Study Protocol Cover Page

Official Study Title:	A Phase lllb, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects with Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program
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DE-109
Protocol 32-009
Original

TITLE: A Phase IIIb, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects with Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program

SPONSOR:	STUDY DRUG:
SANTEN INCORPORATED 2100 Powell Street, 16th Floor Emeryville, CA 94608	2.0% DE-109 injectable solution (440 µg of sirolimus)

I have read the 32-009 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: _____

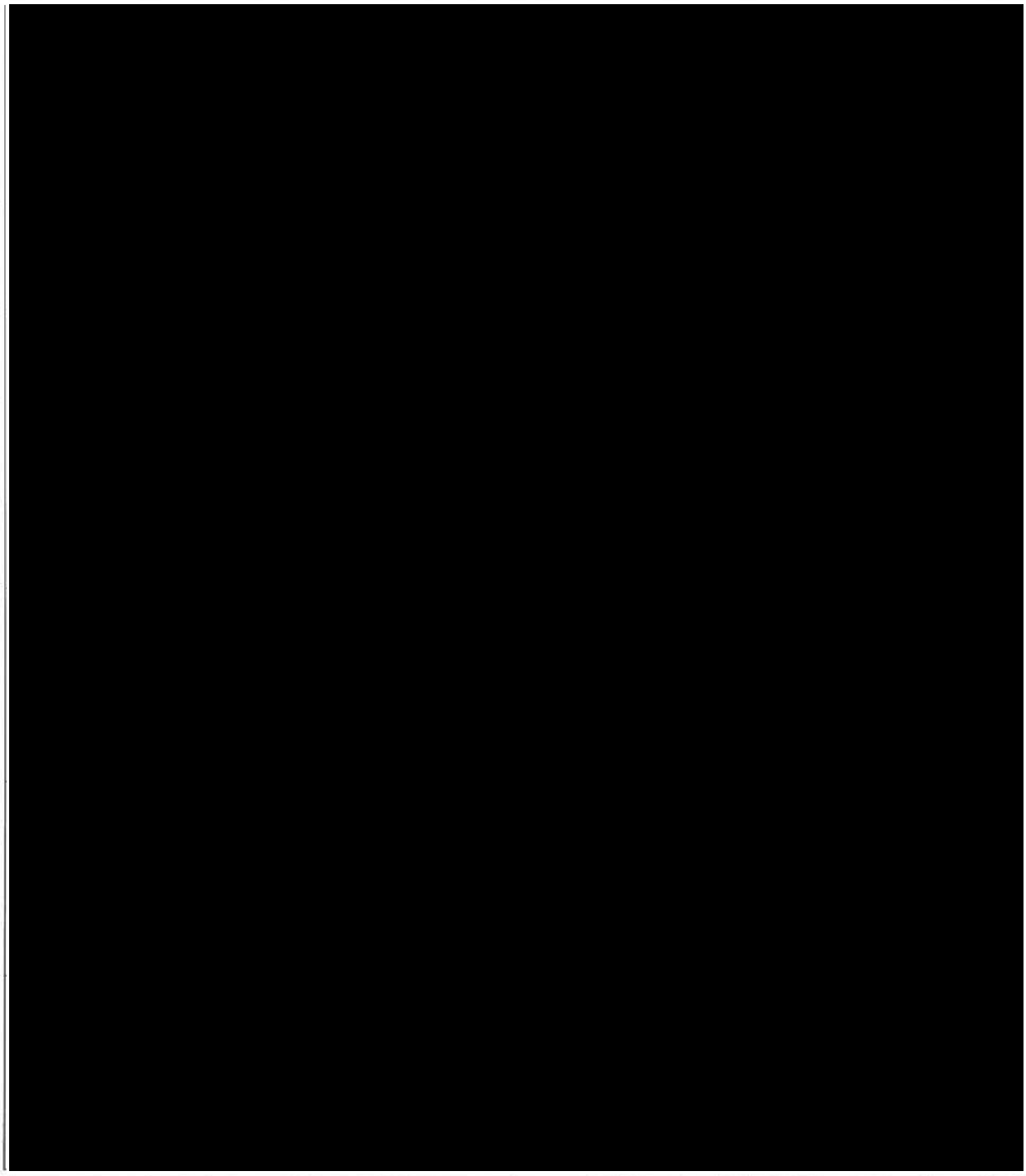
_____

Phone: _____

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

COMPANY/SPONSOR APPROVERS

Company/Sponsor Address
Santen, Incorporated
2100 Powell Street, 16th Floor
Emeryville, CA 94608



1. PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

2. SYNOPSIS

Name of Sponsor/Company:	**Santen Incorporated** 2100 Powell Street, 16th Floor Emeryville, CA 94608
Name of Investigational Product: DE-109 injectable solution	
Name of Active Ingredient: Sirolimus	
Title of Study: A Phase IIIb, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects with Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program	
Study Period (years): Estimated date first subject enrolled: August 2014 Estimated date last subject completed: November 2017	**Phase of Development:** Phase IIIb Safety Study

Objective:

The objective of this extension study is to evaluate the long-term safety of treatment with DE-109 (440 µg) in subjects with non-infectious uveitis of the posterior segment of the eye who have participated in the SAKURA development program.

Methodology:

This is a multicenter, open-label, extension study of intravitreal injections of the 440 µg dose of DE-109 in subjects with non-infectious uveitis of the posterior segment who received any dose of DE-109 and exited the SAKURA program under Santen Protocol 32-007, Amendment 05.

Subjects who were randomized and received at least two injections of DE-109 during the first five months of the SAKURA program and obtained clinical benefit from the study medication, as determined by the Investigator, may be considered for entry in this 12-month extension study. The minimum time lag from last injection in the SAKURA program to entry into the current protocol is 60 days.

The study eye to be treated in this extension study will be the same as the eye treated during the SAKURA program.

Study assessments will be conducted for all subjects at Day 1 (Baseline) and Month 12. Each subject will be followed according to the Investigator's standard clinical practice at non-study visits. DE-109 treatment may be administered in the study eye at the Investigator's discretion during the 12-month study period but no more frequently than every 60 days.

If the Investigator administers a DE-109 injection to the subject, the visit will be considered a Post-Baseline PRN Treatment Visit and procedures will be performed and recorded as specified in this protocol.

All subjects will exit the study at Month 12, unless terminated early. Adverse events will be recorded and collected throughout this extension study, up to the Month 12 exit visit.

Administration of DE-109:

- The study eye will be the eye treated in the SAKURA program.
- DE-109 should NOT be administered to the fellow eye.

Rescue therapy:

During the study, rescue therapy may be used at the discretion of the Investigator.

Masking: This is an open-label extension study. All subjects in this unmasked study will receive the 440 µg dose of DE-109.

Number of Subjects (planned): The number of subjects to be enrolled in the study will be approximately 200.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

At Day 1, a subject from the SAKURA program must meet all of the following inclusion criteria:

1. Have a subject number from participation in the SAKURA program
2. Exited the SAKURA program under Amendment 05
3. Have received at least two injections of DE-109 in the first five months of the SAKURA program
4. Received clinical benefit from treatment with DE-109 as determined by the Investigator
5. Female participants of childbearing potential must not be pregnant or breast-feeding, have a negative pregnancy test at Day 1 and must be willing to undergo pregnancy tests throughout the study
6. Both female participants of childbearing potential and male participants able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, must abstain from intercourse or must agree to practice acceptable methods of contraception throughout the course of the study
7. Ability to give informed consent and attend all study visits

Exclusion Criteria:

A subject from the SAKURA program with any of the following conditions is not eligible to participate in the study:

Ocular:

1. Active infectious uveitis. However, 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.
2. Any implantable corticosteroid-eluting device (e.g. Ozurdex, I-vation, Iluvien, fluocinolone acetonide [FA] intravitreal implant) in the study eye:
    a. If the Investigator confirms the device has no demonstrable efficacy as indicated in the package insert, the subject will be eligible
    b. If a Medidur implant, Iluvien or Retisert has been implanted no less than 3 years and 90 days prior to Day 1, the subject will be eligible
    c. If a Ozurdex implant has been implanted no less than 180 days prior to Day 1, the subject will be eligible
3. Clinically suspected or confirmed central nervous system or ocular lymphoma
4. Progressive glaucoma which is unresponsive to treatment.
5. Intraocular pressure of > 21 mmHg while on medical therapy, or chronic hypotony (< 6 mmHg)
6. Any significant ocular disease that could compromise vision in the study eye. These include, but are not limited to:
    a. Diabetic retinopathy: proliferative diabetic retinopathy (PDR) or non-proliferative diabetic retinopathy (NPDR) that compromises vision. Subjects with NPDR or PDR

that does not compromise vision are not excluded from the study;
   b. Wet age-related macular degeneration;
   c. Myopic degeneration with active subfoveal choroidal neovascularization
7. Any of the following treatments to the study eye:
   a. Intravitreal injections in the past 14 days
   b. Intravitreal injections of DE-109 in the past 60 days
8. Ocular surgery within the past 30 days
9. Ocular or periocular infection in either eye
10. History of or active herpetic infection in the study eye or adnexa
11. Presence of known active, inactive toxoplasmosis or toxoplasmosis scar in either eye
12. Presence of any form of ocular malignancy in the either eye including choroidal melanoma
13. History of vitrectomy in the study eye

Non-Ocular:

14. Allergy or hypersensitivity to study drug product or other study related procedures/medications
15. Participation in other investigational drug (SAKURA is an exception) or device clinical trials within 30 days prior to Day 1, or planning to participate in other investigational drug or device clinical trials for the entire duration of the study. This includes both ocular and non-ocular clinical trials.
16. Any recent systemic infection within 30 days of Day 1
17. Known to be immunocompromised
18. History of cytomegalovirus infection or clinical evidence of active cytomegalovirus infection at Day 1
19. 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
20. 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)
21. 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)
22. Use of medically prescribed marijuana or other illegal medication
23. Active systemic sarcoidosis within the last 30 months (i.e. subjects with uveitis secondary to sarcoidosis will be eligible as long as systemic sarcoidosis is not active and systemic immunosuppressive therapy has not been given in the last 30 months)
24. Therapeutic radiation to the head or neck within 90 days prior to Day 1 and throughout the study

In addition, the Investigator or Santen Medical Monitor may declare a subject ineligible for any sound reason.

