SYNOPSIS

Name of Sponsor/Company: Santen, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: DE-109 Injectable Solution		
Name of Active Ingredient: Sirolimus		

Title of Study: A Phase III, Multinational, Multicenter, Randomized, Double-Masked Study Assessing the Safety and Efficacy of Intravitreal Injections of DE-109 (3 Doses) for the Treatment of Active, Non-Infectious Uveitis of the Posterior Segment of the Eye

Principal Investigators:
81 Principal Investigators

Study centers: 81 sites in 17 countries

Studied Period (years): Date first subject screened: 12 March 2013 Date last subject completed End of Study Visit: 14 September 2016	**Phase of development:** Phase III

Objectives:
Primary:

- To evaluate the safety and efficacy of the intravitreal (IVT) injection of 440 µg DE-109 as compared with 44 µg DE-109 for the treatment of active, non-infectious uveitis of the posterior segment of the eye

Exploratory:

- To evaluate the safety and efficacy of the IVT injection of 880 µg DE-109 as compared with 44 µg DE-109 for the treatment of active, non-infectious uveitis of the posterior segment of the eye.

Methodology:

Protocol 32-007, Amendments #2-#5, SAKURA Study 2; through End of Study Visit Results

SAKURA was a multinational, multicenter, randomized, double-masked program assessing the safety and efficacy 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. The program consisted of 2 Phase III studies, SAKURA Study 1 and Study 2, which were conducted under Protocol

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32-007, Amendments #2, #3, #4, and #5. No subjects were randomized or treated under the original protocol or Protocol Amendment #1. This report describes findings from SAKURA Study 2. Results from SAKURA Study 1 are provided in a separate report.

In SAKURA Study 2, 245 subjects with active, non-infectious posterior, intermediate or panuveitis were randomized at 81 sites. Before implementation of Amendment #5, eligible subjects were randomized in a 1:1:1 ratio to receive DE-109 in 44, 440, or 880 µg dose by IVT injection at Day 1, Month 2, and Month 4 (Double-Masked Treatment Period). Under Amendment #5, eligible subjects were randomized in a 1:1 ratio to receive 44 or 440 µg dose. The primary endpoint assessment was conducted at Month 5.

A planned unmasked analysis of SAKURA Study 1 was conducted on the 6-month data of the 47 randomized subjects. In the overall analysis, the 440 µg dose demonstrated the most favorable benefit:risk profile.

Number of Subjects (planned and analyzed):

Approximately 250 subjects with active, non-infectious posterior, intermediate or panuveitis were planned for randomization to the 44, 440, or 880 µg dose group in SAKURA Study 2, with approximately 180 subjects in the 44 µg and the 440 µg dose groups combined.

A total of 245 study subjects at 81 sites were randomized in SAKURA Study 2.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

1. Ability to give informed consent and attend all study visits
2. Males or females ≥ 18 years of age
3. Had diagnosis of active uveitis of the posterior segment determined by the Investigator to be non-infectious based on the subject's medical history, history of present illness, ocular examination, review of systems, physical examination, and any relevant, pertinent laboratory evaluations. If an anterior component was present, it must be less than the posterior component
4. Had active uveitis defined as a > 1+ (excluding 1+) VH score (Standardized Uveitis Nomenclature [SUN] photographic scale) in the study eye

Name of Sponsor/Company: Santen, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: DE-109 Injectable Solution		
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5. Best-corrected Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity letter score of 19 letters or more (20/400 Snellen equivalent) or better in study eye
6. Female participants of childbearing potential must not have been pregnant or breastfeeding, must have a negative pregnancy test at Screening, and must be willing to undergo pregnancy tests throughout the study
7. 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
8. Subjects must have vision ≥ 20/200 in the non-study eye

Exclusion Criteria:

Ocular:

