# Statistical Analysis Plan Cover Page

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|---|---|
| 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 |
| NCT Number: | NCT02251938 |
| Date of the document: | November 15, 2017 |

# STATISTICAL ANALYSIS PLAN

## SPRING STUDY

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| **Protocol 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 |
| **Product:** | 2.0% DE-109 injectable solution (440 µg of sirolimus) |
| **Protocol Number:** | 32-009 |
| **Sponsor:** | Santen Inc.<br><br>6401 Hollis Street, Suite 125<br>Emeryville, CA 94608<br>U.S.A. |
| **Date:** | November 15, 2017 |
| **Status:** | Version 1.0 |

CONFIDENTIAL

# APPROVAL SIGN-OFF SHEET

**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**

**DE-109 Study 32-009**

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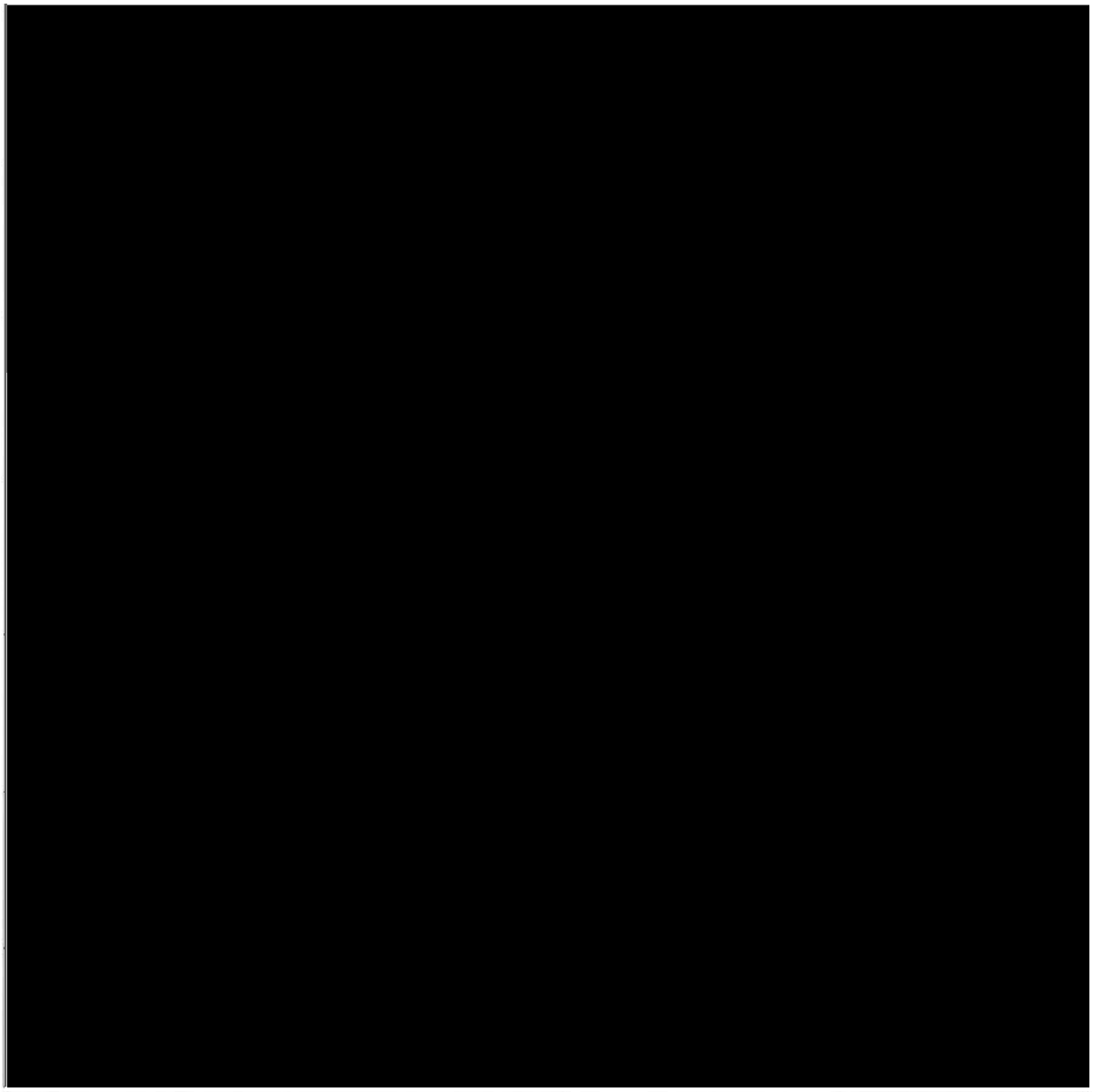

