Study Protocol 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
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DE-109

Protocol 010906IN

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.**

PROTOCOL NUMBER: 010906IN

COMPOUND NUMBER: DE-109 injectable solution

STUDY PHASE: Phase III

SPONSOR: SANTEN INCORPORATED

LEGAL REGISTERED ADDRESS: 6401 Hollis Street, Suite 125, Emeryville, CA 94608

REGULATORY AGENCY IDENTIFIER NUMBER(S): IND Number: 070496

PROTOCOL VERSION/DATE: ORIGINAL: 10SEP2018

AMENDMENT 1: 26MAR2019

AMENDMENT 2: 29SEP2020

AMENDMENT 3: 14JUL2021

I have read the 010906IN protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

INVESTIGATOR:

Date: _____

Signature: _____

Name: _____

Address: _____

_____

Phone: _____

This study will be conducted in accordance with applicable Good Clinical Practices (GCP), United States Code of Federal Regulations, International Council for Harmonisation (ICH) guidelines, and the Declaration of Helsinki.

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1.1. Synopsis

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.

Table 2: Study Objectives, Estimands, and Endpoints

Study Objectives and Estimands	Corresponding Study Endpoints
Primary objective (efficacy vs. sham): The primary objective of this study is to evaluate the efficacy of intravitreal injection of 440 µg DE-109 every 2 months as compared with sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye. **Primary estimand**: Vitreous haze 0 (VH0) 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 event 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. **Treatment policy estimand**: VH0 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 event. For study eyes that had missing data due to any reason, imputation by the multiple imputation-based approach will be used. **Composite estimand**: 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	**Primary efficacy endpoint**: • VH 0 response[a] at Month 5 **Key secondary efficacy endpoints:** • Composite endpoint[b] at Month 5 • VH 0 response at Month 3 • Composite endpoint at Month 3 Note: Overall Type I error rate will be maintained at 0.05 (two-sided) across primary and key secondary efficacy endpoint treatment comparisons. **Other secondary efficacy endpoints:** • VH 0 or 2-unit response[c] at Month 5 • VH 0 or 2-unit response at Month 3 • VH 0 or 0.5+ response[d] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering success[e] with resolution at Month 5 • Corticosteroid tapering success with resolution at Month 3 • BCVA (Best-Corrected Visual Acuity) 3-line response[f] at Month 5 • BCVA 3-line response at Month 3 • Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT • Change from baseline in CST at Month 3 as measured by OCT • Use of rescue therapy before Month 5 • Use of rescue therapy before Month 3 Note: Additional secondary and exploratory efficacy endpoints will be specified in the Statistical Analysis Plan.

Table 2: Study Objectives, Estimands, and Endpoints (Continued)

Study Objectives and Estimands	Corresponding Study Endpoints
• 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 event prior to the specified visit Score = 0 if otherwise	
Secondary (long-term efficacy): A secondary objective of this study is to evaluate the long-term efficacy (> 6 months and up to one year) of intravitreal injection of 440 µg DE-109 every 2 months for the treatment of active, non-infectious uveitis of the posterior segment of the eye.	Secondary efficacy 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 Additional secondary and exploratory endpoints assessing long-term efficacy will be specified in the Statistical Analysis Plan.
Secondary (safety): A secondary objective of this study is to evaluate the safety of intravitreal injection of 440 µg DE-109 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.	Safety of DE-109 will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, 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.

Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale.

[a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale.

[b] Refer to composite score scales defined in the composite estimand in this table.

[c] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale.

[d] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale.

[e] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at 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).

[f] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).

Overall 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.

The study will begin with a 30 days 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.

The hypothesis of the double-masked period is that the test arm (DE-109 440 µg dose every 2 months) will demonstrate superior efficacy versus the sham control arm. To preserve the masking of treatment assignments, there will be separate, unmasked and masked investigators (and designated staff) during the double-masked period. At visits at which investigational product (IP) is being administered, the unmasked investigator (and designated staff) will administer the IP (DE-109 intravitreal injection and sham procedure) and conduct the post-administration assessments; the masked investigator (and designated staff) will conduct the assessments prior to IP administration.

Open-label period: 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., 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.

Study Population:

For study eligibility, active uveitis is defined as having a vitreous haze (VH) score of at least 1.5+ based on the modified SUN scale. If anterior segment inflammation is present, it must be less severe than the posterior component. Subjects receiving systemic (oral) corticosteroid therapy will be eligible to enroll in the study; these subjects will be required to have received a 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 the first day of dosing (Day 1). Similarly, subjects receiving topical corticosteroid eye drops (other than difluprednate ophthalmic emulsion), topical non-steroidal anti-inflammatory eye drops, or certain immunosuppressants will be eligible and will be required to have received a stable dose/frequency of the therapy for at least 1 week (7 days) prior to Day 1 (Inclusion criteria Section 5.1, #6 and #8; Exclusion criteria Section 5.2, #14).

If both of an eligible subject's eyes meet all eligibility criteria, both eyes can be randomized into the study (i.e., both eyes can be study eyes) and will be assigned to the same treatment arm. The investigator will determine whether to enroll both eyes into the study after eligibility has been confirmed. The study randomization will include stratification by number of eyes enrolled (one eye or two eyes) as well as baseline systemic (oral) corticosteroid use (yes/no) and region (US or non-US). There will be separate drug supplies, records, and assessments for each study eye.

If a fellow eye (non-study eye of a subject in the study) has uveitis at baseline or develops active uveitis during the study, the investigator should treat the eye with standard of care local therapies; systemically administered therapies should not be used to treat the fellow eye unless deemed to be medically necessary. DE-109 may not be administered to a fellow eye.

Study Assessments:

Study assessments will include fundus photography (FP), slit-lamp biomicroscopy, indirect ophthalmoscopy, optical coherence tomography (OCT), intraocular pressure (IOP), best-corrected visual acuity (BCVA), fluorescein angiography (FA), the National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25), assessment of adverse events, laboratory tests (serum chemistry, hematology, and urinalysis), physical examination, vital signs, and pregnancy testing (serum and urine pregnancy tests for women of childbearing potential).

Tapering of Systemic (Oral) Corticosteroid Use:

Starting on Day 1, subjects receiving systemic (oral) corticosteroids at a stable prednisone-equivalent dose between ≥15 mg/day and ≤40 mg/day will taper over a maximum of 8 weeks to a prednisolone-equivalent dose of 0 mg/day. Corticosteroid tapering success with resolution of VH will be assessed in these subjects. The study randomization will include stratification by baseline systemic (oral) corticosteroid use (yes/no) as well as the number of eyes enrolled (one eye or two eyes) and region (US or non-US).

Protocol-Specified Rescue Therapy Criteria:

Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS. Rescue therapy is prohibited during the study unless there is worsening of uveitis as demonstrated by one or more of the following three rescue criteria:

1. 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.
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.

When deemed medically necessary, rescue therapy may be administered at the discretion of the investigator, even if none of the protocol-specified rescue criteria noted above are satisfied. The investigator should contact the medical monitor to discuss the rescue treatment plan prior to the administration of rescue therapy. If the investigator is unable to reach the medical monitor, rescue treatment should be administered per the investigator's clinical judgment and the medical monitor should be notified as soon as possible to discuss future on-study treatment plans for the subject.

Interim Analyses, Primary Analysis, and Analysis of Open-Label Period:

An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. There are two goals for this interim analysis (1) to assess for futility; and (2) to re-assess the sample size. Sample size re-assessment will be performed with the "promising zone" approach as follows (Mehta et al., 2011). If the conditional power at the interim analysis is between 50% and 80%, the suggested sample size increase may be up to 100 subjects (i.e., 50% of the original sample size). If, on the other hand, the conditional power is > 80% or < 50%, no change to the sample size will take place. If the conditional power is <30%, then the Data Monitoring Committee (DMC) would recommend stopping the trial due to futility. The DMC could recommend stopping the trial due to safety concerns at any of the DMC meetings and the interim analysis. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the DMC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.

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 primary analysis will be conducted after all subjects have completed the Month 6 visit or prematurely discontinued from the study prior to Month 6. An interim clinical study report will be written documenting the primary analysis results.

Analysis of the open-label period of the study will be performed after the end of the study and documented in the final clinical study report.

Data Monitoring Committee:

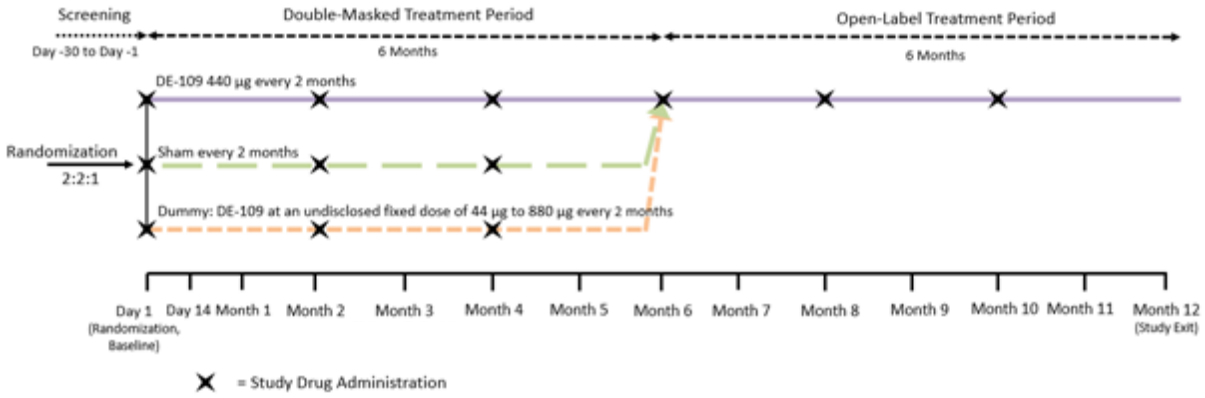
An independent Data Monitoring Committee (DMC) whose members will not be participating in the LUMINA study conduct will serve as an advisory board to the Santen senior management team. The DMC will periodically review and make recommendations based on interim data; unmasked data will only be reviewed in closed DMC sessions without participation of Santen

personnel. The organization, responsibilities, and procedures of the DMC will be specified in a governing charter.

1.2. Schema

Figure 1 provides an overview of the study design.

Figure 1: Study Schema



1.3. Schedule of Activities (SoA)

The schedule of activities (SoA) is provided in Table 3.

Table 3: Schedule 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]

Table 3: Schedule 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 Termination**
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]													
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

Table 3: Schedule of Activities (Continued)

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 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.

2. INTRODUCTION

DE-109 is a formulation of sirolimus administered by intravitreal injection that is being developed for the treatment of non-infectious uveitis of the posterior segment of the eye (intermediate, posterior, and panuveitis). Sirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) and acts as an immunoregulator.

2.1. Study Rationale

Phase III study 010906IN (LUMINA) will evaluate the efficacy and safety of intravitreal injection of DE-109 440 µg administered every 2 months for the treatment of active, non-infectious uveitis of the posterior segment of the eye (NIU-PS). In two Phase III studies conducted previously in this indication, three doses of DE-109 were evaluated (44 µg, 440 µg, and 880 µg, each administered every 2 months); the 440 µg dose demonstrated the optimal benefit-risk profile. The 6-month, double-masked period of Phase III study LUMINA is being conducted to confirm the efficacy and safety of DE-109 440 µg administered every 2 months when compared to a sham control. The 6-month, 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.

2.2. Background

Non-infectious uveitis of the posterior segment of the eye (NIU-PS) is a heterogeneous group of intraocular inflammation disorders with both exogenous (infection, trauma) and endogenous (autoimmune, idiopathic) etiologies that affects up to 730 people per 100,000 (Durrani et al., 2004; Jabs et al., 2005). In chronic uveitis, cumulative structural damage and loss of vision result from recurrent episodes of inflammation. Thus, active uveitis requires urgent treatment to control inflammation.

Historically, the primary treatment for NIU-PS has been systemic corticosteroid therapy. More recently, ocular implants that deliver corticosteroid locally have become available. Systemic corticosteroid therapy is associated with known comorbidities (e.g., osteoporosis, hypertension, and diabetes, as well as cataracts and glaucoma) that may escalate with dose and frequency of use. The available corticosteroid ocular implants are associated with a high rate of increased intraocular pressure (IOP), the attendant risk of glaucoma, and with increased risk of cataract development. Other systemic immunosuppressive therapies (antimetabolites, T-cell inhibitors, alkylating agents, and biologics) may be appropriate as monotherapy in certain patients, or these agents may be used to lower the corticosteroid dose, however close monitoring is required due to potentially serious side effects such as hepatotoxicity, myelosuppression, or malignancy. Given the treatment-limiting side effects of current therapies, there remains an unmet medical need in NIU-PS for therapies that can be used on a long-term basis to address the chronicity of the disease.

Sirolimus (also known as rapamycin) is a macrolide antibiotic that inhibits the mammalian target of rapamycin (mTOR), a multifunctional kinase. Inhibition of mTOR and its downstream signaling molecules by sirolimus results in immunosuppression, primarily by interrupting the inflammatory cascade that leads to T-cell activation and proliferation. Emerging evidence

suggests that sirolimus also promotes immune tolerance by inducing regulatory T-cells (Tregs), which may contribute to the treatment of non-infectious uveitis because of the potential dysfunction of Tregs in autoimmune diseases. Sirolimus received initial US regulatory approval in 1999 (as Rapamune®) for the prophylaxis of organ rejection in renal transplant patients; sirolimus is also the active ingredient in a drug-eluting stent (the CYPHER® Sirolimus-eluting Coronary Stent) marketed for improving coronary luminal diameter in patients with symptomatic ischemic disease. Evidence of the efficacy of sirolimus in treating uveitis was first obtained in an investigator-sponsored study, the SAVE study (Ibrahim et al., 2015; Nguyen et al., 2013). In this study of 30 subjects with non-infectious uveitis, sirolimus administered by either intravitreal or subconjunctival injection was generally well tolerated and showed bioactivity in reducing vitreous haze and cells, in improving visual acuity, and in decreasing the need for systemic corticosteroids.

DE-109 is a formulation of sirolimus that forms a depot which localizes in the inferior portion of the vitreous humor, providing sirolimus exposure to the retina/choroid for approximately two months. Santen has conducted a nonclinical and clinical development program of DE-109 through Phase III to demonstrate the efficacy and safety of DE-109 in the treatment of NIU-PS. A detailed description of the chemistry, pharmacology, efficacy, and safety of DE-109 is provided in the DE-109 Investigational Brochure.

2.3. Benefit/Risk Assessment

Two Phase III studies have been completed (SAKURA Program: SAKURA Study 1 and SAKURA Study 2) which evaluated three doses of DE-109 (44 µg, 440 µg, and 880 µg, each administered every 2 months) in subjects with active NIU-PS. A total of 590 randomized, treated study eyes (590 subject IDs, 589 subjects) received at least one injection of DE-109 (i.e., integrated Safety population). In the integrated Safety population of the two studies, 459 treated study eyes were exposed to the 440 or 880 µg dose of DE-109 for at least 6 months (defined as staying in study under either dose for at least 173 days after the first 440 or 880 µg dose) and 318 treated study eyes were exposed to the 440 or 880 µg dose for at least 1 year (defined as staying in study for at least 346 days after the first 440 or 880 µg dose). The DE-109 440 µg dose exhibited the optimal benefit/risk profile in Study 1 and performed similarly in Study 2. The efficacy and safety data in these large Phase III studies support the 440 µg dose as the most appropriate dose of DE-109 for treating active NIU-PS. For the primary endpoint (VH score of 0 at Month 5), the response rate in the 440 µg dose group was appreciable and consistent across the two studies (22.8% and 19.1% in Study 1 and Study 2, respectively).

The safety data from the SAKURA program demonstrated a reasonable safety profile of the 440 µg dose of DE-109, with few risks directly related to its use. Risks associated with the use of DE-109 are non-infectious endophthalmitis, which was observed mostly with the 880 µg dose and successfully treated with corticosteroids and surgical intervention, and the presence of drug depot in the visual axis, which, if it occurs, is a self-limiting event that may resolve as the drug depot dissolves and moves out of the visual axis. At all three doses (44 µg, 440 µg, and 880 µg, each administered every 2 months), DE-109 had minimal effect on IOP with repeat dosing and the systemic exposures after intravitreal dosing were well below the levels required for immunosuppression, thereby minimizing the possibility of systemic side effects.

The undisclosed, fixed dose of DE-109 in the Dummy arm will be within the range of doses evaluated in the previous Phase III studies (44 μg to 880 μg), all of which have demonstrated an acceptable safety profile.

The control arm for the 6-month, double-masked period of this study is a sham procedure, which mimics an intravitreal injection without penetrating the eye. The protocol allows for the administration of rescue therapy for any subject in the study who experiences a worsening of uveitis.

Refer to the DE-109 Investigational Brochure for detailed descriptions of completed studies of DE-109 and the safety and efficacy data relevant to the clinical use of DE-109 in NIU-PS.

3. STUDY OBJECTIVES AND ENDPOINTS

Table 4: Study Objectives, Estimands, and Endpoints

Study Objectives and Estimands	Corresponding Study Endpoints
Primary objective (efficacy vs. sham): The primary objective of this study is to evaluate the efficacy of intravitreal injection of 440 µg DE-109 every 2 months as compared with sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye. **Primary estimand**: Vitreous haze 0 (VH0) 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 event 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. **Treatment policy estimand**: VH0 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 event. For study eyes that had missing data due to any reason, imputation by the multiple imputation-based approach will be used.	**Primary efficacy endpoint**: • VH 0 response[a] at Month 5 **Key secondary efficacy endpoints:** • Composite endpoint[b] at Month 5 • VH 0 response at Month 3 • Composite endpoint at Month 3 Note: Overall Type I error rate will be maintained at 0.05 (two-sided) across primary and key secondary efficacy endpoint treatment comparisons. **Other secondary efficacy endpoints:** • VH 0 or 2-unit response[c] at Month 5 • VH 0 or 2-unit response at Month 3 • VH 0 or 0.5+ response[d] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering success[e] with resolution at Month 5 • Corticosteroid tapering success with resolution at Month 3 • BCVA (Best-Corrected Visual Acuity) 3-line response[f] at Month 5 • BCVA 3-line response at Month 3 • Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT • Change from baseline in CST at Month 3 as measured by OCT • Use of rescue therapy before Month 5 • Use of rescue therapy before Month 3 **Note: Additional secondary and exploratory efficacy endpoints will be specified in the Statistical Analysis Plan.**

Table 4: Study Objectives, Estimands, and Endpoints (Continued)

Study Objectives and Estimands	Corresponding Study Endpoints
Composite estimand: 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 event prior to the specified visit • Score = 0 if otherwise	
Secondary (long-term efficacy): A secondary objective of this study is to evaluate the long-term efficacy (> 6 months and up to one year) of intravitreal injection of 440 µg DE-109 every 2 months for the treatment of active, non-infectious uveitis of the posterior segment of the eye.	Secondary efficacy 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 Additional secondary and exploratory endpoints assessing long-term efficacy will be specified in the Statistical Analysis Plan.

Table 4: Study Objectives, Estimands, and Endpoints (Continued)

Study Objectives and Estimands	Corresponding Study Endpoints
Secondary (safety): A secondary objective of this study is to evaluate the safety of intravitreal injection of 440 µg DE-109 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.	Safety of DE-109 will be assessed by adverse events (AEs), slit-lamp biomicroscopy, indirect ophthalmoscopy, 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.

Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale.

[a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale.

[b] Refer to composite score scales defined in the composite estimand in this table.