1. Active infectious uveitis. However, if the uveitis was the consequence of a previous infectious disease, such as Tuberculosis, the previous infectious disease must be confirmed as no longer active.
2. Clinically suspected or confirmed central nervous system or ocular lymphoma
3. Primary diagnosis of anterior uveitis
4. Uncontrolled glaucoma, evidenced by an intraocular pressure (IOP) of > 21 mmHg while on medical therapy, or chronic hypotony (< 6 mmHg)
5. Any implantable corticosteroid-eluting device (e.g., Ozurdex®, I-vation, triamcinolone acetonide IVT implant) in the study eye:
   a. If the Investigator confirmed the device had no demonstrable efficacy as indicated in the package insert, the subject was eligible;
   b. If a Medidur™ implant or Retisert® had been implanted no less than 3 years and 90 days respectively prior to Day 1, the subject was eligible
6. Any significant ocular disease that could compromise vision in the study eye. These included, but were not limited to:
   a. Diabetic retinopathy: proliferative diabetic retinopathy (PDR) or non-proliferative

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Name of Finished Product: DE-109 Injectable Solution		
Name of Active Ingredient: Sirolimus		

diabetic retinopathy (NPDR) that compromised vision. Subjects with NPDR or PDR that did not compromise vision were not excluded from the study;

b. Wet age-related macular degeneration;
c. Myopic degeneration with active subfoveal choroidal neovascularization

7. Lens opacities or obscured ocular media other than VH upon enrollment such that reliable evaluations and grading of the posterior segment could not be performed
8. Intraocular surgery within 90 days prior to Day 1 in the study eye
9. Capsulotomy within 30 days prior to Day 1 in the study eye
10. Any of the following treatments within 90 days prior to Day 1 or anticipated use of any of the following treatments to the study eye:
    a. IVT injections (including but not limited to steroids or anti-vascular endothelial growth factors);
    b. Posterior sub-tenon steroids
11. Ocular or periocular infection in either eye
12. Pupillary dilation inadequate for quality stereoscopic fundus photography in the study eye
13. Media opacity that would limit clinical visualization, intravenous fluorescein angiography (IVFA), or optical coherence tomography (OCT) evaluation in the study eye
14. History of herpetic infection in the study eye or adnexa
15. Presence of known active, inactive toxoplasmosis or toxoplasmosis scar in either eye
16. Presence of any form of ocular malignancy in the either eye including choroidal melanoma
17. History of vitrectomy in the study eye

Exclusion Criteria Non-

Ocular:

1. Allergy or hypersensitivity to study medication product, fluorescein dye or other study related procedures/medications
2. Participation in other investigational drug or device clinical trials within 30 days prior

Name of Sponsor/Company: Santen, Inc.	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Finished Product: DE-109 Injectable Solution		
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to Day 1, or planning to participate in other investigational drug or device clinical trials for the entire duration of the study. This included both ocular and non-ocular clinical trials.

3. Treatment with a monoclonal antibody or any other biologic therapy (i.e., Etanercept, Tocilizumab, Adalimumab, Rituximab, etc.) within the previous 30 days, or with alemtuzumab within the previous 12 months from Day 1
4. Immunosuppressive therapy (e.g., methotrexate, cyclosporine, cyclophosphamide, chlorambucil, mycophenolate mofetil, tacrolimus azathioprine, or colchicine) other than prednisone or other corticosteroids for the treatment of uveitis within 30 days of the first study medication administration (Day 1)
5. Any recent systemic infection within 30 days of Screening
6. Known to be immunocompromised
7. History of cytomegalovirus infection or clinical evidence of active cytomegalovirus infection at Screening and/or Day 1
8. History of other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease condition that could contraindicate the use of an investigational drug, might affect the interpretation of the results of the study, or could render the subject at high risk for treatment complications
9. Malignancy in remission for < 5 years prior to study participation (except basal cell or squamous cell skin cancer, or treated melanoma of the skin < 24 months since last treatment)
10. Females who were pregnant or lactating and females of child-bearing potential who were not using adequate contraceptive precautions (i.e., intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the Investigator)
11. Use of medically prescribed marijuana or other illegal medication
12. Active systemic sarcoidosis within the last 30 months (i.e., Subjects with uveitis secondary to sarcoidosis were eligible as long as systemic sarcoidosis was not active and systemic immunosuppressive therapy had not been given in the last 30 months)