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## ABBREVIATIONS

| | |
|---|---|
| AE(s) | Adverse Event(s) |
| ATC | Anatomical-Therapeutic-Chemical |
| BCVA | Best-Corrected Visual Acuity |
| CDISC | Clinical Data Interchange Standards Consortium |
| CSR | Clinical Study Report |
| eCRF | Electronic Case Report Form |
| EMEA | Europe, the Middle East and Africa |
| ESI(s) | Event(s) of Special Interest |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| IOP | Intraocular Pressure |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mmHg | Millimeter of Mercury |
| OCT | Optical Coherence Tomography |
| OD | Oculus Dexter (right eye) |
| OS | Oculus Sinister (left eye) |
| OU | Oculus Uterque (both eyes) |
| PRN | Pro Re Nata (as needed) |
| SAE(s) | Serious Adverse Event(s) |
| SAKURA | Santen Protocol 32-007 |
| SAP | Statistical Analysis Plan |
| SAR(s) | Suspected Adverse Reaction(s) |
| SAS | Statistical Analysis System |
| SOC | System Organ Classification |
| SUN | Standardized Uveitis Nomenclature |
| US | United States |
| VH | Vitreous Haze |
| WHO-DDE | World Health Organization Drug Dictionary Enhanced |

# 1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope of Santen's Protocol 32-009 (SPRING), "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".

This SAP applies to the study protocol 32-009 US Amendment 01 dated 02 June 2016 and provides details of the descriptive statistical analyses of data collected from this Open-Label study. Results from the descriptive statistical analyses will become the basis of the Clinical Study Report (CSR) for Protocol 32-009.

# 2. 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.

# 3. STUDY DESIGN

## 3.1. General Study Design

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. In addition, 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 SPRING program is 60 days. Any subjects can enter into protocol 32-009 US Amendment 01 if that subject is from U.S. and the time lag from exiting the SAKURA program to entry into protocol 32-009 is no more than 6 months.

Each subject retains the same subject ID as had been previously assigned in the SAKURA program. The study eye to be treated in this extension study is the same as the eye treated during the SAKURA program.

Study assessments are conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10 and Month 12. Additional visits may be conducted according to the Investigator's standard clinical practice at interim unscheduled visits. DE-109 treatment may be 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. Treatment of the fellow eye with alternative local therapies is at the Investigator's discretion. However, administration of DE-109 to the fellow eye is a protocol deviation, and is counted as such.

## 3.2. Randomization and Masking

This is an open-label study. Randomization is not employed in this study. At the investigator's discretion, an injection of DE-109 (440 µg) may be administered. The study drug container has a unique number and is dispensed in sequential ascending order by each center.

## 3.3. Sample Size Planning

There is no statistical consideration regarding the sample size. The original defined number of subjects for SPRING study was approximately 200 subjects. Due to slow enrolment, the sample size has been adjusted to 60 subjects. The enrollment was completed by 18 November 2016. Of the 60 subjects, 13 signed the consent of Protocol US Amendment 01.

## 3.4. Visits and Assessments

The assessments to be conducted at each visit can be found in Table 1.