Investigational product, dosage and mode of administration:

Investigational product: DE-109 injectable solution, 440 µg.

Subjects will be treated at the discretion of the Investigator, but no more frequently than every 60 days.

Route of Administration: 20 µL intravitreal injection in the study eye.

Duration of the Study: 12 months or commercial availability of DE-109, whichever comes first.

Criteria for Evaluation:

Safety: The long-term safety of DE-109 440 µg will be assessed based on adverse events, visual acuity, intraocular pressure, indirect ophthalmoscopy variables, vitreous haze and the use of rescue therapy.

Efficacy: Efficacy is not the main objective of this extension study. The long-term efficacy of DE-109 440 µg may be explored by vitreous haze.

Safety Parameters:

- Adverse event incidence rate
- Change in best-corrected visual acuity
- Change in intraocular pressure
- Change in indirect ophthalmoscopy findings
- Change in vitreous haze
- Proportion of safety subjects who were rescued

Statistical Methods:

This extension study is implemented to provide subjects with access to DE-109 to benefit those who have received at least two injections of DE-109 during the first 5-month treatment of the SAKURA development program and to evaluate the long-term safety of DE-109 440 µg in subjects with non-infectious uveitis of the posterior segment of the eye.

No statistical hypotheses will be tested in this study.

The safety data will be summarized descriptively. The Safety population will include all enrolled subjects with any safety data collected during the study, whether or not they ever receive any injection of DE-109 (440 µg). It will be the analysis population for safety summaries.

The formal definition of rescue therapy will be adequately documented based on clinical data review of this extension study prior to database lock.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 2: Abbreviations and Specialist Terms

Abbreviation/Term	Definition
AE	Adverse Event
Baseline	Earliest Assessment of Each Measure on Day 1
BCVA	Best-Corrected Visual Acuity
DE-109	Sirolimus Injectable Solution
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
FDA	Food and Drug Administration
FKBP-12	FK binding protein 12
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IOP	Intraocular Pressure
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major Histocompatibility Complex
mTOR	Mammalian Target of Rapamycin
NEI	National Eye Institute
NPDR	Non-Proliferative Diabetic Retinopathy
PDR	Proliferative Diabetic Retinopathy
SAE	Serious Adverse Event
SAKURA	Santen Protocol 32-007
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SUN	Standardized Uveitis Nomenclature Photographic Scale
USA	United States of America
VH	Vitreous Haze

5. INTRODUCTION

Uveitis is a heterogenous group of intraocular inflammation disorders with both exogenous (infection, trauma) and endogenous (autoimmune disorders, idiopathic) etiologies. The most widely used classification of uveitis is based on the anatomical location of the inflammation within the eye. Anterior uveitis is the most common type and can involve the cornea, iris, and/or ciliary body. Intermediate uveitis affects the middle portion of the eye, such as the ciliary body, anterior vitreous and peripheral retina. Posterior uveitis can involve the vitreous, choroid, retina, and/or optic nerve. Panuveitis, also referred to as diffuse, involves the anterior and posterior segments.

Uveitis is responsible for approximately 10% of the visual handicap in Western countries (Nussenblatt, 1990). The prevalence of posterior uveitis and its associated ocular morbidity is not well characterized. However, one study of an Israeli population and another of a Netherlands population approximated that 15 to 22% of uveitis affect the posterior segment (Rothova et al., 1996; Weiner et al., 1991), while the study of Veterans Affairs patients estimated 10% with posterior uveitis (Suhler et al., 2008). The study of the Netherlands population also found that in patients with posterior uveitis, 46% experienced visual loss of <20/40 or greater and 28% experienced macular edema (Rothova et al., 1996). In chronic uveitis, cumulative structural damage and loss of vision result from recurrent episodes of inflammation. T-cell infiltration is primarily responsible for the inflammation (Barton et al., 1995). T-cells release cytokines including various interleukins (IL-2, IL-4, and IL-10) and interferon gamma (Barton et al., 1995). Major histocompatibility complex molecules (MHC Class I and II) and adhesion molecules are upregulated by the cytokine release (Charteris et al., 1992; George et al., 1997; Whitcup et al., 1992a). In experimental uveitis models, adhesion molecules have been found on ocular resident cells before leukocytes reach the inside of the eye (Whitcup et al., 1993; Whitcup et al., 1992b). Thus, adhesion molecules enable leukocytes to migrate to the site of inflammation, contributing to the inflammatory cascade that occurs with active uveitis.

Corticosteroids are the mainstay of treatment for active, non-infectious uveitis. Corticosteroids are administered topically, by periocular injection, via intravitreal injection and implant, or systemically. Topical corticosteroids are useful for the management of anterior uveitis. In general, periocular corticosteroid injections are appropriate for intermediate uveitis. Retisert™ is a fluocinolone acetonide intravitreal implant which releases drug slowly over a period of months. This product was approved by the Food and Drug Administration (FDA) in 2005 for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. Long-term data shows that subjects who receive fluocinolone acetonide implants sometimes require cataract extraction and a significant percentage require treatment to reduce IOP (Callanan et al., 2008). Even though this newer treatment approach is now available, many patients with chronic, posterior uveitis are more difficult to manage and require systemic corticosteroids due to recurring inflammation. Co-morbidities from systemic corticosteroid use are well known, such as Cushingoid syndrome, diabetes, osteoporotic bones, and metabolic disturbances (Anglade et al., 2007). Systemic immunosuppressive agents, although they require close monitoring, are therefore sometimes utilized for their steroid-sparing capabilities. Immunosuppressive agents can be categorized into three (3) main classes: T-cell inhibitors (cyclosporine, tacrolimus), antimetabolites (azathioprine, methotrexate, mycophenolate mofetil, leflunomide), and alkylating

agents (cyclophosphamide, chlorambucil). More recently, biologic agents have been explored for use in uveitis, including tumor necrosis factor-α inhibitors (infliximab, etanercept, and adalimumab), anti-lymphocyte agents (rituximab and alemtuzumab), and an interleukin-2 receptor blocker (daclizumab).

Currently corticosteroids are the only approved drug class in the United States for non-infectious uveitis. Systemic cyclosporine which blocks T-cell activation and inhibits the production of cytokines has been approved in Germany and a few other countries for treatment-refractory uveitis but is not approved in the United States. Although a variety of treatment options are available, the co-morbidities associated with corticosteroids and the inconvenience of close monitoring required with systemic immunosuppressive and biologic agents warrant more treatment options.

Sirolimus for ocular administration is being tested with a proprietary formulation, DE-109 for the treatment of non-infectious, posterior uveitis. This proprietary formulation was originally developed by MacuSight, Inc. and in June 2010, Santen, Inc. acquired the worldwide rights to the formulation. The formulation provides drug exposure to the retina/choroid for up to approximately 2 months, and is amenable to delivery by the intravitreal route of administration. The active pharmaceutical ingredient in the formulation is sirolimus. Sirolimus, also known as rapamycin, was isolated in the 1970's from *Streptomyces hygroscopicus* in soil samples from Easter Island (Napoli et al., 2001). Sirolimus is the active pharmaceutical ingredient in 2 products approved by the FDA, specifically Rapamune®, an immunosuppressive agent used in renal transplant patients, and the CYPHER® sirolimus-eluting Coronary Stent approved for improving coronary luminal diameter in patients with symptomatic ischemic disease.

The mechanism of action of sirolimus in inmmunoregulation has been described extensively in the literature (Kahan, 2001; Napoli et al., 2001; Sehgal, 1998; Sehgal, 2003). Sirolimus blocks T-lymphocyte activation and smooth muscle and endothelial cell proliferation that occurs in response to antigenic and cytokine (IL-2, IL-4 and IL-15) stimulation employing either Ca^{2+}-dependent or Ca^{2+}-independent pathways (Rapamune, 2009; Sehgal, 1995; Sehgal, 1998). Sirolimus arrests cell cycle progression by direct interaction with 2 intracellular proteins, specifically the immunophilin FK binding protein 12 (FKBP-12) and the mammalian target of rapamycin (mTOR), a multifunctional serine-threonine kinase (Napoli et al., 2001). In cells, sirolimus binds to FKBP-12, and the resulting sirolimus: FKBP-12 complex then binds to and inhibits mTOR. The inhibition of mTOR blocks IL-2 mediated signal transduction pathways that prevent cell cycle progression from G1 to S phase in T cells, endothelial cells, osteosarcoma cells, myogenic cell lines and smooth muscle cells (Kwon et al., 2005; Sehgal, 1998). In addition, sirolimus inhibits the production of antibodies (Sehgal, 1995; Sehgal, 1998). Sirolimus has also been shown to down-regulate the expression of many genes related to inflammation such as interleukin-8, endothelial-monocyte activating polypeptide II, granulocyte chemotactic protein 2, cyclooxygenase 1 and 2, and inducible nitric oxide synthas (Adamis, 2002; Attur et al., 2000; Joussen et al., 2004; Nuhrenberg et al., 2005).