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

<table>
<tr><td>Name of Sponsor/Company:
Santen, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
DE-109 Injectable Solution</td></tr>
<tr><td>Name of Active Ingredient:
Sirolimus</td></tr>
<tr><td colspan="3">Test Product, Dose and Mode of Administration, Batch Number:
Test product: DE-109 injectable solution
Dose and mode of administration:
44, 440, and 880 µg doses. All doses were administered via IVT injection into the study eye.
Batch number:
0.2% DE-109 injectable solution (used for 44 µg dose); batch number 3-FIN-1094
2% DE-109 injectable solution (used for 440 µg dose); batch number 3-FIN-1029
4% DE-109 injectable solution (used for 880 µg dose); batch number 3-FIN-1031 or 3-FIN-1338</td></tr>
<tr><td colspan="3">Duration of Treatment:
Under Amendment #2, the duration of the study was 12 months with 2 post-randomization treatment periods: the 6-month Double-Masked Treatment Period and the 6-month DoubleMasked PRN Treatment Period.
Under Amendments #3 and #4, the duration of the study was 24 months with 3 postrandomization treatment periods: the 6-month Double-Masked Treatment Period, the 6-month Open-Label Treatment Period, and the 12-month Open-Label Retreatment Period.
Under Amendment #5, the duration of the study was 6 months with 1 post-randomization treatment period: the 6-month Double-Masked Treatment Period.</td></tr>
<tr><td colspan="3">Reference Therapy, Dose and Mode of Administration, Batch Number:
Not applicable</td></tr>
<tr><td colspan="3">Criteria for Evaluation:
<u>Efficacy:</u>
Efficacy of DE-109 was assessed by evaluation with slit-lamp biomicroscopy, tapering of systemic corticosteroids, use of rescue therapies, best-corrected visual acuity (BCVA), OCT, and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).</td></tr>
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Name of Finished Product: DE-109 Injectable Solution		
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Safety:

Safety of DE-109 was assessed by AEs and evaluation with slit-lamp biomicroscopy, endothelial cell count (at selected sites only), indirect ophthalmoscopy, BCVA, IOP, OCT, fundus photography, fluorescein angiography, laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, and vital signs.

Criteria for Evaluation:

Efficacy:

Efficacy of DE-109 was assessed by evaluation with slit-lamp biomicroscopy, tapering of systemic corticosteroids, use of rescue therapies, best-corrected visual acuity (BCVA), OCT, and National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).

Safety:

Safety of DE-109 was assessed by AEs and evaluation with slit-lamp biomicroscopy, endothelial cell count (at selected sites only), indirect ophthalmoscopy, BCVA, IOP, OCT, fundus photography, fluorescein angiography, laboratory tests (serum chemistry, hematology, and urinalysis), physical examinations, and vital signs.

Statistical Methods:

SAKURA Study 2 comprised all subjects randomized on or after 01 April 2013. Data collected from 185 subjects randomized under Protocol Amendment #2, #3, or #4 and 60 subjects randomized under Protocol Amendment #5 were analyzed to assess the efficacy and safety of 3 DE-109 doses (44 µg, 440 µg, and 880 µg).
The primary efficacy endpoint, vitreous haze (VH) 0 response, was defined as having a VH score of 0 at Month 5 (modified SUN scale). The Pearson's chi-square test for a 2×2 contingency table was conducted for the following pair of testing hypotheses:

$$\boldsymbol{H}_0: \pi_{44} = \pi_{440} \text{ vs. } \boldsymbol{H}_1: \pi_{44} \neq \pi_{440}$$