**Table 1 Assessment Schedule**

| | **Day 1 Screening/ Baseline** | **Post-Baseline PRN Treatment Visits** | **Month 2/4/6/8/10 Post-Baseline PRN Treatment Visits[h]** | **Month 12 or Early Termination[d]** |
|---|---|---|---|---|
| Assessment window (Days) | - | ≥60 days since last injection | ±7<br>Note: ≥60 days since last injection | ±14 |
| Informed consent[a] | x | | | |
| Demographics | x | | | |
| Medical/surgical history | x | | | |
| Medications | x | x | x | x |
| Urine pregnancy test, if appropriate | x[b] | x[b] | x[b] | x[b] |
| Inclusion/exclusion criteria | x | | | |
| Best-corrected visual acuity | x | x | x | x |
| Intraocular pressure | x[c] | x[c] | x[c] | x[c] |
| Indirect ophthalmoscopy[e] | x | x | x | x |
| Vitreous haze | x | x | x | x |

| | Day 1 Screening/ Baseline | Post-Baseline PRN Treatment Visits | Month 2/4/6/8/10 Post-Baseline PRN Treatment Visits[h] | Month 12 or Early Termination[d] |
|---|---|---|---|---|
| Slit lamp biomicroscopy[h] | x | x | x | x |
| DE-109 administration, if needed (PRN) | x | x | x | |
| Enodothelial cell count (only at selected sites)[h] | x | x | x | x |
| Adverse events | x[f] | x[f] | x[f] | x[f] |
| Imaging[h]: OCT (including CRT), FA, FP | x[g] | x[g] | x[g] | x[g] |

Abbreviations:
[a] Informed consent is be obtained prior to conducting any study-related activities.
[b] Urine pregnancy tests are to be performed on all women of childbearing 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.
**Error! Reference source not found.** Indirect ophthalmoscopy is performed prior to each study drug injection and then again within 30 minutes after study drug injection.
**Error! Reference source not found.** On days when DE-109 injections are administered AEs are elicited before and after DE-109 injection.
[g] Performed at investigator's discretion.
[h] For subjects under Protocol US Amendment 01 only.

# 4. DEFINITIONS

## 4.1. Time-Related Terms

### 4.1.1. Baseline Visit

The *baseline visit* of the SPRING study is the first scheduled visit on Day 1.

### 4.1.2. Study Exit Visit

The *study exit visit* of the SPRING study is the Month 12 visit or early termination visit. If both are missing, the last visit before exit date will be considered as study exit visit. For subjects who don't have any visits after Day 1, Day 1 visit will be considered as both Baseline Visit and Study Exit Visit.

### 4.1.3. Study Day / Days on Study / Days on Treatment

The *study day* variable describes the relative day of the observation starting with Day 1 as the reference date. There will be no Day 0. The study day will be calculated as follows:

- For events occurring on or after the reference date

  Study Day = (Date – Baseline Visit Date) + 1

- For events occurring before the reference date

  Study Day = (Date – Baseline Visit Date)

*Days on Study* measures the duration each subject remains in the study and will be calculated as follows:

Days on Study = (Study Exit Date – Baseline Visit Date) + 1.

*Days on Treatment* measures the duration between the date of first exposure to DE-109 and exit date of each subject and will be calculated as follows:

Days on Treatment = (Study Exit Date – Date of First Exposure to Treatment in SPRING Study + 1.

### 4.1.4. Post-baseline PRN Treatment Visit

A *Post-Baseline PRN Treatment visit* is defined as any visit at which a subject received an intravitreal injection of DE-109 (440 µg) in the study eye, or the scheduled Post-Baseline PRN Treatment Visits at Month 2, Month 4, Month 6, Month 8, and Month 10 for subjects under US Amendment 01. Therefore, it is not necessary to receive an injection in a Post-baseline PRN Treatment Visits for subjects under US Amendment 01.