[c] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale.

[d] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale.

[e] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at 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).

[f] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).

4. STUDY DESIGN

4.1. Overall 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.

The study will begin with a 30 days 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.

The study objectives and endpoints are provided in Section 3. The hypothesis of the double-masked period is that the test arm (DE-109 440 µg dose every 2 months) will demonstrate superior efficacy versus the sham control arm. To preserve the masking of treatment assignments, there will be separate, unmasked and masked investigators (and designated staff) during the double-masked period. At visits at which IP is being administered, the unmasked investigator (and designated staff) will administer the IP (DE-109 intravitreal injection and sham procedure) and conduct the post-administration assessments; the masked investigator (and designated staff) will conduct the assessments prior to IP administration.

Open-label period: Subjects completing the Month 6 pre-dose evaluations (the final evaluations of 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., 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.

Study Population:

For study eligibility, active uveitis is defined as having a vitreous haze (VH) score of at least 1.5+ based on the modified SUN scale. If anterior segment inflammation is present, it must be less severe than the posterior component. Subjects receiving systemic (oral) corticosteroid therapy will be eligible to enroll in the study; these subjects will be required to have received a stable prednisone-equivalent dose between ≥15 mg/day and ≤40 mg/day that has remained stable for at least 1week (7 days) prior to and including on Day 1. Similarly, subjects receiving topical corticosteroid eye drops (other than difluprednate ophthalmic emulsion), topical non-steroidal anti-inflammatory eye drops, or certain immunosuppressants will be eligible and will be required to have received a stable dose/frequency of the therapy for a specified duration prior to Day 1 (inclusion criteria Section 5.1, #6 and #8; exclusion criteria Section 5.2, #14).

If both of an eligible subject's eyes meet all eligibility criteria, both eyes can be randomized into the study (i.e., both eyes can be study eyes) and will be assigned to the same treatment arm. The investigator will determine whether both eyes are eligible for randomization into the study. Additional guidance regarding the enrollment of both or one of two eligible eyes is provided in Section 5. The study randomization will include stratification by number of eyes enrolled (one eye or two eyes) as well as baseline systemic (oral) corticorsteroid use (yes/no) and region (US or non-US). There will be separate drug supplies, records, and assessments for each study eye.

If a fellow eye (non-study eye of a subject in the study) has uveitis at baseline or develops active uveitis during the study, the investigator should treat the eye with standard of care local therapies; systemically administered therapies should not be used to treat the fellow eye unless deemed to be medically necessary. DE-109 may not be administered to a fellow eye.

Overview of Study Assessments:

Study assessments will include fundus photography (FP), slit-lamp biomicroscopy, indirect ophthalmoscopy, optical coherence tomography (OCT), intraocular pressure (IOP), best-corrected visual acuity (BCVA), fluorescein angiography (FA), the National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25), assessment of adverse events, laboratory tests (serum chemistry, hematology, and urinalysis), physical examination, vital signs, and pregnancy testing (serum and urine pregnancy tests for women of childbearing potential).

Tapering of Systemic (Oral) Corticosteroid:

Starting on Day 1, subjects receiving systemic (oral) corticosteroids at a stable prednisolone-equivalent dose between ≥15 mg/day and ≤40 mg/day will taper over a maximum of 8 weeks to a prednisolone-equivalent dose of 0 mg/day according to the tapering regimen described in Section 6.5.3 (the dose of corticosteroid must remain stable for 1 week [7 days] prior to and including on Day 1). Corticosteroid tapering success with resolution of VH will be assessed in these subjects. The study randomization will include stratification by baseline systemic (oral) corticosteroid use (yes/no) as well as the number of eyes enrolled (one eye or two eyes) and region (US or non-US).

Protocol-Specified Rescue Therapy Criteria:

Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS (detailed definition in Section 6.5.6). Rescue therapy is prohibited during the study unless there is worsening of uveitis as demonstrated by one or more of the following three rescue criteria:

1. 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 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.

When deemed medically necessary, rescue therapy may be administered at the discretion of the investigator, even if none of the protocol-specified rescue criteria noted above are satisfied. The investigator should contact the medical monitor to discuss the rescue treatment plan prior to the administration of rescue therapy. If the investigator is unable to reach the medical monitor, rescue treatment should be administered per the investigator's clinical judgment and the medical monitor should be notified as soon as possible to discuss future on-study treatment plans for the subject.

Interim Analyses, Primary Analysis, and Analysis of Open-Label Period:

An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. There are two goals for this interim analysis (1) to assess for futility; and (2) to re-assess the sample size. Sample size re-assessment will be performed with the "promising zone" approach as follows (Mehta et al., 2011). If the conditional power at the interim analysis is between 50% and 80%, the suggested sample size increase may be up to 100 subjects (i.e., 50% of the original sample size). If, on the other hand, the conditional power is > 80% or < 50%, no change to the sample size will take place. If the conditional power is <30%, then the Data Monitoring Committee (DMC) would recommend stopping the trial due to futility. The DMC could recommend stopping the trial due to safety concerns at any of the DMC meetings and the interim analysis. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the DMC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.

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 primary analysis will be conducted after all subjects have completed the Month 6 visit or prematurely discontinued from the study prior to Month 6. An interim clinical study report will be written documenting the primary analysis results.

Analysis of the open-label period of the study will be performed after the end of the study and documented in the final clinical study report.

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.

4.2. Scientific Rationale for Study Design

The double-masked, randomized, parallel design of the 6-month, comparative period of this study is a recognized standard in the evaluation of experimental drug therapies. A subsequent single-arm, open-label period, as used in this study, is also a frequently chosen strategy to allow evaluation of longer-term efficacy and safety of an experimental drug regimen without requiring long-term treatment with a placebo/sham control.

Given the potential risks associated with intravitreal injections, a sham administration procedure is used as a control during the study's double-masked period rather than an intravitreal injection of placebo medication. Sham administration has been routinely used as a control arm in Phase III studies of other intravitreally administered therapies for ocular diseases, including uveitis. To preserve the masking of the investigator conducting the study assessments, a separate, unmasked investigator (and designated staff) will administer the IP (intravitreal injection of DE-109 or sham procedure) during the double-masked period. Inclusion of an additional arm (the dummy arm), in which subjects receive intravitreal injections of DE-109 at a single, undisclosed fixed dose every 2 months, will help to ensure masking in this sham-controlled study. The dose in this arm will not vary between participating sites or subjects randomized to this arm.

Vitreous haze has been previously used as a primary efficacy endpoint in the clinical development of other medicinal products for uveitis. Vitreous haze (VH) is a descriptive term for the obscuration of fundus details by vitreous cells and protein exudation and was selected as the primary efficacy measure because it is strongly linked to inflammation. An assessment of the amount of haze is used as a surrogate marker for the degree of inflammation. A six-step scale of VH was created at the National Eye Institute in 1985 (Nussenblatt et al., 1985). This scale was approved by the Standardization of Uveitis Nomenclature (SUN) Working Group in 2005 as an acceptable method of grading VH in clinical research (Sun Working, 2005).

The primary efficacy endpoint is defined as a VH score of 0 (resolution of inflammation) at Month 5; a VH score of 0 at Month 3, composite score at Month 3 and at Month 5 are key secondary efficacy endpoints. Month 5 (one month after the Month 4 injection) and Month 3 (one month after the Month 2 injection) were selected as pre-specified endpoints for evaluating VH based on tissue distribution studies which demonstrated that peak levels of sirolimus are maintained at the target tissue for up to two months after intravitreal injection of DE-109.

Secondary efficacy assessments include benefit as measured by the ability to taper from corticosteroids and achieve resolution of VH, which is evaluated in the subgroup of subjects receiving systemic (oral) corticosteroids at baseline. Accordingly, to help ensure balance across the treatment arms within this subgroup, the study randomization will be stratified by subject's

systemic (oral) corticosteroid use at baseline (yes/no) as well as the number of eyes enrolled (one eye or two eyes) and region (US or non-US).

In this study which includes a sham control during the double-masked period, rescue therapy is allowed for subjects who experience worsening of disease or vision per protocol-specified criteria, or at the investigator's judgement. In the analysis of VH endpoints including the primary endpoint, the use of rescue therapy prior to the evaluation of a VH endpoint will be accounted for by considering the subject to be a non-responder.

An independent Data Monitoring Committee (DMC) will periodically review unmasked aggregated and individual-level data during the conduct of the trial to help ensure safety and data integrity. An independent statistical and programming team will be used to perform these interim analyses of unmasked data.

Use of the 6-month, single-arm, open-label period after completion of the 6-month double-masked, controlled period allows the evaluation of the efficacy and safety of intravitreal injection of DE-109 440 µg every 2 months for longer duration than appropriate for a placebo or sham control.

4.3. Justification for Dose

The first evidence of the favorable benefit-risk profile of intravitreal injection of sirolimus in treating non-infectious uveitis was provided by the SAVE study (Ibrahim et al., 2015; Nguyen et al., 2013). In SAVE, 30 subjects with active or quiescent non-infectious uveitis were randomized to receive intravitreal or subconjunctival injections of sirolimus every 60 days through day 120 and at dosing intervals ≥ 2 months from month 6 up to month 12. The SAVE study indicated that local administration of sirolimus, including an intravitreal dose of 352 µg every 60 days, was generally well tolerated and showed bioactivity in reducing vitreous haze, in improving visual acuity, and in decreasing the need for systemic corticosteroids.

In the two Phase III clinical trials conducted previously by Santen (SAKURA 1 and SAKURA 2), the efficacy and safety of three doses of DE-109 (44 µg, 440 µg, and 880 µg) administered every 2 months were evaluated for the treatment of NIU-PS. The primary efficacy endpoint evaluation was at Month 5. A total of 590 randomized, treated study eyes (590 subject IDs, 589 subjects) received at least one injection of DE-109. The 440 µg dose of DE-109 (administered to a total of 208 study eyes) demonstrated the optimal benefit-risk profile. The 6-month, double-masked period of Phase III study LUMINA is being conducted to confirm the efficacy and safety of DE-109 440 µg administered every 2 months when compared to a sham control.

4.4. End of Study Definition

A subject is considered to have completed the study if he/she has completed all periods of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (Section 1.3). The end of the study is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

The study will be conducted at up to approximately 100 investigative sites globally.

The study inclusion and exclusion criteria are specified below. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, will not be permitted.

Guidance regarding enrollment of both eyes:

If both of an eligible subject's eyes meet all eligibility criteria, both eyes can be randomized into the study (i.e., both eyes can be study eyes). The investigator will determine whether to enroll both eyes into the study after eligibility has been confirmed.

- **Both eyes eligible, enrolling both of the subject's eyes:**
  - Both eyes should be enrolled on a single Day 1 (Baseline) visit.
  - The IWRS will assign both eyes to the same treatment arm.
  - There will be separate drug supplies, records, and assessments for each study eye.
- **Both eyes eligible, enrolling only one of the subject's two eligible eyes:**
  - The eye with the higher Day 1 (Baseline) VH score should be enrolled.
  - If the VH scores are the same, the right eye should be enrolled.

5.1. Inclusion Criteria

1. Ability to give informed consent and attend all study visits.
2. Males or females of at least 18 years of age.
3. Have diagnosis of active uveitis of the posterior segment determined by the investigator to be non-infectious based on the subject's medical history, history of present illness, ocular examination, review of systems, physical examination, and any relevant, pertinent laboratory evaluations. If anterior segment inflammation is present, it must be less severe than the posterior component.
4. Have active uveitis at the Day 1 visit defined as a ≥ 1.5+ VH score (modified SUN scale) in the study eye(s), as assessed by the investigator and confirmed by a central reading center.
5. Have a BCVA ≥ 20 ETDRS letters (20/400 Snellen equivalent or better) and ≤ 75 ETDRS letters (20/32 Snellen equivalent or worse) in the study eye(s) at the Day 1 visit.
6. Subjects being treated with one of the following: methotrexate, azathioprine and mycophenolate mofetil (or an equivalent drug, e.g., mycophenolic acid) may be enrolled if the dose has remained stable for at least 30 days prior to Day 1 and is anticipated to remain stable until the end of the trial. Subject that satisfy this Inclusion criteria may not be treated with any other systemic immunosuppressant therapy and consequently cannot also satisfy the criteria described in Inclusion criteria #7.

7. Subjects being treated with systemic (oral) corticosteroids must have received a stable oral 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. These subjects will comprise the Intent-to-Taper population and will be required to taper from oral corticosteroids starting on Day 1. Subject that satisfy this Inclusion criteria may not be treated with any other systemic immunosuppressant therapy and consequently cannot also satisfy the criteria described in Inclusion criteria #6.
8. Subjects being treated with topical corticosteroid eye drops (excluding difluprednate ophthalmic emulsion) or topical non-steroidal anti-inflammatory eye drops must have received stable dosing (same medication type and frequency of use) for at least 7 days prior to Day 1 in the study eye(s). Decreases and termination of dose are allowed during the study.
9. Female subjects of childbearing potential must not be pregnant or breast-feeding, must have a negative serum pregnancy test at screening, and must be willing to undergo pregnancy tests throughout the study.
10. Female subjects of childbearing potential and male subjects able to father children must (a) have (or have a partner who has) had a hysterectomy or vasectomy, (b) abstain from intercourse throughout the course of the study, or (c) agree to practice acceptable methods of contraception throughout the course of the study (i.e., intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the investigator).

5.2. Exclusion Criteria

Ocular Infections:

1. Confirmed or suspected infectious uveitis in either eye. If the uveitis is the consequence of a previous infectious disease, such as tuberculosis, the previous infectious disease must be confirmed as no longer active and not latent.
2. Ocular or periocular infection in either eye including (but not limited to).
    a. History of herpetic infection in the study eye(s) or adnexa.
    b. Presence of known active or inactive toxoplasmosis or toxoplasmosis scar in either eye.
    c. History of cytomegalovirus infection or clinical evidence of active cytomegalovirus infection at screening and/or Day 1.

Ocular Conditions:

3. Primary diagnosis of anterior uveitis in the study eye(s).
4. The following ocular inflammatory conditions in the study eye(s):
    a. Ocular inflammation associated with Behcet's Disease
    b. Serpiginous Choroiditis
    c. Punctate Inner Choroidopathy (PIC)
    d. Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

5. Pupillary dilation inadequate for quality stereoscopic fundus photography in the study eye(s).
6. Media opacity (other than vitreous haze) that would limit clinical visualization or OCT evaluation in the study eye(s).
7. Any existing lens opacity in the study eye(s) that, in the opinion of the investigator, could:
    a. require surgical intervention during the 5-month study period to prevent or treat visual loss, or,
    b. interfere with the grading of vitreous haze, or,
    c. preclude evaluation of the posterior pole via fundus photography or OCT assessment.
8. Corneal opacity in the study eye(s) that would preclude reliable assessment of the posterior segment.
9. Uncontrolled glaucoma in the study eye(s) on Day 1, evidenced by an intraocular pressure (IOP) > 21 mmHg while on medical therapy, or chronic hypotony (IOP < 6 mmHg).
10. Any active ocular disease other than uveitis that could compromise vision in the study eye(s). These include, but are not limited to:
    a. Diabetic retinopathy
    b. Wet age-related macular degeneration
    c. Myopic degeneration with active subfoveal choroidal neovascularization
11. History of vitrectomy in the study eye(s).
12. Presence of epiretinal membrane that according to investigator's judgement is significant enough to limit improvement of macular edema.
13. Any ocular condition in the study eye(s) that would prevent improvement in visual acuity.

Concomitant Medications:

14. Use of difluprednate ophthalmic emulsion eye drops in the study eye(s) within 7 days prior to Day 1. Difluprednate ophthalmic emulsion eye drops are prohibited throughout the duration of the study.
15. Any of the following treatments prior to Day 1 or anticipated use of any of the following treatments to the study eye(s):
    a. Intravitreal injections of anti-vascular endothelial growth factors (bevacizumab, aflibercept, ranibizumab, pegaptanib, etc.) within 30 days of Day 1.
    b. Intravitreal or posterior subtenon steroids within 90 days of Day 1.
16. Any implantable corticosteroid-eluting device (e.g. Ozurdex, Iluvien or equivalent, triamcinolone acetonide [TA] intravitreal implant) in the study eye(s) with the following exceptions:
    a. Ozurdex implanted at least 6 months prior to Day 1 will be allowed.

   b. Fluocinolone acetonide implant (Iluvien, Retisert, Yutiq) implanted at least 3 years prior to Day 1 will be allowed.

17. Immunosuppressive therapy (e.g., cyclophosphamide, chlorambucil, tacrolimus or colchicine) within 30 days of Day 1, other than prednisone or equivalent or permitted immunosuppressants described in Inclusion Criteria #6.
18. Treatment with a monoclonal antibody or any other biologic therapy (i.e. etanercept, tocilizumab, adalimumab, rituximab, etc.) within 90 days prior to Day 1.
19. Use of topical ocular application of marijuana and marijuana derivatives including, but not limited to, cannabidiol topical eye drops.

Surgical:

20. Any intraocular surgery (excluding eyelid surgery and refractive laser surgery) in the study eye(s) within 90 days prior to Day 1.
21. Capsulotomy in the study eye(s) within 30 days prior to Day 1.

Malignancies:

22. Clinically suspected or confirmed central nervous system or ocular lymphoma in either eye.
23. Presence of any form of ocular malignancy in the either eye including choroidal melanoma.
24. Malignancy in remission for less than 5 years prior to study participation (except basal cell or squamous cell skin cancer or treated melanoma of the skin less than 24 months since last treatment).

Non-Ocular Conditions:

25. Allergy or hypersensitivity to investigational product or other study related procedures/medications.
26. Any recent systemic infection within 30 days of Day 1.
27. Known to be immunocompromised.
28. Active systemic sarcoidosis. Subjects with uveitis secondary to sarcoidosis will be eligible if either of the following conditions are met:
    a. Systemic sarcoidosis is not active and systemic immunosuppressive therapy has not been given in the last 6 months.
    b. Systemic sarcoidosis has remained inactive for at least 6 months and the subject isbeing treated with permitted immunosuppressants as described in Inclusion Criteria #6.
29. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that contraindicates the use of an investigational drug, might affect the interpretation of the results of the study, or renders the subject at high risk for treatment complications.
30. Any uncontrolled systemic disease.

Pregnancy:

31. Females who are pregnant or lactating and females of child-bearing potential who are not using adequate contraceptive precautions (i.e., intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the investigator).

Participation in Other Clinical Trials:

32. Participation in other investigational drug (oral or topical therapy) or device clinical trials within 30 days prior to Day 1 and/or participation in other investigational drug (intravitreal injection therapy) within 3 months or 5 half-lives (whichever is longer) prior to Day 1, or planning to participate in other investigational drug or device clinical trials during a time which would overlap with the duration of the study. This includes both ocular and non-ocular clinical trials. Exposure to investigational biologics should be discussed with medical monitor.

In addition, the investigator or Santen medical monitor may declare a subject ineligible for any sound reason.

5.3. Lifestyle Considerations

5.3.1. Contraception Requirements

There are no controlled data with the IP in human pregnancy. It is required that females of childbearing potential and male subjects able to father children abstain from intercourse or agree to practice acceptable methods of contraception throughout the course of the study (i.e., intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the investigator).

5.3.2. Fasting Prior to Blood Draws for Hematology and Chemistry Laboratory Tests

Requirements for fasting 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at visits is specified in the SoA (Table 3).

5.4. Screen Failures and Rescreening

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to IP. The following screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities: demography, screen failure details, eligibility criteria, and any SAEs reported during screening. The final study report will include screen failure information in support of these requirements.

