Statistical Analysis Plan Cover Page

Official Study Title:	LUMINA: A Phase III, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 µg DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye.
NCT Number:	NCT03711929
Date of the document:	16 Aug 2022

STATISTICAL ANALYSIS PLAN

DE-109 LUMINA

Protocol Title:	LUMINA: A Phase III, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 µg DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye
Product:	DE-109
Protocol Number:	010906IN
Sponsor:	Santen Incorporated 6401 Hollis Street, Suite 125 Emeryville, CA 94608 USA.
Date:	August 16, 2022
Status:	Version 2.0

CONFIDENTIAL

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
ANCOVA	analysis of covariance
AR(1)	autoregressive (covariance structure)
ARH(1)	heterogeneous autoregressive (covariance structure)
ATC	Anatomical-Therapeutic-Chemical
BCVA	Best-Corrected Visual Acuity
CI	Confidence Interval
CM	Concomitant Medications
CMH	Cochran-Mantel-Haenszel
CSR	Clinical Study Report
CST	Central Subfield Thickness
DM	Double-Masked
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ESI(s)	Event(s) of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
EXCH	exchangeable (correlation structure)
ET	Early Termination
FAS	Full Analysis Set
GEE	Generalized Estimating Equation
IOP	Intraocular Pressure
IP	Investigational product
LOCF	Last-observation-carried-forward
LogMAR	Logarithm of the Minimum Angle of Resolution
LS	least squares
MAR	Missing at random
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
MH	Medical History
mmHg	Millimeter of Mercury

ABBREVIATIONS (Continued)

Abbreviation	Explanation
MMRM	mixed-effects model for repeated measures
NEI	National Eye Institute
NIU-PS	non-infectious uveitis of the posterior segment of the eye
OCT	Optical Coherence Tomography
OHT	Ocular Hypertension
OD	Oculus Dexter (right eye)
OL	Open-Labeled
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
PP	Per-Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
SUN	Standardized Uveitis Nomenclature
TOEP	Toeplitz (covariance)
TOEPH	heterogeneous Toeplitz (covariance)
UN	unstructured (correlation structure)
US	United States
VEGF	Vascular endothelial growth factor
VH	Vitreous haze
VFQ	Visual Functioning Questionnaire
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 LUMINA study within the scope of Santen's Protocol 010906IN, "LUMINA: A Phase III, Multicenter, Sham-Controlled, Randomized, Double-Masked Study Assessing the Efficacy and Safety of Intravitreal Injections of 440 µg DE-109 for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye." It applies to the study protocol Amendment 3, dated 14 JUL 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, ESTIMANDS, AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of intravitreal injection of DE-109 440 µg every 2 months as compared with Sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye.

2.1.2. Secondary Objectives

2.1.2.1. Long-term Efficacy Objective

To evaluate the long-term efficacy (>6 months and up to one year) of intravitreal injection of DE-109 440 µg every 2 months for the treatment of active, non-infectious uveitis of the posterior segment of the eye.

2.1.2.2. Safety Objective

To evaluate the safety of intravitreal injection of DE-109 440 µg every 2 months for up to one year of dosing for the treatment of active, non-infectious uveitis of the posterior segment of the eye.

2.2. Estimands

2.2.1. Primary estimand

Vitreous haze (VH) 0 response rate in DE-109 440 µg group vs. Sham group at Month 5 in all study eyes that received at least one dose of the study treatment where all eyes that were rescued due to worsening of uveitis or discontinued from the study due to lack of efficacy or due to adverse events before Month 5 will be treated as non-responders. For study eyes that were rescued for any other reasons or had missing data due to other reasons, imputation by the multiple imputation-based approach will be used.

2.2.2. Treatment policy estimand

Vitreous haze (VH) 0 response rate in DE-109 440 µg group vs. Sham group at Month 5 in all study eyes that received at least one dose of the study treatment regardless of whether subjects have received rescue therapy or discontinued from the study due to lack of efficacy or due to adverse events. For study eyes that had missing data due to any reason, imputation by the multiple imputation-based approach will be used.

2.2.3. Composite estimands

Mean composite score in DE-109 440 µg group vs. Sham group at Month 3 and at Month 5 in all study eyes that received at least one dose of study treatment. Each study eye will be assigned one of the following scores:

- Score = 3 if a study eye achieved VH score of 0 at the specified visit without taking any rescue therapies that could affect VH score prior to the specified visit

- Score = 2 if a study eye had at least improved by 2 units in VH (compared to baseline) at the specified visit without taking any rescue therapies that could affect VH score prior to the specified visit
- Score = 1 if a study eye achieved VH score of 0.5+ at the specified visit without taking any rescue therapies that could affect VH score prior to the specified visit
- Score = -1 if a study eye got rescued due to worsening of uveitis or discontinued from the study due to lack of efficacy or due to adverse events prior to the specified visit
- Score = 0 if otherwise

2.3. Endpoints

2.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint, *vitreous haze (VH) 0 response*, is defined as having a VH score of 0 at Month 5 based on the modified Standardized Uveitis Nomenclature (SUN) scale.

2.3.2. Key Secondary Efficacy Endpoints

The following key secondary endpoints will be assessed:

- Mean composite score at Month 5: mean of composite scores of all study eyes by the composite scoring system (defined in Section 2.2.3)
- VH 0 response at Month 3: having a VH score of 0 at Month 3 (modified SUN scale)
- Mean composite score at Month 3: mean of composite scores of all study eyes by the composite scoring system (defined in Section 2.2.3)

2.3.3. Secondary Efficacy Endpoints

The secondary endpoints to be assessed for the Double-Masked analysis period include:

- VH 0 or 2-unit response at Month 5: having a VH score of 0 or a decrease (improvement) of at least 2 units (i.e., 2+ to 0, 3+ to 1+, or 4+ to 2+) from baseline in VH score at Month 5 (modified SUN scale)
- VH 0 or 2-unit response at Month 3: having a VH score of 0 or a decrease (improvement) of at least 2 units from baseline in VH score at Month 3 (modified SUN scale)
- VH 0 or 0.5+ response at Month 5: having a VH score of 0 or 0.5+ at Month 5 (modified SUN scale)
- VH 0 or 0.5+ response at Month 3: having a VH score of 0 or 0.5+ at Month 3 (modified SUN scale)
- Change from baseline in VH score at post-baseline visits up to Month 6
- Corticosteroid tapering success with resolution at Month 5 (for the Intent-to-Taper population as defined in Section 6.4): having a prednisone-equivalent oral dose of

0 mg/day and a VH score of 0 at Month 5 without taking any rescue therapies that could affect VH score

- Corticosteroid tapering success with resolution at Month 3 (for the Intent-to-Taper population as defined in Section 6.4): having a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 at Month 3 without taking any rescue therapies that could affect VH score
- BCVA (Best-Corrected Visual Acuity) 3-line response at Month 5 (for the Vision 20/40 or Worse population as defined in Section 6.6): having an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA
- Change from baseline in BCVA at post-baseline visits up to Month 6
- Central subfield thickness (CST) 50-micron response at Month 5 (for the Macular Edema population as defined in Section 6.5): having a decrease (improvement) of at least 50 microns from baseline in CST at Month 5
- Change from baseline in central subfield thickness (CST) at Month 5 as measured by optical coherence tomography (OCT)
- Change from baseline in CST at Month 3 as measured by OCT
- Change from baseline in the National Eye Institute (NEI) Visual Functioning Questionnaire-25 (VFQ-25) composite score at Month 5
- Use of rescue therapy before Month 5
- Use of rescue therapy before Month 3

Secondary endpoints assessing long-term efficacy will include the following:

- VH 0 response at each visit after Month 6
- VH 0 or 2-unit response at each visit after Month 6
- VH 0 or 0.5+ response at each visit after Month 6

2.3.4. Safety Endpoints

Safety of DE-109 will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, best-corrected visual acuity (BCVA), optical coherence tomography (OCT), fundus photography (FP), fluorescein angiography (FA), intraocular pressure (IOP), laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, and vital signs.

2.3.5. Exploratory Endpoints

Binary endpoints for best-corrected visual acuity (BCVA) at Month 3 and Month 5 for the Macular Edema population as defined in Section 6.5:

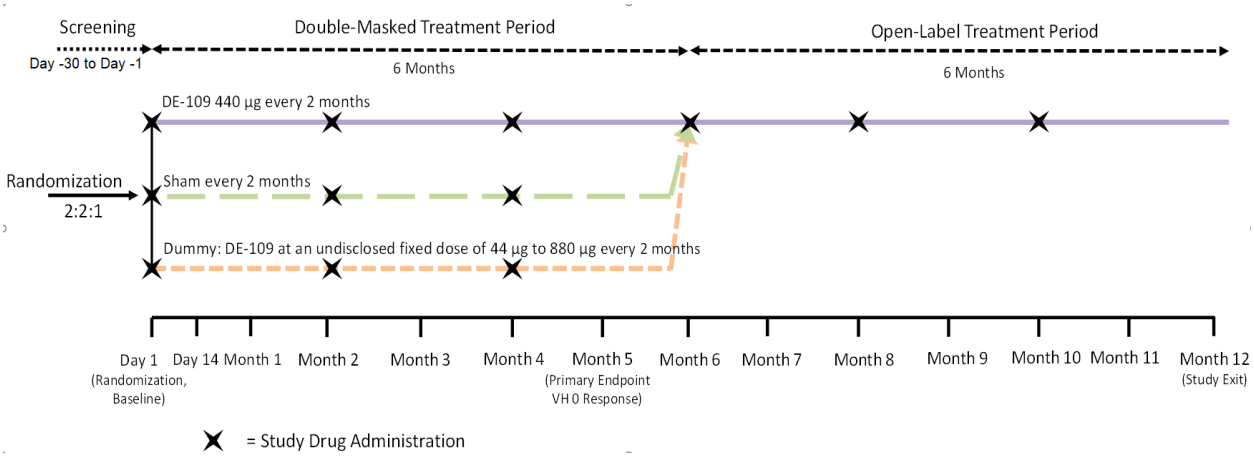
- BCVA x-line response: having an increase (improvement) of at least 5x ETDRS letters, where x = 1 to 3;
- BCVA x-line worsening: having a decrease (worsening of at least 5x ETDRS letters, where x = 1 to 3;
- BCVA maintaining: have a change of > -5 and < 5 EDTRS letters

3. STUDY DESIGN

3.1. General Study Design

This is a Phase III study to assess the efficacy and safety of DE-109 440 µg every 2 months in subjects with active, non-infectious uveitis of the posterior segment of the eye (NIU-PS). The 12-month study consists of a 6-month, randomized, double-masked, parallel design, sham-controlled evaluation of DE-109 440 µg every 2 months followed by a 6-month, open-label period in which all subjects will receive DE-109 440 µg every 2 months (Figure 1).