### 4.1.5. Analysis Visit and Analysis Window

*Analysis visit* is a timing variable to be used for tables and listings involving visits. In SPRING study, possible values of analysis visit include Baseline, Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12. The *analysis window* will be used to determine the analysis visit of an assessment based on the study day of the assessment. The analysis window usually is slightly wider than the corresponding assessment window specified in the protocol for analysis purposes. Table 2 shows the analysis windows for post-baseline visits in SPRING study. Detailed definitions of analysis visit and analysis window will also be provided in the ADaM specifications document.

**Table 2 Analysis Visit and Analysis Window**

| Analysis Visit | Visit Window | Analysis Window |
|---|---|---|
| Baseline (Day 1) | 1 | 1 |
| Month 2 (Day 60) | [53, 67] | [2, 67] |
| Month 4 (Day 120) | [113, 127] | [68, 127] |
| Month 6 (Day 180) | [173, 187] | [128, 187] |

| | | |
|---|---|---|
| Month 8 (Day 240) | [233, 247] | [188, 247] |
| Month 10 (Day 300) | [293, 307] | [248, 307] |
| Month 12 (Day 360) | [346, 374] | >=308 |

In SPRING study, all Post-Baseline Visits including PRN and Unscheduled visits with any study assessments will be mapped to any of the analysis visits according to the table above. For example, an assessment collected at an Unscheduled Visit may be mapped to the analysis visit "Month 4" if the study day of the Unscheduled Visit is 125. Another example, an assessment collected at an Early Termination visit may be mapped to the analysis visit "Month 10" if the study day of the Early Termination visit is 250.

A subject may have more than one visit that is mapped to Month 12. However, only the Month 12 visit with latest date is considered as study exit visit. When summarizing VH and BCVA, Month 12 visit refers to this last Month 12 Visit.

## 4.2. Safety- Related Definitions

### 4.2.1. Study Eye and Fellow Eye

The *study eye* is the eye designated as the study eye in the SAKURA program.

The *fellow eye* is the non-study eye.

### 4.2.2. Baseline Score

For each measure, the *baseline score* of the SPRING study is the observed measurement prior to the injection of DE-109 (440 µg) at Day 1 if an injection is given at Day 1, or the observed measurement by Day 1 otherwise.

### 4.2.3. Change from Baseline

The *change from baseline* in a measure at a post-baseline visit will be derived as:

Change from Baseline at a Post-Baseline Visit = (Score at the Post-Baseline Visit) – (Baseline Score).

For any measure assessed before and after injection at visits, only the pre-injection scores will be used to derive the change-from-baseline variable.

### 4.2.4. Change after Injection

For any measure assessed before and after injection at injection visits, the *change after injection* at an injection visit will be derived as:

Change after Injection = Post-Injection Score at the Visit – Pre-Injection Score at the Visit.

## 4.3. Efficacy Related Definitions

The long-term efficacy of DE-109 (440 µg) may be explored by VH. There are no efficacy-related endpoints that need to be defined in this document.

## 4.4. Safety Related Definitions

### 4.4.1. Adverse Event

Under Protocol 32-009, an AE is defined as 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 any time 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 in Spring Study up to the last study visit. Treatment-emergent AEs are a subset of on-study AEs.

The severity of each AE will be graded by the Clinical Investigator as Mild (aware or unaware of event, but easily tolerated), Moderate (discomfort enough to cause interference with usual activity), or Severe (incapacitating; unable to work or perform usual activity). Each AE will be classified into a system organ classification (SOC) and coded to a preferred term using Medical Dictionary for Regulatory Activities (MedDRA 16.0).

#### 4.4.1.1. Ocular Adverse Event

An AE will be counted as an *ocular AE* if the Clinical Investigator selected 'OD', 'OS', or 'OU' under Item 2 (Eye(s) affected) on the AE eCRF.