where π_{44} and π_{440} denote the response rate for the primary endpoint (i.e., proportion of subjects with VH score of 0 at Month 5) for 44 µg DE-109 and 440 µg DE-109, respectively. The same test was repeated for the comparison between 880 µg DE-109 and 44 µg DE-109. Since the comparison between 880 µg DE-109 and 44 µg DE-109 was exploratory, no multiplicity adjustment was made to control the family-wise Type I error rate. Subjects rescued before Month 5 were treated as non-responders. Missing data of subjects who were not

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rescued before Month 5 were imputed using the last-observation-carried-forward (LOCF) approach.

All efficacy and safety outcomes were summarized descriptively.

Summary – Conclusions:

Efficacy Results: The dose response in Study 2 was similar to the dose response observed in Study 1, wherein the greatest response rate was achieved with the 440 µg dose group. However, due to the larger-than-expected response in the 44 µg dose group, the difference between 44 µg and 440 µg dose groups did not reach the statistical significance (17.6% with 44 µg vs 19.1% with 440 µg, p-value = 0.783). Other clinically relevant endpoints also supported the efficacy of the 440 µg dose: 47% of the subjects achieved remission of inflammation (VH 0 or 0.5+) at Month 5 without the use of rescue therapy. In the Intent-toTaper population, 60% of subjects completely tapered off systemic corticosteroids at Month 5, with two-thirds of these tapering successes also achieving remission of inflammation. On average, subjects in the 440 µg dose group gained 1-line of visual acuity at Month 5. There was resolution of macular edema as demonstrated by a mean reduction of 79.3 microns in CRT at Month 5, which was more than 2-fold the mean reduction in the 44 µg and 880 µg dose groups. There was also a clinically meaningful improvement in visual function as measured by VFQ-25. All results were achieved with the use of the 440 µg dose of DE-109 as a monotherapy.

Safety Results: The overall AE rates, including ocular and non-ocular AE rates, were similar among the dose groups in SAKURA Study 2, with some dose-related trends noted for the PTs of Iridocyclitis, Vitreous opacities, Cataract subcapsular, and Medication Residue. Overall, SAEs in the study eye during the Double-Masked analysis period demonstrated a dosedependent trend, with higher incidence of PTs of Uveitis, Non-infectious endophthalmitis, Intermediate uveitis, and Medication residue in the 880 µg dose group. A slightly higher rate of SARs were reported for the 880 µg dose group compared to the 44 µg and 440 µg dose groups during the Double-Masked analysis period, with dose-related trends for the SARs of Vitreous opacities, Cataract, and Medication residue and with an inverse dose-related trend observed for the PT Eye pain. The effect of all 3 doses of DE-109 on IOP was minimal. Taken together, the AEs, SAEs, and suspected adverse reactions (SARs) reported, along with results from all

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Name of Finished Product: DE-109 Injectable Solution		
Name of Active Ingredient: Sirolimus		

clinical assessments (e.g., slit-lamp biomicroscopy, indirect ophthalmoscopy, IOP measurements) are consistent with the episodic nature of non-infectious posterior segment uveitis and with treatments administered via IVT injection, and are mostly similar to the safety profile established in Study 1.

Conclusions: Efficacy and safety data from SAKURA Study 2 supports the findings from SAKURA Study 1, which clearly demonstrated that the 440 µg dose had the most favorable benefit:risk profile among the 3 doses. The consistent response with the 440 µg dose across studies and analysis populations, its corticosteroid-sparing abilities, as well as the clinically relevant improvements in inflammation, visual acuity, macular edema, and quality of life deems it as the most suitable dose among the 3 studied doses, and thus supports its use as the first non-corticosteroid, immunoregulatory therapy to treat the Orphan disease of noninfectious uveitis of the posterior segment.

Date of the Report: 27 January 2017