In this study, a subject who fails screening may be considered for rescreening in consultation with the Sponsor or its designee and providing that the subject undergoes re-consent. In no case will a subject be allowed to be rescreened more than once. If a subject is to be rescreened after failing screening, a new screening period will begin, and all study eligibility criteria will need to be re-assessed and confirmed prior to randomization into the study. Rescreened subjects will be assigned a new subject number.

6. STUDY INTERVENTION

Study intervention is a general term that refers to any investigational intervention(s), marketed product(s), placebo, sham, or medical device(s) intended to be administered to a study subject according to a study protocol. In this protocol, the term Investigational Product (IP) is generally used to refer to the study interventions, which are the following three DE-109/sham regimens, one of which is randomly assigned to each subject's study eye(s) during the double-masked period: (1) DE-109 440 µg administered by intravitreal injection every 2 months, (2) sham procedure administered every 2 months, and (3) dummy (DE-109 at an undisclosed fixed dose of 44 µg to 880 µg) administered by intravitreal injection every 2 months (at the Day 1, Month 2, and Month 4 visits). During the open-label period, the IP received will be the same for all subjects: DE-109 440 µg administered by intravitreal injection every 2 months (at the Month 6, Month 8, and Month 10 visits).

6.1. Investigational Product Administered, Formulation, Packaging, and Labelling

Investigational product descriptions are provided in Table 5, including formulation, packaging, and labelling.

Table 5: Investigational Product Descriptions

Arm Abbreviated Name: Description	**DE-109: DE-109 440 µg every 2 months**	**Sham: Sham procedure every 2 months**	**Dummy: DE-109 at an undisclosed, fixed dose of 44 µg to 880 µg every 2 months**
Intervention Name	DE-109	Sham	DE-109
Investigational Medicinal Product	Sirolimus intravitreal injection, 22 mg/mL	Not applicable (empty vial)	Sirolimus intravitreal injection, 2.2 mg/mL to 44 mg/mL
Type	Drug	Other	Drug
Use	Experimental	Sham comparator	To help ensure masking of treatment assignments
Dose Formulation	Solution for injection	Not applicable	Solution for injection
Unit Dose	440 µg	Not applicable	44 µg to 880 µg
Frequency of administration	every 2 months	every 2 months	every 2 months
Number of administrations during the 6-month double-masked period	3 (Day 1, Month 2, Month 4)	3 (Day 1, Month 2, Month 4)	3 (Day 1, Month 2, Month 4)

Table 5: Investigational Product Descriptions (Continued)

Arm Abbreviated Name: **Description**	**DE-109:** **DE-109 440 µg every 2 months**	**Sham:** **Sham procedure every 2 months**	**Dummy:** **DE-109 at an undisclosed, fixed dose of 44 µg to 880 µg every 2 months**
Number of administrations during the subsequent, 6-month open-label period	During the open-label period, all subjects will receive DE-109 440 µg every 2 months for a total of 3 administrations (Month 6, Month 8, Month 10).		
Route of Administration	Intravitreal injection	Not applicable	Intravitreal injection
Sourcing	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee	Provided centrally by the Sponsor or designee
Packaging and Labeling	DE-109 solution is filled (0.2 mL) in 2 mL Type 1 glass vial, with 13 mm gray butyl stopper with B2-40 coating, and sealed with 13 mm colored Flip-Off Truedge. One vial will be placed in a unit carton. The vial and unit carton labeling will include protocol number, kit number, and storage conditions. A sterile, single-use 250 µL syringe custom marked at 20 µL as well as two needles (21G and 30G) will be placed in a carton and provided as a kit for injection use.	The vial and carton for Sham is the same as DE-109 except no DE-109 solution is filled in the Sham vial. The empty vial and unit carton labeling will include protocol number, kit number, and storage conditions. The same kit including syringe and needles will be provided for Sham as for DE-109. (Note: The sham procedure mimics an intravitreal injection without penetrating the eye [the blunt end of an empty syringe is pressed against an anesthetized eye]).	DE-109 solution is filled (0.2 mL) in 2 mL Type 1 glass vial, with 13 mm gray butyl stopper with B2-40 coating, and sealed with 13 mm colored Flip-Off Truedge. One vial will be placed in a unit carton. The vial and unit carton labeling will include protocol number, kit number, and storage conditions. A sterile, single-use 250 µL syringe custom marked at 20 µL as well as two needles (21G and 30G) will be placed in a carton and provided as a kit for injection use.

6.2. Investigational Product Storage, Preparation, Administration, Accountability, Handling, and Disposal

Refer to the Investigational Product Manual for detailed instructions regarding receipt, handling, management, storage, administration, and return/disposal of IP, as well as information regarding other clinical supplies provided by Santen.

6.2.1. Investigational Product Storage

Investigational product will be received frozen and should remain frozen in a secure, locked, dark, temperature-controlled freezer at -20°C ± 5°C (with allowable temperature excursions up to -35°C). Investigational product must be stored with access limited to the authorized site staff until the time of use.

6.2.2. Investigational Product Preparation

On study visits during the double-masked period at which IP is administered (see SoA, Table 3), the unmasked investigator or designee will perform the IP preparation and administration.

IP Preparation for Test Arm (DE-109 440 µg) and Dummy Arm (DE-109 at an undisclosed, fixed dose of 44 µg to 880 µg):

The vial of IP (unique vial number is assigned to a subject's specific study eye by IWRS) will be removed from the freezer and thawed by rotating the vial between the palms of the hands for a minimum of approximately 5 minutes, or by setting the vial at room temperature for a minimum of approximately 30 minutes. Care should be taken to protect the product from light. After the product is thawed, mix the product by gently inverting the vial a few times. Investigational product should be drawn into the provided single-use plastic syringe within 60 minutes after removing the vial from the freezer. Investigational product should be injected within 2 hours of being drawn up into the single-use syringe.

DE-109 drug product is dispensed from a 2 mL vial. Each vial contains enough IP to inject one study eye. Each vial will be used one time only.

A sterile, single-use 250 µL syringe custom marked at 20 µL as well as two needles (21G and 30G) will be provided as a kit. Each dose of DE-109 should be administered within 2 hours of being drawn up into the single-use plastic syringe. Instructions for filling the syringe are as follows:

1. Remove the sterile, single-use 250 µL syringe custom marked at 20 µL from the packaging.
    a. Attach a 21-gauge x 1 ½ inch needle to the syringe.

Figure 2: 

2. Using sterile technique, carefully draw up **more than 20 µL** of DE-109 into the plastic syringe. It should be noted that due to the slight viscosity, drawing up DE-109 will be slow.
3. Replace the needle with a 30-gauge x 0.5 inch needle in preparation for the DE-109 intravitreal injection.
   a. Ensure that the 30-gauge by 0.5 inch needle is affixed tightly to the syringe.
   b. **ALIGN THE TOP EDGE OF THE RED O RING OF THE PLUNGER WITH THE 20 µL BLACK MARK ON THE SYRINGE (See Figure 3).**
   c. PLEASE ENSURE THAT THERE ARE NO AIR BUBBLES WITHIN THE SYRINGE OR THE NEEDLE HUB PRIOR TO INJECTION.

Figure 3:

IP Preparation for Control Arm (Sham):

Removal and thawing procedures are the same for Sham as for DE-109. A syringe loading procedure similar to DE-109 should be performed; no drug product will be drawn up into the syringe.

6.2.3. Investigational Product Administration

During the double-masked period, the unmasked investigator will perform all IP administrations (DE-109 440 µg, Sham, and Dummy [an undisclosed, fixed dose of DE-109 in the range of 44 µg to 880 µg]).

The procedures for IP administration to a single study eye are shown in Table 6. Note that the subjects' pupils will already have been dilated by the masked investigator/staff prior to the conduct of the pre IP administration assessments. Detailed guidance regarding IP administration, including administration to both eyes, is provided in the Investigational Product Manual.

Table 6: Investigational Product Administration Procedure

Notes	DE-109 440 µg and Dummy (an undisclosed, fixed DE-109 dose in the range of 44 µg to 880 µg)	Sham
Note: The unmasked investigator or designee should ensure that the subject's pupils are dilated prior to IP administration. The use of sterile gloves and face mask by the unmasked study staff is recommended.		
	1. Administer at least 1 drop of topical anesthetic (topical 0.5% proparacaine hydrochloride ophthalmic solution or an equivalent topical ophthalmic anesthetic is recommended. Adjunctive administration of subconjunctival anesthesia is permitted at the discretion of the unmasked Investigator.	Same as DE-109
	2. Administer 5% povidone iodine to the study eye.	Same as DE-109
	3. Use a sterile cotton-tipped applicator to remove excess fluid from the lower conjunctival sac.	Same as DE-109
Step #4 may be omitted per the unmasked investigator's discretion.	4. Take 2 sterile cotton tipped applicators and thoroughly soak with 0.5% proparacaine topical anesthetic eye drops or an equivalent topical ophthalmic anesthetic. Place the soaked applicators, side by side, gently but firmly on the conjunctival surface at the area of the entry site described below in Step 10 and hold in place for approximately 1 minute.	Same as DE-109
	5. Insert sterile eyelid speculum.	Same as DE-109
	6. Place sterile eye drape over study eye.	Same as DE-109
	7. Prior to starting the injection procedure, DE-109 should have been prepared as described in Section 6.2.2, with the appropriate dose of IP drawn into a 250 µL single-use plastic syringe. ENSURE THAT THERE ARE NO AIR BUBBLES IN THE SYRINGE OR NEEDLE HUB.	Removal and thawing procedures are the same for Sham as for DE-109 (Section 6.2.2). A syringe loading procedure similar to DE-109 should be performed; no drug product will be drawn up into the syringe.
	8. If the subject is phakic, the entry site is recommended to be 3.5 mm to 4.0 mm peripheral to the limbus. If the subject is aphakic or pseudophakic the entry site is recommended to be 3.0 mm to 3.5 mm peripheral to the limbus. An inferior injection site is recommended. A caliper may be used to identify the needle entry site. The intravitreal injection site may be modified at the unmasked investigator's discretion.	Not applicable

Table 6: Investigational Product Administration Procedure (Continued)

Notes	DE-109 440 µg and Dummy (DE-109 44 µg to 880 µg)	Sham
	9. Insert the needle perpendicular to the eye wall at the location specified in Step 10. The needle shaft should be inserted deep enough into the eye so as to ensure that the study drug enters into the vitreous body.	Press the blunt end of the empty syringe against the anesthetized eye and hold for approximately 10 seconds.
	10. Very slowly, inject the entire IP volume and hold for 5 seconds prior to slowly withdrawing the needle. Do not pull back on the plunger at any time prior to withdrawing the needle.	
	11. Briefly apply pressure for approximately 1 minute to the needle entry site with a sterile cotton tipped applicator.	Briefly apply pressure for approximately 1 minute to the recommended entry site (as described in this step for DE-109) with a sterile cotton tipped applicator.
	12. Remove the eyelid speculum.	Same as DE-109
	13. Patch the study eye at the unmasked investigator's discretion.	Same as DE-109
Immediately after each IP administration, the unmasked investigator or designee will conduct a safety check (finger count, hand motion, and light perception).		
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.		

6.2.4. Investigational Product Accountability

The investigator or designee is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The form documenting receipt of clinical supplies should be completed, signed, and returned as directed. A copy must be maintained at the site for the investigator's records.

The investigator or designee is responsible for ensuring that a current record is kept of the inventory and dispensing of all IP. This record will be made available to the study monitor (or designee) to account for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the investigator site must be accounted for and in no case will IP be used in any unauthorized situation. It is the responsibility of the investigator to return any used and unused supplies to the Santen (or designee) at the end of the study.

6.2.5. Investigational Product Handling and Disposal

All used/un-used vials of IP supplied by Santen must be fully accounted for by the study monitor. Accountability will be documented by use of drug accountability forms. During the

study as directed by Santen and/or when the trial is completed, used/un-used vials will be returned to Santen or designee, or destroyed at the site at the direction of Santen.

6.3. Measures to Minimize Bias: 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 44 µg to 880 µg (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.

Separate IP supplies will be assigned to each study eye. At each visit at which IP is to be administered, if one eye is enrolled, the IWRS will assign one specific IP vial for administration to the subject's study eye; if both eyes are enrolled, the IWRS will assign one specific IP vial for administration to the subject's left study eye and one specific IP vial for administration to the subject's right study eye.

A central Reading Center will be used for the fluorescein angiography, fundus photography, and OCT assessments. All central readers will be masked to each subject's IP assignment.

In case of an emergency, the investigator has the sole responsibility for determining if unmasking of a subject's treatment assignment is warranted. If the investigator decides that unmasking is warranted, the investigator should make every effort to contact the medical monitor (Table 1) prior to unmasking a subject's treatment assignment unless this could delay emergency treatment of the subject. Santen must be notified as soon as possible if the IP masking of a subject is broken. The date, time, and reason for the unmasking must be recorded in the source

documents. For unmasking, the randomized treatment assignment of a subject can be obtained from the IWRS by designated individuals following a specific IWRS unmasking procedure.

An independent statistical and programming team will be used to perform the planned interim analysis of unmasked data and the Data Monitoring Committee (DMC) will review the results and make recommendations based on the findings. To unmask the data for the analysis, a designee from the independent statistical and programming team will obtain the randomization codes directly from the external randomizer, without involvement of Santen. Review of unmasked data by the DMC will only occur in closed DMC sessions without participation of Santen personnel. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.

6.4. Investigational Product Compliance

Compliance with the dosing schedule specified in this protocol is critical to obtain reliable efficacy and safety data. The administration of each dose of IP to each subject's study eye(s) will be documented by the investigator/staff and recorded in the electronic Case Report Forms (eCRFs). The study monitors will verify eCRFs and other pertinent data to confirm each subject is attending visits, undergoing procedures, and receiving treatment with IP per protocol.

6.5. Concomitant Therapy

6.5.1. Collection of Prior and Concomitant Medication Information

At Screening, information on prior and concomitant medications taken within the previous 90 days will be collected. At each study visit, subjects should be questioned concerning any new medications or changes in their current medications since their previous study visit and the information should be recorded in the eCRF. Medications given specifically for antiseptic preparation of the study eye should be recorded as concomitant medications.

For all medications, the generic name, indication, route of administration, frequency, dose, start date, and stop date (if applicable) will be collected; for combination products, the brand name will also be documented.

6.5.2. Subjects with Glaucoma: Continuation of Ocular Hypotensive Medication

Subjects with glaucoma are permitted to continue their prescribed ocular hypotensive medication during the study. Any required changes to prescribed ocular hypotensive medications and/or discontinuation of ocular hypotensive medications are allowed during the study, per the investigator's judgement.

6.5.3. Tapering of Systemic Corticosteroid Therapy

For study eligibility, subjects receiving systemic (oral) corticosteroid therapy will be required to titrate the dose as needed such that they remain on a stable oral 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 Day 1. The Intent-to-Taper population is defined as those subjects who are receiving oral corticosteroid therapy on Day 1. Starting on Day 1, the corticosteroid dose of these subjects should be reduced weekly over a maximum of 8 weeks to discontinuation (0 mg/day) according to the following tapering schedule:

- Reduce by 10 mg weekly until a dose of 20 mg is reached
- Then reduce by 5 mg weekly until a dose of 10 mg is reached
- Then reduce by 2.5 mg weekly until reaching 0 mg

If the above-suggested tapering scheme needs to be amended significantly, the investigator must consult with the study medical monitor.

6.5.4. Continuation of Stable Doses of Topical Ocular Corticosteroid Medication, Topical Ocular Non-Steroidal Anti-Inflammatory Medication, or Selected Immunosuppressants

Use of difluprednate ophthalmic emulsion eye drops in the study eye(s) within 7 days prior to Day 1 is prohibited. Difluprednate ophthalmic emulsion eye drops are prohibited throughout the duration of the study. Subjects being treated with other topical corticosteroid eye drops or with topical non-steroidal anti-inflammatory eye drops must have received stable dosing (same medication type and frequency of use) for at least 7 days prior to Day 1 in order to be eligible for enrollment in the study. These subjects will be allowed to continue the therapy at stable dosing during the study (same medication type and frequency of use). Decreases and termination of dose are allowed during the study. Similarly, subjects being treated with one of the following: methotrexate, azathioprine, or mycophenolate mofetil must have received a stable dose for at least 30 days prior to Day 1 with the expectation that the dose will remain stable until the end of the trial. These subjects should continue the therapy at a stable dose during the study.

6.5.5. Protocol-Specified Medications Pre and Post Investigational Product Administration

Below are medications to be administered pre and post IP administration.

Pre IP administration:

- **Pupil dilation:** 1% Mydriacyl and 2.5% phenylephrine or equivalent
- **Ocular antisepsis:** 5% povidone iodine (also see Table 6, IP administration procedure)
- **Topical anesthetic**: recommended 0.5% proparacaine hydrochloride or equivalent (also see Table 6, IP administration procedure).

Adjunctive administration of subconjunctival anesthesia is permitted at the discretion of the unmasked Investigator.

Post IP administration:

- **Topical corticosteroid:** 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. Subjects that are already receiving a stable dose of prednisolone acetate eye drops as concomitant therapy should contact the medical monitor prior to IP administration to discuss adjusting of the dosing frequency.

6.5.6. Rescue Therapy

Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS, other than intravitreal DE-109. Other protocol-allowed or specified medications that are not considered rescue therapy are listed in Section 6.5.7.

The following are examples of rescue therapies:

- Systemic corticosteroid therapy (except as described in Section 6.5.7)
- New systemic treatment with an immunosuppressant agent
- Increase in dose of ongoing therapy with methotrexate, azathioprine, or mycophenolate mofetil (see inclusion criteria Section 5.1, #6)
- Anti-vascular endothelial growth factor therapy (anti-VEGF)
- New or increased dose/frequency of topical ocular corticosteroid to the study eye (see inclusion criteria Section 5.1, #8)
- New or increased dose/frequency of topical ocular nonsteroidal anti-inflammatory agent to the study eye (see inclusion criteria Section 5.1, #8)
- 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

Because rescue therapies such as those noted above may or will have a therapeutic effect on the uveitis in the posterior segment, they are prohibited unless 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 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.
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.

When deemed medically necessary, rescue therapy may be administered at the discretion of the investigator, even if none of the protocol-specified rescue criteria noted above are satisfied. The investigator should contact the study medical monitor to discuss the rescue treatment plan prior to the administration of rescue therapy. If the investigator is unable to reach the medical monitor, rescue treatment should be administered per the investigator's clinical judgment and the medical monitor should be notified as soon as possible to discuss future on-study treatment plans for the subject.

If both eyes are enrolled and rescue therapy for one of the two enrolled study eyes is required, local rather than systemic therapy is encouraged, if appropriate, because systemic therapies will affect the response in the other study eye.

If rescue therapy is administered, the generic name, indication, route of administration, frequency, dose, start date, and stop date (if applicable) will be recorded in the eCRF.

Satisfaction of any of the protocol-specified rescue criteria noted above also satisfies the definition of an ESI of clinically significant new or worsening of uveitis, requiring reporting within 24 hours of knowledge of the event as described in Section 8.2.13.

6.5.7. Protocol-Allowed or Specified Medications not Considered Rescue Therapy

Protocol-allowed or specified medications NOT considered rescue therapy are as follows:

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

6.5.8. Prohibited Concomitant Medications or Treatments

Any treatment that would have a therapeutic effect on the uveitis in the posterior segment is prohibited, as described in Section 6.5.6.