#### 4.4.1.2. Serious Adverse Event

Serious Adverse Events (SAEs) are defined as any findings that suggest a significant hazard, contraindication, side effect, or precaution. An AE will be counted as a *serious adverse event* (SAE) if the Clinical Investigator selected 'Yes' under Item 5 (Is the adverse event serious?) on the AE eCRF. 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 AE* is defined as any ocular AE that places the subject at immediate risk of permanent vision loss in either the study eye or the fellow eye. See more in Section 4.4.1.2.1;
- 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.

#### 4.4.1.2.1. Sight-Threatening Adverse Event

The *sight-threatening AE* is defined as any ocular AE that places the subject at immediate risk of permanent vision loss in either the study eye or the fellow eye. In this extension study, the following serious ocular AEs will be reported as sight-threatening AEs:

- 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.

#### 4.4.1.3. Suspected Adverse Reaction

An AE will be counted as a *suspected adverse reaction* (SAR) if the Clinical Investigator selected either of the two options on the AE eCRF listed in Section 4.4.1.3.1 and Section 4.4.1.3.2.

#### 4.4.1.3.1. Study-Medication Related Adverse Event

- "Related" under Item 11 (Relation to Study Drug)

#### 4.4.1.3.2. Injection-Procedure Related Adverse Event

- "Related to the injection procedure" under Item 12 (Attributable Causes)

#### 4.4.1.4. Events of Special Interest

*Events of Special Interest* (ESIs) in this study include study drug administration error and Pregnancy.

### 4.4.2. Other Safety Assessments

All the other safety measures besides AE to be evaluated for the SPRING study are listed in Table 3.

**Table 3 Other Safety Assessments**

| Safety Measures | Note |
|---|---|
| Slit-lamp Biomicroscopy: Vitreous haze | VH is assessed for each eye using the modified SUN scale as 0, 0.5+, 1+, 1.5+, 2+, 3+, or 4+. A decrease in VH score |

| | |
|---|---|
| | indicates improvement in the vitreous inflammation. |
| Best-corrected visual acuity | BCVA measures the acuteness or clearness of best-corrected vision in ETDRS letters (e.g., 75 letters). An increase in BCVA indicates improvement in the best-corrected vision. A 5-letter difference in visual acuity is equivalent to one Snellen line. A BCVA score of 85 ETDRS letters is equivalent to 20/20 vision, which is considered normal vision. |
| Intraocular pressure (IOP) | IOP, the fluid pressure inside the eye, is recorded in mmHg with one decimal point (e.g., 24.0 mmHg). If DE-109 is administered, a second assessment of IOP is made after injection. |
| Indirect ophthalmoscopy:<br>*lens and cataract* | The lens of an eye is classified as Phakic, Aphakic, or Pseudophakic. Phakic lens is assessed for the presence of cataract (Yes or No). |
| Indirect ophthalmoscopy:<br>*Retina,*<br>*macula,*<br>*choroid,*<br>*optic nerve* | Retina, macula, choroid, and optic nerve, if able to be assessed, are graded as Normal or Abnormal. If DE-109 is administered, these ophthalmoscopy parameters are performed again after injection. |
| Slit-lamp biomicroscopy[a]:<br>*Lid Hyperemia,*<br>*Lid Edema,*<br>*Conjunctival Hyperemia,*<br>*Chemosis,*<br>*Corneal Edema,*<br>*Conjunctival Discharge*<br>*Exudate,*<br>*Anterior Chamber Flare* | The status of each of these biomicroscopy parameters is rated as 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe. For each abnormal record, the clinical significance (Clinically Significant or Not Clinically Significant) is also determined. |
| Slit-lamp biomicroscopy[a]:<br>*Pupil,*<br>*Lashes,*<br>*Ocular Motility,*<br>*Iris* | The status of each of these biomicroscopy parameters is determined as Normal or Abnormal. For each abnormal record, the clinical significance (Clinically Significant or Not Clinically Significant) is also determined. |
| Slit-lamp biomicroscopy[a]:<br>*Vitreous Cell Count* | This measure is rated as 0 = 0 cells, 0.5+ = 1-10 cells, 1+ = 11-20 cells, 2+ = 21-30 cells, 3+ = 31-100 cells, or 4+ = ≥100 cells. |
| Slit-lamp biomicroscopy[a]:<br>*Anterior Chamber Cell* | This measure is rated as 0 = <1 cell, 0.5+ = 1-5 cells, 1+ = 6-15 cells, 2+ = 16-25 cells, 3+ = 26-50 cells, or 4+ = ≥50 cells. |
| Central retinal thickness | At investigator's discretion, assessments of both eyes by OCT |

