Statistical Analysis Plan Cover Page

Official Study Title:	ANGEL-2: A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension.
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STATISTICAL ANALYSIS PLAN

DE-126 ANGEL-2 Study

Protocol Title:	A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma or Ocular Hypertension
Product:	DE-126 ophthalmic solution 0.002%
Protocol Number:	012604IN
Sponsor:	Santen Inc. 6401 Hollis Street, Suite 125 Emeryville, CA 94608 USA.
Date:	November 15th, 2021
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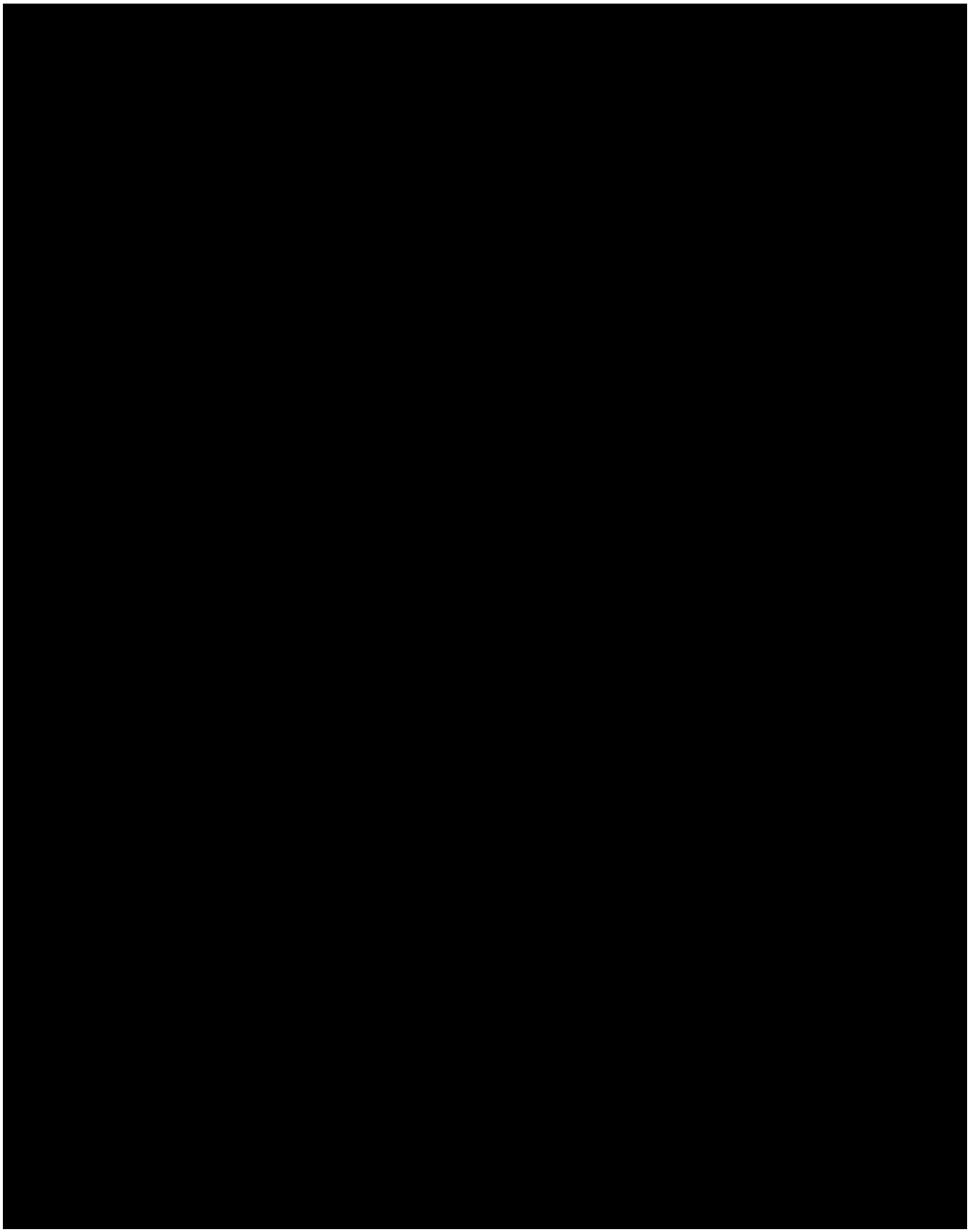
CONFIDENTIAL



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ABBREVIATIONS

ACE	Angiotensin-Converting Enzyme
ADaM	Analysis Data Model
AE	adverse event
ATC	Anatomical-Therapeutic-Chemical
BCVA	Best-Corrected Visual Acuity
BID	twice a day
CFR	Code of Federal Regulations
CI	confidence interval
CSR	Clinical Study Report
eCRF	electronic Case Report Form
ESI	event of special interest
ET	early termination
FAS	full analysis set
GQL-15	Glaucoma Quality of Life –15
IOP	intraocular pressure
logMAR	logarithm of the minimum angle of resolution
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeter of mercury
MI	multiple imputation
MMRM	Mixed-effects Model for Repeated Measures
OHT	ocular hypertension
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)
POAG	primary open-angle glaucoma
PMM	pattern-mixture model
PPS	per-protocol set
PT	preferred term
QD	once daily
RTSM	Randomization and Trial Supply Management system
SAE	serious adverse event
SAP	statistical analysis plan

SAR	suspected adverse reaction
SAS	Statistical Analysis System
SOC	system organ class
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from the 012604IN study within the scope of Santen's Protocol 012604IN, "A Phase IIb, Randomized, Double-Masked, Active-Controlled, Parallel-Group, Multicenter Study Assessing the Efficacy and Safety of DE-126 Ophthalmic Solution 0.002% Compared with Timolol Maleate Ophthalmic Solution 0.5% in Subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OHT)". It applies to the Study Protocol Amendment 1 dated 18 February 2021 and provides detailed instructions as to how each analysis will be performed.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this 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

The primary objective of this study is to investigate whether the IOP lowering efficacy of DE-126 ophthalmic solution 0.002% dosed once daily (QD, in the evening at 20:00) is non-inferior to that of Timolol maleate ophthalmic solution 0.5% dosed twice daily (08:00 and 20:00) in subjects with POAG or OHT after treatment for 3 months. If non-inferiority is met, superiority will be tested.

