EYEPOINT
PHARMACEUTICALS

# Cover Page Statistical Analysis Plan (SAP)

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| **SAP Title:** | Statistical Analysis Plan – A Multi-Center, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment |
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**pSivida Corp.**

**PSV-FAI-005**

# A Multi-Center, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment of the Eye

**10 MARCH 2017**

Statistical Analysis Plan
For US

**Version 2.0**

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# List of Abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ATC | Anatomical Therapeutic Chemical |
| BCVA | Best Corrected Visual Acuity |
| CFT | Central Foveal Thickness |
| CSFT | Central Subfield Thickness |
| eCRF | Electronic Case Report Form |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluocinolone Acetonide |
| FAI Insert | Fluocinolone Acetonide Intravitreal Insert |
| FDA | Food and Drug Administration |
| HLT | High Level Term |
| IOP | Intraocular Pressure |
| ITT | Intent to Treat |
| IVRS | Interactive Voice Response System |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| OCT | Optical Coherence Tomography |
| PP | Per-Protocol |
| PT | Preferred Term |
| ROW | Rest of World |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TEAE | Treatment-Emergent Adverse Event |
| US | United States of America |
| WHO | World Health Organization |
| VA | Visual Acuity |

# 1. Introduction

pSivida Corp. is developing a drug product candidate to treat chronic non-infectious uveitis affecting the posterior segment of the eye. This includes posterior uveitis, intermediate uveitis, with or without anterior uveitis, and panuveitis. pSivida's product candidate is an intravitreal insert that contains 0.18 mg of Fluocinolone Acetonide (FA) and releases FA into the vitreous humor for 36 months.

Uveitis is defined as inflammation of the uveal tract (iris, ciliary body, choroids) or adjacent structures. The cause of inflammatory reaction of the inner eye can be infectious, traumatic, neoplastic or autoimmune. According to the classification scheme recommended by the International Uveitis Study Group, the disease can be classified on the basis of anatomic locations: anterior, intermediate, posterior, or panuveitis.

Generally, posterior uveitis occurs in all age groups and affects people of different ethnic origins. The inflammation that affects the choroid and retina may be a primary intraocular process or may be an ocular manifestation of systemic disease. Posterior uveitis accounts for most of the loss of vision in eyes with uveitis, due to any one or more of the following: cystoid macular edema, choroidal neovascularization, glaucoma, retinal detachment, subretinal fibrosis, cataract, or optic disk atrophy.

Uveitis is often a chronic disease requiring long-term medical therapy. Currently, medical management of chronic non-infectious uveitis affecting the posterior segment generally includes local administration of corticosteroid (topical, intra or periocular, and intravitreal) and/or systemic administration of steroids or immunosuppressants. The goal of therapy is to suppress the inflammation in the back of the eye.

There are disadvantages associated with each of these therapies and their route of administration. All corticosteroid therapy, including systemic, is associated with ocular side effects, including cataract and elevated intraocular pressure (IOP); these side effects are more commonly observed with local therapy. Topical corticosteroid delivery is not effective in the treatment of intermediate or posterior uveitis due to its limited intraocular penetration. Periocular corticosteroid injections may be required frequently and have the additional potential risk for globe perforation, orbital fibrosis, endophthalmitis and ptosis.

A product that is relatively simple to administer and delivers corticosteroid locally for an extended period of time may offer significant benefits over existing local and systemic steroid therapies.

The FAI insert to be used in the present study is virtually identical to Iluvien®, an intravitreal fluocinolone acetonide product candidate that has been inserted into the eyes of over 800 subjects with diabetic macular edema, retinal vein occlusion, wet age-related macular degeneration or dry age-related macular degeneration.

Additionally, Retisert, a Food and Drug Administration (FDA) approved intraocular product that requires surgical implantation, also contains the same active ingredient as the FAI insert. Compared to the FAI insert, Retisert delivers approximately 3 times as much FA at rates approximately 3 times faster. Retisert has been approved by FDA for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye [Retisert prescribing information (June 2001)].

pSivida Corp. is developing the FAI insert to provide local steroid therapy with an improved benefit/risk profile for patients with chronic non-infectious uveitis affecting the posterior segment of the eye.

