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 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</td></tr>
<tr><td colspan="3">Principal Investigators: A total of 28 investigators enrolled subjects into the study.</td></tr>
<tr><td colspan="3">Study centers: 28 sites in 6 countries: United States, India, Italy, France, Austria and Turkey.</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Studied period (years):
Date first subject enrolled: 29Sep2014
Date last subject completed: 01Nov2017</td><td>Phase of development:
Phase IIIb Safety Study</td></tr>
<tr><td colspan="3">Objectives:
Primary: The objective of this extension study was 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 previously participated in the SAKURA development program.</td></tr>
<tr><td colspan="3">Methodology:
This was 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.
Subjects who were randomized and received at least two injections of DE-109 during the first 5 months of the SAKURA program and obtained clinical benefit from the study medication, as determined by the Investigator, were 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 was 60 days.
The study eye which could be treated in this extension study was the same as the eye treated during the SAKURA program.
Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12. Additional visits could have been conducted according to the Investigator’s standard clinical practice at interim unscheduled visits. DE-109 treatment could have been administered in the study eye at the Investigator’s discretion on Day 1 and/or any of the Post-Baseline PRN Treatment Visits at Month 2-10 but no more frequently than every 60 days.</td></tr>
<tr><td colspan="3">All subjects exited the study at Month 12, unless terminated early. Adverse events and sight-threatening events were recorded and collected throughout this extension study, up to the Month 12 exit visit.
Administration of DE-109:
• The study eye was the eye treated in the SAKURA program.</td></tr>
</table>

- DE-109 was NOT administered to the fellow eye.

Rescue therapy:

During the study, rescue therapy could have been used at the discretion of the Investigator.

Number of subjects (planned and analyzed):

Planned: Approximately 200 subjects were planned, 60 subjects enrolled.

Analyzed: 60 subjects were analyzed in the safety analysis. (32 subjects received treatment during the study.)

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

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

1. Had a subject number from participation in the SAKURA program
2. Had exited the SAKURA under Amendment 05. Exited the SAKURA program no more than 6 months ago if enrolled under Amendment 01 of the Spring Study. (For subjects enrolled prior to Amendment 01, there was no maximum time since the subject exited the SAKURA program.)
3. Had received at least two injections of DE-109 in the first 5 months of the SAKURA program
4. Received clinical benefit from treatment with DE-109 as determined by the Investigator
5. If female of childbearing potential, were not pregnant or breast-feeding, had a negative pregnancy test at Day 1 and had to be willing to undergo pregnancy tests throughout the study
6. Both female participants of childbearing potential (non -childbearing potential was defined by at least 1-year post-menopause, i.e., 2 years post last menstrual period defined by date of the last menstrual period) and male participants able to father children must have (or have a partner who has) had a hysterectomy or vasectomy, were required to abstain from intercourse or agreed to practice acceptable methods of contraception throughout the course of the study
7. Were able to give informed consent and attend all study visits.

Exclusion Criteria:

A subject from the SAKURA program with any of the following conditions was not eligible to participate in the study: infectious uveitis, implantable corticosteroid-eluting device, glaucoma, elevated intraocular pressure (≥ 21 mmHg while on medical therapy) or chronic hypotony, ocular diseases which could compromise vision in the study eye or systemic diseases which were contraindicated and other criteria.

Test product, dose and mode of administration, batch number:

Test product: DE-109 injectable solution

Dose and mode of administration: 440 µg by 20 µL intravitreal injection in the study eye,

Batch number: 3-FIN-1029 and 3-FIN-1332

Duration of treatment: Maximum duration of treatment was 12 months.

Reference therapy, dose and mode of administration, batch number:

Reference therapy: None

Criteria for evaluation:

Safety: The long-term safety of DE-109 (440 µg) was assessed based on adverse events; best-corrected visual acuity (BCVA); intraocular pressure (IOP); indirect ophthalmoscopy variables; bio-microscopy variables including vitreous haze; endothelial cell count; and the use of rescue therapy. Additionally, available ocular imaging by Optical Coherence Tomography (OCT) including measurement of central retinal thickness (CRT), Fluorescein Angiography (FA), and/or Fundus

photography (FP) have been collected during the study but are not summarized herein due the limited amount of data and absence of baseline data.

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 subjects who were rescued and not previously rescued in the SAKURA program
- Change in slit-lamp bio-microscopy findings
- Change in endothelial cell counts (selected sites)
- Change in ocular imaging measurements: OCT (including CRT), FA, and FP

Efficacy: Efficacy was not the main objective of this extension study and was not evaluated.

Statistical methods:

No statistical hypotheses were tested in this study.

The safety data were summarized descriptively. Continuous variables were summarized using descriptive statistics such as number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables were tabulated using frequency (n) and percent (%).