The secondary objectives of this study are:

- to compare the mean diurnal IOP between DE-126 ophthalmic solution 0.002% and Timolol maleate ophthalmic solution 0.5% after 3 months of treatment. If non- inferiority is met, superiority will be tested.
- to evaluate the changes and percent changes in IOP from baseline at all post-baseline visits.
- to evaluate proportions of subjects achieving target pressure reductions expressed as either in percent reductions of $\geq 20\%$, $\geq 25\%$, or $\geq 30\%$ or in achieving a target IOP value of IOP ≤ 18 mmHg.

The safety objective of this study is to evaluate the safety of DE-126 ophthalmic solution 0.002% as compared to Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.

The exploratory objective of this study is to explore the Quality of Life in subjects with POAG or OHT based on the Glaucoma Quality of Life (GQL)–15 Questionnaire when given DE-126 or Timolol for 3 months.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is IOP in the study eye measured at the specified time points: 08:00, 10:00, and 16:00 at Week 2, Week 6, and Month 3 visits.

2.2.2. Key Secondary Efficacy Endpoint

The key secondary efficacy endpoint is mean diurnal IOP in the study eye at Month 3 (Visit 5).

2.2.3. Other Secondary Efficacy Endpoints

Other secondary endpoints include:

- Mean diurnal IOP in the study eye at Week 2 (Visit 3) and Week 6 (Visit 4)
- Change and percent change from baseline (Visit 2, Day 1) in IOP in the study eye at each timepoint of each post-baseline visit
- Change and percent change from baseline in mean diurnal IOP in the study eye at each post-baseline visit,
- Having a mean diurnal IOP reduction ≥ 20%, ≥ 25%, or ≥ 30% from Baseline (Visit 2, Day 1) in the study eye at each post-baseline visit
- Having a mean diurnal IOP ≤ 18mmHg in the study eye at each post-baseline visit

2.2.4. Safety Endpoints

The safety of DE-126 will be evaluated by

- AEs and serious AEs (SAEs), including both ocular and non-ocular AEs,
- Visual acuity: measured by best-corrected visual acuity (BCVA),
- Slit-lamp biomicroscopy,
- Ophthalmoscopy examination results,
- Vital signs,

2.2.5. Exploratory Endpoint

Exploratory endpoints to be summarized are the GQL-15 total score and 4 domain scores obtained from the GQL-15 Questionnaire. The 4 domains are central and near vision, outdoor mobility, peripheral vision, and dark adaption and glare.

3. STUDY DESIGN

3.1. General Study Design

This is a Phase IIb, randomized, double-masked, active-controlled, parallel-group, and multicenter study assessing the efficacy and safety of DE-126 ophthalmic solution 0.002% compared with Timolol maleate ophthalmic solution 0.5% in subjects with POAG or OHT.

Subjects diagnosed with POAG or OHT who meet eligibility criteria at Visit 1 (Screening) will washout of their current topical IOP-lowering medication(s) if any. After completing the required washout period, subjects will return for Visit 2 (Baseline, Day 1). Subjects who meet all eligibility criteria at baseline will be randomized to receive treatment for 3 months.

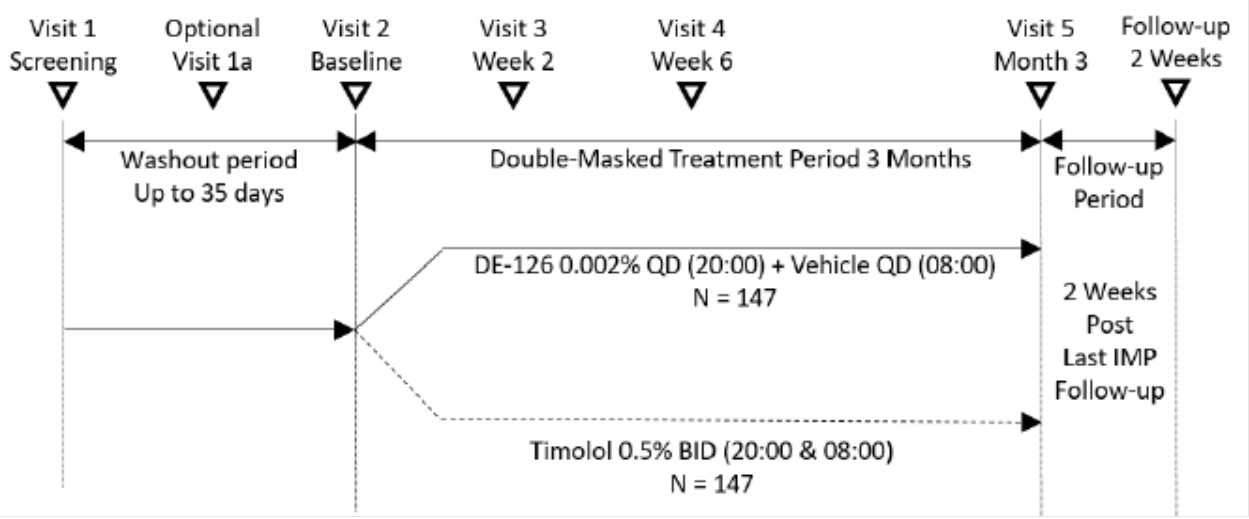
Approximately 294 adult subjects with POAG or OHT who meet all eligibility criteria will be randomized in a 1:1 ratio to receive either:

- DE-126 Ophthalmic Solution 0.002% QD (20:00) and Vehicle QD (08:00), or
- Timolol Maleate Ophthalmic Solution 0.5% BID, twice daily (20:00 and 08:00)

In the Double-Masked Treatment Period, Timolol maleate ophthalmic solution 0.5% will be used as active control.