Refer to the inclusion and exclusion criteria (Section 5.1 and Section 5.2) for other specific prohibited concomitant medications or treatments.

6.6. Dose Modification

In this study, the IP dose/regimen is assigned by randomization. Dose titration or modification is not allowed. Rescue therapy is allowed for worsening of uveitis as described in Section 6.5.6.

6.7. Intervention after the End of the Study

No subsequent intervention is currently planned for subjects completing this 12-month study.

7. DISCONTINUATION OF INVESTIGATIONAL PRODUCT AND SUBJECT DISCONTINUATION/WITHDRAWAL FROM STUDY

7.1. Discontinuation of Investigational Product

Subjects may be discontinued from IP administration for adverse events, non-compliance with study drug, protocol deviation, lack of efficacy, withdrawal by subject, lost to follow-up, study termination, or other reasons. The investigator or Santen medical monitor may discontinue a subject from further IP administration for reasons related to the best interest of the subject. If a subject is discontinued from IP administration at any point during the study, he or she will be encouraged to remain in the study and attend all scheduled visits for safety follow up, including ocular procedures other than IP administration, through Month 12. If a subject decides not to enter into the open-label period, the investigator should discuss the option of early termination with the medical monitor. Subjects that have received at least one open-label treatment are encouraged to remain in the study and attend all scheduled visits for safety follow up through Month 12.

7.2. Subject Early Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. At the time of discontinuing from the study, if possible, an early termination visit will be conducted to collect the data as shown in the SoA (Table 3); the subject will be permanently discontinued both from the IP and from the study at that time.

If the subject withdraws consent for disclosure of future information, Santen may retain and continue to use any data collected before such a withdrawal of consent. If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.

- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or discontinuation of the study is handled as indicated in Section 10.1.9.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 3). Protocol waivers or exemptions from study inclusion/exclusion criteria are not allowed. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

8.1. Visit Details and Efficacy Assessments

8.1.1. Visit Details

The SoA (Table 3) provides a high-level overview of the visits. The sections below provide visit guidance/details by visit.

8.1.2. Screening Visit, Day -30 to Day -1

Subjects taking oral corticosteroids: To be randomized into the study, subjects being treated with systemic (oral) corticosteroids must be on a stable oral 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. Tapering of oral corticosteroids will begin on Day 1 according to the tapering regimen described in Section 6.5.3

Visit details:

- Explain the purpose and details of the study to the subject and obtain written informed consent prior to performing any study-related procedures.
- Obtain the subject's demographic information, medical and surgical history (including history of NIU-PS), current ocular and systemic conditions, and medication history (including systemic corticosteroid status).
- Perform physical examination.
- Record vital signs.
- If the subject is a woman of child-bearing potential, collect blood for serum pregnancy test.
- Collect fasting or non-fasting blood for serum chemistry and hematology tests for laboratory analysis as described in the SoA (Table 3).
- Obtain urine sample for urinalysis.
- Assess BCVA using ETDRS charts.
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography for submission to reading center.
- Assess for adverse events (occurring after the signing of the informed consent).

- Record concomitant medications (including systemic corticosteroid medication status).
- Review the inclusion and exclusion criteria. **Do not continue with screening procedures in any subject who does not meet the screening eligibility requirements.**
- Enter the subject information into the EDC system (Medidata) for the Screening visit to obtain the Subject ID.

Rescreening after screen failure: Depending on the reason(s) for screen failure, rescreening of a subject may be allowed; see Section 5.4.

8.1.3. Double-Masked Treatment Period, Day 1

At all study visits at which masked IP is administered:

- The masked investigator or designee performs assessments in both eyes that are prior to IP administration.
- The unmasked investigator or designee performs IP administration (DE-109 intravitreal injection / sham procedure), the safety check immediately after IP administration (finger count, hand motion, and light perception), and the post-administration assessments.

Visit details:

Verify that central laboratory results from blood and urine collected at screening have been obtained and reviewed.

Perform the following assessments prior to randomization and prior to administration of IP:

- If the subject is a woman of child-bearing potential, conduct urine pregnancy test. A positive pregnancy test requires exclusion from the study.
- Assess BCVA using ETDRS charts to confirm study eye(s) eligibility (inclusion Section 5.1, #5)
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Administer the VFQ-25.
- Obtain fundus photography for immediate submission to reading center.
- Measure IOP.
- Perform slit-lamp biomicroscopy. Assess intended study eye(s) eligibility with respect to VH score (≥ 1.5+ in each intended study eye).
- Perform indirect ophthalmoscopy.
- Perform OCT.
- Perform fluorescein angiography (recommended post investigator eligibility confirmation).

- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Confirm qualifying VH score for each of the subject's intended study eyes has been obtained from the Reading Center based on fundus photography at Day 1. Perform final review of inclusion/exclusion criteria. If the subject and the subject's intended study eye(s) meet all eligibility criteria, randomize the eye(s) into the study using the EDC system (Medidata, including IWRS component) to obtain the assigned vial number(s) to be dispensed to the study eye(s).

The unmasked investigator or designee performs IP preparation and administration as specified in Section 6.2.2 and Section 6.2.3.

Perform the following post IP administration assessments in both eyes:

- Within 30 minutes after the administration of IP:
  - Perform slit-lamp biomicroscopy
  - Perform indirect ophthalmoscopy
- Measure IOP as follows: At approximately 40 (±10) minutes following administration of IP, measure IOP by applanation tonometry. If there is an increase of ≥ 10 mmHg at 40 (±10) minutes post IP administration compared to prior to IP administration, administer topical IOP-lowering drops until the subject returns for follow-up, per the investigator's discretion. (An unscheduled visit may apply). Note that IOP increase of ≥ 10 mmHg should be reported as an adverse event.
- Initiate administration of prednisolone acetate eye drops, for 8 days following each IP administration, 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.
- Assess for adverse events.
- Record concomitant medications.

8.1.4. Double-Masked Treatment Period, Day 14

Allowable visit window: Day 14 ± 2 days

Visit details:

If the subject has consented to the pharmacogenomics sampling protocol, collect blood for pharmacogenomics. Pharmcogenomic 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.

Perform the following assessments in both eyes:

- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).

- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Record the study visit in the EDC system (Medidata) for Day 14.

8.1.5. Double-Masked Treatment Period, Month 1

Allowable visit window: Day 30 ± 3 days

Visit details:

Perform the following assessments in both eyes:

- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Record the study visit in the EDC system (Medidata) for Month 1.

8.1.6. Double-Masked Treatment Period, Month 2

At all study visits at which masked IP is administered:

- The masked investigator or designee performs assessments in both eyes that are prior to IP administration.
- The unmasked investigator or designee performs IP administration (DE-109 intravitreal injection / sham procedure), the safety check immediately after IP administration (finger count, hand motion, and light perception), and the post-administration assessments.

Allowable visit window: Day 60 ± 3 days

Visit details:

Perform the following assessments/procedures in both eyes prior to administration of IP:

- If the subject is a woman of child-bearing potential, conduct urine pregnancy test. A positive 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.
- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Use the EDC System (Medidata, including IWRS component) to record the Month 2 visit and obtain the vial number(s) assigned to the subject's study eye(s).

The unmasked investigator or designee performs IP preparation and administration as specified in Section 6.2.2 and Section 6.2.3.

Perform the following post IP administration assessments in both eyes:

- Within 30 minutes after the administration of IP:
  - Perform slit-lamp biomicroscopy
  - Perform indirect ophthalmoscopy
- Measure IOP as follows: At approximately 40 (±10) minutes following administration of IP, measure IOP by applanation tonometry. If there is an increase of ≥ 10 mmHg at 40 (±10) minutes post IP administration compared to prior to IP administration, administer topical IOP-lowering drops until the subject returns for follow-up, per the investigator's discretion. (An unscheduled visit may apply). Note that IOP increase of ≥ 10 mmHg should be reported as an adverse event.
- Initiate administration of prednisolone acetate eye drops, for 8 days following each IP administration, 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.
- Assess for adverse events.

- Record concomitant medications.

8.1.7. Double-Masked Treatment Period, Month 3

Allowable visit window: Day 90 ± 3 days

Visit details:

Perform the following assessments in both eyes:

- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform fluorescein angiography.
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Record the study visit in the EDC system (Medidata) for Month 3.

8.1.8. Double-Masked Treatment Period, Month 4

Allowable visit window: Day 120 ± 3 days; other procedures/details are the same as for Month 2 (Section 8.1.6).

8.1.9. Double-Masked Treatment Period, Month 5

Note: Subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at Month 5.

Allowable visit window: Day 150 ± 3 days

Visit details:

Perform the following assessments in both eyes:

- Perform physical examination. Note: if this was performed at Month 3 under a previous version of the protocol it does **not** need to be repeated.
- Record vital signs. Note: if this was performed at Month 3 under a previous version of the protocol it does **not** need to be repeated.

- Collect fasting blood for serum chemistry and hematology tests for laboratory analysis. Note: if these samples were collected at Month 3 under a previous version of the protocol they do **not** need to be repeated.
- Obtain urine sample for urinalysis. Note: if this sample was collected at Month 3 under a previous version of the protocol it does **not** need to be repeated.
- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Administer the VFQ-25. Note: if this was performed at Month 3 under a previous version of the protocol it does **not** need to be repeated.
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform fluorescein angiography.
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Record the study visit in the EDC system (Medidata) for Month 5.

8.1.10. Double-Masked Treatment Period, Month 6

Allowable visit window: Day 180 ± 7 days; other procedures/details are the same as for Month 2

8.1.11. Open-Label Treatment Period, Month 7

Allowable visit window: Day 210 ± 7 days; other procedures/details are the same as for Month 1 (Section 8.1.5).

8.1.12. Open-Label Treatment Period, Month 8

Allowable visit window: Day 240 ± 7 days; other visit procedures/details are the same as for Month 2 (Section 8.1.6).

8.1.13. Open-Label Treatment Period, Month 9

Allowable visit window: Day 270 ± 7 days; other visit procedures/details are the same as for Month 1 (Section 8.1.5).

8.1.14. Open-Label Treatment Period, Month 10

Allowable visit window: Day 300 ± 7 days; other visit procedures/details are the same as for Month 2 (Section 8.1.6).

8.1.15. Open-Label Treatment Period, Month 11

Allowable visit window: Day 330 ± 7 days; other visit procedures/details are the same as for Month 1 (Section 8.1.5).

8.1.16. Month 12/Exit/Early Termination Visit

Allowable visit window for Month 12 visit: Day 360 ± 7 days

Visit details:

Perform the following procedures/assessments in both eyes at Month 12 or at early termination from study if a subject discontinues both study participation and IP after Day 1 and before the Month 12 visit:

- Perform physical examination.
- Record vital signs.
- If the subject is a woman of child-bearing potential, collect blood for serum pregnancy test.
- Collect fasting or non-fasting blood for serum chemistry and hematology tests for laboratory analysis as described in the SoA (Table 3).
- Obtain urine sample for urinalysis.
- Assess BCVA using ETDRS charts.
- Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically).
- Administer the VFQ-25.
- Measure IOP.
- Perform slit-lamp biomicroscopy.
- Perform indirect ophthalmoscopy.
- Obtain fundus photography.
- Perform fluorescein angiography
- Perform OCT.
- Assess for adverse events.
- Record concomitant medications (including systemic corticosteroid medication status).

Record the study visit in the EDC system (Medidata) for the Month 12/Exit/Early Termination visit.

8.1.17. Unscheduled Visits

If a subject requires evaluation between scheduled visits, applicable study procedures may be performed as specified in the protocol (e.g., if performed, assessment in both eyes for visual acuity must follow protocol-specified BCVA evaluation using ETDRS chart). At a minimum, unscheduled visits should include (1) assessment for adverse events and (2) recording of concomitant medications. DE-109 will not be administered at an unscheduled visit.

8.1.18. Efficacy Assessments

These sections provide descriptions of assessments from which one or more efficacy endpoints are determined (VH, BCVA, OCT, and use of systemic corticosteroids) as well as the patient reported outcome (VFQ-25). Note that BCVA and OCT are also assessments of safety. Planned time points for all assessments are provided in the SoA (Table 3) and details by visit are provided in Section 8.1.1.

8.1.19. Vitreous Haze

Vitreous haze (VH) will be assessed using the modified SUN scale, as follows:

Table 7: Vitreous Haze (VH), Modified SUN Scale

Step	Description
0	No inflammation
0.5+	Trace Inflammation (slight blurring of the optic disc margins and or loss of nerve fiber layer reflex)
1+	Mild blurring of the retinal vessels and optic nerve
1.5+	Optic nerve head and posterior retina view obstruction greater than 1+ but less than 2+
2+	Moderate blurring of the optic nerve head
3+	Marked blurring of the optic nerve head
4+	Optic Nerve head not visible
A VH score of 1.5+ will be used to categorize subjects with a VH score of greater than 1+ but less than 2+	

VH scores will be recorded during slit-lamp biomicroscopy evaluations. Study eligibility with respect to VH will be confirmed by central reading of fundus photographs; the reading center procedures are detailed in a procedure manual.

8.1.20. Best-Corrected Visual Acuity

The best-corrected visual acuity (BCVA) will be recorded (for both eyes) using ETDRS charts and the total number of letters at 4 meters and 1 meter will be recorded. If a subject's visual acuity is so poor that he/she cannot read any chart letters when tested at 1 meter, then the subject's ability to count fingers, detect hand motion, or have light perception should be evaluated. Refer to Section 12.2 for details of the visual acuity assessments.

8.1.21. Optical Coherence Tomography

Optical Coherence Tomography (OCT) will be performed for both eyes. Central subfield thickness will be recorded. OCT will be performed using reading center certified photographers, equipment, and standardized protocols. Refer to the reading center procedure manuals for the complete protocol.

8.1.22. Use of Systemic Corticosteroids

Subjects use of systemic corticosteroids will be collected and this information will be used in determining efficacy endpoints assessing corticosteroid tapering success.

8.1.23. National Eye Institute Visual Functioning Questionnaire – 25 (VFQ-25)

The National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25), version 2000, including the appendix questions, will be administered (National_Eye_Institute, 2000). The VFQ-25 is a patient reported outcome that was designed to measure the dimensions of self-reported vision-targeted health status that are most important for persons who have chronic eye diseases. The VFQ-25 is provided in Section 12.1.

8.2. Safety Assessments

This section describes the following safety assessments: slit-lamp biomicroscopy, indirect ophthalmoscopy, IOP, fundus photography, fluorescein angiography, laboratory tests (serum chemistry, hematology, and urinalysis), pregnancy testing, physical examination, and vital signs. Assessment of AEs and SAEs is described in Section 8.3. Assessment of BCVA and OCT are described in Section 8.1.20 and Section 8.1.21, respectively. Planned time points for all assessments are provided in the SoA (Table 3) and details by visit are provided in Section 8.1.1.

8.2.1. Slit-Lamp Biomicroscopy

Slit-lamp biomicroscopy will be used to examine eye structures for both eyes during screening and at each follow-up study visit. At visits when IP is administered, slit-lamp biomicroscopy will be performed prior to IP administration and then again within 30 minutes after IP administration. Areas to be assessed include vitreous, lids, conjunctiva, cornea, anterior chamber cells and flare, iris, pupil, lashes, ocular motility, lens, and cataract status.

8.2.2. Vitreous Cells

Slit-lamp biomicroscopy will be used to assess vitreous cells. The following SUN scale for vitreous cell count will be used to measure vitreous cells:

Vitreous Cell Count Scale
(1 mm x 3 mm beam in anterior vitreous)

0	0 cells
0.5+	1-10 cells
1+	11-20 cells
2+	21-30 cells
3+	31-100 cells
4+	>100 cells

8.2.3. Anterior Chamber Cells

Slit-lamp biomicroscopy will be used to assess anterior chamber cells. The following scale will be used to measure anterior chamber cells:

Anterior Chamber Cells
(1 mm x 1 mm slit beam)

0	0 cells
0.5+	1-5 cells
1+	6-15 cells
2+	16-25 cells
3+	26-50 cells
4+	>50 cells

8.2.4. Anterior Chamber Flare

Slit-lamp biomicroscopy will be used to assess anterior chamber flare. The following scale will be used to measure anterior chamber flare:

Anterior Chamber Flare

0	None
1+	Faint
2+	Moderate (iris and lens details clear)
3+	Marked (iris and lens details hazy)
4+	Intense (fibrin or plastic aqueous)

8.2.5. Terminology for Biomicroscopy Findings

Consistency in the recording of biomicroscopy findings will be facilitated by providing a selection of possible terms on the eCRF for each area to be assessed; additional terms may be recorded as needed. Whenever possible, consistency should be maintained in the use of terms between examinations.

8.2.6. Indirect Ophthalmoscopy

Indirect ophthalmoscopy will be used to examine the retina of each eye during screening and at each follow-up study visit, and will be performed with pupil dilation. At visits when IP is administered, indirect ophthalmoscopy will be performed prior to IP administration and then again within 30 minutes after IP administration. Areas to be assessed include retina vessels, macula, fovea, periphery, optic nerve, and vitreous. Consistency in the recording of findings will be facilitated by providing a selection of possible terms on the eCRF for each area to be assessed; additional terms may be recorded as needed.

8.2.7. Intraocular Pressure

Intraocular Pressure (IOP) will be measured during screening and at each follow-up study visit. The examiner will measure IOP in each eye and record results in mmHg (e.g., 24). A single measurement is made to obtain a determination of IOP. The same contact tonometer employing the investigator's standard technique will be used throughout the study.

At visits when IP is administered, IOP will be measured prior to IP administration and at approximately 40 (±10) minutes after IP administration. See the visit details of dosing visits (e.g., Day 1 visit details, Section 8.1.3).

Tonometer calibration: The tonometer must be calibrated for accuracy before the first subject undergoes screening, and periodically according to manufacturer's instructions thereafter, until the last subject has exited the study. For checking calibration, follow the manufacturer's instructions. If when checked, the variation is within ±2 mmHg, the tonometer is considered adequately calibrated. However, if the variation exceeds this amount, the tonometer should be sent for repair and a different, adequately calibrated instrument should be used for IOP measurement. The date of each calibration, along with the name and signature (or initials) of the person who performed the calibration, must be documented. The tonometer calibration record will be retained as a part of the study record.

8.2.8. Fundus Photography

At each visit, digital color fundus photography will be taken of both eyes using reading center certified photographers, equipment, and standardized protocols. Fundus photographs will be submitted to a central reading center. The procedures are detailed in the reading center procedure manual.

8.2.9. Fluorescein Angiography

Wide field fundus fluorescein angiography (FA) will be taken of both eyes using reading center certified photographers (Day 1), equipment and a standardized protocol at the visits as specified in the SoA (Table 3). Refer to the reading center procedure manual for the complete protocol.

8.2.10. Clinical Safety Laboratory Assessments

- Fasting or non-fasting blood samples and urine samples will be obtained for laboratory assessments according to the SoA (Table 3). Samples will be sent for analysis to the designated central laboratory. Note: Blood and urine samples should be collected before injection of fluorescein.

- See Section 10.2 for the clinical laboratory tests to be performed.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease (uveitis), unless judged by the investigator to be more severe than expected for the subject's condition. Lab shifts within the range of normal should generally not be considered AEs.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 60 days after the last IP administration should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Santen medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and Santen notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Table 3).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

A retest of screening laboratory tests is permitted only if there is reason to believe the initial value was either due to a sample processing error or an extenuating circumstance.

8.2.11. Physical Examination

A full body systematic physical examination will be conducted by the investigator/designee.