Similar to cyclosporine, sirolimus blocks T-cell activation and inhibits the production of inflammatory cytokines. Moreover, tacrolimus, another immunomodulatory agent closely related to sirolimus, has shown effectiveness in uveitis refractory to cyclosporine (Kilmartin et al., 1998; Sloper et al., 1999). Since sirolimus provides an inhibitory effect on inflammation, it may be beneficial in the treatment of active, non-infectious uveitis.

Sirolimus has been administered to patients with non-infectious intermediate, posterior uveitis, or panuveitis in an investigator-sponsored protocol trial known as the SAVE study (Nguyen et al., 2013). This was an initial Phase I study evaluating intravitreal and subconjunctival administration of sirolimus and the results of the study supported the continued development of DE-109.

The SAKURA development program is a multinational, multicenter, randomized, double-masked protocol (Santen Protocol 32-007) assessing the safety and efficacy of three doses of DE-109 (44 µg, 440 µg and 880 µg) administered every 2 months in subjects with active, non-infectious uveitis of the posterior segment of the eye. A planned unmasked analysis of 6-month data of 347 subjects has been completed. In the analysis, both the 440 µg and 880 µg doses of DE-109 demonstrated efficacy in the treatment of non-infectious uveitis affecting the posterior segment of the eye. The 440 µg dose demonstrated statistically significant differences for the primary and key secondary endpoints when compared to the 44 µg dose. Efficacy results for the 880 µg dose regimen were not as significant compared to the 44 µg dose. Additionally, there was a tendency towards increased reporting of AEs associated with intraocular inflammation following intravitreal administration with the 880 µg dose. In the overall analysis, the 440 µg dose demonstrated a more favorable Benefit-Risk profile than the 880 µg dose. The SAKURA development program is on-going and continues to enroll.

This study (Santen, Protocol 32-009) is being initiated to allow subjects continued access to DE-109 (440 µg) following participation in the SAKURA program and to obtain additional long-term safety data on the to be developed dose.

6. OBJECTIVES

The objective of this extension study is to evaluate the long-term safety of treatment with DE-109 (440 μg) in subjects with non-infectious uveitis of the posterior segment of the eye.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is a multicenter, open-label, extension study of intravitreal injections of the 440 µg dose of DE-109 in subjects with non-infectious uveitis of the posterior segment who received any dose of DE-109 and exited the SAKURA program under Santen Protocol 32-007, Amendment 05.

Subjects who were randomized and received at least two injections of DE-109 during the first five months of the SAKURA study and obtained clinical benefit from the study medication, as determined by the Investigator, may be considered for entry in this 12-month extension study. The minimum time lag from last injection in the SAKURA program to entry into the current protocol is 60 days.

The study eye to be treated in this extension study will be the same as the eye treated during the SAKURA program.The study eye must meet all eligibility criteria of the extension study.

DE-109 should NOT be administered to the fellow eye. If the fellow eye requires treatment during the study, alternative local therapies (e.g., intravitreal or periocular injection of triamcinolone acetonide, Ozurdex, Iluvien, anti-VEGF treatments or photodynamic therapy, etc) may be administered to that eye. The regimen and frequency of treatments for the fellow eye will be at the Investigator's discretion.

Study assessments will be conducted for all subjects at Day 1 (Baseline) and Month 12. Each subject will be followed according to the Investigator's standard clinical practice at non-study visits. DE-109 treatment may be administered in the study eye at the Investigator's discretion during the 12-month study period but no more frequently than every 60 days.

If the Investigator administers a DE-109 injection to the subject, the visit will be considered a Post-Baseline PRN Treatment Visit and procedures will be performed and recorded as specified in this protocol (See Table 3).

All subjects will exit the study at Month 12, unless terminated early. Adverse events (AEs) will be recorded and collected throughout this extension study, up to the Month 12 exit visit.

It is anticipated that approximately 200 subjects from the SAKURA program may be enrolled in this study. Subjects will be screened for eligibility and written informed consent will be obtained before any study related procedures are performed.

7.1.1. Discussion of Study Design

This study is designed to provide access to DE-109 (440 µg) for those subjects who received treatment during the SAKURA program. In addition the study will evaluate the long-term safety of DE-109.

The 440 µg dose of DE-109 will be the only dose utilized in this open-label study. Subjects will be evaluated for treatment with DE-109 as needed, but may not receive an injection of DE-109 more frequently than every 60 days. DE-109 may only be administered to the study eye.

Rescue treatment for the study eye and all treatments for the non-study eye are to be administered at the discretion of the Investigator. The long-term safety of DE-109 (440 µg) will

be assessed based on adverse events (AEs), best-corrected visual acuity (BCVA), intraocular pressure (IOP), indirect ophthalmoscopy variables, VH and the use of rescue therapy.

The final safety data evaluation will be assessed at Month 12. Interim analyses may be performed by the Sponsor at various times during the study.

7.2. Number of Subjects

The number of subjects to be enrolled in the study will be approximately 200 subjects.

7.3. Treatment Assignment

This is an open-label study and all subjects will receive the 440 μg dose of DE-109.

7.4. Criteria for Study Termination

This study may be stopped by Santen at any time following appropriate notification.

7.5. Study Procedures

All subjects must sign a written informed consent form (ICF) before undergoing any study-related procedure. Each subject will be assigned the same patient number assigned to them in the SAKURA program.

A Schedule of Events is provided in Table 3 and detailed procedures for examinations can be found in Section 21.4.

Table 3: Schedule of Events

	Visit 1 Day 1 Screening/Baseline	Post-Baseline PRN Treatment Visits	Visit 2 Month 12 or Early Termination[d]
Assessment Window (Days)	-	≥60 days since last injection	±14
Informed Consent[a]	X		
Demographics	X		
Medical/Surgical history	X		
Medications	X	x	x
Urine pregnancy test, if appropriate	x[b]	x[b]	x[b]
Inclusion/exclusion criteria	X		
Best-Corrected Visual Acuity	X	x	x
Intraocular pressure	x[c]	x[c]	x
Indirect ophthalmoscopy[e]	X	x	x
Vitreous haze	X	x	x
DE-109 administration, if needed	x	x	
Adverse events	x[f]	x[f]	x

a. Informed consent will be obtained prior to conducting any study-related activities.
b. Urine pregnancy tests are to be performed on all women of child-bearing potential.
c. On days when DE-109 injections are administered perform IOP before and 40 (±10) minutes after DE-109 injection.
d. For Early Termination Visits please complete the procedures for the Month 12 visit.
e. Indirect ophthalmoscopy will be performed prior to each study drug injection and then again within 30 minutes after study drug injection
f. On days when DE-109 injections are administered AEs will be elicited before and after DE-109 injection.

7.5.1. Visit 1 - Day 1 - Screening/Baseline

- Explain the purpose and details of the study to the subject and obtain written informed consent prior to the subject's participation in any extension study related activity.
- Determine if the subject has:
    - A subject number from participation in the SAKURA program, Amendment 05
    - Received at least two treatments of DE-109 in the first five months of the SAKURA program
    - Received clinical benefit from treatment with DE-109 as determined by the Investigator.
- Record subject's demographics, medical and surgical history and medications.
- If the subject is a woman of child-bearing potential, perform a urine pregnancy test.
- Review the inclusion and exclusion criteria. If the subject has met the inclusion/exclusion criteria, the subject may continue in the study.
- Perform the following assessments:

    For subjects exiting the SAKURA program at this visit, the following assessments will be obtained from the SAKURA Termination Visit. Please skip to "Evaluation of Need for Treatment."

    - BCVA
    - IOP
    - Indirect ophthalmoscopy
    - VH.
- **Evaluation of Need for Treatment** - If in the judgment of the investigator, the subject needs DE-109 treatment, it has been at least 60 days since the last treatment, and the results of the urine pregnancy test were negative (for women of child-bearing potential), perform the study drug administration procedures as described in Section 10.4 and 10.5.
- The following assessments must be performed after the administration of study drug:
    - Indirect ophthalmoscopy within 30 minutes following injection
    - IOP 40 (±10) minutes following injection
    - AEs

7.5.2. Visit 2 - Month 12 or Early Termination

- At Day 360 (±14) or if the subject is exiting the study early, perform the following assessments:
    - Update medications
    - Urine pregnancy test for women of child-bearing potential

- BCVA
- IOP
- Indirect ophthalmoscopy
- VH
- AEs.

- Exit the subject from the study.

7.5.3. Post-Baseline PRN Treatment Visit

The subject may receive DE-109 treatments at the discretion of the Investigator, but no more frequently than every 60 days. If a subject receives treatment with DE-109 between scheduled study assessments, the following procedures will be performed:

- Update medications
- If the subject is a woman of child-bearing potential, perform a urine pregnancy test
- BCVA
- IOP
- Indirect ophthalmoscopy
- VH
- AE.