| | |
|---|---|
| (CRT)[a] | imaging methods are performed. Measurement of CRT in microns is obtained from the OCT reading. Equipment type is specified. Images are collected into a central repository |

[a] For subjects under US Amendment 01 only.

## 4.5. Other Definitions

### 4.5.1. Rescue Therapy and Rescue Rate

*Rescue therapy* refers to any treatment that would have a therapeutic effect on the uveitis in the posterior segment (e.g., systemic treatment with an immunosuppressant agent, or a corticosteroid injection in the study eye) other than intravitreal DE-109. Topical ocular corticosteroid medication is not considered rescue therapy. Data related to rescue therapies will be reviewed and documented by the Medical Monitor prior to database lock to make the final determination of whether a medication will be classified as rescue therapy. *Rescue rate* is defined as the percentage of subjects who receive rescue therapy during the SPRING study among all subjects.

### 4.5.2. Prior and Concomitant Medications

*Prior medications* are non-study medications started and ended prior to the enrollment (Day 1) of the study. *Concomitant medications* are non-study medication taken during the study, i.e., the treatment period of a concomitant medication taken by a subject needs to overlap with the observation period from Day 1 to the Study Exit of the subject.

All medications are coded using the World Health Organization Drug Dictionary Enhanced (WHO-DDE) March 2014 version. Each medication will be classified using the Anatomical-Therapeutic-Chemical (ATC) classification system and mapped to a WHO-DDE preferred drug name.

# 5. STUDY POPULATION

## 5.1. Safety Population

*Safety Population* will include all enrolled subjects with any safety assessment data (defined in Section 4.4) collected during the SPRING study, regardless of receiving an injection of DE-109 (440 μg) or not in this study. It will be the analysis population for descriptive summaries of all safety measures.

# 6. GENERAL CONSIDERATIONS

All variables will be summarized by the last dose received in SAKURA study and overall. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, medium, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

All data manipulations and descriptive summaries will be performed using SAS Version 9.4 or later.

## 6.1. Adjustments for covariates

No inferential analysis is planned for this study. Therefore, no covariate will be adjusted.

## 6.2. Handling of Missing Data

### 6.2.1. Safety Measures

Descriptive summaries of safety measures will be based on observed data only. No imputation of missing scores will be implemented.

### 6.2.2. Dates for Medical Events and Medications

Completely or partially missing onset and resolution dates for medical events including medical history and AEs will be imputed in a conservative fashion as in Table 4.

**Table 4 Handling of Missing Date**

| Date | Type of Missing Date | Handling of Missing Date |
|---|---|---|
| Event onset date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. |
| | Only YYYY is available | Use the first day of YYYY to impute the missing month and date parts of the onset date |
| | YYYY and MM are available but DD is missing | Use the first day of MM to impute the missing date part of the onset date |
| Event resolution date (e.g., YYYY-MM-DD) | Completely missing | No imputation will be applied. The event will be considered ongoing (i.e., not resolved) at the last visit date. |
| | Only YYYY is available | Use the last day of YYYY to impute the missing month and date parts of the resolution date |
| | YYYY and MM are available but DD is missing | Use the last day of MM to impute the missing date part of the resolution date |

The same rules will be followed to impute completely or partially missing start and end dates of concomitant medications.

## 6.3. Multi-Center Studies

This is a multi-center study enrolling subjects from sites in multiple countries, including the US, India, and Europe.