Figure 1: Study Design Diagram



The study will begin with a 30-day screening period (Day -30 to Day -1) which will be followed by the 6-month double-masked treatment period. In the double-masked period, approximately 200 eligible subjects will be randomized in a 2:2:1 ratio to three arms:

1. **Test arm**: Intravitreal injection of DE-109 440 µg in the study eye(s) every 2 months (Day 1, Month 2, and Month 4) (approximately 80 subjects).
2. **Control arm**: Sham procedure administered to the study eye(s) every 2 months (Day 1, Month 2, and Month 4) (approximately 80 subjects). The sham procedure mimics an intravitreal injection without penetrating the eye (the blunt end of an empty syringe is pressed against an anesthetized eye).
3. **Dummy arm**: Intravitreal injection of DE-109 at an undisclosed, fixed dose (within the range of 44 µg to 880 µg) in the study eye(s) every 2 months (Day 1, Month 2, and Month 4) (approximately 40 subjects). This study arm (which has the same route of administration and frequency as the test arm) is included in the study to help ensure masking of treatment assignments. The dose used in this arm will be chosen from a range of DE-109 doses (44 µg to 880 µg) previously demonstrated to have an acceptable safety profile. The dose in this arm will not vary between participating sites or subjects randomized to this arm.

Subjects completing the Month 6 pre-dose evaluations (the final evaluations in the double-masked period) will begin the open-label period of the study, in which all subjects will receive intravitreal injection of DE-109 440 µg in the study eye(s) every 2 months for an additional 6 months of dosing (i.e., investigational product (IP) injections at Month 6, Month 8, and Month 10 with a final follow-up evaluation at Month 12). The same study eye(s) treated during the double-masked period will be treated during the open-label period. The open-label period of the study will allow evaluation of the long-term (> 6 months and up to one year) efficacy and safety of DE-109 440 µg every 2 months in subjects with NIU-PS.

3.2. Randomization and Masking

For the double-masked period, eligible subjects (total sample size of approximately 200 subjects) will be randomized in a 2:2:1 ratio to the DE-109 440 µg arm (80 subjects), the Sham arm (80 subjects), and the Dummy arm (40 subjects). The randomization will be stratified by baseline systemic (oral) corticosteroid use (yes/no), number of subject's enrolled eyes (1 eye/2 eyes), and region (US/non-US). A separate permuted-block randomization with a fixed block size will be generated for each stratum. A computer algorithm for random number generation will be used to generate the randomization and an IWRS will be used to administer the randomized assignment of subject eyes to treatment arms. Subjects with both eyes enrolled will be assigned to the same treatment arm in both eyes.

The 6-month, comparative period of the study is double-masked and sham-controlled. The sham procedure mimics an intravitreal injection (the blunt end of an empty syringe is pressed against an anesthetized eye). To retain the masking of the investigator, a separate, unmasked investigator will be responsible for administering the IP (DE-109 intravitreal injections and sham). The masked investigator will conduct assessments prior to IP administration; the unmasked investigator will administer the IP and conduct the post-administration assessments. Thus, the treatment assignments will be masked to Santen (except Clinical Supply and Quality Assurance personnel, as required), study subjects, and masked investigators.

The dummy arm is included in the double-masked period of the study to help ensure masking of treatment assignment given the use of a sham control. All subjects randomized to the dummy arm receive intravitreal injections of DE-109 every 2 months at an undisclosed fixed dose of 44µg to 880µg (doses of DE-109 in this range have previously been shown to have an acceptable safety profile). The dose in this arm will not vary between participating sites or subjects randomized to this arm. Except for a limited number of Santen employees in Clinical Supply and Quality Assurance as required, the dose of DE-109 in the dummy arm will remain undisclosed to investigators, CROs, and Santen employees involved in the study conduct.

3.3. Sample Size Planning

Assuming a 30% VH 0 response rate for DE-109 440 µg group and a 12% response rate for the sham treatment group, 160 subjects (80 subjects per arm) is required to achieve 80% power to detect such a difference in response rate between the DE-109 440 µg group and the sham treatment group using the Pearson's Chi-square test (two-sided, $\alpha = 0.05$). Including approximately 40 subjects in the dummy arm, a total of approximately 200 subjects with active NIU-PS will be randomized in a 2:2:1 ratio to DE-109 440 µg, sham, and dummy arms. Because some subjects will contribute two study eyes to this study, the planned sample size of 80 subjects

in both the test (DE-109 440 µg) and control (sham procedure) arms will achieve more than 80% power.

3.4. Visits and Assessments

The schedule of activities (SoA) is provided in Table 1.

Table 1: Table of Activities

	Screening	Double-Masked Period Visits							Open-Label Period Visits					
	Screening (Within 30 days prior to D1; i.e., D -30 to D -1)	**D1 (Baseline)**		**D14**	**M1**	**M2, M4**		**M3**	**M5**	**M6** [a]		**M7, M9, M11**	**M8, M10**		**M12/ Exit/ Early Termination**
Study day		D1		D14	D30	D60, D120		D90	D150	D180		D210, D270, D330	D240, D300		M12: D360
Visit window in days	NA	NA		±2	±3	±3		±3	±3	±7		±7	±7		M12: ±7
IP (DE-109, Sham, Dummy) administration		**x** [b]				**x** [b]				**x**			**x**		
Time relative to IP administration		pre	post			pre	post			pre [a]	post [a]		pre	post	
Signed and dated informed consent	**x** [c]														
Inclusion/exclusion criteria	**x**	**x**													
Medical/surgical history, history of NIU-PS	**x**														
Demographics	**x**														
Physical examination and vital signs	**x**								**x**[d]						**x**
VFQ-25		**x**							**x**[d]						**x**
Serum pregnancy test [e]	**x** [e]														**x** [e]
Urine pregnancy test [e]		**x** [e]				**x** [e]				**x** [e]			**x** [e]		
Laboratory safety tests (hematology, chemistry, urinalysis) [f]	**x** [f]								**x** [d, f]						**x** [f]
Blood sample for pharmacogenomics [g]				**x** [g]											
Time relative to IP administration		pre	post			pre	post			pre [a]	post [a]		pre	post	
Randomization [h]		**x** [h]													

Table 1: Table of Activities (Continued)

	Screening	Double-Masked Period Visits								Open-Label Period Visits					
	Screening (Within 30 days prior to D1; i.e., D -30 to D -1)	**D1 (Baseline)**		**D14**	**M1**	**M2, M4**		**M3**	**M5**	**M6** [a]		**M7, M9, M11**	**M8, M10**		**M12/ Exit/ Early Termina-tion**
Best-corrected visual acuity (ETDRS)	x	x		x	x	x		x	x	x		x	x		x
Slit-lamp biomicroscopy	x	x	x [i]	x	x	x	x [i]	x	x	x	x [i]	x	x	x [i]	x
Intraocular pressure	x	x	x [j]	x	x	x	x [j]	x	x	x	x [j]	x	x	x [j]	x
Indirect ophthalmoscopy	x	x	x [i]	x	x	x	x [i]	x	x	x	x [i]	x	x	x [i]	x
Optical Coherence Tomography		x		x	x	x		x	x	x		x	x		x
Fundus photography	x	x		x	x	x		x	x	x		x	x		x
Fluorescein angiography [k]		x						x	x						x
Systemic corticosteroid medication status	x [l]	x		x	x	x		x	x	x		x	x		x
Other prior or concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prednisolone acetate eye drops [m]			x [m]				x [m]				x [m]			x [m]	
Adverse events [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

IP = Investigational product; NA = not applicable; M=Month; D=Day; pre=prior to IP administration; post = after IP administration.

[a] The double-masked period ends with the pre-dose evaluations at Month 6; the first open-label dose of DE-109 is at Month 6.

[b] On study visits during the double-masked period at which IP is administered, the unmasked investigator will perform the IP preparation and administration.

[c] Signed and dated informed consent form must be obtained prior to conducting any study-related activities.

[d] If physical examination and vital signs, VFQ-25 and/or laboratory safety tests were performed at Month 3 under a previous version of the protocol these assessments do not need to be performed at Month 5.