- If in the judgment of the Investigator, the subject needs DE-109 treatment, it has been at least 60 days since the last treatment, and the results of the urine pregnancy test were negative (for women of child-bearing potential), perform the study drug administration procedures as described in Section 10.4 and Section 10.5.
- The following assessments must be performed after the administration of study drug:
  - Indirect ophthalmoscopy within 30 minutes following injection
  - IOP 40 (±10) minutes following injection
  - AEs.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

Eligible subjects must meet all eligibility criteria described in Section 8.1 and Section 8.2.

8.1. Inclusion criteria

At Day 1, a subject from the SAKURA program must meet all of the following inclusion criteria:

1. Have a subject number from participation in the SAKURA program
2. Exited the SAKURA program under Amendment 05
3. Have received at least two injections of DE-109 in the first five months of the SAKURA program
4. Received clinical benefit from treatment with DE-109 as determined by the Investigator
5. Female participants of childbearing potential must not be pregnant or breast-feeding, have a negative pregnancy test at screening and must be willing to undergo pregnancy tests throughout the study
6. Both female participants of childbearing potential and male participants able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, must abstain from intercourse or must agree to practice acceptable methods of contraception throughout the course of the study.
7. Ability to give informed consent and attend all study visits

8.2. Exclusion criteria

A subject from the SAKURA program with any of the following conditions if not eligible to participate in the study:

Ocular:

1. Active infectious uveitis. However, 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.
2. Any implantable corticosteroid-eluting device (e.g. Ozurdex, I-vation, Iluvien, fluocinolone acetonide [FA] intravitreal implant) in the study eye:
    a. If the Investigator confirms the device has no demonstrable efficacy as indicated in the package insert, the subject will be eligible
    b. If a Medidur implant, Iluvien or Retisert has been implanted no less than 3 years and 90 days prior to Day 1, the subject will be eligible
    c. If a Ozurdex implant, has been implanted no less than 180 days prior to Day 1, the subject will be eligible
3. Clinically suspected or confirmed central nervous system or ocular lymphoma
4. Progressive glaucoma which is unresponsive to treatment

5. Intraocular pressure of > 21 mmHg while on medical therapy, or chronic hypotony (<6 mmHg)
6. Any significant ocular disease that could compromise vision in the study eye. These include, but are not limited to:
    a. Diabetic retinopathy: proliferative diabetic retinopathy (PDR) or non-proliferative diabetic retinopathy (NPDR) that compromise vision. Subjects with NPDR or PDR that does not compromise vision are not excluded from the study;
    b. Wet age-related macular degeneration;
    c. Myopic degeneration with active subfoveal choroidal neovascularization
7. Any of the following treatments to the study eye:
    a. Intravitreal injections in the past 14 days
    b. Intravitreal injections of DE-109 in the past 60 days
8. Ocular surgery within the past 30 days
9. Ocular or periocular infection in either eye
10. History of herpetic infection in the study eye or adnexa
11. Presence of known active, inactive toxoplasmosis or toxoplasmosis scar in either eye
12. Presence of any form of ocular malignancy in the either eye including choroidal melanoma
13. History of vitrectomy in the study eye

Non-Ocular:

14. Allergy or hypersensitivity to study drug product or other study related procedures/ medications
15. Participation in other investigational drug (SAKURA is an exception) or device clinical trials within 30 days prior to Day 1, or planning to participate in other investigational drug or device clinical trials for the entire duration of the study. This includes both ocular and non-ocular clinical trials.
16. Any recent systemic infection within 30 days of Day 1
17. Known to be immunocompromised
18. History of or active cytomegalovirus infection or clinical evidence of active cytomegalovirus infection at Day 1
19. 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

20. 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)
21. 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)
22. Use of medically prescribed marijuana or other illegal medication
23. Active systemic sarcoidosis within the last 30 months (i.e. subjects with uveitis secondary to sarcoidosis will be eligible as long as systemic sarcoidosis is not active and systemic immunosuppressive therapy has not been given in the last 30 months).
24. Therapeutic radiation to the head or neck within 90 days prior to Day 1 and throughout the study.

In addition, the Investigator or Santen Medical Monitor may declare a subject ineligible for any sound reason.

8.3. Subject Withdrawal Criteria

An early termination occurs when a subject who provides written informed consent ceases participation in the study, regardless of circumstances, before the completion of the study. Subjects may voluntarily withdraw from the study at any time for any reason. In addition, the Investigator or the Medical Monitor may terminate a subject's study participation for reasons related to the best interest of the subject. Subjects who terminate from the study will not be replaced. Subjects may be terminated from the study due to any of the following reasons:

- Non-compliance
- Lack of efficacy
- Lost to follow-up
- Protocol violation
- Withdrawal by subject
- AE
- Death
- Other

If a subject is discontinued from the study before completing Month 12, then to the extent possible, all assessments, including safety, that are scheduled to be performed at Month 12 should be performed on the day of discontinuation.

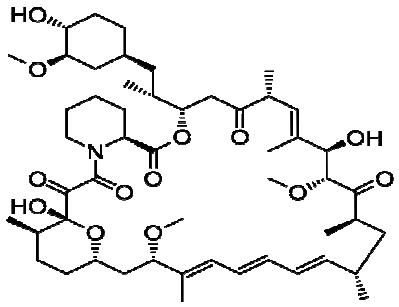
Subjects who discontinue prematurely will not be replaced.

9. TREATMENT OF SUBJECTS

9.1. Description of Study Drug

DE-109 is a depot formulation of sirolimus, an immunomodulatory agent which inhibits the mammalian target of rapamycin (mTOR), a serine/threonine protein kinase that regulates cell growth, proliferation, motility and survival through changes in transcription and protein synthesis.

Figure 1: DE-109 Chemical Structure



Investigational Product: 2.0% DE-109 injectable solution (440 µg)

9.2. Concomitant Medications

The use of any concomitant prescription or over-the-counter medication will be recorded during the study. Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator during the study. Whenever possible, concomitant medications should be administered in dosages that remain constant throughout the study. The generic name, indication, route of administration, frequency, dose, start date and stop date (if applicable) will be recorded for each medication.

9.2.1. Prohibited Medications or Treatments

The decision to administer a prohibited concomitant medication or treatment during the study should be made with the safety of the subject as the primary consideration. There may be prohibited therapies not mentioned below.

The following medications or treatments are prohibited:

- Participation in other investigational drug (SAKURA is an exception) or device clinical trials within 30 days prior to Day 1 or planning to participate in other investigational drug or device clinical trials for the duration of the study. This includes both ocular and non-ocular clinical trials.
- Therapeutic radiation to the head or neck within 90 days prior to Day 1 and throughout the study.
- Use of medically prescribed marijuana or other illegal medication within 30 days prior to Day 1 and throughout the study.

9.2.2. Rescue Therapy

Rescue therapy may be used at the discretion of the Investigator.

9.3. Treatment Compliance

The Investigator is not required to administer DE-109 at any visit. DE-109 treatments may be given, as needed, at the discretion of the Investigator; however, DE-109 treatments may not be given more frequently than every 60 days.

The Investigator is responsible for scheduling the subject for follow-up visits based on the Investigator's standard clinical procedures and these visits are not study visits. If a subject receives treatment with DE-109 (440 µg) between scheduled study assessments, the visit will be a Post-Baseline PRN Treatment Visit and procedures will be performed and recorded as specified in this protocol (See Table 3).

Study monitors will verify pertinent data to confirm the study is conducted according to the protocol.

9.4. Randomization and Masking

Randomization is not employed in this study. The decision to administer study drug on any given study day is at the discretion of the Investigator. All subjects who are dosed will receive the same open-label dose of DE-109 (440 µg). Study drug will contain a unique number and should be dispensed in sequential, ascending order by each center.

10. STUDY DRUG MATERIALS AND MANAGEMENT

10.1. Study Drug

10.1.1. Test Article

DE-109 (440 µg) is formulated as clear, non-aqueous solutions of the drug substance, sirolimus, in a vehicle composed of polyethylene glycol 400 (PEG 400) and ethanol. Both PEG 400 and ethanol are widely used as solubilizing excipients in injectable formulations (Strickley, 2004).

The dosage of sirolimus to be administered in this extension study will be 440 µg DE-109 as shown in Table 4.

Table 4: DE-109 Dosing

Injection Volume of:	Will deliver approximately:
20 µL of 22 µg/µL (2.0%) intravitreally	440 µg of sirolimus

DE-109 (440 µg) will be supplied frozen either as 0.3 mL of sterile injectable solution in 0.5 mL vials or 0.3 mL of sterile injectable solution in 2 mL vials. Investigator must use the syringes and needles supplied by the sponsor.

10.1.2. Study Drug Complaint Reporting

Complaints regarding the study drug should be reported to Santen Product Complaint at 415-268-9100 or the study monitor.

10.2. Study Drug Packaging and Labeling

DE-109 (440 µg) injectable solutions are filled in Type 1 Glass (borosilicate) clear vials, capped with 13 mm Gray Butyl stoppers with B2-40 coating, and sealed with a 13 mm colored Flip-Off Truedge. Each single use vial will be placed in a unit carton, and the labeling will include protocol number, unique kit number, and storage conditions.