The Safety population included all enrolled subjects with any safety data collected during the SPRING study, whether or not they received any injection of DE-109 (440 µg) during the SPRING study. It was the analysis population for safety summaries.

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

Summary – Conclusions:

Safety Results:

The SPRING Study enrolled 60 subjects: 32 subjects who received treatment and 28 subjects who did not receive treatment. The SPRING Study provides long-term safety data for 32 subjects who received a total of 64 intravitreal treatments during the study.

Common Ocular AEs of the 32 Subjects who Received DE-109 during SPRING Study

The most common ocular AEs in the study eye for the 32 subjects who received DE-109 were uveitis (12.5%), cystoid macular edema (9.4%), cataract (6.3%), IOP increased (9.4%) and IOP decreased (9.4%). All these events, which could be due to recurrent uveitis and its treatment, were considered mild or moderate in severity. Two subjects who received study drug had serious ocular AEs in the study eye: IOP increased in both eyes of one subject and procedural complication (wound leak due to use of incorrect needle). Neither event was considered related to study drug; however, the use of the incorrect needle was a procedural complication. Five subjects experienced sight threatening AEs. Of these, two subjects experienced serious sight threatening events in the study eye. There were no deaths and 2 subjects withdrew due to non-ocular AEs.

Common Ocular AEs for the 28 subjects who did NOT receive DE-109 while enrolled in the SPRING Study

The common ocular AEs in the study eye for the 28 subjects who did not receive treatment with DE-109 while enrolled in the SPRING Study were intermediate uveitis in 3 (10.7%), uveitis in 2 (7.1%) and cystoid macular edema in 2 (7.1%).

Changes in VH from Baseline to Month 12

Eight study eyes showed a worsening in VH from baseline to Month 12; of these, one eye (44/440 µg) shifted from a score of 0 at baseline to a score of 3+ at Month 12. Overall, most subjects that completed the Month 12 study visit had either no change in VH in the study eye from baseline to Month 12 (18 of 43 eyes) or had a favorable shift in VH from baseline to Month 12 (17 of 43 eyes).

Changes in BCVA from Baseline to Month 12

At Month 12, a mean decrease from baseline in BCVA in the study eye was observed in the 440/440 µg group (0.9 letters), and mean increases (i.e., improvement) from baseline in BCVA in the study eye were observed in the overall group (2.1 letters) and the 44/440 µg (4.0 letters) and 880/440 µg (2.8 letters) groups.

Nine (20.9%) subjects who completed Month 12 had a ≥ 5-letter worsening in BCVA from baseline to Month 12 in the study eye. Five (11.6%) subjects had a ≥ 10-letter worsening in BCVA, and 3 (7.0%) subjects had a ≥ 15-letter worsening in BCVA from baseline to Month 12 in the study eye. None of the subjects in the 44/440 µg group had a worsening in BCVA ≥ 5 letters in the study eye.

Changes in IOP from Baseline to Month 12

At Month 12, minimal mean increases from baseline in IOP in the study eye were observed in the overall group (0.3 mmHg) and the 44/440 µg (0.5 mmHg) and 440/440 µg (0.5 mmHg) groups.

Overall, 4 (6.7%) subjects had elevated IOP reported as an AE in the study eye. Four (6.7%) subjects also had an increase in IOP ≥10 mmHg from baseline to any post-baseline visit. The proportion of subjects who had an absolute IOP ≥ 25 mmHg at any post-baseline visit was 6.7%; the proportions of subjects who had an absolute IOP ≥ 30 mmHg or IOP ≥ 35 mmHg were 5.0% and 3.3%, respectively. No appreciable differences were observed among treatment groups for the occurrence of IOP-related events.

Changes in Ophthalmoscopy Parameters from Baseline to Month 12

Almost all study eyes exhibited either no change or had a favorable shift in the ophthalmoscopy parameters from baseline to Month 12. No more than 3 (5%) study eyes had a shift to an abnormal finding for the macula, optic nerve, and/or retina; none showed such a shift for the choroid.

Use of Rescue Medication during the SPRING Study

A total of 9 (15.0%) subjects received rescue medication during the study. Median time to use of first rescue medication was 98.0 days (range: 2 to 183 days).

Conclusions:

For subjects that who received 1 or more intravitreal injections of DE-109 (440 µg) during the SPRING Study, the study drug was well tolerated. As compared to the SAKURA program, no new safety signals were identified in the SPRING study. The most commonly reported ocular study eye AEs were assessed as mild or moderate in severity. The incidences of SAEs, treatment-related serious SARs, serious sight threatening AEs, and abnormal findings in ocular investigational parameters were low. There were no deaths and only 2 subjects withdrew from the study due to an AE (both of which were non-ocular AEs). Overall, within the setting of this limited exposure study, the use of DE-109 440 µg on a PRN basis demonstrated an acceptable safety profile.

Date of the report: 16 Jul 2018