[e] Serum and urine pregnancy tests are to be performed on all females of child-bearing potential. Urine pregnancy test (hCG) is to be performed prior to each IP administration. A positive pregnancy test at screening or Day 1 (Baseline) requires exclusion from the study. At subsequent visits, a positive urine pregnancy test requires immediate discontinuation from the study. Pregnancy is an event of special interest and requires follow-up by Santen until the outcome is known.

[f] At Month 5 subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests. At Screening, and Month 12/Exit/Early termination visit, lipid may be obtained in the fasting or non-fasting state.

[g] This is only applicable if the subject has consented to collection of blood for pharmacogenomics (approximately 10 mL of blood). This sample should be collected at the Day 14 visit, but may be collected at any time during the study or at a separate post study visit, if necessary.

[h] Refer to Section 8.1.3 of the protocol for assessments and requirements prior to randomization.

[i] After IP administration, slit-lamp biomicroscopy is performed first and then indirect ophthalmoscopy, in both eyes within 30 minutes of IP administration.

[j] Intraocular pressure (IOP) is measured in both eyes at approximately 40 ± 10 minutes after IP administration. If IOP is increased ≥10 mmHg 40±10 minutes after IP administration compared to prior to IP administration, administer topical IOP lowering medication for use until the subject returns for follow-up per the investigator's discretion. (An unscheduled visit may apply). IOP increase of ≥10 mmHg at any visit compare to the Baseline (Day 1) assessment should be reported as an AE.

[k] Any required blood or urine sample is to be collected before injection of fluorescein.

[l] Subjects receiving systemic (oral) corticosteroid therapy will be required to titrate the dose as needed such that they remain on a stable prednisone-equivalent dose between ≥15 mg/day and ≤40 mg/day that has remained stable for at least 1 week (7 days) prior to and including on Day 1.

[m] Prednisolone acetate eye drops are to be started after each IP administration and continued for 8 days, according to the following schedule: 4 times per day for 4 days (including the day of IP administration) followed by 2 times per day for 4 days, then stop.

[n] Adverse events (AE) will be recorded starting after the signing of the informed consent form. During the double-masked period, regardless of the source of the reported occurrence of an AE in a subject, the masked investigator will assess the causality of the AE.

4. TIME-RELATED TERMS

4.1. Baseline Visit

The *Baseline Visit* is the visit when a randomized subject receives the first administration of an investigational product (IP) (either an injection of DE-109 or a sham procedure).

4.2. Injection Visit

The injection visit is defined as the visit at which a subject received an investigational product (IP) in the study eye. Note that if a subject did not receive any IPs at a visit where an administration of IP was scheduled per protocol, the visit will not be considered an injection visit for the subject. In the LUMINA study, Day 1, Months 2, 4, 6, 8, and 10 visits may be injection visits

4.3. Study Day and Analysis Visit

The *study day* describes the relative day of an observation starting with the reference date designated as Study Day 1. In this study, the reference date is the baseline visit date. Thus, the study day will be calculated as:

- For a pre-baseline date, Study Day = Date – Baseline Visit Date
- For a post-baseline date, Study Day = Date – Baseline Visit Date + 1

Analysis visit is a timing variable to be used for analyses involving visits. For this study, the analysis visit is the same as the nominal visit.

4.4. Treatment Period, Treatment Start Date, and Treatment End Date

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

Treatment Period	Treatment Start Date	Treatment End Date
Double-Masked (DM) Treatment Period	The date at which a randomized subject received the first injection of DE-109 or the first Sham procedure	The date of the last double-masked injection of DE-109 + 120 days, the date of the first injection of the open-label DE-109 440 µg, or the Study Exit date, whichever came first
Open-Label (OL) Treatment Period	The date of the first open-label injection of DE-109 440 µg	The date of the last open-label injection of DE-109 440 µg + 120 days, or the Study Exit date, whichever came earlier
Entire Study	The date at which a randomized subject received the first injection of DE-109 or the first Sham procedure	The date of the last open-label injection of DE-109 440 µg + 120 days, or the Study Exit date, whichever came earlier

4.5. Treatment Exposure

The treatment exposure to DE-109 will be reflected by the number of injections received. The treatment exposure to Sham will be the number of administered Sham procedures.

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

Details in covariates to be included in the statistical model for each individual statistical analysis are provided in Section 8.

5.2. Handling of Missing Data

5.2.1. Efficacy Measures

For the analysis of VH 0 response at Month 5 (primary endpoint) and at Month 3 (key secondary endpoint), study eyes will be treated as non-responders if they meet at least one of the following criteria:

1. A study eye is rescued due to the protocol-specified worsening of uveitis (Section 8.1.6)
2. A subject discontinued from the study due to lack of efficacy or adverse events
3. A study eye meets the protocol-specified worsening of uveitis rescue criteria (Section 8.1.6) regardless whether the eye received any rescue therapies

Study eyes which were rescued due to worsening of uveitis specified under previous protocol versions but did not meet the rescue criteria under the current version will be treated as rescued due to other reasons and censored the data after being rescued. The multiple imputation-based approach (Section 8.2.1) will be applied to impute missing VH score data of study eyes which

were not rescued and treated as non-responders. The VH 0 response status will then be determined based on the observed or imputed VH score.

The same approach will be applied to the inferential analyses of other VH response endpoints.

For the analysis of composite score (at Month 3 and at Month 5), study eyes with missing VH score at a given visit will be assigned with a score of 0, unless the study eyes got rescued due to protocol-specified worsening of uveitis or corresponding subjects discontinued the study due to adverse events or lack of efficacy (in this case, the score will be -1).

For the analysis of corticosteroid tapering success on the Intent-to-Taper population, study eyes rescued before Month 5/Month 3 will be treated as corticosteroid tapering failures. The Last-Observed-Carried-Forward (LOCF) approach will be applied to impute missing data of study eyes not rescued before Month 5/Month 3, i.e., the missing overall prednisone-equivalent dose at Month 5/Month 3 will be imputed by last derived overall dose. The tapering status at Month 5/Month 3 will then be determined based on the derived or imputed overall dose.

No imputation is needed for the analysis of the binary endpoint "use of rescue therapy before Month 5/Month 3".

To assess the impact of missing data on the primary analysis results for VH 0 response at Month 5, the following imputation approaches will be applied to some sensitivity analyses:

- The LOCF approach for any FAS study eyes with missing VH score at Month 5
- Treatment policy approach: The primary analysis will be performed on FAS study eyes regardless whether they get rescued. That is, no censoring of observed VH score after a rescue will be implemented. Other missing VH scores will be imputed with multiple imputation-based approach.

For analyses of "change from baseline in central subfield thickness at Month 5 as measured by OCT" and "change from baseline in the NEI VFQ-25 composite score at Month 5", the LOCF approach will be applied for any FAS study eyes with missing score at Month 5.

"Change from baseline in VH score at post-baseline visits up to Month 6" and "change from baseline in BCVA at post-baseline up to Month 6" will be analyzed using the mixed-effects model for repeated measures (MMRM) on observed cases. No imputation of missing data will be needed.

Subgroup analyses of all binary endpoints will employ the same imputation approach for the primary analysis of that endpoint. Other descriptive efficacy summaries will be based on observed data, unless otherwise specified.

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 or *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.
- If the duration of event is needed, the following approach may be considered:

- If *year* (or resolution date is completely missing): do not impute
- If *year* is not missing but *month* and *day* are missing: impute the last day of the *year*
- If *year* and *day* are not missing but *month* is missing: impute the last month of the *year* for the missing *month*
- If *year* and *month* are not missing but *day* is missing: impute the last day of the *month* of the *year*

5.3. Multi-Center Studies

This is a multicenter study with approximately 72 centers, among which a maximum of 35 centers are planned to be outside of the United States. The number of subjects per site might be small. Therefore, there are no analyses adjusting for sites.

5.4. Multiple Comparisons / Multiplicity

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

A. Conduct the statistical testing for the primary comparison between DE-109 440 µg and Sham treatment arm on the primary endpoint (VH 0 response) at the significance level of 0.05 (two-sided)

B. If the result of the primary comparison on the primary endpoint is positive (i.e., *p*-value < 0.05), then conduct the statistical testing for the primary comparison between DE-109 440 µg and Sham treatment arm on the following key secondary endpoints in a hierarchical fashion:

    1. Mean composite score at Month 5
    2. VH 0 response at Month 3
    3. Mean composite score at Month 3

    The primary comparison on the $(i+1)^{th}$ key secondary endpoint will be performed inferentially ONLY IF the result of the primary comparison in the i^{th} key secondary endpoint is positive, where i = 1 or 2.

5.5. Interim Analysis and Data monitoring Committee

An independent data monitoring committee (DMC) whose members will not be participating in the LUMINA study conduct will serve as an advisory board to the Santen senior management team. The DMC will periodically review and make recommendations based on interim data; unmasked data will only be reviewed in closed DMC sessions without participation of Santen personnel. The organization, responsibilities, and procedures of the DMC will be specified in a governing charter.

An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. The DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will

receive information about interim results only if they need to know for the safety of their patients.

5.5.1. Interim Analysis

The objectives of the interim analysis are to assess for futility and to re-assess the sample size. No analyses are planned for the purpose of stopping the study early for efficacy. The futility and sample size re-assessment are based on evaluation of conditional power in relationship to pre-specified decision rules defined by ranges of attainable conditional power values under the "promising zone" approach (Mehta et al., 2011). If the conditional power is less than 30%, futility will be recommended and the study may stop for futility. If the conditional power is between 50% and 80%, the sample size will be increased up to 100 extra subjects. If the conditional power between 30% and 50% or greater than 80%, no change to the sample size will take place.