10.3. Study Drug Storage

DE-109 (440 µg) will be received frozen. DE-109 (440 µg) must be stored and should remain frozen in a secure, locked, dark, temperature controlled, -20ºC ± 5ºC (with allowable temperature excursions up to -35º C) freezer with restricted access until the time of use.

10.4. DE-109 Preparation

The vial of study drug will be removed from the freezer and thawed by rotating the vial between the palms of the hands for a minimum of 5 minutes, or by setting the vial at room temperature for a minimum of 30 minutes. Care should be taken to protect the product from light. Study drug should be drawn into the provided single-use plastic syringe within 60 minutes after removing

the vial from the freezer. Study drug should be injected within 2 hours of being drawn up into the single-use syringe.

Each vial contains enough study drug to inject one subject. Each vial will be used one time only.

A sterile, single-use 250 µL syringe custom marked at 20 µL will be provided separately for intravitreal injection use. These will be used for intravitreal injections of DE-109. 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. If the drug product is dispensed from a 0.5 mL vial, attach a 23-gauge x 1 inch or 25-gauge x 5/8 inch needle to the syringe.

    Figure 2: 0.3 mL fill in a 0.5 mL vial

    b. If the drug product is dispensed from a 2 mL vial, attach a 21-gauge x 1 ½ inch needle to the syringe.

    Figure 3: 0.3 mL fill in a 2 mL vial

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. For DE-109 (440 µg) preparation, replace the needle with a 30-gauge x 0.5 inch needle for the intravitreal injection.
    a. Ensure that the 30-gauge x 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 4).**
    c. PLEASE ENSURE THAT THERE ARE NO AIR BUBBLES WITHIN THE SYRINGE OR THE NEEDLE HUB PRIOR TO INJECTION.

Figure 4: The alignment of the syringe

10.5. Administration

10.5.1. Instructions for Intravitreal Injection of DE-109

10.5.1.1. Eye Preparation

The subject may receive DE-109 (440 µg) treatments at the discretion of the Investigator, but no more frequently than every 60 days. Instructions for ocular antisepsis are provided below.

1. Dilate pupil (1% Mydriacyl and 2.5% phenylephrine or equivalent applied topically) approximately 10 minutes prior to injection;
2. Administer 1 eye drop of topical anesthetic (0.5% proparacaine hydrochloride ophthalmic solution or an equivalent topical ophthalmic anesthetic);
3. Administer 5% povidone iodine to the study eye immediately prior to injection.
4. Use a sterile cotton-tipped applicator to remove excess fluid from the lower conjunctival sac;
5. 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 superotemporal conjunctival surface at the area of the entry site described below in Step 10 and hold in place for approximately 1 minute;
6. Administer a subconjunctival injection of 0.25 mL of 2% lidocaine without epinephrine or equivalent to the superotemporal quadrant to the area of the entry site described below in Step 10 (Steps #*5 and* 6 may be omitted per the Investigator's discretion);

7. Insert sterile eyelid speculum;
8. Place sterile eye drape over study eye;
9. Prior to starting the injection procedure, DE-109 should have been prepared as described in Section 10.4, with the appropriate dose of study drug drawn into a 250 µL single-use plastic syringe. **ENSURE THAT THERE ARE NO AIR BUBBLES IN THE SYRINGE OR NEEDLE HUB;**
10. If the subject is phakic, the entry site is recommended to be 3.5 mm to 4.0 mm peripheral to the inferotemporal 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 inferotemporal limbus. A caliper may be used to identify the needle entry site. The intravitreal injection site may be modified at the Investigator's discretion.
11. Insert the needle perpendicular to the eye wall at the location specified in Step 10.
12. Very slowly, inject the entire study drug 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;
13. Briefly apply pressure for approximately 1 minute to the needle entry site with a sterile cotton tipped applicator;
14. Remove the eyelid speculum;
15. Patch the study eye at the Investigator's discretion;

Prescribe fluoroquinolone equivalent antibiotic eye drops 3 times per day for 2 days following each injection (Aiello et al., 2004).

10.6. Study Drug Accountability

The Investigator is responsible for ensuring that an inventory is conducted upon receipt of the clinical supplies. The temperature recorder from the shipment will be deactivated and authorized study staff will verify that the temperature was maintained at -20°C or lower during transit. The clinical supplies shipment form should be completed, signed, and returned as directed. A copy must be maintained at the site for the Investigator's records.

The Investigator will keep a current record of the inventory, storage conditions and dispensing of all study drugs. This record will be made available to Santen (or designee) for the purpose of accounting for all clinical supplies. Any significant discrepancy and/or deficiency must be recorded with an explanation.

All supplies sent to the Investigator must be accounted for and in no case will study drugs be used in any unauthorized situation. It is the responsibility of the Investigator to ensure that any used and unused supplies are available to Santen (or designee) throughout the study.

10.7. Study Drug Handling and Disposal

All investigational products including unused vials of study drug supplied by Santen will be returned to Santen or designee and be fully accounted for by the monitor with the help of the person responsible for dispensing the study drug. Accountability will be documented by use of drug accountability forms.

The used vials of study drug will be stored at the investigational site upon completion of accountability procedures and returned to Santen or designee, or destroyed at the site at the direction of Santen, after the trial is completed.

11. ASSESSMENT OF EFFICACY

The long-term efficacy of DE-109 (440 µg) may be explored by VH.

12. ASSESSMENT OF SAFETY

12.1. Adverse Events, Serious Adverse Events and Events of Special Interest

12.1.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with study drug. An AE therefore can be an unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

In clinical studies, an undesirable medical condition occurring at any time, including baseline or wash-out period, may be recorded as an AE even if no study drug has been administered.

Any significant change in a subject's condition from baseline, regardless of causality, is to be considered an AE, unless the change is determined to be a continuation of a pre-existing condition that is documented in the subject's medical history. However, a clinically significant worsening in severity, intensity, or frequency of a pre-existing condition may indicate an AE.

Lack of efficacy of the study drug for the condition being investigated is not considered an AE unless a clinically significant change is assessed by the Investigator. In addition, any elective surgical procedure scheduled or planned prior to study entry is not considered an AE and the underlying diagnosis for which surgery is to be performed should be captured in the medical history as a pre-existing condition.

For this protocol, an AE is any *on-study* untoward medical occurrence (e.g. sign, symptom, disease, syndrome, intercurrent illness) that occurs in a study subject, regardless of the suspected cause and regardless of timing of DE-109 (440 µg) administration. An on-study AE can occur anytime after the date of informed consent through the last study visit. An AE will be considered as *treatment-emergent* if the AE occurred on or after the date of the first DE-109 (440 µg) treatment up to the last study visit. Treatment-emergent AEs are a subset of on-study AEs. Both on-study and treatment-emergent AEs will be reported.

12.1.1.1. Assessment of Adverse Events

Investigators will seek information on AEs at each subject contact. Subjects should be asked using a general, non-direct question if there has been any change in their general health or well-being. Direct questioning and examination should then be performed as appropriate.

Severity of the AE should be assessed according to the following criteria:

Mild: Aware or unaware of event, but easily tolerated

Moderate: Discomfort enough to cause interference with usual activities

Severe: Incapacitating; unable to work or perform usual activity.

Regardless of severity, some AEs may also meet regulatory serious criteria. Refer to definitions and reporting of serious adverse events (SAEs) in Section 12.1.2.

An Investigator who is qualified in medicine must make the determination of relationship to the study drug for each AE (related or not related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the study drug caused the AE/SAE based on facts, evidence, science-based rationales, and clinical judgment. When assessing causality, the Investigator may consider the following information when determining the relationship to the study drug for each AE: mechanism of action, biologic plausibility, confounding risk factors (i.e., medical history, concomitant medications), temporal relationship, dechallenge/rechallenge, and lack of alternative explanation.

- The AE may be recorded as **Related** to study drug if there is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject's clinical state, inter-current illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
- Reporting the AE as **Not Related** to study drug may be considered if, for example, there is good evidence that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, inter-current illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

12.1.1.2. Reporting Adverse Events

AEs, whether spontaneously reported by the subject or noted by authorized study personnel, will be recorded in the subject's medical record and on the appropriate AE eCRF. Each recorded AE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria if applicable, suspected relationship to the study drug, and actions taken.

AEs that occur after any subject has provided written informed consent up to Month 12 must be recorded. If an adverse event is ongoing at the time of study exit, then the Investigator should perform reasonable follow-up efforts as necessary (e.g. telephone contact, post-study office visit) to determine the outcome of the event. To improve the quality and precision of acquired AE data, Investigators should observe the following guidelines:

- Whenever possible, use recognized medical terms when recording. Do not use colloquialisms and/or abbreviations.
- If known, record the diagnosis (i.e., disease or syndrome) rather than component signs and symptoms (e.g., record congestive heart failure rather than dyspnea, rales, and cyanosis). However, other events that are considered unrelated to an encountered syndrome or disease should be recorded as individual AEs (e.g., if congestive heart failure and severe headache are observed at the same time and are clinically unrelated, each event should be recorded as an individual AE).
- AEs occurring secondary to other events (e.g., sequelae) should be identified by the primary cause. A primary AE, if clearly identifiable, generally represents the most accurate clinical term. If a primary AE is recorded, events occurring secondary to the primary event should be described in the narrative description of the case.

For example:

The subject developed orthostatic hypotension and subsequently fainted and fell to the floor wherein she experienced a head trauma and neck pain.

The primary AE in this example is orthostatic hypotension.