As shown in the Study Design Diagram (Figure 1), this study consists of a Screening Period of up to 35 days including a washout period of up to 28 days (+ 7 days window) and a 3-month Double-Masked Treatment Period.

Figure 1: Study Design Diagram



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

Final eligibility for randomization will be determined at Visit 2 (Baseline, Day 1) after all necessary washout from prior IOP-lowering medications have been completed.

Approximately 294 eligible adult subjects will be randomized to receive either DE-126 ophthalmic solution 0.002% QD in the evening and vehicle QD in the morning or Timolol maleate ophthalmic solution 0.5% BID in a 1:1 ratio. Randomized subjects will be treated for 3 months with scheduled visits at Visit 2 (Baseline, Day 1), 3 (Week 2), 4 (Week 6), and 5 (Month 3). Subjects will be contacted approximately 2 weeks post last study drug administration by a phone call to confirm AE.

3.2. Randomization and Masking

A stratified permuted-block randomization will be employed to randomize eligible subjects in a 1:1 ratio to either DE-126/Vehicle arm or Timolol Maleate arm. The randomization will be stratified by mean diurnal IOP in the study eye at baseline visit (Visit 2): <25 mmHg vs. ≥25 mmHg.

The randomization schedule will be generated and implemented using central randomization via Interactive Response Technology (Medidata Rave RTSM). Each randomized subject will receive numbered study medication kits as assigned by Medidata Rave RTSM (Randomization and Trial Supply Management system).

This is a double-masked study. The subjects, Investigators, Examiners, and Santen personnel involved in the conduct of the study will be masked to the study treatment. An authorized unmasked study staff member at the investigative site who is not the Investigator or Examiner will dispense and collect study medication(s) and will query about dosing compliance.

Subjects will be instructed not to show the eye drop bottles or discuss the eye drops to either the Investigator or the Examiner or other study subjects. The active control treatment (Timolol Maleate) bottles will be over-labeled and packaged in the same secondary package (e.g., cardboard carton) as the investigational treatment (DE-126). Subjects in DE-126/Vehicle arm will receive a kit containing 2 bottles labeled “morning” for the morning dose and 2 bottles labeled “evening” for the evening dose. Subjects on Timolol arm will receive a kit containing 2 bottles labeled morning/evening for the BID dosing.

Each eligible subject will receive a numbered study medication kit assigned by Central randomization via Interactive Response Technology (Medidata Rave RTSM) at Visit 2 (Baseline, Day 1) and at Visit 4 (Week 6).

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

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

3.3. Sample Size Planning

The sample size calculation was based on a two-sided Type I error rate of 5% and a non-inferiority margin of 1.5 mmHg. Assuming a between-treatment difference of 0 mmHg, SD of 4.0 mmHg and a correlation coefficient of 0.6 among repeated measures, approximately 280 adult subjects in total (140 subjects per treatment arm) will provide 70% power to demonstrate non-inferiority of DE-126 Ophthalmic Solution 0.002% to Timolol maleate ophthalmic solution 0.5%. Assuming a drop-out rate of 5%, the final needed sample size will be 294 in total, i.e. 147 subjects/arm.

3.4. Visits and Assessments

There are 5 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 Month 3 (Visit 5, Day 91 ± 3), to the extent possible, all assessments scheduled for Visit 5 will be performed at the early termination (ET) visit. Subjects who have an on-going study medication-related serious adverse event (SAE) at study completion or at ET from the study will be followed by the Clinical Investigator until the event is resolved or determined to be irreversible, chronic, or stable.

Table 1: Schedule of Events and Procedures

	Screening Phase		Double-Masked Treatment Phase				Follow-up Period
	Visit 1 Screening *	Optional Visit 1a	Visit 2 Eligibility / Baseline (Day 1) *	Visit 3 Week 2	Visit 4 Week 6	Visit 5 Month 3 or Early Termination[a]	2 weeks of post-Last Study Drug Administration
Study day	**D-28**		**D1**	**D14**	**D42**	**D90**	**Study Exit + D14**
Visit window in days	**+7**		**NA**	**±3**	**±3**	**±7**	**+7**
Signed and dated informed consent [b]	X						
Inclusion/Exclusion Criteria [b]	X		X				
Demographics and Medical History, including prior PGA[c]	X						
Other prior or Concomitant Medications/Therapies/ Procedures	X	X	X	X	X	X	
Dosing Compliance Check				X	X	X	
Adverse Events [d]	X	X	X	X	X	X	X
Pregnancy Test [e]	X		X				
Vital Signs (blood pressure/heart rate) [f]	X		X (08:00)			X (08:00)	
Refraction [g]	X						
BCVA [g]	X	X	X (08:00)	X (08:00)	X (08:00)	X (08:00)	
Slit-lamp Biomicroscopy [h]	X		X (08:00)	X (08:00)	X (08:00)	X (08:00)	
IOP [i]	X	X	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	08:00 10:00 16:00	
Pachymetry [j]	X						
Instill study medication after IOP measurement at site by unmasked site staff and record dosing				X (08:00)	X (08:00)	X (08:00)	
Gonioscopy [k]	X						
Visual Field [l]	X						
Ophthalmoscopy [m]	X		X (16:00)			X (16:00)	
Blood Sampling for PGx [n]			X				
Dispense Study Medication & Diary			X		X		
Collect Study Medication & Diary					X	X	
Phone call [o]				X	X	X	X
GQL-15 questionnaire [p]			X			X	

* Visit 1 (Screening) and Visit 2 (Eligibility/Baseline, Day 1) may be combined into one visit for treatment-naïve subjects as long as the additional requirements of Visit 2 (Eligibility/Baseline, Day 1) are fulfilled, and assessment started at 8:00 (±60 min) on the day of the combined visit.