The futility and sample size re-assessment analysis will be evaluated for the primary endpoint, vitreous haze (VH) 0 response at Month 5 based on subjects who were randomized, received at least one dose of IP at baseline, and reached or completed Month 3 visit of the study. Missing VH status at the interim analysis will be handled using the multiple imputation approach in the similar manner as specified in Section 8.2.1. However, only number of enrolled eye will be used as the stratification factor in the Cochran-Mantel-Haenszel (CMH) test procedure (Yu et al., 2020).

The conditional power at the interim analysis, denoted by $\mathrm{CP}_{\widehat{\delta_1}}(z_1, \widetilde{n_2})$, can be defined by the following equation (Mehta et al., 2011):

$$\mathrm{CP}_{\widehat{\delta_1}}(z_1, \widetilde{n_2}) = 1 - \Phi\left(\frac{z_{\alpha/2}\sqrt{n_2} - z_1\sqrt{n_1}}{\sqrt{\widetilde{n_2}}} - \frac{z_1\sqrt{\widetilde{n_2}}}{\sqrt{n_1}}\right)$$

where n_1 is the number of evaluable subjects at the interim analysis, n_2 is the total number of subjects at the final analysis, $\widetilde{n_2} = n_2 - n_1$, $z_{\alpha/2} = \Phi^{-1}(1 - \alpha/2)$, and z_1 is the squared root of the CMH test statistic as computed at the interim analysis of n_1 evaluable subjects. Define the estimated treatment difference, $\widehat{\delta_1} = \hat{\pi}_{440} - \hat{\pi}_{\text{sham}}$ at interim analysis, where $\hat{\pi}_{440}$ and $\hat{\pi}_{\text{sham}}$ are Mantel-Haenszel weighted response rates of DE-109 440 µg and Sham arms at interim analysis, respectively.

The primary analysis of this study is the analysis of the data from the 6-month, double-masked period. These data will be quality-checked, soft-locked, and the analysis for double-masked period will be conducted after all subjects have completed the Month 6 visit or prematurely discontinued from the study prior to Month 6.

6. STUDY POPULATION

6.1. Safety Population

For analyses of ocular adverse events (AEs) and safety parameters assessed per eye, the Safety population will consist of all study eyes which received at least one administration of investigational product (IP) and study eyes will be classified by the actual treatment received. For analyses of non-ocular AEs and safety parameters assessed per subject, the Safety population will consist of all subjects which received at least one administration of IP and subjects will be classified by the actual treatment received.

6.2. Full Analysis Set

The Full Analysis Set (FAS) will consist of all study eyes that are randomized and received at least one administration of study treatment. The efficacy analyses will be performed using the FAS and study eyes will be classified by the randomized treatment assignment, irrespective of the actual treatment received. For analyses of other parameters assessed per subject, the FAS population will consist of all subjects whose study eye(s) are randomized and received at least one IP administration and subjects will be classified by the planned treatment assignment.

6.3. Per-Protocol Population

The Per-Protocol (PP) Population will be a subset of the FAS population. The PP population will be the analysis population for sensitivity analyses and will use treatment as randomized. Any study eye affected by a significant protocol deviation (such that the outcome to treatment could be altered) will be excluded from the PP Population. In addition, any study eye without the Month 5 VH score will be excluded from the PP Population.

Before database lock and the unmasking of treatment assignments, Santen's study team will review all protocol deviations, identify study eyes with any protocol deviation that could impact the efficacy outcome, and determine whether or not to exclude the study eye from the PP population.

When data are presented at the subject level, PP Population is referred to subjects who have all of their study eyes qualified for the PP Population.

6.4. Intent-to-Taper Population

The Intent-to-Taper population will be a subset of the FAS population, consisting of study eyes from subjects who were taking systemic (oral) corticosteroids at a stable prednisone-equivalent dose between ≥15 mg/day and ≤40 mg/day for at least 1 week (7 days) prior to and including on Day 1. The Intent-to-Taper population will be used for the analysis of tapering success performed using eyes as randomized.

When data are presented at the subject level, Intent-to-Taper Population is also referred to subjects who have their study eye(s) qualified for the Intent-to-Taper Population.

6.5. Macular Edema Population

The Macular Edema population will be a subset of the FAS population and will consist of study eyes with central subfield thickness (CST) ≥ 300 microns at baseline. It will be the analysis population for the analysis of CST 50-micron response to be performed with study eyes classified by randomized treatment assignments.

When data are presented at the subject level, Macular Edema Population is also referred to subjects who have at least one of their study eyes qualified for the Macular Edema Population.

6.6. Vision 20/40 or Worse Population

The Vision 20/40 or Worse population will be a subset of the FAS population and will consist of study eyes with BCVA ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse) at baseline. It will be the analysis population for the analysis of BCVA 3-line response to be performed with study eye classified by randomized treatment assignments.

When data are presented at the subject level, Vision 20/40 or Worse Population is also referred to subjects who have at least one of their study eyes qualified for the Vision 20/40 or Worse Population.

6.7. Open-Label Safety Population

The Open-Label Safety population will include all Safety subjects who received at least one open-label injection of the DE-109 440 µg. It will be the analysis population for safety analyses for the Open-Label analysis period to be performed with subjects as treated.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject and Study Eye Disposition

The subject and study eye disposition of FAS population will be summarized by treatment period (double-masked and open-label) and by planned treatment assignments (for double-masked period) and overall.

The FAS and the FAS subsets including the PP Population, Intent-to-Taper Population, Vision 20/40 or Worse Population, and Macular Edema Population, Safety Population, subjects who were taking systemic corticosteroid at baseline, and subjects who completed vitreous haze (VH) assessment at Month 3, Month 5, Month 6, and Month 12 will be tabulated at the subject level. In addition, subjects who discontinued the study before Month 3, Month 5, Month 6, and Month 12 will be tabulated separately by the primary discontinuation reason. Subjects whose study eye(s) are in the FAS will also be summarized by country.

7.2. Demographics and Baseline Characteristics

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

- Age at randomization (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)
- Study eye (categorical: OD, OS, or OU)
- Laterality of uveitis (bilateral or unilateral)
- Overall prednisone-equivalent dose (mg/day) for subjects whose study eye(s) are in the Intent-to-Taper population

Baseline characteristics will also be descriptively summarized for eye-level FAS by number of enrolled eyes. The following variables will be summarized:

- Baseline VH score for the study eye and the fellow eye
- Anatomic location of uveitis of the study eye (intermediate, posterior, intermediate + posterior, or panuveitis)
- Etiology of uveitis of the study eye
- Duration of uveitis of the study eye in months derived as [Day 1 Visit Date – Uveitis Onset Date (observed or imputed)]/30. Partially missing uveitis onset dates, if any, will be imputed using the approach specified in Section 5.2.3.
- Baseline BCVA of the study eye for
  - FAS population

  - Vision 20/40 or Worse population
- Baseline CST of the study eye for
  - FAS population
  - Macular Edema population

Other baseline characteristic variables may be summarized as suggested by the data.

7.3. Medical and Surgical History

For this study, medical history (i.e., medical events) will be coded using MedDRA 23.1, 2020 and summarized for the FAS population. Each medical event will be classified into a system organ class (SOC) and mapped to a preferred term (PT).

Subjects reporting any medical history events will be tabulated by SOC and preferred term specified in MedDRA for each planned double-masked treatment assignment and overall. In addition, subjects reporting any medical history events ongoing at baseline, any medical history events in study eyes that are linked to SOC *Eye disorders,* and any medical history events ongoing at baseline in study eyes that are linked to SOC *Eye disorders* will also be tabulated. Any subject with more than one medical and/or surgical term within the same SOC (or mapped to the same preferred term) will be counted only once for that SOC (or preferred term).

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Informed Consent
- Inclusion/Exclusion Criteria
- Study Drug
- Protocol Procedures/Safety
- Endpoint Data
- Visit Window
- Prohibited Med/Procedures
- 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 first administration of study treatment. *Concomitant medication* for an analysis period is defined as any non-study medication taken concurrently with the study medication during that analysis period.

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

Treatment compliance will be summarized only for the Double-Masked analysis period. For each subject in the Full Analysis Set (FAS), the treatment compliance at Day 1, Month 2, and Month 4 will be considered achieved if: 1) subject received an administration of study medication in the study eye ('Yes' to the eCRF question "Has the study eye been injected?"), and 2) the dose actually received was the planned dose. A subject will be considered fully compliant with double-masked treatment if the treatment compliance was achieved at all scheduled injection visits, up to Month 4 or Study Exit, which ever came earlier.

The treatment compliance will be summarized for the FAS population by planned Double-Masked treatment and overall. The treatment compliance statuses will also be listed by planned Double-Masked treatment, subject ID, and visit.

7.8. Treatment Exposure

The treatment exposure to DE-109 will be reflected by the number of injections received. The treatment exposure to Sham will be the number of administered Sham procedures. For the Double-Masked analysis period, Safety Population study eyes will be tabulated by the number of injections (1, 2, and 3) for each actual Double-Masked treatment and overall. The numbers of injections received during the Double-Masked, Open-Label, and the Entire Study analysis periods will also be listed for the Safety Population.

