run-in Period Population

The *Run-in Period Population* will include all subjects who signed informed consent, met the eligibility criteria at the start of a Run-in Period (Visit 2), and received at least one dose of latanoprost ophthalmic solution 0.005%.

10.1.2. Time-Related Terms for Exploratory Analyses

For exploratory analyses, the *Run-in Period Baseline* is the Visit 2, the start of the Run-in Period, when Run-in Period Population subjects takes the first dose of latanoprost ophthalmic solution 0.005%. Analysis visit of a measurement during the Run-in Period (i.e., Visit 2 and Visit 3) are the same as the study visit at which the measurement was collected, specified by the protocol. Analysis timepoint and analysis timepoint window are defined in the same manner as in Section 4.5.

10.1.3. Endpoint-Related Terms for Exploratory Analyses

For IOP measurements, the Run-in Period baseline score is the observed measurement at Visit 2. The change and the percent change from Run-in Period baseline in IOP at subsequent visits will be derived as:

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

Safety-related definitions used in the exploratory analyses are the same as defined in Section 9.1.

10.2. Summary of Run-in Period Population

10.2.1. Subject Disposition

The disposition of the Run-in Period Population subjects will be summarized for the Run-in Period. The summary will include the number and percentage of subjects who completed Washout Period and entered Run-in Period (Visit 2), subjects who reached midpoint of the Run-in Period and eligible to stay on the study (Visit 3), and subjects who completed Run-in Period but did not meet inclusion/exclusion criteria (Visit 4). Screen failure subjects and their failure reasons will also be summarized and listed.

10.2.2. Demographics

Subject demographics will also be summarized for the Run-in Period Population in the same manner as described in Section 7.2.

10.3. Exploratory Efficacy Analyses

10.3.1. Analysis of Efficacy Measurements in the Run-in Period

The IOP and mean diurnal IOP for both eyes (OD and OS) at Visit 1, 2, 3 and 4, as well as their changes and percent changes from the start of the Run-in Period (Visit 2) will be summarized for the following three sets of subjects:

1. Subjects who met the eligible criteria at the Baseline Visit (Visit 4) and enter the Treatment Period.
2. Subjects who completed the Run-in Period but failed to meet the eligible criteria at the Baseline Visit (Visit 4).
3. Subjects in the Run-in Period Population.

Summaries of IOP and mean diurnal IOP for the first set of subjects will be provided for study eye and fellow eye separately, while those for second and third sets will be provided for OD and OS separately.

10.3.2. Other Exploratory Analyses

The following exploratory efficacy endpoints will be analyzed for the FAS subjects:

- Change and percent change from Run-in Period baseline (Visit 2) in mean diurnal IOP at Week -4 (Visit 3), Baseline (Visit 4), Week 2 (Visit 5), Week 6 (Visit 6) and Month 3 (Visit 7)
- Change and percent change from Run-in Period baseline (Visit 2) in IOP at each timepoint of Week -4 (Visit 3), Baseline (Visit 4), Week 2 (Visit 5), Week 6 (Visit 6) and Month 3 (Visit 7)

For these endpoints, descriptive statistics will be provided including the number of subjects (n), mean, standard deviation, median, minimum, and maximum.

10.4. Safety Analyses

AEs, SAEs, ADRs, serious ADRs, and significant AEs (AEs leading to study drug discontinuation and AEs leading to death) will be tabulated by type of AEs for all AEs, ocular AEs, and non-ocular AEs separately. The Run-in Period Population will be used for AEs summary during the Run-in Period.

In addition, AEs emerged in the Run-in Period will be tabulated separately by SOC and preferred term on the Run-in Period Population. No other safety measurements will be summarized for the Run-in Period Population.

11. SUMMARY OF CHANGES TO THE PROTOCOL

11.1. Adding Exploratory Analyses

The exploratory analyses were added to the SAP to explore the demographics, efficacy and safety measures of the study targeted population, latanoprost low/non-response. A new study population was proposed along with descriptive summary and analyses in Section 10. In addition, efficacy analyses for FAS in the entire study from screening to the end of the study were added in Section 10.3.2, for exploratory purpose.

11.2. Change in Handling Missing Data

PROTOCOL: Missing IOP data at Month 3 will be imputed by last observed post-base IOP. The protocol did not specify on how to handle missing data when all post-baseline IOP data are missing.

SAP: Add detail on how to handle missing IOP data at Month 3 when none of post-baseline IOP data is available. Specifically, the baseline IOP can be used for imputation in this scenario.

11.3. Change in Safety Population

PROTOCOL and SAP: The eligibility criteria at baseline (Visit 4, Day 1) was removed for Safety Population. The updated Safety Population includes all subjects who signed informed consent and received at least one dose of the study medication, DE-117.

11.4. Change in Sample Size Planning

PROTOCOL and SAP: The planned sample size was changed from 150 to 100. Using one sample t-test with a significant level of 5%, a sample size of 100 will have 75% power to detect a mean diurnal IOP reduction of 1.0 mmHg from baseline with a standard deviation 3.5 mmHg, after taking into account of up to 12% dropouts.

12. APPENDIX