## 6.4. Multiple Comparisons / Multiplicity

Multiplicity adjustment is not applicable to the descriptive summaries of this study.

## 6.5. Interim Analysis

No formal interim analysis is planned for this study.

# 7. SUMMARY OF STUDY POPULATION DATA

## 7.1. Subject Disposition

The subject disposition for all enrolled subjects will be tabulated by Safety population. Safety population will be further tabulated by subjects who completed study exit assessment and Month 12 Visit completers. Non-completers at Month 12 will be tabulated by the primary discontinuation reason and will be listed by subject ID. Days to premature discontinuation will also be summarized.

The subject enrollment will be summarized by geographic region and country, if applicable.

## 7.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be descriptively summarized for the Safety Population. Subject demographics collected under Protocol 32-009 include age at entry, gender and geographic region. Race and ethnicity for the Safety Population will be carried over from the SAKURA program.

For baseline characteristics, the baseline scores of the following variables will be summarized:

- Baseline VH score of study eye
- Anatomic location of uveitis of study eye (intermediate, posterior or panuveitis)
- Presence of cataract in the study eye (Phakic lens only) (yes or no)
- Baseline BCVA of study eye
- Use of systemic corticosteroid
- Rescued in SAKURA study
- Entered open-label period in SAKURA study

Other baseline characteristic variables may be summarized as suggested by the data.

## 7.3. Medical and Surgical History

The medical history events will be coded using the MedDRA Version 16.0 and summarized for the Safety population.

Subjects reporting any medical history events will be tabulated by System Organ Class (SOC) and preferred term specified in MedDRA. In addition, the following subsets of medical history events will be tabulated:

- SOC *Eye Disorders* medical events in study eye by Preferred Term and Lowest Level Term
- Medical events ongoing at baseline by SOC and Preferred Term

- SOC Eye Disorders medical events ongoing at baseline in study eye by Preferred Term and Lowest Level Term

Any subject with more than one medical and/or surgical term within the same SOC (or mapped to the same preferred term) will be counted only once for that SOC (or preferred term).

## 7.4. Protocol Deviations

Protocol deviation(s) will be listed by geographic region (US, EMEA, or India) and subject. Major protocol deviations will be tabulated by deviation category.

## 7.5. Prior and Concomitant Medications

For Safety subjects, all non-study medications will be tabulated by ATC level and WHO-DDE preferred drug name. A subject will be counted at most once for each non-study medication, even if the subject received the same medication on multiple occasions. Details of those non-study medication usages will be listed including subject information, start and end date of the medication, unit, dose and frequency.

## 7.6. Treatment Exposure

The extent of exposure to DE-109 (440 μg) in the SPRING study will be assessed by the number of DE-109 injections (0, 1, 2, 3, 4, 5, or 6) together with days on treatment (<60, ≥60 and <120, ≥120 and <180, ≥180 and <240, ≥240 and <300, or ≥300).

# 8. SAFETY ANALYSES

Safety measures collected in this extension study include:

- On-Study AEs
- VH
- BCVA
- IOP
- Indirect ophthalmoscopy
- Treatment exposure
- Use of rescue therapy
- Slit-lamp Biomicroscopy
- Central Retinal Thickness

Unless specified otherwise, safety measures collected from both eyes will be summarized for study eyes and fellow eyes separately.

## 8.1. Adverse Event

All AE(s) will be coded by MedDRA 16.0, 2013. All analysis will focus on on-study AEs given the PRN nature of this study. The information that whether an AE is treatment emergent or not

will be provided in all the AE related listings. All AE tables will be summarized by last dose received in SAKURA study, received injection or not in SPRING study, and overall.

Besides the overall summary of AEs, subjects with any AE(s) will be tabulated by SOC, preferred term, and maximum severity. A subject who experienced multiple AEs within a SOC or preferred term will be counted only once for that SOC or preferred term. SAEs, SARs, Serious SARs, study-medication related AEs, and injection-procedure related AEs will be tabulated similarly.