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 an investigational product (IP) at baseline (Day 1). For subjects who enrolled both eyes in the study and both eyes received IPs at baseline (Day 1), both of their eyes will be considered as study eyes. Number of enrolled study eyes for each subject is defined as the number of eyes that received an IP administration at baseline (Day 1).

For subjects who enrolled one eye in the study, the other eye which did not receive an IP at baseline (Day 1) will be the non-study eye, or *fellow eye*. In a case when a subject enrolled in the study with both eyes eligible but only one of his/her eyes received an IP during the Double-Masked period, the eye which received an IP will be considered study eye, the eye which did not received any IPs will be considered fellow eye.

8.1.2. Baseline Score

For any measure, the *baseline score* is the last observed measurement prior to the first administration of the IP.

8.1.3. Change and Percent Change from Baseline

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

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

8.1.4. Change after Injection

For any measure assessed pre and post administration of an IP at injection visits, the *change after injection* at an injection visit will be derived as:

- Change after injection = (Post-Administration score) – (Pre-Administration score)

If multiple pre-injection or post-injection scores were collected at an injection visit, then the score closest to the injection time will be used to derived the change after injection variable.

8.1.5. Efficacy Measures

Table 2 lists all the efficacy measures that were evaluated in LUMINA study.

Table 2: Efficacy Measures

Efficacy measure	Note
Vitreous haze (VH)	VH was graded using the modified SUN scale as 0, 0.5+, 1+, 1.5+, 2+, 3+, or 4+. A decrease in VH score indicates improvement in the vitreous inflammation.
Overall prednisone-equivalent dose	The overall prednisone-equivalent dose (mg/day) of all eligible systemic corticosteroids in each day
Best-corrected visual acuity (BCVA)	BCVA measures the acuteness or clearness of best-corrected vision, with a range of [0, 110] in ETDRS letters. An increase in BCVA indicates improvement in the best-corrected vision. A 5-letter difference in visual acuity is equivalent to one Snellen line. A BCVA score of 85 ETDRS letters is equivalent to 20/20 vision, which is considered normal vision.
Central Subfield Thickness (CST)	For each eye, the CST was measured using Optical Coherence Tomography (OCT). OCT was performed using reading center certified photographers, equipment, and standardized protocols.
NEI VFQ-25: Composite score and 12 subscales (General Health, General Vision, Ocular Pain, Near Activities, Distance Activities, Vision-Specific Social Functioning, Vision-Specific Mental Health, Vision-Specific Role Difficulties, Vision-Specific Dependency, Driving, Color Vision, Peripheral Vision)	As shown in Appendix A, each NEI VFQ item was recorded to a 0-100 scale. The composite score and subscales will be derived based on the recorded items. An increase in the NEI VFQ-25 composite score or subscale indicates improvement in certain visual function. Note that the 39-item NEI VFQ (VFQ-25 + optional items) conducted at the US sites will be used to derive the VFQ-25 composite score and subscales (double-check).

8.1.6. Rescue Therapy

Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS, other than intravitreal DE-109.

- Systemic corticosteroid therapy (except during the tapering window)
- New systemic treatment with an immunosuppressant agent
- Increase in dose of ongoing therapy with methotrexate, azathioprine, or mycophenolate mofetil (or an equivalent drug, e.g., mycophenolic acid)
- Anti-vascular endothelial growth factor therapy (anti-VEGF)
- New or increased dose/frequency of topical ocular corticosteroid to the study eye
- New or increased dose/frequency of topical ocular nonsteroidal anti-inflammatory agent to the study eye
- Ocular or periocular corticosteroid injection to the study eye

- Use of difluprednate ophthalmic emulsion eye drops in the study eye
- Vitrectomy in the study eye

Other protocol-allowed or specified medications that are not considered rescue therapy are listed as follows:

- Investigational product (DE-109, Sham, Dummy).
- Oral corticosteroids administered in accordance with the protocol-specified tapering schedule (refer to Protocol Section 6.5.3).
- Ongoing stable dose/frequency of corticosteroid eye drops is permitted (exception of difluprednate), non-steroidal anti-inflammatory eye drops, methotrexate, azathioprine, or mycophenolate mofetil are allowed by the protocol.
- The protocol-specified administration of prednisolone acetate eye drops following each IP administration.

Rescue therapies will be performed when worsening of uveitis in the study eye is observed satisfying one or more of the following three rescue criteria:

1. Worsening of uveitis in the study eye as indicated by at lease a 2-step increase in VH score (i.e., 0 to ≥2+, 0.5+ to ≥3+, 1+ to ≥3+, 1.5+ to ≥4+, or 2+ to ≥4+) as compared to the baseline (Day 1) VH score or the best achieved VH score post baseline.
2. Severe deterioration of vision in the study eye due to worsening of uveitis that is indicated by at least doubling of the visual angle (BCVA loss of 3 or more lines [≥15 ETDRS letters]) as compared to baseline (Day 1) BCVA.
3. New or worsening retinal or choroidal uveitic lesion(s) in the study eye determined by clinical examination, as compared to baseline.

These three above criteria are generally referred to as *protocol-specified rescue criteria.*

When subjects got rescued when deemed medically necessary even if none of the protocol-specified rescue criteria were satisfied, all of the reasons will be pooled together and referred to as *Other* rescue criterion. Further breakdown of reasons under the "Other" category might be performed if deemed necessary.

8.1.7. Response Endpoint and Response Rate

Three VH response endpoints will be evaluate at Month 3, Month 5, Month 6, and at each visit after Month 6 in this study. VH response endpoints are defined as follows:

- VH 0 response: having a VH score of 0 (modified SUN scale). Study eyes which met this criterion are called *VH 0 responders*.
- VH 0 response: having a VH score of 0 or 0.5+ (modified SUN scale). Study eyes which met this criterion are called *VH 0 or 0.5+ responders*.
- VH 0 response: having a VH score of 0 or a decrease (improvement0 of at least 2 units from baseline in VH score (modified SUN scale). Study eyes which met this criterion are called *VH 0 or 2-unit responders*.

For response endpoints at Month 6 and at visits of the Open-Label analysis period, subjects who were rescued before the visit when the endpoint is evaluated will be treated as non-responders. The response rate will be estimated as the proportion of responders in the corresponding treatment group.

8.1.8. Intent-to-Taper Subject and Corticosteroid Tapering Success

Subjects who were taking systemic (oral) corticosteroid(s) at baseline (Day 1) with the overall prednisone-equivalent dose between 15 mg/day and 40 mg/day are called *Intent-to-Taper* subjects. An Intent-to-Taper study eye will be considered a corticosteroid taper success if the corresponding subject's overall prednisone-equivalent dose was tapered off to 0 mg/day and the study eye achieved VH score of 0 at Month 5. Intent-to-Taper study eyes which were rescued before Month 5 will be treated as corticosteroid tapering failures.

The *tapering success rate* will be estimated as the proportion of corticosteroid tapering successes among Intent-to-Taper study eyes in the corresponding treatment group.

8.1.9. Best-corrected Visual Acuity Response

The BCVA response endpoint is defined as a study eye having an increase (improvement) of at least 15 ETDRS letters (i.e., 3 lines) at Month 5. The BCVA response endpoint will be summarized for Vision 20/40 or Worse Population.

8.1.10. Central Subfield Thickness Response

In the study, subjects with the CST in the study eye ≥ 300 microns at baseline (Day 1) are called macular edema subjects. CST 50-micron response is defined for macular edema subjects as having a decrease (improvement) of at least 50 microns in CST at Month 5.

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, VH 0 response, is defined as having a VH score of 0 at Month 5 (modified SUN scale). For the primary endpoint, the VH 0 response rate will be evaluated in accordance with the following null (versus alternative) hypothesis:

$$\mathrm{H}_0: \pi_{\mathrm{sham}} = \pi_{440}$$

versus

$$\mathrm{H}_A: \pi_{\mathrm{sham}} \neq \pi_{440}$$

where π_{sham} and π_{440} denote the response rate for sham and 440 µg DE-109, respectively.

The Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic (Yu et al., 2020), stratified by pooled strata based on the number of enrolled eyes from a subject (one eye or two eyes), baseline systemic (oral) corticosteroid use (yes or no), and region (US or non-US). Such pooling is needed to avoid the situation where subjects in too small strata might all have the same responses (either success or failure); hence, do not contribute to the test. To guarantee that

a pooled stratum has at least one success and one failure, the pooling algorithm will be performed as follows:

- Determine the number of subjects in each stratum, defined by crossing the number of enrolled eyes, baseline systemic corticosteroid use, and region.
- Within each combination of number of enrolled eyes and region, if one or both strata, stratified by corticosteroid use, have less than 25 subjects, then those strata will be pooled.
- Within each stratification factor level based on number of enrolled eyes, if at least one of (pooled/unpooled) strata have less than 25 subjects, then those strata will be pooled together.

The pooling algorithm will be performed based on the available data prior to the unmasking of the randomization. At the interim analysis, only number of enrolled eyes will be used as the stratification factor.

Study eyes will be treated as non-responders if they meet at least one of the following criteria:

1. A study eye is rescued due to the protocol-specified worsening of uveitis (Section 8.1.6)
2. A subject discontinued from the study due to lack of efficacy or adverse events
3. A study eye meets the protocol-specified worsening of uveitis rescue criteria (Section 8.1.6) regardless whether the eye received any rescue therapies

Study eyes which were rescued due to worsening of uveitis specified under previous protocol version but did not meet the rescue criteria under the current version will be treated as rescued due to other reason and censored the data after being rescued. The multiple imputation-based approach will be applied to impute missing VH score data of study eyes which were not rescued and treated as non-responders. The VH 0 response status will then be determined based on the observed or imputed VH score.

