SYNOPSIS

<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">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</td></tr>
<tr><td colspan="3">Principal Investigators:
103 Principal Investigators</td></tr>
<tr><td colspan="3">Study centers: 103 sites in 15 countries</td></tr>
<tr><td colspan="2">Studied Period (years):
Date first subject screened: 25 May 2011
Date last subject completed End of Study visit: 01 April 2015</td><td>Phase of development:
Phase III</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To evaluate the safety and efficacy of intravitreal (IVT) injection of 3 doses of DE-109 (44 μg, 440 μg, and 880 μg) for the treatment of active, non-infectious uveitis of the posterior segment of the eye
Secondary:
• To evaluate the long-term safety of multiple IVT injections of 880 μg dose of DE-109
• To evaluate the durability of effect of 880 μg dose(s) of DE-109</td></tr>
<tr><td colspan="3">Methodology:
Protocol 32-007, Amendments #2-#5, SAKURA Study 1; 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 32007, 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</td></tr>
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Study 1. Results from SAKURA Study 2 are provided in a separate report.

In SAKURA Study 1, 347 subjects with active, non-infectious posterior, intermediate or panuveitis were randomized at 103 sites. 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). The primary efficacy endpoint assessment was conducted at Month 5.

A planned unmasked analysis of SAKURA Study 1 was conducted on the 6-month data of the 347 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 (1:1:1) to the 44, 440, or 880 µg dose group in SAKURA Study 1.

A total of 347 study subjects at 103 sites were finally randomized in SAKURA Study 1. The increase in sample size to > 300 subjects was the result of re-evaluation of the original assumptions based on masked analysis and the elapsed time the changes to the program were discussed and approved by the Food and Drug Administration (FDA) at the 07 March 2013 Type C meeting.

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

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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 be pregnant or breast-feeding, 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 are not limited to:
   a. Diabetic retinopathy: proliferative diabetic retinopathy (PDR) or non-proliferative diabetic retinopathy (NPDR) that compromised vision. Subjects with NPDR or

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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 studyrelated procedures/medications

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2. Participation in other investigational drug 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 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.

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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-FIN1338

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.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable

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-25 (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.

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Statistical Methods:

SAKURA Study 1 comprised all subjects randomized by 31 March 2013. Data collected from all 347 subjects randomized in Study 1 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 Fisher's Exact test for a 2×2 contingency table was conducted for each pair of the following testing hypotheses:

$$\boldsymbol{H_{0A}}: \pi_{44} = \pi_{440} \text{ vs. } \boldsymbol{H_{1A}}: \pi_{44} \neq \pi_{440}$$

and

$$\boldsymbol{H_{0B}}: \pi_{44} = \pi_{880} \text{ vs. } \boldsymbol{H_{1B}}: \pi_{44} \neq \pi_{880}$$

where π_{44}, π_{440}, and π_{880} 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, 440 µg DE-109 and 880 µg DE-109, respectively.

The Hochberg step-up procedure was followed to control the family-wise Type I error rate at the 0.05 level (2-sided). Subjects rescued before Month 5 were treated as non-responders. Missing data of subjects not rescued before Month 5 were imputed using the last-observationcarried-forward (LOCF) approach.

All efficacy and safety outcomes were summarized descriptively.

Summary – Conclusions:

Efficacy Results: SAKURA Study 1 demonstrated the efficacy of the 440 and 880 µg doses of DE-109 as compared to the 44 µg dose for the treatment of non-infectious uveitis of the posterior segment. The 440 µg dose was statistically significantly more favorable than the 44 µg dose for the primary and key secondary VH endpoints, with approximately 23% of subjects achieving resolution of inflammation and over half of all subjects achieving remission (VH 0 or 0.5+) at Month 5 without the use of rescue therapy. Additionally, majority of subjects in the 440 µg dose group had either improvement or preservation of vision. In the Intent-to-Taper population, 77% of the subjects treated with the 440 µg dose successfully tapered from systemic corticosteroids at Month 5, with 60% of these tapering successes also achieving remission of inflammation. Efficacy benefits for the 880 µg dose were clinically

apparent, although not statistically significant as compared to the 44 µg dose.

Safety Results: The overall AE rates, including ocular and non-ocular AE rates, were similar among the dose groups in SAKURA Study 1, with the exception of certain events of exacerbated ocular inflammation for which a dose-related escalating trend was observed. This same result was observed for ocular AEs reported in the study eye and serious adverse events (SAEs) reported in the study eye, with some dose-related trends noted for non-infectious endophthalmitis. There was a tendency towards increased reporting of AEs associated with worsening of the baseline disease due to treatment failure and inflammatory reactions following IVT administration with the 880 µg dose. 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 clinical assessments (e.g., slit-lamp biomicroscopy, indirect ophthalmoscopy, IOP measurements) are consistent with the episodic nature of noninfectious posterior segment uveitis and with treatments administered via IVT injection, and represent a reasonable safety profile for all 3 doses.

Conclusions: The efficacy and safety findings from SAKURA Study 1 clearly demonstrated that the 440 µg dose had the most favorable benefit:risk profile among the 3 doses, and thus supports its use as the first non-corticosteroid, immunoregulatory therapy to treat the Orphan disease of non-infectious uveitis of the posterior segment.

Date of the Report: 27 January 2017