[a] Optional at unscheduled visit, required for early terminated subjects.

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

[c] Prostaglandin naive subjects are defined as subjects who are not known to have used prostaglandin as their glaucoma treatment. The previous use of prostaglandin should be confirmed by either subject's medical records or subject history.

[d] AE will be recorded starting after the signing of the informed consent form until 2 weeks post Last Study Drug Administration. Regardless of the source of the reported occurrence of an AE in a subject, the masked investigator will assess the causality of the AE.

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

[f] Vital signs (resting blood pressure and pulse rate) will be collected in sitting position anytime at Visit 1 (Screening), and approximately at 08:00 for Visit 2 (Baseline, Day 1), and Visit 5 (Month 3)/exit or early termination before the morning dose.

[g] Refraction will be performed at the screening visit anytime. 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.

[h] Slit-lamp Biomicroscopy examination must be completed before IOP is measured at 08:00. Aqueous flare and cell evaluation will be performed before fluorescein instillation.

[I] IOP measurements using Goldmann applanation tonometer will be performed at 08:00 (±60 min), 10:00 (±60 min), and 16:00 (±60 min) at all visits except for Visit 1 (Screening), and Optional Visit 1a (mid-washout).

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

[k] 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. If needed, Gonioscopy will be performed after IOP measurement at Visit 1 (Screening).

[l] 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.

[m] Ophthalmoscopy with pupil dilation will be performed at Visit 1 (Screening) anytime, Visit 2 (Baseline), and Visit 5 (Month 3)/exit or early termination at the 16:00 (±60 min) after IOP measurements.

[n] Blood sampling for the PGx laboratory research study may be performed at any visit after PGx informed consent obtained, subject randomized, and study drug dosing has begun.

[o] At Visit 3, 4, and 5, subject will be reminded to take evening dose on the day before each visit. At follow-up Period, subject will be contacted by a phone call to confirm AE after 2 weeks post last study drug administration.

[p] GQL-15 questionnaire will be administered by subject.

4. DEFINTIONS

4.1. Time-Related Terms

4.1.1. Screening Visit

The *Screening visit* is Visit 1 when subjects will be screened against the inclusion and exclusion criteria. Eligible subjects will be instructed to discontinue use of all IOP-lowering medications, if any, during a washout period.

4.1.2. Baseline Visit

The *Baseline visit* is Visit 2 (Day 1) when the subjects are randomized.

4.1.3. Treatment Start and End Dates, Extent of Exposure (Days)

Treatment start date is the date at which a randomized subject takes the first dose of the study medication. *Treatment end date* is the date at which a randomized subject takes the last dose of the same study medication. For all treatment arms except the placebo arm, if the date of the last dose is missing, then

- The date prior to Month 3 (Visit 5) will be considered the treatment end date for subjects who completed the study, and
- the date prior to ET visit will be used for subjects who prematurely discontinued the study. If the ET visit date of a non-completer is not available, then the date prior to last available visit date will be considered the treatment end date.

The treatment end date will be set to missing if the treatment start date is missing.

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.

4.1.4. 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, for efficacy analyses, the randomization date is the reference day and the study day will be calculated as:

- For days prior to the randomization date, Study Day = Date – Randomization Date.
- For days on/after the randomization date, Study Day = Date – Randomization Date + 1.

For safety analyses, the treatment start date is the reference day and the study day will be calculated as:

- For days prior to the treatment start date, Study Day = Date – Treatment Start Date.
- For days on/after the treatment start date, Study Day = Date – Treatment Start Date + 1.

Note that there is no Study Day 0.

4.1.5. Days on Study

The *days on study* measures the duration of stay since randomization in the study. For each randomized subject, the days on study will be derived as:

Days on Study = (Study Exit date – Baseline Visit Date) + 1.

4.1.6. Analysis Visit Window and Out-of-Window Measurements

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

Analysis visit is a timing variable to be used for analyses involving visits. For each analysis visit, an *analysis window* is set up to determine the analysis visit a measurement should be mapped to. 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 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* for post-baseline visits will be applied to minimize the amount of missing data for analysis purposes:

Table 2: Post-Baseline Analysis Visit and Analysis Window

Post-Baseline Analysis Visit (Target Assessment Date)	***Protocol Visit Window***	***Analysis Window***
Week 2 (Day 14)	[11, 17]	[2-25]
Week 6 (Day 42)	[39, 45]	[26-61]
Month 3 (Day 90)	[83, 97]	[62-

For analyses involving post-baseline visits, if there are two or more measurements that fall into the same analysis window of a post-baseline visit, then a visit in which IOP are measured at all the scheduled timepoints (8:00, 10:00 and 16:00) will be selected for that analysis visit. In case that there are two or more such visits within the same analysis window, the measurement closest to the target assessment day will be selected for that analysis 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.

4.1.7. Analysis Timepoint Window and Out-of-Window Measurements

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*
8:00	[7:00, 9:00]	- 8:59]
10:00	[9:00, 11:00]	[9:00, 12:59]
16:00	[15:00, 17:00]	[13:00 -

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.

4.2. Efficacy-Related Definitions

4.2.1. Study Eye

The *study* eye will be the eye that qualifies per eligibility criteria at Visit 2 (Baseline, Day 1). If both eyes meet the eligibility criteria, the eye with the higher mean diurnal IOP at Visit 2 (Baseline, Day 1) will be designated as the study eye. For example, IOP must be ≥ 22 mmHg at all IOP measurement time-points (08:00, 10:00 and 16:00). If both eyes meet the eligibility criteria and have the same mean diurnal IOP, the right eye will be designated as the study eye.