This US-specific statistical analysis plan (SAP) uses a revised definition of the primary efficacy endpoint that aligns with FDA guidance. Detailed rationale is provided in Appendix 13.3.

# 2. Objectives

The primary objectives of this study are to evaluate the safety and efficacy of a FAI insert in the management of subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

## 2.1. Primary Objective

To assess the efficacy of FAI insert by comparing the proportion of subjects who have a recurrence of uveitis (as defined under "Primary Efficacy Endpoint") in the study eye within 6 months following the treatment.

## 2.2. Secondary Objective

To assess the safety of FAI insert within the 36 months following the treatment.

# 3. Investigational Plan

## 3.1. Overall Study Design and Plan

This trial is a 36 month, Phase 3, multi-center, randomized, masked (subject and outcome assessor), controlled study to evaluate the safety and efficacy of either the FAI insert or a Sham injection, administered post screening on Day 1, in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye. Clinical sites in India only will participate in this study. A total enrollment of approximately 150 subjects is planned for this study. On Day 1, subjects will be randomized in a 2:1 ratio to treatment with either FAI insert or Sham injection and then will receive standard care for the next 36 months; subjects will be assessed according to the schedule presented in Appendix 13.1

Analyses of study data will be performed at the following three time points during the study:

1. After all subjects have completed the Month 6 visit (or have been discontinued from the study prior to this visit). The primary analysis of efficacy will occur at the Month 6 time point.
2. After all subjects have completed the Month 12 visit (or have been discontinued from the study prior to this visit).

3. After all subjects have completed the Month 36 visit (or have been discontinued from the study prior to this visit).

Details on masked and unmasked personnel at the two time points are provided in Section 4.2.1.

### 3.2. Study Endpoints

The primary efficacy endpoint is the proportion of subjects who have a recurrence of uveitis in the study eye within 6 months following treatment. Recurrence is captured on the Recurrence of Uveitis eCRF page.

The FDA has requested a definition of recurrence for the primary efficacy analyses that differs from the ROW definition of recurrence in PSV-FAI-005. For US/FDA reporting, recurrence is defined as:

- An increase in the vitreous haze of ≥ 2 steps, compared to baseline or any visit time point prior to Month 6
  OR
- A deterioration in visual acuity of at least 15 letters best-corrected visual acuity (BCVA), compared to baseline or any visit time point prior to Month 6

Any criterion used to define recurrence must be attributable only to noninfectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis begin after the study Day 7 visit.

The exploratory efficacy endpoints include:

- Proportion of subjects who have a recurrence of uveitis in the study eye within 12 months and 36 months
- Proportion of subjects who have a recurrence of uveitis in the fellow eye (within 6 months, 12 months and 36 months)
- Mean change from baseline in BCVA letter score in the study eye (at 6 months, 12 months and 36 months)
- Number of recurrences of uveitis (within 6 months, 12 months and 36 months)
- Time to recurrence of uveitis in the study eye (within 6 months, 12 months and 36 months)
- Number of adjunctive treatments required to treat recurrences of uveitis (within 6 months, 12 months and 36 months)
- Resolution of macular edema, as measure by OCT imaging (at 6 months, 12 months and 36 months)

In addition, the following safety endpoints will be included in the analysis:

- Systemic adverse events
- Ocular adverse events, including IOP elevation
- Medications/procedures required to control elevated IOP
- Development or worsening of cataract
- Cataract-related procedures
- Clinically significant ocular change
- Treatment related adverse events

# 4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e. n, mean, standard deviation, median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by treatment group.

Subjects will be identified in the listings by the subject identification number concatenated with the investigator number.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted "Missing" will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis population of interest, unless otherwise specified.

Unless otherwise specified, baseline will be defined as the last non-missing evaluation prior to or on the date of treatment injection (Day 1). The study day will be calculated as assessment date – date of treatment injection (Day 1) + 1.