For missing VH score due to any other reasons other than protocol-specified worsening of uveitis, the multiple imputation approach will be applied as follows:

1. Use Markov chain Monte Carlo (MCMC) to create monotone missingness first with VH score on the logarithm scale. Then obtain standard multiple imputations under MAR assumptions for missing VH scores using monotone regression on the logarithm scale. The imputed values will be then converted into an eligible VH score based on the absolute distance. The missing data are filled in and 50 complete datasets are created. The seed that will be used in the SAS program is 135711.
2. Each of 50 complete datasets will then be analyzed separately. The CMH test statistic, response rate for each treatment group, and the rate difference will be calculated for each complete sets.
3. The final CMH test statistic, obtained from each complete dataset, will be transformed using Wilson-Hilferty transformation and combined for inference purposes (O'Kelly et al., 2014). Rates and rate differences will also be combined without any transformations.

The Mantel-Haenszel weighted response rate (%) of each treatment group, the Mantel-Haenszel weighted rate difference, the corresponding asymptotic 95% confidence interval (CI) and the CMH's p-value will be reported.

The main part of the SAS code for the specified CMH test procedure and the multiple imputation are provided in Appendix C, respectively.

8.2.2. Sensitivity Analyses

The following sensitivity analyses will be performed to assess the robustness of the results from the primary analysis:

- The primary analysis will be repeated on the PP Population.
- The CHM test stratified by the same pooled strata as in the primary analysis will be performed on the FAS population the missing data due to other reasons handled using the Last-Observation-Carried-Forward (LOCF) approach. Subjects who were rescued due to the protocol-specified worsening of uveitis or discontinued from the study due to lack of efficacy or adverse events prior to Month 5 will be treated as non-responders.
- Treatment policy strategy: The CHM test stratified by the same pooled strata as in the primary analysis will be performed on the FAS population regardless whether study eyes get rescued. The missing VH score will be imputed using multiple-imputation approach in the similar manner as described in Section 8.2.1.
- A generalized estimating equation (GEE) method will be used on observed cases up to Month 6 using identity link function. The GEE might be applied on the imputed data (via the same imputation approach as in primary analysis) if there are considerable large amount of missingness. The model will include pooled geographic region (US vs non-US), baseline VH score of the study eye (1.5+, 2+, '3+ or 4+'), treatment, visit, and treatment-by-visit as explanatory variables. An unstructured (UN) correlation structure will be used to model the correlation of the responses from subjects. For subjects rescued before Month 6, all VH scores of study eye collected after the start date of rescue therapy will be excluded from the analysis.
- If the UN correlation structure fails to converge, then an exchangeable (EXCH) correlation structure will be used to model the correlation. If the EXCH model fails to converge, then the independent model will be used.
- Multiple imputation with tipping point analysis will be performed to assess the impact of missing data on the primary analysis results. The following steps will be performed to generate different possible imputation scenarios:
  - Use Markov chain Monte Carlo (MCMC) to create monotone missingness first with VH score on the logarithm scale. Then obtain standard multiple imputations under MAR assumptions for missing VH scores using monotone regression on the logarithm scale. The missing data are filled in and 50 complete datasets are created. The seed that will be used in the SAS program is 135711.

- The imputed values for the treatment group will be added a different amount of 0.05, 0.10, 0.15, 0.20, and 0.25. The newly derived imputed values will be then converted into a eligible VH score based on the absolute distance.
- For each possible imputed scenario (associated with different added amounts), the primary analysis will be repeated and the p-values as well as the response rates will be obtained to determine whether the outcome under the scenario is positive or negative. The larger the added amount that required to reverse the conclusion of the primary analysis, the more robust the conclusion is considered to be.

No multiplicity adjustment will be made to these sensitivity analyses.

8.2.3. Analyses of Key Secondary Efficacy Endpoints

The following key secondary endpoints will be analyzed:

- Composite score at Month 5
- VH 0 response rate at Month 3
- Composite score at Month 3

All the key secondary endpoints will be analyzed using CMH test in the similar manner as the primary endpoint analysis. Study eyes with missing VH score at a given visit will be assigned with a score of 0 in the composite score system. For each composite score analysis, the raw mean score, Mantel-Haenszel weighted mean score, corresponding mean difference, its asymptotic 95% confidence interval, and p-values will be reported.

8.2.4. Analyses of Secondary Efficacy Endpoints

8.2.4.1. Analyses of Binary Secondary Endpoints

All binary secondary VH response endpoints and use of rescue therapy before Month 5 will be analyzed on the FAS using similar approach to the primary analysis.

For each of these binary endpoints, the frequency (n) and percent (%) of each treatment group will be reported. The Mantel-Haenszel weighted rates and rate difference and it 95% CI will also be reported.

BCVA binary endpoint defined in Section 8.1.9 will be descriptively summarized on observed cases for the Vision 20/40 or Worse Population. CST binary endpoint defined in Section 8.1.10 will be descriptively summarized on observed cases for the Macular Edema Population.

8.2.4.2. Analyses of Continuous Secondary Endpoints

The following secondary endpoints will be analyzed using MMRM on observed cases up to Month 6:

- Change from baseline in VH score at a post-baseline visit up to Month 6
- Change from baseline in BCVA score at a post-baseline visit up to Month 6

For the analysis of change from baseline in VH score, the MMRM model will include country (US or non-US), baseline systemic (oral) corticosteroid use status, study eye, treatment, visit, and

treatment-by-visit as fixed effects, baseline VH score and baseline-by-visit as covariates. Correlations of change from baseline in VH score due to eyes and study visits within a subject will be modeled using a direct product structure, which is constructed by taking the Kronecker product of an unstructured matrix (modeling the correlation across study eyes) and an unstructure matrix (modeling the correlation across study visits). For subjects rescued before Month 6, all VH scores of the study eye collected after the start date of rescue therapy will be excluded from the analysis.

For the analysis of change from baseline in BCVA score, the MMRM model will include country (US or non-US), baseline systemic (oral) corticosteroid use status, baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+'), study eye, treatment, visit, and treatment-by-visit as fixed effects, baseline BCVA score and baseline-by-visit as covariates. Correlations of change from baseline in BCVA due to eyes and study visits within a subject will be modeled using a direct product structure, which is constructed by taking the Kronecker product of an unstructured matrix (modeling the correlation across study eyes) and an unstructure matrix (modeling the correlation across study visits). For subjects rescued before Month 6, all BCVA of the study eye collected after the start date of rescue therapy will be excluded from the analysis.

For each MMRM model, the denominator degrees of freedom for fixed effects will be estimated using the Kenward-Roger approximation (Kenward et al., 1997). An unstructured (UN) covariance matrix will be used to model the within-subject correlation due to study eyes and study visits. If the UN model fails to converge, then an autoregressive of order 1 (AR(1)) covariance matrix will be used to model the within-subject correlation due to study visits while study eye-related within-subject correlation structure remains unchanges. If the AR(1) model fails to converge, then the compound symmetry model will be used.

The following secondary endpoints will be analyzed using the analysis of covariance (ANCOVA) with missing data at Month 5 being imputed by the LOCF approach:

- Change from baseline in CST at Month 5 as measured by OCT
- Change from baseline in the NEI VFQ-25 composite score and subscales at Month 5

For the analysis of change from baseline in CST at Month 5, the ANCOVA model will include study eye, country (US or non-US), baseline systemic (oral) corticosteroid use status, and treatment as factors and baseline CST score as a covariate. Correlations of change from baseline in CST within a subject due to eyes will be modeled using UN structure.

For the analysis of changes from baseline in the NEI VFQ-25 composite score and subscales at Month 5, the ANCOVA model will include country (US or non-US), baseline systemic (oral) corticosteroid use status, baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+') or the worse study eye (i.e., higher VH score) for subjects who enrolled both eyes, number of enrolled study eyes, and treatment as factors and baseline VFQ-25 score as a covariate.

For each of these continuous endpoints, the least squares (LS) mean change from baseline of each DE-109 group with its standard error will be reported. For each treatment comparison, the LS mean difference with the 95% CI will be reported.

8.3. Subgroup Analyses

The homogeneity of treatment effects among prospectively defined subgroups will be assessed via descriptive statistics of VH 0 response rate, including Mantel-Haenszel weighted rates and rate difference and it 95% CI, by the number of treated eyes for the following subgroups:

- Age (< 65 or ≥ 65 years)
- Sex (males or females)
- Race (White or non-White)
- Country (US or non-US)
- Baseline VH score of the study eye (1.5+, 2+, or '3+ or 4+')
- Anatomic location of uveitis of study eye at baseline (intermediate, posterior, intermediate + posterior, or panuveitis)
- Intent-to-taper status at baseline (yes or no)
- Mean diurnal IOP at baseline (< 25 or ≥ 25 mmHg)
- Baseline BCVA score of the study eye (≤70 letters or >70 letters)
- Baseline BCVA score of the study eye (≤65 letters or >65 letters)
- Presence of macular edema in the study eye at baseline (yes [CST ≥ 300 microns] or no [CST < 300 microns])

Similarly, subgroup analyses will also be performed for the composite score. Other subgroup analyses may be performed as deemed necessary.

8.4. Exploratory Analyses

8.4.1. Analysis of combined total drug group

A total drug group consists of all FAS subjects who were randomized into either the DE-109 440 µg arm or the DE-109 fixed dose (dummy) arm. The analysis of primary endpoint and key secondary endpoints will be applied on the total drug study group in comparison to the Sham arm.