4.2.2. Efficacy Measure

IOP (in mmHg) is the efficacy measure for this study. For the IOP at each timepoint of measurement, a mean of two consecutive measurements using the Goldmann applanation tonometer will be used. If the two measurements differ by 3 mmHg or more, then a third measurement will be made, and the median of the three consecutive measurements will be used.

The mean diurnal IOP at each visit is defined as the mean of the three scheduled timepoints 8:00, 10:00, and 16:00 at the visit. If there are one or more missing IOP measurement at timepoints, the mean diurnal IOP will not be calculated.

To assess the efficacy of DE-126, the mean/median IOP at each scheduled timepoint (8:00, 10:00, 16:00) and the mean diurnal IOP in the study eye will be analyzed. In addition, changes and percent changes from baseline in IOP at each timepoint and the mean diurnal IOP in the study eye will also be analyzed.

4.2.3. Baseline Score

For any measure, the *baseline score* is the last observed measurement or derived score prior to the first dose of study medication.

4.2.4. IOP Response Endpoints and Response Rate

Four IOP response endpoints shown in Table 3 will be evaluated at each post-Baseline visit of Week 2 (Visit 3), Week 6 (Visit 4), or Month 3 (Visit 5).

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 visit.

Table 3 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

4.3. Safety-Related Definitions

4.3.1. Adverse Event

Events reported on the AE electronic Case Report Form (eCRF) will be assessed according to the recently amended Food and Drug Administration regulations 21 CFR Parts 312 and 320.

Under Protocol 012601IN, an AE is defined as any untoward medical occurrence that occurs in a study subject, regardless of the suspected cause and regardless of timing of 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 the 2 days (twice the scheduled dosing interval) after treatment end date. Treatment-emergent AEs are a subset of on-study AEs. Both on-study and treatment-emergent AEs will be recorded, but only treatment-emergent AEs will be tabulated.

The severity of each AE will be graded by the Clinical Investigator as Mild, Moderate, or Severe.

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 23.1 published in 2020.

4.3.1.1. Serious Adverse Event

An AE will be counted as a *serious adverse event* (SAE) if the Clinical Investigator selected "Yes" under Item 5 (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)
- Inpatient hospitalization and/or prolonged hospitalization

- 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)
- A congenital anomaly/birth defect in the offspring of a study subject who was exposed to study therapy prior to conception or during pregnancy
- Sight threatening event
- Other medically important event (e.g. requires medical or surgical intervention to prevent one or more of the listed above)

4.3.1.2. Ocular Adverse Event

An AE will be counted as an *ocular AE* if the Clinical Investigator selected "OD", "OS", or "OU" under 'Item 2 (Eye(s) affected)' on the AE eCRF.

4.3.1.3. Suspected Adverse Reaction

An AE will be counted as a *suspected adverse reaction* (SAR) if the Clinical Investigator selected answered 'Related' to the AE eCRF Item 10 (Relationship to Study Drug).

4.3.1.4. Events of Special Interest

Events of special interest (ESI), such as pregnancy, study medication administration error, and AEs leading to study discontinuation or unmasking, will be identified throughout the study.

4.3.2. Safety Measures

Table 4: Safety AssessmentsTable 4 lists the safety measures to be evaluated for this study.

Table 4: Safety Assessments

Safety Measures	***Note***
BCVA	BCVA will be measured prior to the 08:00 IOP measurement at all visits except Visit 1 (Screening)/ 1a (Optional visit) using visual acuity chart (Early Treatment Diabetic Retinopathy Study [ETDRS] chart) and the logMAR scoring. For Visit 1/1a, the corrected visual acuity is performed prior to IOP measurement.
Slit-lamp biomicroscopy: anterior chamber cells anterior chamber flare lid hyperemia lid edema conjunctival (palpebral and bulbar) hyperemia conjunctival chemosis corneal edema	Anterior Chamber Cells will be graded as 0 = No cells, 0.5 = 1-5cells, 1 = 6-15 cells, 2 = 16-25 cells, 3 = 26-50 cells, or 4 = > 50 cells. Anterior Chamber Flare will be graded as 0 = None, 1 = Faint, 2 = Moderate, 3 = Marked, or 4 = Intense. The other biomicroscopy parameters will be graded as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe.

corneal staining (with fluorescein) keratic precipitate lens anterior synechiae of iris posterior synechiae of iris iris color abnormalities eyelash abnormalities eyelid abnormalities	
Ophthalmoscopy glaucomatous optic nerve	Damage to optic nerve will be graded as 0 = None 1 = Mild, 2 = Moderate, 3 = Severe.
Vital signs: systolic blood pressure diastolic blood pressure pulse rate	Systolic blood pressure and diastolic blood pressure will be measured in mmHg. Pulse rate will be measured by beats/minute.

4.4. Other Definitions

4.4.1. 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's needs to overlap with his/her treatment period of the study medication.

4.4.2. Concurrent Medical Conditions

Concurrent medical conditions are those ongoing conditions or diseases that are present at the signing of informed consent.

5. STUDY POPULATION

Analysis populations utilized for this study are defined below.

The ***Full Analysis Set*** (FAS) includes all randomized subjects who received at least one dose of the study medication (test or control medication) and had at least one post-baseline efficacy assessment of the study eye during the study. 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.

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

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

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.

6. GENERAL CONSIDERATIONS

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 summarized using frequency (n) and percent (%).

The statistical testing will be conducted at a significance level of 0.05 (2-sided) unless specified otherwise. No statistical testing will be conducted for safety measures.

6.1. Adjustments for Covariates

In general, baseline IOP score 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. Efficacy Measure

For each IOP endpoint, no imputation is needed for the MMRM analyses. For sensitivity analysis purpose multiple imputation will be adopted in some analyses.