8.2.12. Vital Signs

Systolic and diastolic blood pressure should be measured only after the subject has been in a sitting position for at least 5 minutes, and will be recorded in millimeters of mercury (mmHg). Measurement with an automated sphygmomanometer is acceptable.

Heart rate should be measured only after the subject has been in a sitting position for at least 2 minutes, and will be recorded in beats per minute (bpm).

Temperature should be measured.

8.2.13. Events of Special Interest

Events of Special Interest (ESIs) are medical events both anticipated and unanticipated that may have particular impact on the benefit/risk profile of DE-109 and therefore may require more detailed characterization. The DE-109 Investigational Brochure is the source for defining the DE-109 ESIs and should be consulted for further information.

The DE-109 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).

  Note: When documenting clinically significant new or worsening uveitis, the anatomic location (e.g., anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis) should be specified.
- Endophthalmitis / Sterile Endophthalmitis in the study eye – A guided questionnaire is provided as part of the eCRFs to facilitate the documentation of endophthalmitis and sterile endophthalmitis. Endophthalmitis is also to be reported as an SAE (Section 10.4).
- Traumatic cataract in the study eye
- Vitreoretinal hemorrhage in the study eye
- Drug depot in visual axis in the study eye
- Retinal detachment (also to be reported as an SAE, Section 10.4) in the study eye
- Increased IOP (> 10 mmHg as compared to baseline). Note that certain instances of increased IOP are to be reported as an SAE (IOP >35 mmHg that persists for at least 7 days despite pharmacologic therapy, Section 10.4) in the study eye.
- Cataract (new or worsening from baseline) in the study eye
- Investigational product administration error considered to be significant by the investigator (examples include administration of IP from an incorrect kit and IP administration error attributed to some aspect of the instructions provided)
- Pregnancy (see Section 8.2.14)

Additionaly below are the two (pregnancy and medication error) ESIs that need to be reported regardless of the study eye involvement:

Most ESIs are AEs, some ESIs may also be SAEs, and some ESIs may not be AEs (e.g., an IP administration error may not be an AE; pregnancies are not AEs). However, all ESIs should be reported within 24 hours of knowledge of the event using applicable eCRFs and recording as

much information as available. ESIs should be followed by the investigator to the same extent as SAEs, that is, until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained. Monitoring for pregnancy and follow-up of pregnancy is described in Section 8.2.14.

8.2.14. Pregnancy Testing, Monitoring, and Reporting

8.2.15. Pregnancy Testing

If the subject is a woman of child-bearing potential, a blood sample will be obtained during screening for a serum pregnancy test. Samples will be sent for analysis to the central laboratory. Urine samples will be collected for pregnancy tests prior to IP administrations as specified in the SoA (Table 3). Urine samples will be analyzed at the site with results available prior to administration of IP.

8.2.16. Pregnancy Monitoring and Reporting Procedures

Pregnancy in female subjects and female partners of male subjects will be monitored starting from screening through the Month 12/Exit/Early Termination visit.

Although not considered an AE or SAE, pregnancy is an ESI and requires careful monitoring and follow up. If a pregnancy is reported by a study subject (or in the partner of a study subject), the investigator must:

- Inform Santen within 24 hours of learning of the pregnancy.
- If the pregnancy has occurred in a study subject, discontinue further IP administration and/or withdraw the subject from the study.
- Report pregnancy information on the eCRF following instructions.
- Follow the pregnancy until outcome is known. Santen will request specific follow-up on a case-by-case basis.

Additional details regarding collection, reporting, and follow-up of pregnancy is provided below:

Female subjects who become pregnant: The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Santen within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to Santen. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an Event of Special Interest (ESI). Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the IP by the investigator will be reported to Santen. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous

reporting. Any female subject who becomes pregnant while participating in the study will discontinue IP and be withdrawn from the study.

Male subjects with partners who become pregnant: The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to Santen within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Santen. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

8.3. Adverse Events and Serious Adverse Events

The definitions of AE and SAE are provided in Section 10.4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) to the masked or unmasked investigator.

The masked and unmasked investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and following up on-going AEs and SAEs as specified below.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be monitored for and collected at the time points specified in the SoA (Table 3), from the signing of the Informed Consent Form (ICF) until the subject withdrawal or the scheduled exit visit. (Note: Although AEs will be monitored for and collected prior to IP administration, the statistical data analysis will determine and summarize treatment-emergent AEs, i.e., those AEs that began or worsened in severity after the first IP administration.)

All SAEs will be recorded and reported to Santen or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.4. The investigator will submit any updated SAE data to Santen within 24 hours of it being available.

Investigators are not obligated to monitor for new AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify Santen.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.4. 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.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

All reported AEs should be followed by the investigator until resolution or until the subject's participation in the study ends.

More extensive follow-up is required for (1) SAEs and (2) IP related AEs that lead to or cause early withdrawal of a subject from the study. Both of these types of events should be followed by the investigator until the event is determined to be resolved, irreversible, chronic, stable, the subject withdraws consent, or no further information can be reasonably obtained. As described in Section 8.2.13, ESIs are followed up to this same extent.

In addition to the above, Santen (or designee) may request, on a case-by-case basis, follow up of events/subjects beyond the scheduled exit visit.

Prior to database lock, follow-up information on an individual SAE or AE (or ESI) will be entered into the eCRF. When database lock has already been completed, or if information requested by Santen is not part of the eCRF, the site's response to follow-up requests should be emailed or documented on paper and faxed to Santen Global Pharmacovigilance (see Table 1).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Santen of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.

Santen has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Santen will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Santen will prepare investigator safety reports for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Santen policy and forward them to investigators as necessary. An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Santen will review and then file it along with the Investigational Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4. Pharmacogenomics

All subjects participating in the study will have the option to participate in blood sampling for pharmacogenomics and this will be consented to collect this optional test. Subjects who do not wish to participate in the pharmacogenomic sampling may still participate in the study. [redacted] on Day 14 visit, but may be collected at any time during the study or at a separate post study visit, if necessary, as shown in the SoA (Table 3). [redacted]

[redacted]
separate procedure manual.

[redacted]
investigator and participants.

9. STATISTICAL CONSIDERATIONS

Unless specified otherwise, efficacy measures will be summarized by planned (i.e., randomized) treatment and based on the FAS population, and safety measures will be summarized by actual treatment received and based on the Safety population. All efficacy endpoint analyses will be performed on eyes enrolled in the study (referred to as study eyes). Safety assessments that pertain to the eye will be analyzed by the study eye and fellow eye separately. Safety assessments that pertain to the subject will be analyzed at the subject level.

Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, medium, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

Statistical testing is planned for the analysis of efficacy endpoints of the double-masked period only (not safety endpoints) and will assess for superiority of efficacy observed in the test arm (440 µg DE-109 every 2 months) compared to the sham control. Statistical testing will not involve the dummy arm, which is included in the study to help ensure masking of treatment assignments. Unless specified otherwise, the statistical testing will be conducted at a significance level of 0.05 (two-sided). Additional details of the statistical methods will be described in the Statistical Analysis Plan (SAP).

All data manipulations, descriptive summaries, and statistical hypothesis testing will be performed using SAS Version 9.4 or later. FDA guidance regarding case report tabulations (annotated eCRFs, SAS datasets, metadata, and SAS programs) in electronic submissions will be followed. Data definition tables will be created for SDTM and ADaM datasets separately.

9.1. Estimands

- The **primary estimand** is: Vitreous haze 0 (VH0) 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 event 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.
- The **treatment policy estimand** is: VH0 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 event. For study eyes that had missing data due to any reason, imputation by the multiple imputation-based approach will be used.
- The **composite estimand** is: 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 event prior to the specified visit
- Score = 0 if otherwise

9.2. Statistical Hypotheses

The primary efficacy endpoint (VH 0 response at Month 5) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic, stratified by 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). The null (H_0) and alternative (H_1) hypotheses are as follows:

$$H_0: \pi_{sham} = \pi_{440}$$

$$H_1: \pi_{sham} \neq \pi_{440}$$

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

9.3. Sample Size Determination

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.

9.4. Populations for Analyses

The following analysis populations for study analyses are defined: Full Analysis Set (FAS), Safety, Per-Protocol (PP), Intent-to-Taper, Macular Edema, Vision 20/40 or Worse:

- The **FAS population** will consist of all study eyes that are randomized and received at least one administration of study treatment. The FAS population will be the analysis population for the primary analysis and will use treatment as randomized.
- For analyses of ocular AEs and safety parameters assessed per eye, the **Safety population** will consist of all study eyes which received at least one administration of IP. For analyses of non-ocular AEs and safety parameters assessed per subject, the **Safety population** will consist of all subjects who received at least one administration of IP.
- The **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. Eyes to be excluded from the PP population will be identified before the unmasking of treatment assignments.

- 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.
- The **Macular Edema population** will be a subset of the FAS population and will consist of study eyes with CST ≥ 300 microns at baseline.
- 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.

9.5. Statistical Analyses

Details of statistical analyses will be described in the SAP, which will be developed and finalized before database lock. This section is a summary of the planned statistical analyses of the primary and secondary endpoints (see Table 4).

9.5.1. Handling of Missing Values

In the analysis of VH 0, VH 0 or 2-unit decrease (improvement), and VH 0 or 0.5+ responses:

- Subjects who (a) receive rescue therapy for conditions other than worsening of uveitis or (b) are rescued due to the worsening of uveitis but do not meet the protocol-defined rescue criteria, missing VH scores subsequent to receiving rescue therapy will be imputed using a multiple imputation-based approach before receiving rescue therapy.
- Missing VH scores of subjects not rescued before Month 5/Month 3 visit will be imputed using a multiple imputation-based approach.

The multiple imputation model will include vitreous haze measures at preceding visits and baseline characteristics. The response status will then be determined based on the observed or imputed VH scores.

No imputation is needed for composite score analysis as eyes with missing VH scores will be assigned a score of zero, unless they are rescued due to the worsening of uveitis or discontinued from the study due to lack of efficacy or adverse event (which will be assigned with a score of -1).

For medical events including AEs, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. The same rules will be followed to impute completely or partially missing start and end dates of non-study medications.

Unless specified otherwise, descriptive summaries will be based on observed cases. No imputation of missing scores will be implemented.

Additional details on handling of missing data and sensitivity analyses on imputation methods will be provided in the SAP.

9.5.2. Efficacy Analyses

Rescue therapy is defined in Section 6.5.6 and is essentially any treatment that would have a therapeutic effect on NIU-PS other than intravitreal DE-109. Rescue therapy is permitted in the case of worsening of uveitis that satisfies protocol-defined rescue criteria. The use of rescue therapy is considered in assessing the VH response endpoints (VH 0 response, VH 0 or 2-unit improvement, and VH 0 or 0.5+ response). In the analysis of these endpoints at a specific follow-up visit (e.g., Month 5 or Month 3), subjects who met one of the protocol-defined rescue criteria will be assessed as non-responders regardless of whether the subjects were rescued or not.

Table 8: Endpoint Statistical Analysis

Endpoint	Statistical Analysis Methods
Primary endpoint: VH 0 response[a] at Month 5	For the primary analysis of VH 0 response at Month 5, the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by 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) will be conducted. Logistic generalized estimating equation (GEE) model, treatment policy strategy, last-observation-carried-forward (LOCF) imputation, and multiple imputation with tipping point analysis will be used as a sensitivity analysis.
Secondary endpoints: **Key secondary efficacy endpoints**: • Composite endpoint[b] at Month 5 • VH 0 response at Month 3 • Composite endpoint at Month 3	A hierarchical approach will be used to control the overall Type I error rate associated with the multiple comparisons across the primary and the key secondary efficacy endpoints. If the hypothesis testing for the primary endpoint successfully rejects the null hypothesis, the first key secondary efficacy endpoint will be tested, and so on. All the other secondary efficacy endpoints are supportive in nature. Therefore, no formal hypothesis testing will be performed on secondary efficacy endpoints. Two-sided 95% confidence intervals and nominal p-values may be reported for them, and such results will be interpreted descriptively in terms of the support they provide to the treatment comparisons for the primary and the key secondary efficacy endpoints in the sense of logical consistency.

Table 8: Endpoint Statistical Analysis (Continued)

Endpoint	Statistical Analysis Methods
Other secondary efficacy endpoints (double-masked period of study): • VH 0 or 2-unit response[c] at Month 5 • VH 0 or 2-unit response at Month 3 • VH 0 or 0.5+ response[d] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering success with resolution[e] at Month 5 • Corticosteroid tapering success with resolution at Month 3 • BCVA 3-line response[f] at Month 5 • BCVA 3-line response at Month 3 • Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT • Change from baseline in CST at Month 3 as measured by OCT • Use of rescue therapy before Month 5 • Use of rescue therapy before Month 3 **Other secondary efficacy endpoints (open-label period of study):** • 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 Note: Additional secondary/exploratory efficacy endpoints will be specified in the Statistical Analysis Plan.	**For secondary efficacy endpoints during double-masked period:** All binary secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by number of enrolled eyes from a subject (one eye or two eyes), baseline systemic (oral) corticosteroid use (yes or no), and region (US vs. non-US). Change-from-baseline endpoints will be analyzed by a mixed-effects model for repeated measures (MMRM) using observed cases. The statistical model for the analysis of each continuous secondary endpoint may be adjusted if it fails to converge. More details regarding model specifications will be provided in the SAP. **For secondary efficacy endpoints during open-label period:** No formal inferential analysis will be performed. Summary statistics will be provided.

Table 8: Endpoint Statistical Analysis (Continued)

Endpoint	Statistical Analysis Methods
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale.

[a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale.

[b] Refer to composite score scales defined in the composite estimand in this table.

[c] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale.

[d] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale.

[e] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at a stable prednisone-equivalent dose of between ≥15 mg/day and ≤40 mg/day that has remained stable for at least 1 week [7days] prior to and including on Day 1).

[f] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤70 ETDRS letters (Snellen equivalent of 20/40 or worse).

9.5.3. Subpopulation Analyses

All the analyses listed in Section 9.5.2 will be repeated on the PP, Intent-to-Taper, Macular Edema, and Vision 20/40 or Worse sub-populations.

9.5.4. Safety Analyses

All safety analyses will be performed on the Safety Population.

Safety of DE-109 will be assessed by AEs and evaluation with slit-lamp biomicroscopy, indirect ophthalmoscopy, BCVA, intraocular pressure (IOP), fundus photography, fluorescein angiography, laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations and vital signs.

Besides the overall summary of AEs, subjects with any AE(s) will be tabulated by system organ class (SOC) and preferred term specified in MedDRA dictionary. They will also be tabulated by SOC, preferred term, and maximum severity. For AE tables, a subject who experienced multiple AEs within a SOC or preferred term will be counted only once at the maximum severity for that SOC or preferred term. SAEs will be tabulated similarly. Separate summaries for ocular AEs and non-ocular AEs will also be performed. Ocular AEs will be summarized for study eyes and fellow eyes separately. Any ocular AE that occurred simultaneously to both eyes will be counted once for both the study eye and the fellow eye. Injection-procedure related AEs will be tabulated by SOC and preferred term.

AEs leading to death, SAEs, and AEs leading to discontinuation, if any, will be listed separately. Events of special interest will be listed by type of event. For other safety variables, descriptive summaries of observed score or status, change or shift from baseline, and/or change after injection, whichever applicable, will be performed.

9.6. Interim Analyses, Primary Analysis, and Analysis of Open-Label Period of Study

An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. There are two goals for this interim analysis (1) to assess for futility; and (2) to re-assess the sample size. Sample size re-assessment will be performed with the "promising zone" approach as follows (Mehta et al., 2011). If the conditional power at the interim analysis is between 50% and 80%, the suggested sample size increase may be up to 100 subjects (i.e., 50% of the original sample size). If, on the other hand, the conditional power is > 80% or < 50%, no change to the sample size will take place. If the conditional power is <30%, then the Data Monitoring Committee (DMC) would recommend stopping the trial due to futility. The DMC could recommend stopping the trial due to safety concerns at any of the DMC meetings and the interim analysis. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the DMC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.

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 primary analysis will be conducted after all subjects have completed the Month 6 visit or prematurely discontinued from the study prior to Month 6. An interim clinical study report will be written documenting the primary analysis results.

Analysis of the open-label period of the study will be performed after the end of the study and documented in the final clinical study report.

9.6.1. Data Monitoring Committee (DMC)

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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (Declaration_of_Helsinki, 2008) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines (CIOMS_Ethical_Guidelines, 2016).
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations

10.1.2. Obligations of Investigators

In summary, the clinical investigator has agreed to the following obligations:

- Obtaining signed and dated informed consent from every subject prior to the subject's participation in any study related activity and maintaining records of consent as part of the study records.
- Obtaining approval from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and ensuring a copy of the letter indicating IRB/IEC approval is available at the investigational site before involving any subject in any study related activity; submitting verification of the approval to the Sponsor. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Submitting the final report to IRB/IEC and to the Sponsor.
- Approving the protocol and conducting the study according to the protocol and applicable regulations; informing the Sponsor of all deviations from the protocol.
- Informing the IRB/IEC of all protocol amendments/modifications and obtaining approval for the amendment/modification from the IRB/IEC in accordance with local requirements before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects; sending the Sponsor a copy of the letter from the IRB/IEC approving the amendment/modification.
- Reporting to the Sponsor and the IRB/IEC any SAEs or other significant safety findings that occur in the course of the investigation.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

- Keeping careful and accurate records of all clinical study data (study records must be considerably more exact and complete than those kept in ordinary medical practice); maintaining records of all materials submitted to the IRB/IEC study including the subject consent form and recruitment materials; maintaining records of all actions by the IRB/IEC regarding the study.
- Making study records available for inspection by the Sponsor (Santen) and representatives of the FDA and other regulatory agencies; keeping records until notified by the Sponsor that they may be destroyed.
- Maintaining proper control and documentation of all test and control articles.
- Submitting the following records and reporting to the Sponsor:

I. Prior to the Beginning of the Study

- A signed Form FDA-1572, Statement of Investigator.
- A current curriculum vitae (CV) if not submitted to Santen previously or if updated.
- CVs for all sub-investigators listed on the 1572.
- A letter from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) indicating that the protocol was approved, including the name and address of the IRB/IEC.
- A copy of the consent form approved by IRB/IEC.
- A list of current members of the IRB/IEC.
- Financial disclosure (Section 10.1.3).

II. While the Study Is in Progress

- Acknowledgment of receipt of the test and control articles; documentation of disposition of all test and control articles.
- Original Case Report Forms for each subject enrolled in the study.
- Information regarding all deviations from the protocol.
- Information regarding all adverse medical events occurring to a subject while enrolled in the study.
- Annual progress report (if study is ongoing for more than one year). Letter from the IRB/IEC indicating approval of the annual progress report.

III. Once the Study Is Completed

- Disposition of all used and/or unused test and control articles, as well as documentation of all drug accountability.
- A final study report.

10.1.3. Financial Disclosure

Investigators and sub-investigators will provide Santen with sufficient, accurate financial information as requested to allow Santen to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

10.1.4. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study. Each subject should be allowed time to consider the information provided.
- Subjects must be informed that their participation is voluntary and that they are free to discontinue from the study at any time. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The Informed Consent Form must be approved by the governing IRB/IEC.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The subject's signed and dated informed consent must be obtained before any protocol-directed procedures are performed.
- The subject's signature must be witnessed by the authorized person obtaining the informed consent. If the investigator obtains informed consent, then the subject's signature must be witnessed by another individual (e.g., member of the site staff).
- The investigator or authorized person obtaining the informed consent must also sign and date the IRB/IEC-approved Informed Consent Form where designated.
- Subjects must be re-consented to the most current version of the IRB/IEC-approved ICF(s) during their participation in the study.
- The Principal Investigator(s) must maintain the original, signed Informed Consent Form with the study records. A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.
- The ICF will contain a separate section that addresses blood samples collected and stored for subsequent pharmacogenomics analysis by Santen. The investigator or authorized designee will explain to each subject the objectives of this exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

See Section 10.1.4.1 for further details on the content of informed consent.