- For intermittent events (e.g., intermittent headache) and events that occur with each instillation (e.g., eyes burn for 5 minutes after every dose), the event start date should be recorded as the date the subject first started to experience the event. The end date should reflect when the last occurrence resolved or stopped. For example, if a subject had an intermittent headache from 14 MAY 2014 until 21 MAY 2014 and each individual headache lasts 3 hours a day, then the date of resolution is 21 MAY 2014 (not 14 MAY 2014).
- 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.
- If an event occurs with each instillation (e.g., eyes burn mild to moderate for 5 minutes after every dose), record the maximum severity of the individual incident. In the example above, the severity is moderate.

12.1.2. Serious Adverse Events

SAEs are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. Any adverse event is considered a serious adverse event if it results in any of the following outcomes:

- Death
- Life threatening:

  A life-threatening event is any event that places the subject at immediate risk of death from the event as it occurred; it does not refer to an event that hypothetically might have caused death if it were more severe.
- In-subject hospitalization and/or prolonged hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- 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 (See Section 12.1.3).
- Other medically significant events:

  Other medically significant events are events that may not result in death, be life-threatening, or require hospitalization but may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

12.1.3. Sight Threatening Events

For the purposes of this study the following ocular adverse events will be reported as serious adverse events:

- Loss of 6 or more lines of vision (≥30 letters) from Baseline;
- Endophthalmitis;
- Purulent, infectious conjunctivitis;
- Retinal detachment;
- IOP > 35 mmHg that persists for at least 7 days despite pharmacologic therapy;
- Other significant ocular events per Investigator's discretion

12.1.3.1. Reporting Serious Adverse Events

A SAE eCRF must be completed with as much information available within 24 hours of knowledge of the event.

To improve the quality and precision of acquired SAE data, Investigators should observe the following guidelines:

- **Death** - Death is an outcome of an event. The event that resulted in the death should be recorded and reported as a SAE.
- **Hospitalizations for Surgical or Diagnostic Procedures** - The illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the Medical/Surgical History eCRF and be mentioned as part of the action taken in response to the illness.

When new significant information (including the outcome of the event) is obtained, the Investigator should enter the information directly into the eCRF within 24 hours or as soon as possible after knowledge of the information.

Depending on the nature and seriousness of the AE, Santen may request additional documentation, for example, copies of the ophthalmic and medical record of the subject as well as results of laboratory tests. If the subject was hospitalized, the site should summarize the hospital discharge summary and provide to Santen upon request.

12.1.3.2. Expedited Reporting of Serious Adverse Events

Santen (or designee) will provide the Investigator with a reporting cover letter and an anonymized MedWatch 3500A for expedited reporting of SAEs to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The Investigator is responsible for receiving and reviewing expedited safety reports, submitting expedited safety reports to the IRB or IEC, and maintaining copies of expedited safety reports in the study records.

12.1.4. Events of Special Interest

Events of Special Interest (ESIs) are events that may require special attention for the purposes of on-going patient safety review during this study. The following are considered ESIs and should

be reported on the appropriate eCRF with as much information as available within 24 hours of knowledge of the event:

- **Study medication administration error** – Study medication administration errors determined to be significant by the Investigator will be reported and evaluated as ESIs. Examples of study medication administration errors may include, but are not limited to: overdose of study medication and administration of study medication from an incorrect kit.
- **Pregnancy** - There are no controlled data with the investigational product in human pregnancy. It is required that women of childbearing potential use effective contraception during the study and recommended for 12 weeks after the completion of the study. Any pregnancy occurring during study treatment should be reported and the subject removed from the study. The subject should be followed until the end of pregnancy or until the end of the study, whichever is longer.

12.1.5. Follow-up of Adverse Events

All reported AEs at study exit will be followed by the Investigator (or his/her designee) until the event is resolved or determined to be irreversible, chronic, or stable.

In addition, on a case-by-case basis, Santen (or designee) may request follow-up beyond the end of the study.

If Santen Drug Safety requests follow-up on an individual SAE or designated ESI, site response to follow-up requests should be faxed to Santen Drug Safety: 415-276-5882 (fax) or drugsafety@santeninc.com.

12.1.6. Manual Back-Up Reporting Procedures

This study is utilizing an electronic data capture (EDC) system for data entry. In the event that the EDC system is unavailable for electronic reporting, the manual back-up reporting procedures found in Section 21.5 should be followed.

12.2. Safety Parameters

The safety assessments will include the incidence of AEs and SAEs and treatment with rescue therapy. Changes in BCVA, IOP, indirect ophthalmoscopy variables and VH will also be used to evaluate the long-term safety of DE-109.

12.2.1. Adverse Events

AEs will be elicited from the subjects following the signing of informed consent through the end of the study. The information will include at least a description of the event, whether or not it is serious, onset and duration, severity, relation to study drug, relation to injection procedure, location (OD, OS, OU or NA), action taken and outcome. Prior to evaluating the incidences, all AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 16.0, 2013). Ocular and non-ocular AEs will be summarized separately. See Section 12.1 for complete information regarding AE reporting.

12.2.2. Visual Acuity

BCVA will be measured for each eye at Day 1, Month 12 and Post-Baseline PRN Treatment Visits using an ETDRS chart.

12.2.3. Intraocular Pressure

IOP will be measured for each eye using applanation tomometry at Day 1, Month 12 and Post-Baseline PRN Treatment Visits prior to evaluation of need for treatment. If DE-109 (440 μg) is administered, a second assessment will be made 40 (±10) minutes after injection.

12.2.4. Indirect ophthalmoscopy

An indirect ophthalmoscopy will be performed at Day 1, Month 12 and Post-Baseline PRN Treatment Visits to examine the retina of each eye. Indirect ophthalmoscopy will be performed prior to each study drug injection and then again within 30 minutes after study drug injection. Assessments include lens, retina, macula, choroid, and optic nerve. Lens will be assessed for the presence or absence of cataract. All other assessments will be noted as normal or abnormal.

12.2.5. Vitreous Haze

VH will be assessed for each eye at each visit using the modified SUN scale scores of: 0, 0.5+, 1+, 1.5+, 2+, 3+, 4+.

12.2.6. New Treatments with Rescue Therapy

Concomitant medications will be assessed according to the Investigator's standard practice for the incidence of new treatment with rescue therapy, among those subjects not previously treated with rescue therapy in the SAKURA program.

12.2.7. Pregnancy Test

A urine pregnancy test will be conducted at Day 1, Month 12 and Post-Baseline PRN Treatment Visits for all women of childbearing potential.

13. OTHER ASSESSMENTS

13.1. Demographics and Baseline Characteristics

Subject demographics include age, race, sex, and ethnicity. Baseline characteristics include medical history, prior medications, and baseline results of BCVA, IOP, indirect ophthalmoscopy findings, VH and pregnancy test.

13.2. Other Assessments

Other assessments include concomitant medications and exposure to study drug. The number of DE-109 (440 μg) treatments between Day 1 and Month 12 will be evaluated.

14. STATISTICAL METHODS

14.1. General Considerations

This protocol is implemented to evaluate the long-term safety of treatment with DE-109 (440 µg) in subjects with non-infectious uveitis of the posterior segment of the eye among those subjects who received at least two treatments of DE-109 during the first five months of the SAKURA program and received clinical benefit, as determined by the Investigator. The minimum time lag from last injection during the SAKURA program to entry into the current protocol is 60 days.

Study visits for assessment are scheduled at Day 1 and Month 12. At the discretion of the investigator, dosing of DE-109 (440 µg) may take place at Day 1 or at any Post-Baseline PRN Treatment Visit prior to the Month 12 assessment visit.

The descriptive statistics will include number of observations (n), mean, standard deviation, minimum, and maximum for continuous parameter and frequency (n) and percent (%) for categorical parameters. No statistical hypothesis testing will be conducted on any parameter.

Details about the statistical analyses for this study will be provided in the statistical analysis plan (SAP).

All data manipulations and descriptive summaries will be implemented using SAS®, Version 9.1.3 or later.

14.1.1. Analysis Parameters

- AE incidence rate
- Change in BCVA
- Change in IOP
- Change in indirect ophthalmoscopy findings
- Change in VH
- Proportion of safety subjects who were rescued who were not previously rescued in the SAKURA program.

14.1.2. Sample Size

The sample size will not be determined based on statistical considerations.

14.1.3. Statistical Hypotheses and Level of Significance

No statistical hypothesis is defined for this study.

14.1.4. Randomization

Randomization is not employed in this study. The decision to administer study drug on any study day is at the discretion of the Investigator. All subjects who are dosed will receive the same open-label dose (440 µg) of DE-109.

14.1.5. Study Eye

The study eye must meet all eligibility criteria. For analysis purposes, the study eye will be the eye actually treated in this extension study. If a subject receives no injection of DE-109 (440 µg) in this extension study, then the eye designated as the study eye in the SAKURA program is the study eye.

14.2. Study Populations

The Safety population will include all enrolled subjects with any safety data collected during the study, whether or not they ever receive any injection of DE-109 (440 µg). It will be the analysis population for safety summaries.

14.3. Interim Analyses

No formal interim analysis is planned for this study; however, the Sponsor may perform interim analyses throughout the study.

14.4. Handling of Missing Values

For safety measures, missing scores will not be imputed for data summaries.