6.2.2. Safety Measures

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

6.2.3. Dates for Medical Events and Medications

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

Missing onset dates

- Completely missing: No imputation will be applied.
- Only year is available: Use the first day of the year to impute the missing month and date parts of the onset date
- Year and month are available, but day is missing: Use the first day of the month to impute the missing date part of the onset date.

Missing resolution dates

- Completely missing: No imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the last visit date.
- Only year is available: Use the last day of the year to impute the missing month and date parts of the resolution date
- Year and month are available, but day is missing: Use the last day of the month to impute the missing date part of the resolution date

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

6.3. Multi-Center Studies

This is a multi-center study. The number of subjects enrolled from each site will not be pooled in this study.

6.4. Multiple Comparisons / Multiplicity

Fixed sequence procedure will be applied to control the overall Type I error rate across the four hypotheses in the primary and key secondary endpoints at the 0.05 level. Fixed sequence procedure tests hierarchically ordered hypotheses at level 0.05 until the first non-rejection.

The fixed sequence for the four hypotheses in this study is as follows:

1. Hypothesis of non-inferiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the primary endpoint, IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 2, Week 6, and Month 3.
2. Hypothesis of non-inferiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the key secondary endpoint, mean diurnal IOP at Month 3.
3. Hypothesis of superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the key secondary endpoint, mean diurnal IOP at Month 3.
4. Hypothesis of superiority of DE-126 ophthalmic solution 0.002% to Timolol maleate ophthalmic solution 0.5% for the primary endpoint, IOP at each scheduled timepoint (08:00, 10:00, and 16:00) at Week 2, Week 6, and Month 3.

6.5. Interim Analysis

No formal interim analysis is planned for this study.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

The disposition of all randomized subjects will be summarized by treatment and overall. The summary will include the number of subjects in the FAS population the Safety population, and the PP population. The disposition summary will also include the number and percentage of completers and non-completers at Month 3 (Visit 5), by the primary discontinuation reason.

7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for the FAS population by planned treatment, Safety population by 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: Asian, Black or Africa American, or White)

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

- Baseline mean diurnal IOP in the study eye: <25 mmHg vs. ≥25 mmHg.
- Primary ocular diagnosis (categorical: POAG 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, ROCK inhibitor, other, or none)
- Prostaglandin naive (Yes or No)
- Baseline lens status (categorical: phakic or pseudophakic/aphakic)
- Baseline mean diurnal IOP score and baseline IOP score at each scheduled timepoint (08:00, 10:00, and 16:00)
- BCVA (logMAR)
- Baseline central corneal thickness
- Glaucomatous optic nerve findings (categorical: none, mild, moderate, or severe)
- Baseline glaucoma hemifield test result by device (categorical: within normal limits, borderline, or outside normal limits)
- Baseline visual field global indices by device
    - mean deviation
    - pattern standard deviation

7.3. Medical and Surgical History

For this study, medical and surgical history (i.e., medical events) will be coded using MedDRA 23.1, 2020. Each medical event will be classified into a SOC and mapped to a PT.

The medical and surgical history will be summarized for the FAS population. Subjects reporting any medical and surgical history at baseline will be tabulated by SOC and PT for each planned treatment and overall.

Baseline lens status (categorical: phakic or pseudophakic/aphakic)

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
- Randomization
- Safety issues
- Time Window
- Protocol implementation issues
- Other deviations

A protocol deviation is considered major if it may affect the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. Santen's study team will review all protocol deviations and determine the list of major protocol deviations prior to database lock. All randomized subjects with any major protocol deviation(s) will be tabulated by deviation category for each planned treatment and overall.

7.5. Prior and Concomitant Medications

For this study, non-study medications, including prior and concomitant medications, will be coded using World Health Organization Drug Dictionary Enhanced (WHO-DDE) (March 2017). 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

A subject will be considered fully compliant to treatment if he/she responded "0" at all post-baseline visits to the eCRF question "How many doses were missed since the previous visit?"

The treatment compliance rate for a subject at a visit will be as following.

Treatment Compliance Rate (%)

$$= \frac{(\text{Duration} - \text{Total Number of Missed Dose})}{\text{Duration}} \times 100 \quad \textit{if the subject did not withdraw the study medication before this visit}$$

$$= \frac{\text{Duration} - \text{Total Number of Missed Dose} - (\text{Current Visit Date} - \text{Treatment End Date})}{\text{Duration}} \times 100$$

if the subject withdrew the study medication before this visit,

where

- duration is the number of days subjects should have administered study medication, calculated as current visit date – baseline date, and
- total number of missed dose is the total number of days that subject did not follow the proper dosing procedures or dosing schedule since baseline.

For FAS subjects, treatment compliance 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 4.1.3. For Safety subjects, the duration of exposure will be summarized using descriptive statistics for actual treatment received and overall. Frequency and percentage of subjects will also be tabulated by analysis visit.

8. EFFICACY ANALYSES

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

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

8.1. Analyses of Primary Endpoint and Key Secondary Endpoint

8.1.1. Primary Analysis

8.1.1.1. Primary Endpoint

The primary efficacy endpoint is the IOP in the study eye at each scheduled timepoint (08:00, 10:00, and 16:00) at each of three follow-up visits, Week 2, Week 6, and Month 3. The nine combinations of three scheduled timepoints at each of three visits are referred to subsequently as nine timepoints. For the primary endpoint, the following hypotheses will be tested:

$$H_0\colon\ \mu_T - \mu_C > \Delta \quad \textit{for at least one timepoint}$$

versus

$$H_A\colon\ \mu_T - \mu_C \leq \Delta \quad \textit{at all nine timepoints}$$

where μ_T and μ_C denote the mean values of the primary endpoint in the DE-126 arm and the Timolol arm, respectively, and Δ denotes the noninferiority margin of 1.5 mmHg.