10.1.4.1. Elements of Informed Consent

I. Elements of Informed Consent

The following information must be provided to each subject in obtaining informed consent. If written consent is being obtained, the subject (or subject's legal representative) should be provided with a copy of the signed written Informed Consent Form.

1. State that the study involves RESEARCH.
   A. Explain the PURPOSE of the research.
   B. State the expected DURATION of the subject's participation.
   C. Describe the PROCEDURES to be followed.
   D. Identify any EXPERIMENTAL procedures.
2. Describe any reasonably foreseeable RISKS OR DISCOMFORTS to the subject.
3. Describe any BENEFITS to the subject or to others that may reasonably be expected from the research.
4. Note appropriate ALTERNATIVE procedures or courses of treatment, if any, that might be advantageous to the subject.
5. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained. Note that regulatory agencies MAY INSPECT the records.
6. For research involving more than minimal risk, explain if any COMPENSATION or medical treatments are available should injury occur. If so, explain what they consist of, OR where further information may be obtained.
7. Tell whom to contact for ANSWERS to pertinent questions about the research, and research subjects' rights and whom to contact in the event of a research-related INJURY to the subject.
8. State that participation is VOLUNTARY, refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled, and the subject MAY DISCONTINUE participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

II. Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

1. A statement that particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.
3. Any additional costs to the subject that may result from participation in the research.

4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject.
6. The approximate number of subjects involved in the study.

The informed consent requirements in this protocol are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed for informed consent to be legally effective.

Nothing in this protocol is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable Federal, State, or local law.

REFERENCE: 21 CFR Part 50.25 – PROTECTION OF HUMAN SUBJECTS, Elements of Informed Consent.

10.1.5. Data Protection

- Subjects will be assigned a unique identifier by Santen. Any subject records or datasets that are transferred to Santen will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by Santen in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Santen, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.6. Source Documents

The investigator must maintain detailed source documents on all study subjects who are enrolled in the study or who undergo screening. Source documents include subject medical records, hospital charts, clinic charts, investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests, OCT). Data for enrolled subjects will be transcribed on to eCRFs provided by the Sponsor. All data should be transcribed completely, promptly, and legibly on the eCRFs. Data transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Exit forms are to be completed for all enrolled subjects, regardless if they did or did not complete the study (e.g., subject discontinuation, study termination).

The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available. The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number

- The study protocol number and the name of Santen Inc.
- The date that informed consent was obtained
- Evidence that the subject meets study eligibility requirements (e.g., medical history, study procedures and/or evaluations)
- The dates of all study related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of IP accountability
- Occurrence and status of any AEs
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to Santen or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by Santen or inspection by competent authorities.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and contracts.
- Santen or designee is responsible for the data management of this study including quality checking of the data.
- Santen assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until notified by Santen that the records may be destroyed. No records may be transferred to another location or party without written notification to Santen.

10.1.8. Sponsor's Direct Access to Source Data/Documents and IRB/IEC Materials for Monitoring and Audit

10.1.8.1. Study Monitoring

Santen or Santen's designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the monitor to inspect the drug storage area, investigational product stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

Before an investigational site can enter a subject into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Santen or its representatives. This will be documented in a Clinical Study Agreement between Santen or its designee and the investigator.

During the study, a monitor from Santen or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to Santen.
- Confirm non-serious AEs and SAEs have been properly documented on CRFs and confirm any safety information requiring expedited reporting to Santen Inc PVU (including SAEs, ESIs and Pregnancies) have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the investigator(s) or other staff need information or advice.

10.1.8.2. Audits and Inspections

Authorized representatives of Santen, a regulatory authority (national or foreign), an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Council for Harmonisation, and any applicable regulatory requirements. The investigator should contact Santen immediately if contacted by a regulatory agency about an inspection.

10.1.9. Study and Site Closure

Santen's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Santen. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by Santen or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Santen's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further development of the investigational product

10.1.10. Confidentiality and Publication Policy

The existence of this clinical study is confidential, and it should not be discussed with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information supplied to the investigator that is indicated as confidential.

The data generated by this clinical study are the property of Santen, Incorporated (the Sponsor) and should not be disclosed without the prior written permission of Santen. These data may be used by Santen now and in the future for presentation or publication at Santen's discretion or for submission to governmental regulatory agencies. Santen reserves the right of prior review of any publication or presentation of data from this study.

This study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov.

In signing this protocol, the investigator agrees to the release to Santen of the data from this study, and acknowledges the above publication policy.

10.2. Clinical Laboratory Tests

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 9: 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

10.3. Estimated Amount of Blood Collected from Each Subject

[redacted]

10.4. Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Table 10: Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (and not related to progression of underlying disease [uveitis], unless judged by the investigator to be more severe than expected for the subject's condition). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Table 11: Definition of SAE

A SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Sight threatening event: A sight-threatening event is any event that places the subject at immediate risk of permanently losing vision in either eye as a direct result of the event. • Ocular AEs required to be reported as SAEs: For the purposes of this study, the following ocular AEs will be reported as SAEs: – Loss of 6 or more lines of vision (≥30 letters) from baseline – Endophthalmitis (also to be reported as an ESI, Section 8.2.13) – Purulent, infectious conjunctivitis – Retinal detachment (also to be reported as an ESI, Section 8.2.13) – IOP >35 mmHg that persists for at least 7 days despite pharmacologic therapy (also to be reported as an ESI, Section 8.2.13) – Other significant ocular events per Investigator's discretion • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Table 12: Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is not acceptable for the investigator to send photocopies of the participant's medical records to Santen in lieu of completion of the Santen/AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by Santen. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Santen. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Table 12: Recording and Follow-Up of AE and/or SAE (Continued)

AE and SAE Recording
Assessment of Causality Note: 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.
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The following criterial can be used to make a causality judgment: • Related (possibly or probably) o There is a clinically plausible time sequence between onset of the AE and investigational product administration/protocol procedure; and/or o There is a biologically plausible mechanism for investigational product causing or contributing to the AE; and o The AE may or may not be attributed to concurrent/underlying illness, other drugs, or protocol procedures. • Not Related o A clinically plausible temporal sequence is inconsistent with the onset of the AE and Investigational product administration/protocol procedure; and/or o A causal relationship is considered biologically implausible. The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the Investigational Brochure (IB) and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Santen. However, **it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to Santen.** • The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Table 12: Recording and Follow-Up of AE and/or SAE (Continued)

AE and SAE Recording
Procedures for Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Santen to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Santen with a copy of any post--mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to Santen within 24 hours of receipt of the information.

Table 13: Reporting of SAEs

SAE Reporting to Santen via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to Santen will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Santen Global Pharmacovigilance (Table 1). • Contacts for SAE reporting can be found in Table 1. • For SAE supporting information (i.e. X-ray reports, hospital summaries, etc.) that are not included in the EDC format, follow a procedure analogous to the manual SAE reporting process (see next section).
SAE Reporting to Santen via Paper CRF (If Electronic Data Collection Tool is Unavailable)
• Complete both the paper AE and SAE Forms (located in your site regulatory binder) • Attach a Fax Cover Sheet with your contact information and fax to Santen Global Pharmacovigilance (Table 1). • In the rare circumstance of the absence of facsimile equipment, notification by telephone is acceptable with a copy of the paper AE and SAE forms sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Table 1.

10.5. List of Abbreviations and Specialist Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 14: List of Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
µg	Micrograms
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ADaM	Analysis Data Model
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
BCVA	Best-Corrected Visual Acuity
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran–Mantel–Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form (paper or electronic)
CRO	Contract Research Organization
CST	Central subfield thickness
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESI	Event of Special Interest
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAS	Full analysis set
FDA	Food and Drug Administration
FP	Fundus photography
GCP	Good Clinical Practice
GEE	General estimating equation
GGT	Gamma glutamyl transferase
hCG	Human chorionic gonadotropin
HCT	Hematocrit

Table 14: List of Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
HDL	High-density lipoproteins
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low-density lipoproteins
LOCF	Last Observation Carried Forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mL	Milliliters
MMRM	Mixed-effects model for repeated measures
mTOR	Mammalian target of rapamycin
NIU-PS	Non-infectious uveitis of the posterior segment of the eye
NPDR	Non-proliferative diabetic retinopathy
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
PGx	Pharmacogenomic
PLT	Platelets
PP	Per-protocol
PVU	Pharmacovigilance Unit
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities

Table 14: List of Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
SOC	System Organ Class
SDTM	Study Data Tabulation Model
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reaction
VA	Visual Acuity
VFQ-25	Visual Functioning Questionnaire
VH	Vitreous haze
WBC	White blood cell

11. LIST OF REFERENCES

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12. APPENDICES

12.1. Appendix 1: National Eye Institute Visual Functioning Questionnaire – 25 (VFQ-25)

National Eye Institute Visual Functioning Questionnaire - 25 (VFQ-25) version 2000 (Interviewer Administered Format) plus appendix is provided below.

PB/IA

National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)

version 2000

(INTERVIEWER ADMINISTERED FORMAT)

January 2000

Instructions:

I'm going to read you some statements about problems which involve your vision or feelings that you have about your vision condition. After each question I will read you a list of possible answers. Please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses for a particular activity, please answer all of the following questions as though you were wearing them.

Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is*:

(Circle One)

READ CATEGORIES:

Excellent	**1**
Very Good	**2**
Good	**3**
Fair	**4**
Poor	**5**

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

READ CATEGORIES:

Excellent	**1**
Good	**2**
Fair	**3**
Poor	**4**
Very Poor	**5**
Completely Blind	**6**

*** Skip Question 1 when the VFQ-25 is administered at the same time as the SF-36 or RAND 36-Item Health Survey 1.0**

3. How much of the time do you worry about your eyesight?

(Circle One)

READ CATEGORIES:

None of the time	**1**
A little of the time	**2**
Some of the time	**3**
Most of the time	**4**
All of the time?	**5**

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

READ CATEGORIES:

None	**1**
Mild	**2**
Moderate	**3**
Severe, or	**4**
Very severe?	**5**

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

8. How much difficulty do you have reading street signs or the names of stores?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

12. Because of your eyesight, how much difficulty do you have <u>picking out and matching your own clothes</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

13. Because of your eyesight, how much difficulty do you have <u>visiting with people in their homes, at parties, or in restaurants</u> ?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

14. Because of your eyesight, how much difficulty do you have <u>going out to see movies, plays, or sports events</u>?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

15. Now, I'd like to ask about driving a car. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 *Skip To Q 15c*

No 2

15a. IF NO, ASK: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 *Skip To Part 3, Q 17*

Gave up..... 2

15b. IF GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 *Skip To Part 3, Q 17*

Mainly other reasons ..... 2 *Skip To Part 3, Q 17*

Both eyesight and other reasons ... 3 *Skip To Part 3, Q 17*

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all 1
A little difficulty 2
Moderate difficulty 3
Extreme difficulty 4

16. How much difficulty do you have <u>driving at night</u>? Would you say you have: (READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

16a. How much difficulty do you have <u>driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic</u>? Would you say you have:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Have you stopped doing this because of your eyesight	**5**
Have you stopped doing this for other reasons or are you not interested in doing this	**6**

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.

	(Circle One On Each Line)				
READ CATEGORIES:	**All of the time**	**Most of the time**	**Some of the time**	**A little of the time**	**None of the time**
17. Do you accomplish less than you would like because of your vision?	**1**	**2**	**3**	**4**	**5**
18. Are you limited in how long you can work or do other activities because of your vision?	**1**	**2**	**3**	**4**	**5**
19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	**1**	**2**	**3**	**4**	**5**

For each of the following statements, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I stay home most of the time because of my eyesight.....	1	2	3	4	5
21. I feel frustrated a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have much less control over what I do, because of my eyesight.	1	2	3	4	5
23. Because of my eyesight, I have to rely too much on what other people tell me..	1	2	3	4	5
24. I need a lot of help from others because of my eyesight.....	1	2	3	4	5
25. I worry about doing things that will embarrass myself or others, because of my eyesight.....	1	2	3	4	5

That's the end of the interview. Thank you very much for your time and your help.

Appendix of Optional Additional Questions

SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										**Best**

SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms? Would you say:
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: SOCIAL FUNCTION

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?
(READ CATEGORIES AS NEEDED)

(Circle One)

No difficulty at all	**1**
A little difficulty	**2**
Moderate difficulty	**3**
Extreme difficulty	**4**
Stopped doing this because of your eyesight	**5**
Stopped doing this for other reasons or not interested in doing this	**6**

SUBSCALE: DRIVING

A10. [This items, "driving in difficult conditions", has been included as item 16a as part of the base set of 25 vision-targeted items.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, I'd like you to tell me if this is true for you all, most, some, a little, or none of the time.
(READ CATEGORIES AS NEEDED)

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Do you have more help from others because of your vision?	1	2	3	4	5
b. Are you limited in the kinds of things you can do because of your vision?	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please tell me if it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often irritable because of my eyesight.	1	2	3	4	5
A13. I don't go out of my home alone, because of my eyesight.....	1	2	3	4	5

12.2. Appendix 2: ETDRS Visual Acuity Chart Procedure

Tumbling “E” chart is available for subjects who cannot read alphabet.

12.2.1. Procedures for Refraction and Vision Testing

Refraction and visual acuity measurements will be performed for all subjects by trained vision examiners only. The **name and certification number** of the vision examiner should be documented in the subject’s **source document** at each visit. **When possible**, visual acuity examiners should not have access to the subject’s chart or previous visual acuity testing results. Only the previous refraction should be made available. Refraction should be conducted prior to visual acuity testing to obtain best-corrected vision as described below. Best-corrected visual acuity is measured at all trial visits using standard charts, lighting, and procedures. Best correction is determined by careful refraction at that visit according to the standard protocol for refraction described below.

12.2.1.1. Equipment

Refraction equipment required includes:

1. Retro illuminated light box and ETDRS 4-meter distance acuity chart set
2. Trial lens frames
3. Trial lens set with plus or minus cylinder lenses
4. Jackson cross-cylinder of 0.25, 0.50, and 1.00 diopters
5. Pinhole occluder
6. Tissues or eye pads and tape
7. A 1-meter rigid measuring stick

12.2.1.2. Visual Acuity charts

Chart 1 is used for testing the visual acuity of the RIGHT eye; Chart 2 for testing the LEFT eye; and Chart R (or 3) for refraction only. Subjects should not be allowed to see any of the charts before the examination.

12.2.1.3. Visual Acuity Lane and Visual Acuity Box

A distance of **4 meters** is required between the subject’s eyes and the visual acuity charts. With the box light off, not more than **15 foot-candles of light** (161.4 Lux) should fall on the center of the chart. To measure the amount of light, the room is set up for visual acuity testing, but with the box light off. The light meter is placed at the fourth line from the top of the chart, with its back against the chart and the reading is taken. If more than one lane is available for testing visual acuity, the visual acuity of individual subjects should be measured in the same lane at each visit, if possible. If different lanes are used to test visual acuity, they must each meet the same standards.

Retro illuminated ETDRS charts are used in this trial. The illuminator box will be either wall-mounted or mounted on the stand. The light box should be mounted at a height such that top of third row letter is 49±2 inches from floor.

The visual acuity light box is equipped with two General Electric 20-watt fluorescent tubes and ballast. Each tube is partly covered a 14-inch fenestrated sleeve, which is centered on the tube and open in the back. This serves as a "baffle" to produce even illumination over the testing chart. Because of the illumination of the fluorescent tube diminishes by 5 percent during the first 100 hours and by another 5 percent during the next 2000 hours, new tubes should be kept on for 4 days (96 hours) continuously, and should be replaced once a year.

A **sticker** should be placed on the back of the light box, indicating the date on which the present tubes were installed. A spare set of burned in bulbs should be available on sight.

12.2.1.4. Beginning Approximate Refraction

At the baseline visit, the subject's beginning refraction is determined by one of the following ways:

a. If the subject's visual acuity is 20/100 or better and the subject does not require glasses for distance vision, then the beginning approximate refraction should be no lens correction or plano.
b. If the subject's visual acuity is 20/100 or better and the subject requires glasses for distance viewing, the glasses should be measured using a lensometer, and these measurements are used for the beginning refraction.
c. If the subject's visual acuity is less than 20/100 with or without correction, then retinoscopy or auto-refraction should be performed to determine the beginning approximate refraction.
d. If the subject wears contact lenses for refraction, a notation should be made that the refraction was over contact lenses. It is suggested that the subject wear the contact lenses for future examinations. If the subject is not a regular contact lens wearer and wore the lens by mistake, they should be removed, and you should wait at least 30 minutes before beginning the refraction. The subject should be reminded not to wear contact lenses at subsequent visits.

Refractions are performed with either plus or minus cylinder power. Whichever cylinder type is used at baseline (minus or plus) must be used for all subsequent visits. Best correction results should be recorded on Santen-provided worksheet which will be included in the source documents. **At each follow-up visit, the results of the protocol refraction from the previous visits are used as the beginning approximate refraction.** If the previous refraction is not available for some reason, the procedure described immediately above should be used.

The charts used for measuring distance visual acuity must NOT be used for refraction. Refraction for each eye should be performed at **4 meters** unless the subject's visual acuity at 4 meters on the refraction charts (Chart R or Chart 3) is **worse than 20/160. If visual acuity is worse than 20/160 the eye is refracted at 1.0 meter.** If during the refraction process at 1 meter, the subject is reading letters on the eighth line or lower line of the chart, the refraction should be continued at 4 meters. Whenever a subject cannot read any letters on the top line of Chart R or Chart 3 at 1.0 meter the vision should be checked with a pinhole to see whether reduced vision is due, at least in part, to a larger refractive error. If there is no improvement with the pinhole, then the eye is exempt from refraction.

12.2.1.5. Subjective Refraction

Subjective refraction allows one to determine the best correction for a subject to perform the visual acuity tests. The **"push plus"** approach is used. Add minus diopter spherical corrections **only when the subject is able to read at least one more letter** on a line or a letter on a smaller line.