Completely or partially missing onset and resolution dates for AEs and completely or partially missing start and end dates of concomitant medications will be imputed in a conservative fashion that will be detailed in the SAP.

14.5. Demographics and Baseline Characteristics

Age, sex, race, ethnicity, and baseline assessments will be summarized descriptively.

14.6. Safety Analysis

The safety assessments will include the incidence of AEs and SAEs and treatment with rescue therapy. Changes in BCVA, IOP, indirect ophthalmoscopy variables and VH will also be used to evaluate the long-term safety of DE-109. Safety data from both eyes will be included.

Each AE will be classified into a system organ classification (SOC) and coded to a preferred term using the most updated version of MedDRA (MedDRA 16.0, 2013). Subjects with any AE(s) will be tabulated by SOC and preferred term. They will also be tabulated by SOC, preferred term, and maximum severity. In these 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; in addition, ocular AEs will be presented first to be separated from non-ocular AEs. Study-medication-related and injection-procedure-related AEs will be summarized similarly. In addition, AEs, SAEs, and AEs leading to discontinuation and death, if any, will be listed. ESIs, if any, will also be listed by event type.

Ocular safety outcome measures will be summarized using descriptive statistics. Specifically for BCVA, IOP, indirect ophthalmoscopy findings, and VH, scores and changes from baseline will be summarized descriptively; in addition, clinically significant changes from baseline, if any, will be listed.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will allow representatives of Santen's monitoring team (or designee), the governing institutional review board (IRB), the FDA, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's medical records at regular intervals throughout the study. These inspections are for the purpose of verifying adherence to the protocol, completeness, and exactness of the data being entered onto the eCRF, and compliance with the FDA or other regulatory agency regulations.

15.1. Study Monitoring

Before an investigational site can enter a subject into the study, a representative of Santen (or designee) will evaluate the investigational study site to:

- Determine the adequacy of the study facilities.
- Review with the Investigator(s) and authorized study staff their responsibilities with regard to protocol procedures adherence, and the responsibilities of Santen (or designee).

During the study, Santen (or designee) will have regular contact with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Assess adherence to the protocol and GCP.
- Perform investigational product accountability checks and quality control procedures.
- Ensure the on-going implementation of accurate data entry in the eCRF.
- Perform source data verification, including a comparison of the data in the eCRFs with the subject's medical records 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 AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to Santen and those SAEs that met criteria for reporting have been forwarded to the IRB or IEC.

Santen (or designee) may remotely access the eCRFs at any time during the study for centralized monitoring. Santen (or designee) will be available between visits if authorized study staff needs study related information or support.

15.2. Audits and Inspections

The Investigator will allow Santen (or designee), the governing IRB or EC, and applicable regulatory agencies to audit and inspect any aspect of the study, including all study records, eCRFs, recruitment materials, and corresponding portions of the subject's charts and medical records at any time during the study. These study records must be retained at the study site and

made available for audits and inspections. The purpose of these audits and inspections is to verify adherence to the protocol, completeness and accuracy of the eCRF data, and compliance with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements.

The Investigator or authorized study staff will notify Santen (or designee) should the site be audited or inspected by the governing IRB or IEC, and applicable regulatory agencies. Santen (or designee) will also notify the investigational site of any known pending site audits or inspections planned by Santen (or designee), governing IRB or IEC and regulatory agencies.

15.3. Institutional Review Board

The Investigator must obtain IRB or IEC approval for the investigation. Initial IRB or IEC approval, and all materials approved by the IRB or IEC for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

16. QUALITY CONTROL AND QUALITY ASSURANCE

16.1. Quality Control

Santen (or designee) will provide instructional material to the study sites, as appropriate; including but not limited to instruction on the protocol, the completion of eCRFs, and study procedures. Santen (or designee) will communicate regularly with site personnel via mail, email, telephone, and/or fax; and make periodic visits to the study site. During those visits, Santen (or designee) will perform source data verification with the subject's medical records and other records relevant to the study. Upon receiving the eCRFs, Santen (or designee) will review and evaluate eCRF data and use standard system edits and may use centralized monitoring to detect errors in data collection.

16.2. Quality Assurance

Santen (or designee) may conduct a quality assurance audit at any time.

17. ETHICS

17.1. Ethics Review

The final study protocol and the final version of the ICF, and other study related material, as appropriate, must be approved or given a favorable opinion in writing by an IRB or IEC as appropriate. The Investigator must submit written approval to Santen (or designee) before study initiation. See Section 21.1 Appendix A for a list of obligations of Investigators.

The Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local regulations and guidelines. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and at least annually.

The Investigator is also responsible for providing the IRB or IEC with progress reports and notifications of any reportable serious adverse drug reactions from the investigational product.

17.2. Ethical Conduct of the Study

This study will be conducted in compliance with IRB or IEC, and regulatory requirements. This study will also be conducted in compliance with the protocol, GCP guidelines, International Conference on Harmonization (ICH) guidelines, the Declaration of Helsinki, and Health Insurance Portability and Accountability Act of 1996 (HIPAA).

17.3. Written Informed Consent

The Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and possible benefit of the study. Subjects must also be notified that they are free to withdraw from the study at any time. Subjects should be given the opportunity to ask questions and allowed time to consider the information provided. Before participating in any study-related activity, voluntary informed consent must be documented by the use of a written ICF approved by the IRB or IEC and signed and dated by the subject or the subject's legally authorized representative at the time of consent. The original signed and dated ICF will be retained with the study records, and a copy of the signed ICF will be given to the subject or the subject's legally authorized representative (Section 15.2).

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

The Investigator will allow Santen (or designee), the governing IRB or IEC and applicable regulatory agencies to inspect any aspect of the study, including all study records, eCRFs, and corresponding portions of the subject's charts and medical records at any time during the study. The purpose of these inspections is to verify adherence to the protocol, completeness and accuracy of the eCRF data, and compliance with GCP guidelines and applicable regulatory requirements.

18.2. Retention of Records

All records relating to the conduct of this study are to be retained by the Investigator until notified by Santen (or designee) that the records may be destroyed.

18.2.1. Source Documents

The Investigator must maintain detailed source documents on all study subjects who provide informed consent. Source documents include subject medical records, hospital charts, clinic charts, study files, as well as the results of diagnostic tests (e.g., laboratory tests, visual field test printouts).

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 concomitant medications
- Documentation of study drug accountability
- Occurrence and status of any AEs
- The date the subject exited the study and a notation as to whether the subject completed or terminated early from the study, including the reason for early termination

18.2.2. Data Collection

The Investigator must maintain detailed records on all subjects who provide informed consent. Data for screened and eligible subjects will be entered into eCRFs. Review of the eCRFs will be completed remotely by Santen (or designee). At designated intervals, a study monitor will perform source data verification on site. During those visits, Santen (or designee) will monitor the subject data recorded in the eCRF against source documents at the study site. Santen (or designee) will review and evaluate eCRF data and use standard system edits, and may use centralized monitoring evaluations, to detect errors in data collection. At the end of the study, a copy of the completed eCRFs will be sent to the site to be maintained as study records.

19. 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 that is indicated as confidential. Information pertaining to this study will be published on www.clinicaltrials.gov as required by the Food and Drug Administration (FDA).

The data generated by this clinical study are the property of Santen 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.

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

20. REFERENCES

1. Adamis, A. (2002). Is diabetic retinopathy an inflammatory disease? British Journal of Ophthalmology 86(4):363-5.

2. Aiello, L., Brucker, A., Chang, S., Cunningham, E., D'Amico, D., Flynn, H., Grillone, L., Hutcherson, S., Liebmann, J., O'Brien, T., Scott, I., Spaide, R., Ta, C., Trese, M. (2004). Evolving Guidelines for Intravitreous Injections. Retina 24(5):S3-S19.

3. Anglade, E., Yatscoff, R., Foster, R., Grau, U. (2007). Next-generation calcineurin inhibitors for ophthalmic indications. Expert opin. Investig. Drugs 16(10):1525-40.

4. Attur, M., Patel, R., Thakker, G., Vyas, P., Levartovsky, D., Patel, P., Naqvi, S., Raza, R., Patel, K., Abramson, D., Bruno, G., Abramson, S., Amin, A. (2000). Differential anti-inflammatory effects of immunosuppressive drugs: Cyclosporin, rapamycin and FK-506 on inducible nitric oxide synthase, nitric oxide, cyclooxygenase-2 and PGE_2 production. Inflammation Research 49:20-6.

5. Barton, K., McLauchlan, M., Calder, V., Lightman, S. (1995). The Kinetics of Cytokine mRNA Expression in the Retina during Experimental Autoimmune Uveoretinitis. Cellular Immunology 164:133-40.

6. Callanan D., Jaffe, G., Martin, D., Pearson, A., Comstock, T. Treatment of Posterior Uveitis With a Fluocinolone Acetonide Implant *Three-Year Clinical Trial Results*. (2008). Arch Ophthalmol 126(9):1191-1201

7. Charteris, D., Barton, K., McCartney, A., Lightman, S. (1992). $CD4^+$ Lymphocyte Involvement in Ocular Behcet's Disease. Autoimmunity 12(3):201-6.

8. George, R., Chan, C., Whitcup, S., Nussenblatt, R. (1997). Ocular Immunopathyology of Behcet's Disease. Survey of Ophthalmology 42(2):157-62.