The primary analysis of the primary efficacy endpoint will be performed using a MMRM based on the FAS. A separate MMRM will be used for IOP at each scheduled timepoint (8:00, 10:00, or 16:00). For each scheduled *k*th timepoint, the model will include treatment (T_i), analysis visit (V_j), and treatment-by-visit interaction (TV_{ij}) as fixed effects, and the baseline IOP (B_k) as covariates:

$$\mathrm{IOP}_{ijkn} = \mu + T_i + V_j + TV_{ij} + B_k + \varepsilon_{ijkn}$$

where μ denotes the overall mean, and ε denotes the random error associated with the individual subject. The above model allows treatment effect and its variability to vary over study visits.

Correlations of IOP measurements within-subject will be modeled using an unstructured covariance matrix. If there are convergence issues, covariance matrix structures other than unstructured will be tried in the following order: (1) heterogeneous Toeplitz (TOEPH), (2) heterogeneous autoregressive of order 1 (ARH(1)), (3) heterogeneous compound symmetry (CSH), and (4) compound symmetry (CS). The first covariance structure that converges will be used as the primary analysis. Least squares mean IOP values for each treatment arm and differences between least squares treatment arm means and associated 95% confidence intervals will be reported for each of the nine timepoints.

For the subjects who receive IOP-lowering rescue therapy, any IOP values collected after the receipt of rescue therapy will be censored (i.e., treated as missing) in the analyses.

Noninferiority criteria for primary endpoint: With respect to the primary study objective, noninferiority of DE-126 to Timolol is established if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (DE-126 minus Timolol) is ≤ 1.5 mmHg at all nine timepoints and ≤ 1.0 mmHg in majority (five or more) of the nine timepoints.

Superiority of DE-126 to Timolol for the primary efficacy endpoint will be claimed if the upper limit of the two-sided 95% confidence interval for the difference in the mean IOP (DE-126 minus Timolol) is < 0 mmHg at all nine timepoints.

8.1.1.2. Key Secondary Endpoint

The key secondary efficacy endpoint is the mean diurnal IOP in the study eye at Month 3. The following null (versus alternative) hypothesis will be tested:

$$H_{0S}\colon \mu_{TM} - \mu_{CM} > \Delta \quad \text{vs.} \quad H_{AS}\colon \mu_{TM} - \mu_{CM} \leq \Delta$$

where μ_{TM} and μ_{CM} denote the mean diurnal IOP at Month 3 of the DE-126 and Timolol arm, respectively, and Δ denotes the noninferiority margin of 1.5 mmHg. The primary analysis of this key secondary efficacy endpoint will be performed using a MMRM based on the FAS. The model will include treatment, analysis visit (Week 2, Week 6, or Month 3), and treatment-by-visit interaction as fixed effects, and baseline mean diurnal IOP as a covariate. Correlations of mean diurnal IOPs within-subject will be modeled using an unstructured covariance matrix. The mathematical model is analogous to the model in the primary efficacy endpoint.

If there are convergence issues, covariance matrix structures other than unstructured will be tried in the following order: (1) heterogeneous Toeplitz (TOEPH), (2) heterogeneous autoregressive of order 1 (ARH(1)), (3) heterogeneous compound symmetry (CSH), and (4) compound symmetry (CS). The first covariance structure that converges will be used as the primary analysis. Least squares mean diurnal IOP values at Month 3 for each treatment arm and the difference between least squares treatment group means and its 95% confidence interval will be reported.

Noninferiority of DE-126 to Timolol is achieved for this endpoint if the upper limit of the 95% confidence interval for the difference between DE-126 and Timolol (DE 126 minus Timolol) in the mean diurnal IOP at Month 3 is ≤ 1.5 mmHg. Superiority of DE-126 to Timolol is achieved for this endpoint if the upper limit of the 95% confidence interval is < 0 mmHg.

8.1.2. Sensitivity Analyses

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

- Using the analysis population of the PPS
- Using a pattern-mixture model (PMM) with delta-adjustment approach where missing values are imputed by multiple imputation.

To assess the sensitivity to departure from MAR assumption, a PMM with delta-adjustment will be applied, as follows:

a. Use Markov chain Monte Carlo (MCMC) to create monotone missingness first. Then obtain standard multiple imputations under MAR assumptions for missing IOP values using monotone regression. The missing data are filled in and 50 complete datasets are created. The seed that will be used in the SAS program is 13546.

b. For each IOP value that had been missing because of censoring after having received IOP-lowering rescue therapy, or early study discontinuation due to lack of efficacy or AE, these values will adjust by adding delta to the imputed values, where delta = 1.0 mmHg. The seed that will be used in the SAS program is 13546.

c. Each of the 50 complete datasets will then be analyzed separately using the same MMRM as used for the primary analysis.

d. The estimates obtained from the MMRM analysis of each complete dataset are combined for inference purposes.

e. Repeat step b, c, d, with delta = 2.0, 3.0, 4.0, and 5.0 mmHg. The larger the value of delta that is required to reverse the conclusion of the primary analysis, the more robust the conclusion is considered to be.

For the primary endpoint, in addition to the two types of sensitivity analyses described above, if the overall rate of study drug discontinuation due to lack of efficacy or AE is greater than 10% and the difference between the rate in the DE-126 and Timolol arms is greater than 5 percentage points, a trimmed mean analysis (Permutt et al., 2017) will be conducted as a sensitivity analysis.

8.2. Analyses of Other Secondary Endpoints

For continuous secondary endpoints (IOP, mean diurnal IOP, change and percent change from baseline in IOP/mean diurnal IOP) at Week 2, Week 6 and Month 3, both MMRM and descriptive summaries will be performed. The MMRM will be the same as the one for key secondary endpoint but without multiplicity adjustment.