8.4.2. Analysis of exploratory endpoints

For the analysis of BCVA-response endpoints based on Macular Edema population, response rate of each treatment, rate difference and its 95% confidence interval will be reported.

8.4.3. Bayesian analysis of the primary endpoint

8.4.3.1. Prior Data

The DE-109 clinical trial program includes Sakura 1 (32-007-S1) and Sakura 2 (32-007-S2), two randomized controlled trials in which subjects were randomized to the DE-109 study drug at one of three doses: 44 µg, 440 µg and 880 µg. The inclusion/exclusion criteria in Sakura studies are very similar to those in LUMINA study, although inclusion criteria in Sakura studies were

slightly more liberal. The primary endpoint in the study (i.e., LUMINA study) will be analyzed using a Bayesian approach with Sakura data served as prior knowledge.

To ensure the similarity of data from subjects across trials, only Sakura studies' Intent-to-treat subjects who meet the additional following inclusion criteria will be included in the derivation of prior distribution:

- Having a BCVA ≥ 20 ETDRS letters and ≤ 75 ETDRS letters in the study eye(s) at the Day 1 visit.
- Subject being treated with systemic (oral) corticosteroids must have received a stable oral prednisone-equivalent dose between ≥15 mg/day and ≤40 mg/day at Day 1 visit.

The prior distribution representing the prior knowledge learned from a study will be derived based on the number of responders and number of subjects in the study population. If the previous study with N randomized subjects had n responders of the primary endpoint, the prior distribution for the response rate π will be

$$\pi \sim \text{Beta}\big(w \cdot n, w \cdot (N-n)\big),$$

where w represents the weight to compensate for possible variability from previous study and this study.

8.4.3.2. Bayesian Analysis

To assess the superiority of DE-109 440 µg compared to Sham, a Bayesian analysis of the primary endpoint using Sakura studies data as prior knowledge will be employed. The prior distribution for the DE-109 440 µg will be derived from Sakura 1 and Sakura 2 study, separately. For this analysis, the weight to account for possible variability across studies is chosen to be 40%, with other values will be used to assess the robustness of such choice. Prior distribution of Sham's response rate will be Beta (1, 1) as Sham has not been used as a comparator in previous studies. The posterior distribution of response rates will be calculated based on data collected from subjects who received DE-109 440 µg and Sham in this study and the corresponding prior distribution, respectively.

The efficacy of DE-109 440 µg is determined based on whether the posterior probability of DE-109 440 µg superiority is met, that is

$$\text{P}(\pi_{440} - \pi_{\text{sham}} > 0 \mid \text{Data}) > 0.975$$

where π_{440} and π_{sham} are the response rate of the DE-109 440 µg and Sham arm, respectively.

To further assess the robustness of the Bayesian analysis, a sensitivity analysis will be performed where different weights (20%, 30%, 40%, 50%, and 60%) in the derivation of prior distribution will be used. Another sensitivity analysis with prior data including all Sakura studies' intent-to-treat subjects will also be performed.

9. SAFETY ANALYSES

9.1. Safety-Related Definitions

9.1.1. Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical participant, temporally associated with the use of study intervention, whether or not related to the study intervention. An AE reported on the AE eCRF will be considered as *treatment-emergent* if the AE occurred on or after the treatment start date up to 120 days after treatment end date (or the last study visit). In other words, a reported event will not be counted as a treatment-emergent AE if it can be determined that the onset of the event occurred prior to the treatment start date or beyond 120 days after treatment end date. For tabulations of AEs during the Double-Masked analysis period or the Open-Label analysis period, only treatment-emergent AEs will be included. Note that events that occurred before the first administration of investigational product (IP) are considered medical history events and will be tabulated separately.

Each AE will be graded by the Clinical Investigator as Mild (aware or unaware of event, but easily tolerated), Moderate (discomfort enough to cause interference with usual activity), or Severe (incapacitating; unable to work or perform usual activity). AEs will also be rated by the Investigator as to their causality/relationship to the IP.

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.

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 'Event Location' on the AE eCRF.

9.1.1.2. Adverse Drug Reaction

An AE will be counted as an *adverse drug reaction* (ADR) if

- the AE was considered *study medication*-related, i.e., the Clinical Investigator answered 'Related' to the AE eCRF question "Relationship to Study Drug", **OR**
- the AE was considered injection procedure-related, i.e., the Clinical Investigator answered 'Related' to the AE eCRF question "Relationship to Study Drug injection procedure"

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. Sight-Threatening Adverse Event

A *sight-threatening AE* is any SAE that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event. An AE will be counted as a sight-threatening AE if the Clinical Investigator checked an 'Sight-Threatening' option under 'Serious Criteria/Category' question on the SAE eCRF.

9.1.1.5. Events of Special Interest

An *event of special interest* (ESI) is a medical event both anticipated and unanticipated that may have a particular impact on the benefit/risk profile of the study medication. For this study, ESIs are specific to the study eye only and are as follows:

- Clinically significant new or worsening of uveitis, defined as satisfaction of any of the following:
  - Worsening of uveitis in the study eye as indicated by at least a 2-step increase in VH score (i.e., 0 to ≥ 2+, 0.5+ to ≥ 3+, 1+ to ≥ 3+, 1.5+ to ≥ 4+, or 2+ to ≥ 4+) as compared to the baseline (Day 1) VH score or the best achieved VH score post-baseline.
  - Severe deterioration of vision in the study eye due to worsening of uveitis that is indicated by at least doubling of the visual angle (loss of 3 or more lines [≥15 ETDRS letters]) as compared to baseline (Day 1) BCVA.
  - New or worsening retinal or choroidal uveitic lesion(s) in the study eye as compared to baseline (Day 1).
  - New or worsening uveitis otherwise deemed clinically significant by the investigator in the study eye as compared to the baseline (Day 1).
- Endophthalmitis / Sterile Endophthalmitis in the study eye
- Traumatic cataract in the study eye
- Vitreoretinal hemorrhage in the study eye
- Drug depot in visual axis in the study eye
- Retinal detachment in the study eye
- Increased IOP (> 10 mmHg as compared to baseline).
- Cataract (new or worsening from baseline) in the study eye

For regulatory reporting requirement, **pregnancy** and **investigational product administration error** considered to be significant by the investigator are also considered ESIs for this study

9.1.2. Safety Measures

Table 3 lists the safety measures to be evaluated for this study.

Table 3: Safety Assessments

Safety Measures	Note
Slit-lamp biomicroscopy: *vitreous, eyelid, conjunctiva, cornea, anterior chamber cells and flare, iris and pupil, ocular motility*	The status of each of these biomicroscopy parameters was determined as Normal or Abnormal. For each abnormal record, the parameter was rated as 1 = Mild, 2 = Moderate, or 3 = Severe.
Slit-lamp Biomicroscopy: *vitreous cell count*	This measure was rated as 0 = 0 cells, 0.5+ = 1-10 cells, 1+ = 11-20 cells, 2+ = 21-30 cells, 3+ = 31-100 cells, 4+ = >100 cells
Slit-lamp Biomicroscopy: *anterior chamber cells*	This measure was rated as 0 = 0 cells, 0.5+ = 1-5 cells, 1+ = 6-15 cells, 2+ = 16-25 cells, 3+ = 26-50 cells, 4+ = >50 cells
Slit-lamp Biomicroscopy: *anterior chamber flare*	This measure was rated as 0 = None, 1+ = Faint, 2+ = Moderate, 3+ = Marked, 4+ = Intense
Slit-lamp Biomicroscopy: *lens and cataract*	The lens of an eye was classified as Phakic, Aphakic, or Pseudophakic. For phakic lens with cataract, the severity was rates as 1 = Mild, 2 = Moderate, 3 = Severe. In addition, whether cataract affects grading of degree of inflammation (Yes or No) was also determined.
Intraocular pressure	The IOP, the fluid pressure inside the eye, was recorded in mmHg with one decimal point (e.g., 24.0 mmHg). For this study, the elevated IOP, depending on the level of elevation, might be reported as an AE at Clinical Investigator's discretion.
Indirect ophthalmoscopy: *retina vessels, macula, fovea, periphery, optic nerve, cup-to-disc ratio*	The status of retina vessels, macula, fovea, periphery, and optic nerve was determined as Normal or Abnormal. The cup-to-disc ratio was recorded with two decimal points (e.g., 0.80)
Best-corrected visual acuity (BCVA)	BCVA measures the acuteness or clearness of best-corrected vision, with a range of [0, 110] in ETDRS letters. An increase in BCVA indicates improvement in the best-corrected vision. A 5-letter difference in visual acuity is equivalent to one Snellen line. A BCVA score of 85 ETDRS letters is equivalent to 20/20 vision, which is considered normal vision.
Central Subfield Thickness (CST)	For each eye, the CST was measured using Optical Coherence Tomography (OCT). OCT was performed using reading center certified photographers, equipment, and standardized protocols.