9. Joussen, A., Poulaki, V., Le, M., Koizumi, K., Esser, C., Janicki, H., Schraermeyer, U., Kociok, N., Fauser, S., Kirchhof, B., Kern, T., Adamis, A. (2004). A central role for inflammation in the pathogenesis of diabetic retinopathy. The FASEB Journal 18(12):1450-2.

10. Kahan, B. (2001). Sirolimus: a comprehensive review. Expert Opin Pharmacother 2(11):1903-17.

11. Kilmartin, D., Forrester, J., Dick, A. (1998). Tacrolimus (FK506) in failed cyclosporin A therapy in endogenous posterior uveitis. Ocul Immunol Inflamm 6(2):101-9.

12. Kwon, Y., Hong, H., Kim, J., Shin, J., Son, Y. (2005). Inhibitory Effect of Rapamycin on Corneal Neovascularization In Vitro and In Vivo. Investigative Ophthalmology & Visual Science 46(2):454-60.

13. MedDRA 16.0. MedDRA MSSO, Medical Dictionary for Regulatory Activities, Version 16.0.

14. Napoli, K., Taylor, P. (2001). From Beach to Bedside: History of the Development of Sirolimus. Therapeutic Drug Monitoring 23(5):559-86.

15. Nguyen, Q., Ibrahim, M., Watters, A., Bittencourt, M., Yohannan, J., Sepah, Y., Dunn, J., Naor, J., Shams, N., Shaikh, O., Leder, H., Do, D. (2013). Ocular tolerability and efficacy of intravitreal and subconjunctival injections of sirolimus in patients with non-infectious uveitis: primary 6-month results of the SAVE Study. Journal of Ophthalmic Inflammation and Infection 3(32):1-15.

16. Nuhrenberg, T., Voisard, R., Fahlisch, F., Rudelius, M., Braun, J., Gschwed, J., Kountides, M., Herter, T., Bauer, R., Hombach, V., Baeuerle, P., Zohlnhofer, D. (2005). Rapamycin attenuates vascular wall inflammation and progenitor cell promoters after angioplasty. Faseb J 19(2):246-8.

17. Nussenblatt, R. (1990). The natural history of uveitis. International Ophthalmology 14:303-8.

18. Rapamune. Rapamune (sirolimus) Oral Solution and Tables - Package Insert. (2009).

19. Rothova, A., Suttorp-van Schulten, M., Treffers, W., Kijlstra, A. (1996). Causes and frequency of blindness in patients with intraocular inflammatory disease. British Journal of Ophthalmology 80:332-6.

20. Sehgal, S. (1995). Rapamune (Sirolimus, Rapamycin): An Overview and Mechanism of Action. Therapeutic Drug Monitoring 17(6):660-5.

21. Sehgal, S. (1998). Rapamune (RAPA, rapamycin, sirolimus): Mechanism of Action Immunosuppressive Effect Results From Blockage of Signal Transduction and Inhibition of Cell Cycle Progression. Clinical Biochemistry 31(5):335-40.

22. Sehgal, S. (2003). Sirolimus: Its Discovery, Biolgical Properties, and Mechanism of Action. Transplantation Procedings 35(Suppl 3A):S7-S14.

23. Sloper, C., Powell, R., Dua, H. (1999). Tacrolimus (FK506) in the treatment of posterior uveitis refractory to cyclosporine. Ophthalmology 106(4):723-8.

24. Strickley, R. (2004). Solubilizing Excipients in Oral and Injectable Formulations. Pharmaceutical Research 21(2):201-30.

25. Suhler, E., Lloyd, M., Choi, D., Rosenbaum, J., Austin, D. (2008). Incidence and Prevalence of Uveitis in Veterans Affairs Medical Centers of the Pacific Northwest. American Journal of Ophthalmology 146(6):890-6.

26. Weiner, A., BenEzra, D. (1991). Clinical Patterns and Associated Conditions in Chronic Uveitis. American Journal of Ophthalmology 112(2):151-8.

27. Whitcup, S., Chan, C., Li, Q., Nussenblatt, R. (1992a). Expression of Cell Adhesion Molecules in Posterior Uveitis. Arch Ophthalmol 110(5):662-6.

28. Whitcup, S., DeBarge, L., Caspi, R., Harning, R., Nussenblatt, R., Chan, C. (1993). Monoclonal Antibodies against ICAM-1 (CD54) and LFA-1 (CD11a/CD18) Inhibit Experimental Autoimmune Uveitis. Clinical Immunology and Immunopathology 67(2):143-50.

29. Whitcup, S., Wakefield, D., Li, Q., Nussenblatt, R., Chan, C. (1992b). Endothelial Leukocyte Adhesion Molecule-1 in Endotoxin-Induced Uvetis. Investigative Ophthalmology & Visual Science 33(9):2626-30.

21. APPENDICES

21.1. Appendix A - Obligations of Investigators

In summary, the Investigator has agreed to the following obligations:

- Obtaining 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 IRB before involving any subject in any study related activity; submitting verification of the approval to the Sponsor; submitting periodic progress reports (at least annually) and final report to IRB 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 of all protocol amendments/modifications; sending the Sponsor a copy of the letter from the IRB approving the amendment/modification.
- Reporting to the Sponsor and the IRB any adverse experiences that occur in the course of the investigation, this includes Serious Adverse Events within 24 hours.
- 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 and of all action by the IRB regarding the study.
- Making study records available for inspection by the Sponsor (Santen) and representatives of the Food and Drug Administration 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 (Section 21.1).

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 IRB indicating that the protocol was approved, including the name and address of the IRB.
- A copy of the consent form approved by IRB.
- A list of current members of the IRB.

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 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.

21.2. Appendix B - 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 ICF.

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. A. Describe the extent, if any, to which CONFIDENTIALITY of records identifying the subject will be maintained.
   B. Note that the FDA 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 (a) what they consist of, OR (b) where further information may be obtained.
7. A. Tell whom to contact for ANSWERS to pertinent questions about (a) the research, and (b) research subjects' rights.
   B. Tell whom to contact in the event of a research-related INJURY to the subject.
8. State that:
   A. Participation is VOLUNTARY,
   B. Refusal to participate will involve NO PENALTY or loss of benefits to which the subject is otherwise entitled, and
   C. 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.

21.3. Appendix C - Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy

volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

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C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

21.4. Appendix D - Procedures for Examinations

21.4.1. Demographics, Medical History and Medication

Demographics, medical and surgical history, medications, current ocular and systemic conditions will be obtained through subject interviews at Day 1. Medications will be updated at each visit, as appropriate.

21.4.2. Pregnancy Test

A urine pregnancy test will be conducted at Day 1, Month 12 and Post-Baseline PRN Treatment Visits for all women of childbearing potential. Samples will be analyzed at the site with results available prior to administration of study drug.

21.4.3. Visual Acuity

BCVA will be measured for each eye at Day 1, Month 12 and Post-Baseline PRN Treatment Visits under normal room illumination using an ETDRS chart.

21.4.3.1. Procedures for Refraction and Vision Testing

Refraction and visual acuity measurements will be performed for all subjects by trained vision examiners only. 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.

21.4.3.1.1. 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

21.4.3.1.2. 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.

21.4.3.1.3. 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.

21.4.3.1.4. 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 the sponsor-provided worksheet which will be included in the source

documents. At each **follow-up visits, 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 continue 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.

21.4.3.1.5. 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.

21.4.3.1.5.1. 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.

21.4.3.1.6. 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.

21.4.3.1.7. 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.

21.4.3.1.7.1. 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.

21.4.3.1.7.2. 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.

21.4.3.1.7.3. 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."

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	

21.4.4. Intraocular Pressure (IOP)

IOP will be measured for each eye using applanation tomometry at Day 1, Month 12 and Post-Baseline PRN Treatment Visits prior to evaluation of need for treatment. If DE-109 is administered, a second assessment will be made 40 (±10) minutes after injection.

The examiner will measure IOP and record results in mmHg with one decimal place (e.g., 24.0). A single measurement is made to obtain a determination of intraocular pressure. The same contact tonometer employing the Investigator's standard technique, will be used throughout the study. In addition, all reasonable efforts should be made to have the same examiner obtain all IOP measurements for a given subject.

The tonometer must be calibrated for accuracy before the first subject undergoes screening, and at least once every 30 days 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.

21.4.5. Indirect ophthalmoscopy

An indirect ophthalmoscopy will be performed at Day 1, Month 12 and Post-Baseline PRN Treatment Visits to examine the retina of each eye. Indirect ophthalmoscopy will be performed prior to each study drug injection and then again within 30 minutes after study drug injection. Assessments include lens, retina, macula, choroid, and optic nerve. Lens will be assessed for the presence or absence of cataract prior to study drug administration. All other assessments will be noted as normal or abnormal.

21.4.6. Vitreous Haze

VH will be assessed for each eye according to the Investigator's standard practice at Day 1, Month 12 and Post-Baseline PRN Treatment Visits using the modified SUN scale:

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

21.5. Appendix E – Manual SAE Reporting Process

In the event the EDC system is unavailable and your site needs to report a SAE, please follow the manual process described below.

- Complete both the paper AE and SAE forms (located in your site regulatory binder)
- Attach a Fax Cover Sheet with your contact information and address to Santen Drug Safety
- Fax the Cover Sheet, AE form and SAE form to Santen at the appropriate fax number identified below.

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

Table 5: SAE Manual Reporting Fax numbers