12.2.1.5.1. Procedure

1. Measure and record the distance vision of the eye being tested using Chart R while occluding the fellow eye. The fellow eye should be lightly patched with an eye pad or tissue and tape. Subjects should be reminded to blink and encouraged to use eccentric fixation, or their side vision, when necessary.
2. All refraction and vision testing must be done at 4 meters or 1 meter. Distance for 4 meters is 13 feet and 1.5 inches or 157.5 inches. The one-meter distance is 39 and 3/8 inches.
3. All subjects should be seated for testing. A **rigid measuring device** should be used to measure the distance from the subject to the chart if testing is done at **1 meter**. The distance is measured from the outer canthus to the center of the second letter (left eye) or fourth letter (right eye) of the third line of the chart. For **4-meter** testing, **clear and permanent floor markings** should be used to mark the distance for consistency.
4. Place and adjust the trial frame on the subject's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupils. Adjust the lens cells for the proper distance from the cornea. Be sure the trial frame is comfortable on the subject's face.
5. Occlude the left eye by lightly patching with the eye pad or tissue and tape.
    a. Place the spherical lens correction in the compartment closest to the eye.
    b. The cylindrical lens correction, if present, is placed in the compartment in front of the spherical correction. Adjust the axis.
6. **Spherical Correction**: To determine the highest plus or least minus sphere, refract the right eye. **The following refraction steps are recommended for visual acuities of 20/10 to 20/80 with the beginning approximate refraction. For visual acuities less than 20/80, refer to the refraction table for the appropriate sphere and cylinder powers and testing distance and follow a similar procedure.** Note: Whenever visual acuity is improved to a higher range, refraction should be performed with the smaller sphere and cylinder powers given for the better visual acuity level.
    a. Hold a **+0.50 sphere** in front of the subject's right eye. The subject should be looking at the smallest legible line on the visual acuity chart. In these exact words, ask the subject, **"Is this better, worse, or no change?"**
    b. If the subject responds that the vision is **worse or blurred**, remove the +0.50 sphere from in front of the trial frame and **go to Step 6d**.
    c. If the subject responds **better or no change,** remove the +0.50 sphere from in front of the trial frame and replace the spherical lens in the trial frame with a spherical lens

that is one-half diopter more positive. Continue this procedure by returning to Step 6a and repeating this process **until a +0.50 makes the vision worse** or blurred and then go to Step 6d.

d. Hold a **-0.50 sphere** in front of the subject's right eye. In these exact words, ask the subject, "Is this better, worse, or no change?" If the subject replies "worse" or "no change," go to Step 6f. If they reply "better" go to step 6e.

e. Hold the -0.50 sphere in front of the eye. If the subject responds that the vision is better, ask the subject to read the visual acuity chart. **Only when the visual acuity is improved, by at least one letter, may you increase the minus** by 0.50 (or decrease the plus) and repeat Step 6d. Whenever visual acuity is not improved, go to Step 6f.

f. Remove the -0.50 sphere from in front of the eye and hold a +0.50 sphere in front of the right eye. In these exact words, ask the subject, "Is this better, worse, or no change?" If the subject responds that the vision is better or unchanged, then return to Step 6c. Otherwise, go to Step 7. **Spherical testing should always end with a plus lens.**

7. Cylinder Axis: To determine and refine the cylinder axis for **PLUS** cylinder, proceed as follows; (if **minus** cylinders are used, the appropriate technique using minus cylinders must be employed and minus cylinder must be used throughout the trial.)

    a. Have the subject look at a line which is either **one or two lines larger** than the smallest line the subject is able to read. Ask the subject to focus on a rounded letter such as, "C", "D", or "O". The subject should focus on the same letter throughout this procedure.

    b. If a cylinder is present in the beginning approximate refraction, then go to Step 7c. Otherwise, follow the option listed below to determine if cylinder may be needed.

    Testing for cylinder when there is none in the beginning approximate refraction:

    Place a **+0.50 diopter** cylinder with a positive axis first at 90°, then compare this to no cylinder; repeat this procedure for 180°, then 45°, and 135° always comparing to no cylinder after each axis position. If the subject says that the vision is improved at any one of the four axis positions, place a +0.50 cylindrical lens in the trial frame at the preferred axis and go to Step 7c. If the subject prefers no cylinder at all four axis positions, then go to Step 9.

    c. Place the +0.25 diopter hand held cross-cylinder (for VA 20/10 – 20/80) first with the positive axis 45° to the right of the preferred cylinder axis (as determined above), and second with the positive axis 45° to the left of the preferred cylinder axis. Ask the subject, "Which do you like better, position one or position two?" Also, tell the subject that both positions may blur their vision. The subject must choose the least blurred position, either one or two. "Neither" is allowed only if both positions are equally blurred or equally good.

d. If "neither" position is better, and this was the first test of axis position, move the axis of the cylinder in the trial frame 15° to the right or left and return to Step 7c. Otherwise, proceed to Step 7e.

e. When one position is preferred over another, move the cylinder to the preferred positive axis position in the step sizes noted below and return to Step 7c. If no single position is better than another, then go to Step 8.

Cylinder Refinement **Cylinder Power**	**suggested axis step sizes** **Axis Step Sizes**
<1.00D	15º
1.00 - <2.00D	10º
2.00 - <3.00D	5º
3.00 - <5.00D	3º
5.0 - <8.00D	2º

8. **Cylinder Power:** Cylinder power is refined by following the step:

   a. Ask the subject to look at the **smallest line** that can be read on the visual acuity chart.

   b. Test the cylinder power by placing 0.25 diopter cross-cylinder (for vision of 20/10 – 20/80) first with the positive axis and second with the negative axis coincident with the cylinder axis. Ask the subject, "Which is better, position one or position two?" Do not give the subject the choice of neither.

   c. If the subject prefers the minus axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. Repeat the process until the subject cannot choose one of the cross-cylinder positions over the other. If the subject indicates a change that would introduce negative cylinder power, remove all cylinder power and continue testing for positive cylinder power at an axis 90° away from the previous axis. Otherwise, go to Step 8d.

   d. If the subject prefers the plus axis coincident with the cylinder axis, increase the power of the cylinder by 0.25 diopter and return to Step 8b. Otherwise, proceed to Step 8e.

   e. When the subject feels that both positions are equally bad or good, and the cylinder power in the trial frame has changed by more than 0.50 diopter, return to Step 7c and re-check the axis if necessary. Otherwise, proceed to Step 9.

      Note: If the cylinder is changed by more than 0.50 diopter, the **spherical equivalent** should be maintained. (For each 0.50 **plus** CX increase, add -0.25 to the sphere, for each 0.50 **minus** CX increase, add +0.25 to the sphere).

9. **Spherical Correction Refinement:** Recheck, or **"refine"** the power of the sphere by adding +0.25 and -0.25 spheres and changing the spherical power by 0.25 diopter increments of the appropriate sign until the subject cannot detect any improvement in vision. As a reminder, **minus sphere should only be added if the subject can read additional letters** and spherical testing should always begin and end with a plus lens.

10. Record the lens corrections obtained by subjective refraction for the right eye on the examination form in the section for visual acuity measurements as the correction obtained by protocol refraction for the right eye.
11. Repeat the entire process (Steps 1-10) for the left eye and record the refraction results on the VAE worksheet.

12.2.1.6. Best-Corrected Visual Acuity Measures

1. As a reminder, Charts 1, 2, and R (or 3) are used for testing the right eye, left eye, and refraction, respectively. Subjects should not see the charts until the test begins.
2. The lens correction from the subjective refraction should be in the trial frame worn by the subject.
3. **All eyes must be tested at 4 meters first, even if the refraction was performed at 1 meter.**
4. The subject should be seated comfortably directly in front of the chart so that the eyes remain at the 4 meter distance. Testing always begins with the right eye. The fellow eye should be occluded with a folded tissue or eye pad lightly taped over the eye behind the trial frame serves as an effective occlude that allows eccentric fixation without inadvertent use of the covered eye. After testing the right eye, occlusion of the right eye should be done BEFORE Chart 2 is put up for testing the left eye.
5. The subject is asked to read the letters slowly, approximately one letter per second. The subject should be told that only one chance is given to read each letter, but may change their mind before moving to the next letter. If the subject is unsure about the identity of the letter, then the subject should be encouraged to guess.
6. **The subject should begin by reading the top line of the chart and continue reading every letter on each smaller line, from left to right on each line. The subject should be encouraged to continue reading even if making mistakes. Each letter read is counted.** The examiner circles every correct letter read and totals each line and the whole column (0 if no letters are correct) on the data collection form. An X is put through letters read incorrectly. Letters, for which no guess was attempted, are not marked. When a subject reaches a level where he/she cannot guess, the examiner may stop the test provided that the subject has made errors on previous guesses, which is a clear indication that the best visual acuity has been obtained.
7. **When a subject cannot read at least 20 letters on the chart at 4.0 meters, the subject is tested at 1.0 meter.** The distance from the subject to the chart should be measured again using the rigid one meter stick. **The distance is measured from the outer canthus to the center of the fourth letter (right eye) or the second letter (left eye) of the third line of the chart.** The spherical correction in the trial frame should be changed by **adding +0.75** to correct for the closer test distance. The subject may fixate eccentrically or turn or shake his/her head to improve visual acuity. Particular care should be taken to make sure the subject does not move forward when testing at 1 meter. The subject should be reminded to blink.

8. The examiner should not tell the subject if a letter was identified correctly. The subject may be encouraged by neutral comments, such as “good”, “next”, and “OK.”
9. The examiner should not stand close to the chart during testing. Attention should be focused on the subject and data collection form. If the subject has difficulty locating the next line to read, the examiner may go up to the chart and point briefly to the next line to be read, but then must move away from the chart.
10. **When 20 or more letters are read at 4 meters the visual acuity score for that eye is recorded as the number of letters correct at 4 meters plus 30**. The subject **gets credit for the thirty 1 meter letters** even though they did not have to read them. Otherwise, the visual acuity score is the number of letters read correctly at 1.0 meter plus the number, if any, read at 4 meters. If no letters are read correctly at either 4 meters or 1 meter, then the visual acuity score is recorded as 0.

12.2.1.7. Testing for Count Finger Vision, Hand Motion Vision and Light Perception/No Light Perception Vision

If the subject’s visual acuity is so poor that he/she cannot read any chart letters when tested at one meter then the subject’s ability to count fingers, detect hand motion, or have light perception should be evaluated.

12.2.1.7.1. Testing for Count Fingers Vision

In testing for count fingers vision, the examiner’s hand holding 1, 2, or 5 fingers is held steady at a distance of two feet directly in front of the eye being examined. The fellow eye is completely occluded with a patch on the face. A light should be shone directly on the hand from behind the subject. The examiner’s fingers should be presented in random order and repeated five times. Eccentric fixation, if present, should be encouraged. If the subject correctly identifies three of the five presentations, then count fingers vision is noted. If not, then the subject must be tested for hand motion vision.

12.2.1.7.2. Testing for Hand Motion Vision

The examiner’s hand with all fingers spread out should be extended two feet directly in front of the eye being examined. The fellow eye should be occluded with a patch on the subject’s face. A light should be shown directly on the examiner’s hand from behind the subject. The examiner’s hand should be moved in an up-and-down direction (vertically) or in a side-to-side direction (horizontally) at a constant speed of approximately one back and forth presentation per second. The subject is instructed that the examiner’s hand will be presented, and they will have to respond to the question: “What am I doing with my hand?” This should be repeated five times. Three out of five correct responses indicate that hand motion vision is present. If the subject does not correctly identify three of five presentations, then you must test for light perception.

12.2.1.7.3. Testing for Light Perception/No Light Perception Vision

Light perception should be tested with an indirect ophthalmoscope in a darkened room. The fellow eye should be completely patched and covered by the subject’s hand. The indirect ophthalmoscope light should be in focus at 1 meter with the rheostat set at maximum voltage. From that distance the beam should be directed in and out of the subject’s eye at least four times,

and the subject should be asked to respond when he/she sees the light. If the examiner is convinced that the subject perceives the light, vision should be recorded as “light perception,” if not, vision should be recorded as “no light perception.”

Table 15: 4M Refraction Protocol Summary

Refraction Distance	**Check Sphere First then Power**		**Check Cylinder Axis**			**Sphere “Refinement”**	
If VA on “R” chart is between:	**Power (a)**	**Increment**	**Axis (b)**	**Power (c)**	**Increment**	**Power (d)**	**Increment**
20/10 – 20/80 (4 meters)	+.50 -.50	+.50 -.50	.25 JCC	.25 JCC	+.25 -.25	+.25 -.25	+.25 -.25
20/100 – 20/160 (4 meters)	+1.00 -1.00	+1.00 -1.00	.50 JCC	.50 JCC	+.50 -.50	+.50 -.50	+.50 -.50
20/200 – 20/400 (1 meter)	+2.00 -2.00	+2.00 -2.00	1.00 JCC	1.00 JCC	+1.00 -1.00	+1.00 -1.00	+1.00 -1.00
<20/400 (1.0 meters) sequence refraction a-d	+2.00 -2.00	+2.00 -2.00	No cylinder test required			No refinement required	

12.3. Appendix 3: Adverse Event Case Report Form Items and Terms

Concise Description of Event:	A concise description of the signs, symptoms, complaints, or diagnosis of the subject's problem (e.g., nasal congestion). Complete one AE form for related symptoms that can be grouped as one condition (e.g., If a subject complains of sneezing, nasal congestion, watery eyes, the AE is described as cold symptoms). If two independent events occur at the same time, separate AE forms must be completed for each event.
Affected Eye(s):	Indicate if ocular event is OD, OS, or OU. Non-ocular events should be recorded as N/A.
Adverse Event Serious?:	If AE is serious or an Event of Special Interest, Santen must be notified immediately (within 24 hours). Complete both the AE and the SAE eCRFs in the EDC system. In the event the EDC system is unavailable, and your site needs to report an SAE, please follow the manual process described in the body of the protocol under "Reporting of SAEs."
Date of Event Onset:	The date the event started.
Maximum Severity of Event:	Record the severity of the AE according to the following definitions: Mild: Aware or unaware of event, but easily tolerated Moderate: Discomfort enough to cause interference with usual activity Severe: Incapacitating; unable to work or perform usual activity For intermittent events, record the maximum severity of the individual events. For example, if a subject complains of intermittent headaches for one week and the severity of each headache ranges from mild to moderate, then the severity would be moderate. Record that the severity of the headaches ranged from mild to moderate in the comment section of the form. If an event occurs with each injection (e.g., eyes burn mild to moderate for 5 minutes after every injection), record the maximum severity of the individual incident. In the example above, the severity is moderate. Record that the severity of the event ranged from mild to moderate in the comment section of the form.
Action Taken as Related to this AE:	Indicate the action taken as a result of the AE. If the frequency of Investigational product administration was changed or discontinued temporarily or if surgery was required, provide more detailed explanation in the comment section of the form. If "Other" is indicated, specify the action taken.

Outcome of Event:	Indicate the outcome of the AE and provide resolution date or date of death. For intermittent events (e.g., intermittent headache) and events that occur with each injection (e.g., eyes burn for 5 minutes after every injection), the date should reflect when the last occurrence resolved or stopped. For example, if a subject has an intermittent headache from 12/14/2010 until 12/21/2010 and each individual headache lasts 3 hours a day, then the date of resolution is 12/21/2010 (NOT 12/14/2010). If treatment was initiated, then include the treatment and duration in the comments section (e.g., subject took acetaminophen for headache on 12/14/2010, 12/17/2010 and 12/20/2010).
Relationship to Study Drug/Investigational Product:	Indicate if there is a reasonable possibility that the AE may have been caused by the study drug/investigational product with a Yes or No response. A "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug/investigational product and the AE. If response is No, select the possible alternative explanation of the event from the list provided.
Relationship to Injection Procedure:	The event cannot be attributed to the subject's underlying medical condition or other concomitant therapy and there is a compelling temporal relationship between the onset of the event and the injection procedure that leads the investigator to believe there is evidence of a reasonable causal relationship.

For SAE supporting information (i.e., X-ray reports, hospital summaries, etc.) that are not included in the EDC format, follow the same reporting process as for manual SAE reporting.

12.4. Appendix 4: Protocol Amendment 3 Summary of Changes

Global Changes:	Herein is a summary of changes made to protocol amendment 2 dated 29 Septemeber 2020 and reflected in Amendment 3 dated 14JUL2021. New text is identified in ***bold and italicized*** and deleted text with ~~**bold/strikethrough.**~~ • Updated Company/Sponsor Approver(s) • Updated Contact Information. • Updated changes per FDA comments In addition to the changes included in this document, there are administrative updates made throughout the protocol, including clarifications, changes in wording, punctuation, abbreviations, date, number or format for clarity and consistency; these changes are not listed in this document for conciseness.

Section:	**Table 2, Table 4, Footnotes, Section 9.1**
Original Text:	Table 2: Study Objectives and Endpoints Study Objectives Primary (efficacy vs. sham): The primary objective of this study is to evaluate the efficacy of intravitreal injection of 440 µg DE-109 every 2 months as compared with sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye. Corresponding Study Endpoints Primary efficacy endpoint: • VH 0 response[a] at Month 5 Key secondary efficacy endpoints: • VH 0 or 2-unit response[b] at Month 5 • VH 0 response at Month 3 • VH 0 or 2-unit response at Month 3 Note: Overall Type I error rate will be maintained at 0.05 (two-sided) across primary and key secondary efficacy endpoint treatment comparisons. Other secondary efficacy endpoints: • VH 0 or 0.5+ response[c] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering success[d] with resolution at Month 5

	• Corticosteroid tapering success with resolution at Month 3 • BCVA (Best-Corrected Visual Acuity) 3-line response[e] at Month 5 • BCVA 3-line response at Month 3 • Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT • Change from baseline in CST at Month 3 as measured by OCT • Use of rescue therapy before Month 5 • Use of rescue therapy before Month 3 Note: Additional secondary and exploratory efficacy endpoints will be specified in the Statistical Analysis Plan. Footnotes Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale. [a]VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale. [b] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale. [c] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale. [d] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at 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). [e] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).
Revised Text:	Table 2: Study Objectives, ***Estimands***, and Endpoints Study Objectives and ***Estimands*** Primary ***objective*** (efficacy vs. sham): The primary objective of this study is to evaluate the efficacy of intravitreal injection of 440 µg DE-109 every 2 months as compared with sham for the treatment of active, non-infectious uveitis of the posterior segment of the eye. ***Primary estimand: Vitreous haze 0 (VH0) 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 event 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.*** ***Treatment policy estimand: VH0 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 event. For study eyes that had missing data due to any reason, imputation by the multiple imputation-based approach will be used. ***Composite estimand: 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 event prior to the specified visit*** • ***Score = 0 if otherwise*** Corresponding Study Endpoints Primary efficacy endpoint: • VH 0 response[a] at Month 5 Key secondary efficacy endpoints: • ~~**VH 0 or 2-unit response**~~***Composite endpoint***[b] at Month 5 • VH 0 response at Month 3 • ~~**VH 0 or 2-unit response**~~***Composite endpoint*** at Month 3 Note: Overall Type I error rate will be maintained at 0.05 (two-sided) across primary and key secondary efficacy endpoint treatment comparisons. Other secondary efficacy endpoints: • ***VH 0 or 2-unit response***[c] ***at Month 5*** • ***VH 0 or 2-unit response at Month 3*** • VH 0 or 0.5+ ~~**response**~~[e]***response***[d] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering ~~**success**~~[d]***success***[e] with resolution at Month 5 • Corticosteroid tapering success with resolution at Month 3

	• BCVA (Best-Corrected Visual Acuity) 3-line ***response[e]response[f]*** at Month 5 • BCVA 3-line response at Month 3 Footnotes: Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale. [a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale. ***[b] Refer to composite score scales defined in the composite estimand in this table.*** ~~[c]b~~—VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale. ~~[d]c~~ VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale. ~~[e]d~~ Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at 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). ~~[f]e~~BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).
Rationale:	This change is in accordance with the ICH E9 (R1) addendum, to define the primary estimand and other estimands of the study. Key secondary endpoints are modified to be aligned with study estimands.