Table 3: Safety Assessments (Continued)

Safety Measures	Note
Physical examination: *Height, weight*	The physical exam result was determined as Normal, Abnormal, or No Change. The weight and the height were recorded with one decimal point in inch/cm and lb/kg, respectively. The conversion rules "1 lb = 0.453592 kg" and "1 in = 2.54 cm" will be followed to convert lb to kg and into cm, respectively.
Vital signs: *Oral temperature, systolic and diastolic blood pressure, heart rate*	The oral temperature was recorded in °F or °C. The conversion rule "°C = 5/9 × (°F – 32)" will be followed to convert °F to °C. The blood pressure (systolic and diastolic) and the heart rate were recorded in mmHg and beats per minute (bpm), respectively.
Laboratory tests: *Blood chemistry/hematology, urinalysis*	The minimum blood and urine parameters collected in the study are listed in Appendix B. Hematology, chemistry, and urinalysis outcomes were determined by the Clinical Investigator as Normal, Not Clinically Significant Abnormality, or Clinically Significant Abnormality based on the comprehensive review of the relevant laboratory test results.

The safety-related measures collected in this study include AEs, events of special interest (ESIs), slit-lamp biomicroscopy findings, IOP, best-corrected visual acuity, indirect ophthalmoscopy findings, central subfield thickness, physical exam results, vital signs, and laboratory test results. The Safety population will be used for all summaries.

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

9.2. Adverse Events

Subjects with any AE(s) will be tabulated by type of AE(s) and number of enrolled eyes for each actual treatment received and total drug (i.e., the combination of DE-109 440 µg and DE-109 fixed dose arm). Study eyes with any ocular AE(s) will be tabulated by type of AE(s) for each actual treatment received and total drug. For subject-level summaries, any AEs experienced by either eye or both eyes will be counted once for that AE. Unless specified otherwise, ocular AEs in study eyes will be summarized at the eye-level, while overall AEs, ocular AEs in fellow eyes, and non-ocular AEs will be summarized at the subject-level.

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/study eye which experienced multiple AEs within a SOC or preferred term will be counted only once for that SOC or preferred term for subject-level/eye-level summaries. Non-serious AEs (including number of events) will also be summarized by SOC and preferred term. ESIs will be summarized descriptively at the eye-level.

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

9.3. Intraocular Pressure

IOP and change from baseline in IOP will be summarized by analysis visit.

Change after injection in IOP will be summarized by injection visit. Subjects with any increase of ≥10 mmHg in IOP after injection will be 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 worsening (increase) of ≥ 2 units from baseline will be listed. Any clinically significant worsening from baseline in severity will also be listed.

For lid hyperemia, lid edema, conjunctival hyperemia, chemosis, corneal edema, conjunctival discharge/exudate, and anterior chamber flare, shift from baseline in severity rating score will be summarized by analysis visit and shift after injection will be summarized by injection visit. Subjects with any clinically significant abnormality will be listed by biomicroscopic parameter. In addition, subjects with any worsening (increase) of 2 units or more from baseline will also be listed by biomicroscopic parameter.

For pupil, lashes, ocular motility, and iris, shift from baseline in status (Normal or Abnormal) will be summarized by analysis visit and shift after injection will be summarized by injection visit. Subjects with any clinically significant abnormality will be listed by biomicroscopic parameter. In addition, subjects with any change from Normal at baseline to Abnormal in status will also be listed by biomicroscopic parameter.

For vitreous cell count and anterior chamber cells, shift from baseline in rating score will be summarized by analysis visit and shift after injection will be summarized by injection visit.

9.4.1. Lens

For phakic lens only, shift from baseline in cataract severity score will be summarized by analysis visit and shift after injection will be summarized by injection visit. Subjects with any worsening (increase) of 2 units or more from baseline in cataract severity will be listed. In addition, subjects with any cataract that affected grading of degree of inflammation will also be listed.

9.5. Ophthalmoscopy

For retina vessels, macula, fovea, periphery, and optic nerve, shift from baseline in status (Normal or Abnormal) will be summarized by analysis visit and shift after injection will be summarized by injection visit. Subjects with any change from Normal at baseline to Abnormal in status will be listed by ophthalmoscopic parameter.

For vitreous hemorrhage, retinal detachment, and retinal tear, shift from baseline in presence status (None or Present) will be summarized by analysis visit and shift after injection will be summarized by injection visit. Subjects with any change from None at baseline to Present in presence status will be listed by ophthalmoscopic parameter.

For cup/disc ratio, score and change-from-baseline score will be summarized by analysis visit. Change after injection in cup/disc ratio will be summarized by injection visit. Subjects with any worsening (increase) of 0.2 units or more from baseline in cup/disc ratio will be listed.

9.6. Physical Examination and Vital Signs

For weight, height, oral temperature, blood pressure, and heart rate, score and change from baseline score will be summarized by analysis visit. Subjects with any change from Normal at baseline to Abnormal in physical exam result will be listed.

9.7. Laboratory Tests

Hematology results will be summarized by laboratory test and analysis visit. Subjects with any clinically significant abnormality in hematology will be listed.

10. SUMMARY OF CHANGES TO THE PROTOCOL

10.1. Adding Exploratory Endpoints

The visual acuity-related endpoints (presented in Section 2.3.5) were added to explore the treatment effect of DE-109 440 μg among Macular Edema population subjects.

10.2. Adding Exploratory Analyses

In previous studies, DE-109 has showed some evidence of efficacy across different doses. To further explore the overall efficacy of DE-109, the analysis of primary endpoint and the analyses of key secondary endpoints will be repeated on the combined DE-109 μg and DE-109 fixed dose arms versus Sham arm.

Analysis of BCVA-related endpoints was also added in corresponding to the added exploratory endpoints.

11. REFERENCE

1. Kenward, M. G., Roger, J. H. (1997). Small Sample Inference for Fixed Effects from Restricted Maximum Likelihood. Biometrics. 53(3):983-97. PubMed PMID: 9333350.

2. Mehta, C. R., Pocock, S. J. (2011). Adaptive increase in sample size when interim results are promising: a practical guide with examples. Stat Med. 30(28):3267-84.

3. O'Kelly, M., Ratitch, B. Clinical Trials with Missing Data: A Guide for Practitioners: John Wiley & Sons; 2014.

4. Yu, J., Koch, G. (2020). Randomization-Based Methods for Treatment Comparisons for Dichotomous Outcomes for Multiple Anatomical Regions. Statistics in Biopharmaceutical Research. 13(4):1-15. doi: 10.1080/19466315.2020.1750471.

APPENDIX A. VFQ-25 COMPOSITE SCORE AND SUBSCALES

Following steps will be taken to derive the VFQ-25 composite score and subscales:

Step One: Recode Item Scores

Item Numbers on VFQ-25	Original Response[a]	Recode Value
1, 3, 4	1 2 3 4 5	100 75 50 25 0
2	1 2 3 4 5 6	100 80 60 40 20 0
5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 16, 16a, A3[b], A4[b], A5[b], A6[b], A7[b], A8[b], A9[b]	1 2 3 4 5 6	100 75 50 25 0 *[c]
15c[d]	1 2 3 4	100 75 50 25 0
17, 18, 19, 20, 21, 22, 23, 24, 25, A11a[b], A11b[b], A12[b], A13[b]	1 2 3 4 5	0 25 50 75 100
A1[b], A2[b]	0 to 10	0 to 100

[a] Original response choices as printed in the questionnaire

[b] The letter "A" before the item number indicates that this item is an optional item from the Appendix of VFQ-25 questionnaire.

[c] A response of '6' indicates that the person does not perform the activity because of non-vision related problems. If '6' is selected, the item will be recoded as missing.

[d] Item 15c has 4 levels (1, 2, 3, or 4), but it is recoded to 5 levels by incorporating the response choice for Item 15b:
if 15b = 1 then 15c is recoded to 0;
if 15b = 2 or 3 then 15c is recorded to missing.

Step Two: Identify Items Needed to Derive VFQ-25 Composite Score and Subscales

Score or Subscale	Items to be averaged (after step 1)
General Health	1, A1
General Vision	2, A2
Ocular Pain	4, 19
Near Activities	5, 6, 7, A3, A4, A5
Distance Activities	8, 9, 14, A6, A7, A8
Vision Specific Social Functioning	11, 13, A9
Vision Specific Mental Health	3, 21, 22, 25, A12
Vision Specific Role Difficulties	17, 18, A11a, A11b
Vision Specific Dependency	20, 23, 24, A13
Driving	15c, 16, 16a
Color Vision	12
Peripheral Vision	10
Composite Score	All items except Item 1 and A1

Step Three: Derive VFQ-25 Composite Score and Subscales

Score = Sum of all items with a non-missing answer / Total number of items with a non-missing answer, with a range of [0, 100] (0 = Worst possible score; 100 = Best score)

APPENDIX B. CLINICAL LABORATORY PARAMETERS

Serum Chemistry and Hematology

The following is a list of the minimum parameters that will be measured. Other additional parameters may also be reported.

Table 4: Serum Chemistry and Hematology

Chemistry	Hematology
Albumin	red blood cells (RBC)
Creatinine	white blood cells (WBC)
lactate dehydrogenase (LDH)	differential WBC
Glucose	platelets (PLT)
Calcium	hemoglobin (HGB)
Potassium	hematocrit (HCT)
Sodium	mean corpuscular volume (MCV)
cholesterol (total, HDL and LDL)	mean corpuscular hemoglobin (MCH)
Triglycerides	mean corpuscular hemoglobin conc. (MCHC)
urea nitrogen	
bilirubin (total, direct, indirect)	
alkaline phosphatase (ALP)	
alanine aminotransferase (ALT)	
aspartate aminotransferase (AST)	
gamma glutamyl transferase (GGT)	

Urinalysis

The following is a list of the minimum urine parameters that will be measured. Other additional urine parameters may also be reported.

PH	Protein	Erythrocytes	Ketones	Glucose