8.2.1. Responder Rates

For binary secondary endpoints, the responder rates will be summarized at each post-baseline visit. Subjects discontinued study by any reason without response will be treated as non-responder. A sensitivity analysis will be conducted by multiple imputing for discontinued subjects with reasons other than AE or lack of efficacy. DE-126/Vehicle arm will be compared with Timolol Maleate arm using Fisher's exact test, and the differences between the two treatment arms will be reported along with 95% CIs.

8.3. Subgroup Analyses

To assess the homogeneity of treatment effects among subgroups, descriptive summaries for all IOP endpoints will be conducted by the following categories:

- age group (< 65, or ≥ 65 years)
- sex (males or females)

- race (White or non-White)
- mean diurnal IOP in the study eye at baseline visit (<25 mmHg vs. ≥25 mmHg)
- primary ocular diagnosis (primary open-angle glaucoma or ocular hypertension.

If there are a sufficient number of subjects in each subgroup, the test of interaction will be conducted using an MMRM with treatment, visit, treatment-by-visit, subgroup, and treatment-by-subgroup as fixed effects, baseline IOP score (score at the corresponding timepoint or mean diurnal score) as a covariate, and subject as a random effect.

9. SAFETY ANALYSES

The safety-related measures collected in this study include AEs, slit-lamp biomicroscopy, ophthalmoscopy, corrected visual acuity, ocular symptoms, central corneal thickness, iris color, eyelash, and eyelid by photographs, vital signs, and clinical laboratory tests. The Safety population will be used for all safety summaries, where subjects will be classified by actual treatment received. If a subject was administered a different treatment than that which was assigned in the study, this subject will be included in the higher dose of DE-126 arm or Timolol arm if the subject didn't receive any DE-126 in the study.

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 AEs will be tabulated AEs by treatment arm using actual treatment received. Subjects with any AEs will be tabulated by SOC and PT where a subject who experienced multiple AEs within a SOC or PT will be counted only once for that SOC or PT. SAEs, SARs, and Serious SARs will be tabulated similarly.

Subjects with any ocular and non-ocular AEs will be tabulated separately. AEs, ocular, and non-ocular will also be summarized by relationship to treatment and maximum severity. Any ocular AE that occurred simultaneously to both eyes will be counted once.

AE, SARs, ocular and non-ocular AEs will also be summarized by country.

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

9.2. Best-Corrected Visual Acuity

BCVA measures the acuteness or clearness of the best-corrected vision, with a range of [0, 97] in ETDRS letters. An increase in BCVA indicates an improvement in the best-corrected vision.

BCVA will be measured for each eye prior to the 08:00 IOP measurement at each visit at Baeline, Week 2, Week 6, and Month 3 using a Snellen chart using visual acuity chart (Early Treatment Diabetic Retinopathy Study [ETDRS] chart) and the logMAR scoring.

BCVA in Snellen scale will be converted to logMAR scale using the following equation and be used in all the BCVA analyses:

$$\text{LogMAR VA} = -\log_{10}\left(\frac{\text{Snellen numerator}}{\text{Snellen denominator}}\right)$$

BCVA (logMAR scores) and changes from baseline will be summarized by treatment and analysis visit for study eyes and fellow eyes, separately. In addition, any change (worsening or improvement) of ≥ 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 severity rating score will be summarized by actual treatment received and analysis visit for study eyes and fellow eyes, separately. In addition, subjects with improvement (decrease) or worsening (increase) or maintaining from baseline in severity rating score will be tabulated by analysis visit and biomicroscopy parameter. Subjects with worsening of 2 units or more from baseline will be listed.

9.4. Ophthalmoscopy

For cup to disc ratio, scores and changes from baseline will be summarized by actual treatment received and analysis visit for study eyes and fellow eyes, separately.

For glaucomatous optic nerve, frequency and percentage of severity rating score will be summarized by actual treatment received and analysis visit for study eyes and fellow eyes, separately.

9.5. Central Corneal Thickness

Central corneal thickness scores at screening will be summarized by actual treatment received for study eyes and fellow eyes, separately.

9.6. Vital Signs

Blood pressures and pulse rate, and changes from baseline may be summarized by actual treatment received and analysis visit.

10. ANALYSIS OF EXPLORATORY ENDPOINT

Glaucoma Quality of Life-15 (GQL-15) questionnaire (protocol Appendix F) is a 15-item questionnaire measuring the severity of visual disability in glaucoma patients. The GQL-15 will be administered at Baseline (Visit 2, Day 1) and Month 3 (Visit 5).

The GQL-15 total score and 4 domain scores will be summarized descriptively by actual treatment received. In addition, change from baseline will be presented. The 4 domains are central and near vision, outdoor mobility, peripheral vision, and dark adaption and glare.

Table 5 GQL-15 Questionnaire Items Associated with 4 Domains

Domain	Questionnaire Item
Central and near vision	1. Reading newspapers 15. Recognizing faces
Peripheral vision	4. Walking on uneven ground 8. Tripping over objects 9. Seeing objects coming from the side 11. Walking on steps/stairs 12. Bumping into objects 13. Judging distance of foot to step/curb
Glare and dark adaption	2. Walking after dark 3. Seeing at night 5. Adjusting to bright lights 6. Adjusting to dim lights 7. Going from light to dark or vice versa 14. Finding dropped objects
Outdoor mobility	10. Crossing the road

Total score is derived by summing all item-level response scores. Subscale scores are derived by coding the item-level responses on a numerical interval scale ranging from 0 (no difficulty) to 100 (severe difficulty). Subscale scores are average of the sum of scores generated for the item-level subscale responses. Higher subscale scores indicate lower QOL and greater difficulty with subscale specific tasks (Nelson et al, 2003; Sencanic et al, 2018).

11. REFERENCES

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12. APPENDICES