Section:	**Section 1.1, Section 4.1, Section 6.5.6, and Section 8.2.13**
Original Text:	**Protocol-Specified Rescue Therapy Criteria:** Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS. Rescue therapy is prohibited during the study unless

	there is worsening of uveitis as demonstrated by one or more of the following three rescue criteria: 1. Worsening of uveitis in the study eye as indicated by at least a 2-step increase in VH score (i.e., 0 to ≥ 1+, 0.5+ to ≥ 1.5+, 1+ to ≥ 2+, 1.5+ to ≥ 3+, or 2+ to 4+) post baseline as compared to the baseline (Day 1) VH score. **<u>The DE-109 ESIs are specific to the study eye only and are as follows:</u>** • 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 ≥ 1+, 0.5+ to ≥ 1.5+, 1+ to ≥ 2+, 1.5+ to ≥ 3+, or 2+ to 4+) as compared to the baseline (Day 1) VH score or the best achieved VH score post-baseline.
Revised Text:	**Protocol-Specified Rescue Therapy Criteria:** Rescue therapy is defined as any treatment that would have a therapeutic effect on NIU-PS. Rescue therapy is prohibited during the study unless there is worsening of uveitis as demonstrated by one or more of the following three rescue criteria: 11. Worsening of uveitis in the study eye as indicated by at least a 2-step increase in VH score (i.e., 0 to ≥ ~~**1+**~~***2*****+,** 0.5+ to ≥ ~~**1.5+**~~***3*****+,** 1+ to ≥ ~~**2+**~~***3*****+**, 1.5+ to ≥ ***4*****+**~~**3+**~~, or 2+ to ≥ 4+) ~~**post baseline**~~ as compared to the baseline (Day 1) VH score ***or best achieved VH score post baseline.*** **<u>The DE-109 ESIs are specific to the study eye only and are as follows:</u>** • 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 ≥ ~~**1+**~~***2*****+,** 0.5+ to ≥ ~~**1.5+**~~***3*****+,** 1+ to ≥ ~~**2+**~~***3*****+**, 1.5+ to ≥ ***4*****+**~~**3+**~~, or 2+ to ≥ 4+) as compared to the baseline (Day 1) VH score or the best achieved VH score post-baseline.
Rationale:	Updated to reflect that a ½ unit is not recognized as a step change in the vitreous haze, so only whole unit increases in the vitreous haze are used in the rescue criteria and Events of Special Interest definitions.

Section:	Section 1.1, Section 4.1, Section 9.6
Original Text:	**Interim Analyses, Primary Analysis, and Analysis of Open-Label Period:** An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. There are two goals for this interim analysis (1) to assess for futility; and (2) to re-assess the sample size. Alpha spending for this interim analysis will be 0.00001. Sample size re-assessment will be performed with the "promising zone" approach as follows (Mehta et al., 2011). If the conditional power at the interim analysis is between 50% and 80%, the suggested sample size increase would be 100 subjects (i.e., 50% of the original sample size). If, on the other hand, the conditional power is > 80% or < 50%, no change to the sample size will take place. If the conditional power is <10%, then the Data Monitoring Committee (DMC) would recommend stopping the trial due to futility. The DMC could recommend stopping the trial due to safety concerns at any of the DMC meetings and the interim analysis. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the DMC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.
Revised Text:	**Interim Analyses, Primary Analysis, and Analysis of Open-Label Period:** An interim analysis is planned when the first 100 subjects complete their Month 5 Visit. There are two goals for this interim analysis (1) to assess for futility; and (2) to re-assess the sample size. ~~**Alpha spending for this interim analysis will be 0.00001.**~~ Sample size re-assessment will be performed with the "promising zone" approach as follows (Mehta et al., 2011). If the conditional power at the interim analysis is between 50% and 80%, the suggested sample size increase ~~**would be**~~ ***may be up to*** 100 subjects (i.e., 50% of the original sample size). If, on the other hand, the conditional power is > 80% or < 50%, no change to the sample size will take place. If the conditional power is <~~**10%**~~**30%**, then the Data Monitoring Committee (DMC) would recommend stopping the trial due to futility. The DMC could recommend stopping the trial due to safety concerns at any of the DMC meetings and the interim analysis. An independent statistical and programming team will be used to perform this interim analysis of unmasked data and the DMC will review the results and make recommendations based on the findings. The planned interim analysis will be specified in greater detail in the SAP and in the DMC charter.

Rationale:	Change in the futility threshold to allow trial to stop earlier if the treatment does not show enough evidence to provide benefits to the subjects.

Section:	**Section 8.1.7**
Original Text:	**Double-Masked Treatment Period, Month 3** Note: Subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at Month 3. Allowable visit window: Day 90 ± 3 days **Visit details:** Perform the following assessments in both eyes: • Perform physical examination. • Record vital signs. • Collect fasting blood for serum chemistry and hematology tests for laboratory analysis. • Obtain urine sample for urinalysis. • Assess BCVA using ETDRS charts. • Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically). • Administer the VFQ-25. • Measure IOP. • Perform slit-lamp biomicroscopy. • Perform indirect ophthalmoscopy. • Obtain fundus photography. • Perform fluorescein angiography. • Perform OCT. • Assess for adverse events. • Record concomitant medications (including systemic corticosteroid medication status). Record the study visit in the EDC system (Medidata) for Month 3.

Revised Text:	**Double-Masked Treatment Period, Month 3** ~~**Note: Subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at Month 3.**~~ Allowable visit window: Day 90 ± 3 days **Visit details:** Perform the following assessments in both eyes: • ~~**Perform physical examination.**~~ • ~~**Record vital signs.**~~ • ~~**Collect fasting blood for serum chemistry and hematology tests for laboratory analysis.**~~ • ~~**Obtain urine sample for urinalysis.**~~ • Assess BCVA using ETDRS charts. • Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically). • ~~**Adminster the VFQ-25**~~ • Measure IOP. • Perform slit-lamp biomicroscopy. • Perform indirect ophthalmoscopy. • Obtain fundus photography. • Perform fluorescein angiography. • Perform OCT. • Assess for adverse events. • Record concomitant medications (including systemic corticosteroid medication status). Record the study visit in the EDC system (Medidata) for Month 3.
Rationale:	Our primary endpoint has changed from Month 3 to Month 5. Physical exam and vital signs, laboratory safety tests, and VFQ-25 have been moved to align these safety assessments and the patient-reported outcomes with the primary endpoint.

Section:	**Section 8.1.9.**

Original Text:	**Double-Masked Treatment Period, Month 5** Allowable visit window: Day 150 ± 3 days **Visit details:** Perform the following assessments in both eyes: • Assess BCVA using ETDRS charts. • Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically). • Measure IOP. • Perform slit-lamp biomicroscopy. • Perform indirect ophthalmoscopy. • Obtain fundus photography. • Perform fluorescein angiography. • Perform OCT. • Assess for adverse events. • Record concomitant medications (including systemic corticosteroid medication status). Record the study visit in the EDC system (Medidata) for Month 5.
Revised Text:	**Double-Masked Treatment Period, Month 5** ***Note: Subjects must fast 8 hours prior to the blood draw for hematology and chemistry laboratory tests taken at Month 5.*** Allowable visit window: Day 150 ± 3 days **Visit details:** Perform the following assessments in both eyes: • ***Perform physical examination. Note: if this was performed at Month 3 under a previous version of the protocol it does not need to be repeated.*** • ***Record vital signs. Note: if this was performed at Month 3 under a previous version of the protocol it does not need to be repeated.*** • ***Collect fasting blood for serum chemistry and hematology tests for laboratory analysis. Note: if these samples were collected at Month 3 under a previous version of the protocol they do <u>not</u> need to be repeated.***

	• ***Obtain urine sample for urinalysis. Note: if this sample was collected at Month 3 under a previous version of the protocol it does not need to be repeated.*** • Assess BCVA using ETDRS charts. • Administer dilation eye drops (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically). • ***Administer the VFQ-25. Note: if this was performed at Month 3 under a previous version of the protocol it does <u>not</u> need to be repeated.*** • Measure IOP. • Perform slit-lamp biomicroscopy. • Perform indirect ophthalmoscopy. • Obtain fundus photography. • Perform fluorescein angiography. • Perform OCT. • Assess for adverse events. • Record concomitant medications (including systemic corticosteroid medication status). Record the study visit in the EDC system (Medidata) for Month 5.
Rationale:	Our primary endpoint has changed from Month 3 to Month 5. Physical exam and vital signs, laboratory safety tests, and VFQ-25 have been moved to align these safety assessments and patient-reported outcomes with the primary endpoint.

Section:	**Section 8.2.3**
Original Text:	8.2.3.. Anterior Chamber Cells Slit-lamp biomicroscopy will be used to assess anterior chamber cells. The following scale will be used to measure anterior chamber cells:

	Anterior Chamber Cells (1 mm x 1 mm slit beam) 0 <1 cells 0.5+ 1-5 cells 1+ 6-15 cells 2+ 16-25 cells 3+ 26-50 cells 4+ >50 cells
Revised Text:	8.2.3.. Anterior Chamber Cells Slit-lamp biomicroscopy will be used to assess anterior chamber cells. The following scale will be used to measure anterior chamber cells: Anterior Chamber Cells (1 mm x 1 mm slit beam) 0 ***0*** ~~<1~~ cells 0.5+ 1-5 cells 1+ 6-15 cells 2+ 16-25 cells 3+ 26-50 cells 4+ >50 cells
Rationale:	Updated to provide clarity.

Section:	**Section 9.2**
Original Text:	9.1 Statistical Hypotheses The primary efficacy endpoint (VH 0 response at Month 5) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic, stratified by the number of enrolled eyes from a subject (one eye or two eyes) and region (US or non-US). The null (H_0) and alternative (H_1) hypotheses are as follows:
Revised Text:	***9.2*** Statistical Hypotheses

	The primary efficacy endpoint (VH 0 response at Month 5) will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic, stratified by 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). The null (H_0) and alternative (H_1) hypotheses are as follows:
Rationale:	This is addition of language to reflect that subjects are stratified based on baseline systemic (oral) corticosteroid use in addition to number of eyes and region, and that analysis will account for all stratifying factors.

Section:	**Section 9.4**
Original Text:	9.3 Population for Analyses The following analysis populations for study analyses are defined: Intent-to-Treat (ITT), Safety, Per-Protocol (PP), Intent-to-Taper, Macular Edema, Vision 20/40 or Worse: • The **ITT population** will consist of all study eyes. The ITT population will be the analysis population for the primary analysis and will use treatment as randomized. • For analyses of ocular AEs and safety parameters assessed per eye, the **Safety population** will consist of all study eyes which received at least one administration of IP. For analyses of non-ocular AEs and safety parameters assessed per subject, the **Safety population** will consist of all subjects who received at least one administration of IP.
Revised Text:	***9.4*** Population for Analyses The following analysis populations for study analyses are defined: ~~*Intent-to-Treat (ITT)*~~***Full Analysis Set (FAS),*** Safety, Per-Protocol (PP), Intent-to-Taper, Macular Edema, Vision 20/40 or Worse: • The ~~ITT~~***FAS* population** will consist of all study eyes ***that are randomized and received at least one administration of study treatment***. The ~~**ITT**~~ ***FAS*** population will be the analysis population for the primary analysis and will use treatment as randomized.
Rationale:	Change in the definition of the analysis population from Intent-to-treat (ITT) to Full Analysis Set (FAS) to align the analysis population with the study estimands, as deemed acceptable by FDA review comments.

Section:	**Section 9.5.1**
Original Text:	Section 9.4.1 Handling of Missing Values In the analysis of VH 0, VH 0 or 2-unit decrease (improvement), and VH 0 or 0.5+ responses: • Subjects who (a) receive rescue therapy for conditions other than worsening of uveitis or (b) are rescued due to the worsening of uveitis but do not meet the protocol-defined rescue criteria, missing VH scores subsequent to receiving rescue therapy will be imputed using the last observed VH score before receiving rescue therapy. • Missing VH scores of subjects not rescued before Month 5/Month 3 visit will be imputed using a last-observation-carried forward (LOCF) approach. The response status will then be determined based on the observed or imputed VH scores. Sensitivity analyses using other imputation methods will be performed. For medical events including AEs, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. The same rules will be followed to impute completely or partially missing start and end dates of non-study medications. Unless specified otherwise, descriptive summaries will be based on observed cases. No imputation of missing scores will be implemented. Additional details on handling of missing data will be provided in the SAP.
Revised Text:	Section ***9.5.1*** Handling of Missing Values In the analysis of VH 0, VH 0 or 2-unit decrease (improvement), and VH 0 or 0.5+ responses: • Subjects who (a) receive rescue therapy for conditions other than worsening of uveitis or (b) are rescued due to the worsening of uveitis but do not meet the protocol-defined rescue criteria, missing VH scores subsequent to receiving rescue therapy will be imputed using ***a*** ~~**the last observed VH score**~~***multiple imputation-based approach*** before receiving rescue therapy. • Missing VH scores of subjects not rescued before Month 5/Month 3 visit will be imputed using a ***multiple imputation-based approach***~~**last-observation-carried forward (LOCF) approach.**~~

	The multiple imputation model will include vitreous haze measures at preceding visits and baseline characteristics. The response status will then be determined based on the observed or imputed VH scores. ***No imputation is needed for composite score analysis as eyes with missing VH scores will be assigned a score of zero, unless they are rescued due to the worsening of uveitis or discontinued from the study due to lack of efficacy or adverse event (which will be assigned with a score of -1).*** For medical events including AEs, completely or partially missing onset and resolution dates will be imputed in a conservative fashion to be detailed in the SAP. The same rules will be followed to impute completely or partially missing start and end dates of non-study medications. Unless specified otherwise, descriptive summaries will be based on observed cases. No imputation of missing scores will be implemented. Additional details on handling of missing data ***and sensitivity analyses on imputation methods*** will be provided in the SAP.
Rationale:	The approach to missing data will be changed from LOCF to multiple imputation to be aligned with the study estimands.

Section:	**Table 8, Footnotes**
Original Text:	Endpoint Statistical Analysis Secondary endpoints Key secondary efficacy endpoints: • VH 0 or 2-unit response[b] at Month 5 • VH 0 response at Month 3 • VH 0 or 2-unit response at Month 3 Other secondary efficacy endpoints (double-masked period of study): • VH 0 or 0.5+ response[c] at Month 5 • VH 0 or 0.5+ response at Month 3 • Corticosteroid tapering success with resolution[d] at Month 5 • Corticosteroid tapering success with resolution at Month 3 • BCVA 3-line response[e] at Month 5 • BCVA 3-line response at Month 3 • Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT • Change from baseline in CST at Month 3 as measured by OCT • Use of rescue therapy before Month 5

	• Use of rescue therapy before Month 3 Statistical Analysis Methods For the primary analysis of VH 0 response at Month 5, the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by number of enrolled eyes from a subject (one eye or two eyes) and region (US or non-US) will be conducted. Logistic generalized estimating equation (GEE) model will be used as a sensitivity analysis. A hierarchical approach will be used to control the overall Type I error rate associated with the multiple comparisons across the primary and the key secondary efficacy endpoints at the 0.04999 level (two-sided) . If the hypothesis testing for the primary endpoint successfully rejects the null hypothesis, the first key secondary efficacy endpoint will be tested, and so on. For the other secondary endpoints, no multiplicity adjustment will be made. For secondary efficacy endpoints during double-masked period: All binary secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by number of enrolled eyes from a subject (one eye or two eyes) and region (US vs. non-US). Change-from-baseline endpoints will be analyzed by a mixed-effects model for repeated measures (MMRM) using observed cases. The statistical model for the analysis of each continuous secondary endpoint may be adjusted if it fails to converge. More details regarding model specifications will be provided in the SAP. Footnotes: Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale. [a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale. [b] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale. [c] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale. [d] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at a stable prednisone-equivalent dose of 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). [e] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).
Revised Text:	Secondary endpoints: Key secondary efficacy endpoints: • ~~**VH 0 or 2-unit response**~~***Composite endpoint***[b] at Month 5 • VH 0 response at Month 3

- ~~**VH 0 or 2-unit response**~~***Composite endpoint*** at Month 3

Other secondary efficacy endpoints (double-masked period of study):

- ***VH 0 or 2-unit response[c] at Month 5***
- ***VH 0 or 2-unit response at Month 3***
- VH 0 or 0.5+ ~~**response**[e]~~***response[d]*** at Month 5
- VH 0 or 0.5+ response at Month 3
- Corticosteroid tapering success with ~~**resolution**[d]~~ ***resolution[e]*** at Month 5
- Corticosteroid tapering success with resolution at Month 3
- BCVA 3-line ~~**response**[e]~~***response[f]*** at Month 5
- BCVA 3-line response at Month 3
- Change from baseline in central subfield thickness (CST) at Month 5 as measured by OCT
- Change from baseline in CST at Month 3 as measured by OCT
- Use of rescue therapy before Month 5
- Use of rescue therapy before Month 3

Statistical Analysis

For the primary analysis of VH 0 response at Month 5, the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by 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) will be conducted.

Logistic generalized estimating equation (GEE) model, ***treatment policy strategy, last-observation-carried-forward (LOCF) imputation, and multiple imputation with tipping point analysis*** will be used as a sensitivity analysis.

A hierarchical approach will be used to control the overall Type I error rate associated with the multiple comparisons across the primary and the key secondary efficacy endpoints ~~**at the 0.04999 level (two-sided)**~~.

If the hypothesis testing for the primary endpoint successfully rejects the null hypothesis, the first key secondary efficacy endpoint will be tested, and so on.

All the other secondary efficacy endpoints are supportive in nature. Therefore, no formal hypothesis testing will be performed on secondary efficacy endpoints. Two-sided 95% confidence intervals and nominal p-values may be reported for them, and such results will be interpreted descriptively in terms of the support they provide to the treatment comparisons for the primary and the key secondary efficacy endpoints in the sense of logical consistency. ~~**For the other secondary endpoints, no multiplicity adjustment will be made.**~~

For secondary efficacy endpoints during double-masked period:

All binary secondary endpoints will be analyzed using the Cochran-Mantel-Haenszel (CMH) test with Row Mean Scores statistic stratified by number of enrolled eyes from a subject (one eye or two eyes***), baseline systemic (oral) corticosteroid use (yes or no),*** and region (US vs. non-US). Change-from-

	baseline endpoints will be analyzed by a mixed-effects model for repeated measures (MMRM) using observed cases. The statistical model for the analysis of each continuous secondary endpoint may be adjusted if it fails to converge. More details regarding model specifications will be provided in the SAP. Footnotes: Note: Vitreous haze (VH) will be scored using the modified Standardized Uveitis Nomenclature (SUN) scale. [a] VH 0 response (resolution of inflammation) is defined as a VH score of 0 in the study eye at a specified follow up visit based on the modified SUN scale. ***[b] Refer to composite score scales defined in the composite estimand in this table.*** ~~[b]~~[c] VH 0 or 2-unit response is defined as 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 the study eye in VH score at a specified follow up visit based on the modified SUN scale. ~~[c]~~[d] VH 0 or 0.5+ response (remission of inflammation) is defined as a VH score of 0 or 0.5+ in the study eye at a specified follow-up visit based on the modified SUN scale. ~~[d]~~[e] Corticosteroid tapering success with resolution is defined as achievement of a prednisone-equivalent oral dose of 0 mg/day and a VH score of 0 in the study eye at a specified follow-up visit. This endpoint is assessed based on the Intent-to-Taper population (study eyes of subjects who received systemic [oral] corticosteroids at a stable prednisone-equivalent ~~of~~ 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). ~~[e]~~[f] BCVA 3-line response is defined as an increase (improvement) of at least 3 lines (15 ETDRS letters) from baseline in BCVA at a specified follow-up visit. This endpoint is assessed based on eyes with a baseline best-corrected visual acuity (BCVA) ≤ 70 ETDRS letters (Snellen equivalent of 20/40 or worse).
Rationale:	Added the clarification in the analysis of the primary endpoint regarding the stratification factors. Sensitivity analysis strategy is changed to be aligned with the study estimands. Clarification on the multiplicity adjustment for other secondary endpoints is also added.