Ocular AEs, ocular SARs, serious ocular AEs, and serious ocular SARs will be summarized. Any ocular AE that occurred simultaneously to both eyes will be counted once for both the study eye and the fellow eye.

Sight-threatening AEs will be summarized by type of event specified in Section 4.4.1.2.1 .

Eye disorders AEs may be tabulated using lowest level term and preferred term to provide more detailed information.

Non-ocular AEs and serious non ocular AEs will be presented by SOC and preferred term.

All AEs reported during the study will be listed. SAEs, SARs, Ocular AEs, study-medication related AEs, injection-procedure related AEs, AEs leading to death, AEs leading to discontinuation, sight-threatening AEs, and ESIs, if any, will be listed separately.

## 8.2. Vitreous Haze (VH)

VH score, change from baseline, and shift from baseline in VH at Month 12 visit and Study Exit visit will be summarized and listed.

Subgroup analysis will be performed for change from baseline in study eye at study exit by demographics and baseline characteristics in Section 7.2.

Subjects with any score of 3+ or above in VH after Baseline will be listed.

## 8.3. Best-Corrected Visual Acuity (BCVA)

BCVA and change from baseline in BCVA at Month 12 and Study Exit visit will be summarized and listed.

Subjects with improvement or worsening of at least 5 letters, 10 letters, or 15 letters in study eye at Month 12 visit will be tabulated, as well as subjects maintained BCVA within 5 letters of change in study eye.

Subjects with any BCVA score of 0 after baseline will be listed.

## 8.4. Intraocular Pressure (IOP)

IOP, change from baseline in IOP at the Study Exit visit, and change after injection in IOP will be summarized.

Subjects with elevated IOP reported as an AE will be tabulated. Subjects with any increase of $\geq$ 10 mmHg in IOP from baseline at any post-baseline visit, or after injection will be tabulated and listed. In addition, Subjects with IOP of at least 25, 30, or 35 mmHg at any post-baseline visit will be summarized.

## 8.5. Indirect Ophthalmoscopy

For retina, macula, choroid, and optic nerve, shift from baseline in status (Normal or Abnormal) will be summarized at study exit visit and shift after injection will be summarized by injection visit. Subjects with any change from normal at baseline to abnormal in status after baseline will be listed.

For phakic lens only, shift from baseline in presence of cataract (Yes or No) at study exit visit will be summarized. Subjects with no cataract presence at baseline to cataract presence after baseline, if any, will be listed.

## 8.6. Treatment Exposure

The exposure to DE-109 will be evaluated by descriptive summaries of number of injections during the study, time to first injection, and study days on the drug.

## 8.7. Use of Rescue Therapy

Subjects who take any medication qualified as rescue therapy, or who have vitrectomy procedures in study eye will be listed. The rescue rate in SPRING study will be calculated. Time to first rescue from Day 1 for rescued subjects will be summarized descriptively. Subgroup analysis of rescue rate will be performed by rescue status in SAKURA study, and received injection or not in SPRING study.

## 8.8. Slit-lamp Biomicroscopy

Only subjects who are under US Amendment 01 have slit-lamp biomicroscopy assessments. However, none of those subjects have slit-lamp biomicroscopy records at baseline since all of them entered the amendment after day 1. Taking this fact into consideration, all the slit-lamp biomicroscopy parameters (Lid Hyperemia, Lid Edema, Conjunctival Hyperemia, Chemosis, Corneal Edema, Conjunctival Discharge Exudate, Anterior Chamber Flare, Pupil, Lashes, Ocular Motility, Iris, Vitreous Cell Count and Anterior Chamber Cells) will be presented only in listings.

## 8.9. Central Retinal Thickness

Since central retinal thickness assessment is at investigator's discretion and is only for subjects under US Amendment 01, only a few records were collected. Therefore, subjects with central retinal thickness records will simply be listed by type of OCT machine.

# 9. REFERENCE

None.