For all efficacy and safety analyses, analysis visit windows will be used for assigning assessments to an analysis visit, as follows:

| Scheduled Visit | Target Day | Visit Window (Days) |
|---|---|---|
| Screening | -30 to -1 | Not applicable |
| Day 1 | 1 | Not applicable |
| Day 7 | 7 | 5 to 9 |
| Day 28 | 28 | 25 to 31 |
| Month 2 | 60 | 53 to 67 |
| Month 3 | 90 | 83 to 97 |
| Month 6 | 180 | 152 to 208 |
| Month 9 | 270 | 242 to 298 |
| Month 12 | 360 | 332 to 388 |
| Month 18 | 540 | 512 to 568 |
| Month 24 | 720 | 692 to 748 |
| Month 30 | 900 | 872 to 928 |
| Month 36 | 1080 | 1052 to 1108 |

Only those assessments which are assigned to an analysis visit will be included in the summary tables and figures which are presented by visit. For summaries of an event at or before a given time point, such as recurrence at Month 12, all assessments (including unscheduled visits) on or before the upper limit of the corresponding visit window will be considered. All assessments will be presented in the data listings.

For summaries presented by 3 month time intervals through Month 12, the intervals will be defined based on study days and the analysis visit windows, as follows:

- Day 1 to 3 months: Day 1 to Day 97 (upper limit of Month 3 visit window)
- 3 to 6 months: Day 98 to Day 208 (upper limit of Month 6 visit window)
- 6 to 9 months: Day 209 to Day 298 (upper limit of Month 9 visit window)
- 9 to 12 months: Day 299 to Day 388 (upper limit of Month 12 visit window)

For summaries presented by 6 month time intervals, the intervals will be defined based on study days and the analysis visit windows, as follows:

- Day 1 to 6 months: Day 1 to Day 208 (upper limit of Month 6 visit window)
- 6 to 12 months: Day 209 to Day 388 (upper limit of Month 12 visit window)
- 12 to 18 months: Day 389 to Day 568 (upper limit of Month 18 visit window)
- 18 to 24 months: Day 569 to Day 748 (upper limit of Month 24 visit window)
- 24 to 30 months: Day 749 to Day 928 (upper limit of Month 30 visit window)
- 30 to 36 months: Day 929 to Day 1108 (upper limit of Month 36 visit window)

The Month 6 analysis will include all assessments (events, medications, etc.) with a start day on or before the upper limit of the Month 6 visit window (study day 208). The Month 12 analysis will include all assessments (events, medications, etc.) with a start day on or before the upper limit of the Month 12 visit window (study day 388). The analysis at Month 36 will include all data in the database.

For tabulations of data on the Safety population, subjects who were randomized but did not receive treatment will not be included; however data for all subjects in the Safety population will be included in the data listings. In the listings, subjects who did not receive treatment will be grouped separately by their randomized treatment assignment (i.e., FAI Insert - Not Treated, Sham Injection - Not Treated). Percentages for Safety population summaries will be based on the total number of subjects who receive treatment.

All analyses will be conducted using SAS Version 9.2 or higher.

### 4.1. Sample Size

A two group continuity corrected Chi-square test with a 0.05 two-sided significance level will have 95% power to detect the difference between a Sham group recurrence free rate of 0.600 and a FAI treated group recurrence free rate of 0.880 (odds ratio of 0.205) when the sample sizes are 50 and 100, respectively (a total sample size of 150).

### 4.2. Randomization, Stratification, and Masking

Subjects will be randomly assigned in a 2:1 ratio to either the FAI insert or Sham injection through a central Interactive Voice Response System (IVRS). A blocked randomization will be used and randomization will be stratified on the basis of systemic treatment to control uveitis at the time of study entry. The three strata are: Not receiving systemic treatment, Receiving systemic treatment – corticosteroid therapy, and Receiving systemic treatment – immunosuppressive therapy. Stratification will be achieved dynamically through the IVRS.

To minimize bias, two investigators will be used at each study site. The unmasked treating investigator will inject the FAI insert or perform a Sham injection and perform all assessments on study Day 1. The second investigator will serve as the masked assessing investigator and will perform all study assessments after Day 1. Only the unmasked treating investigator will know the assigned study treatment. Study personnel will use every reasonable effort to maintain the study mask.

Unmasking a subject's treatment to the assessing investigator should only be done in emergency situations for reasons of subject safety. In the event that an emergency unmasking is required, the assessing investigator/medically qualified designee has the authority to unmask a subject's treatment using IVRS, or its backup system if IVRS is not functioning. If possible, the assessing investigator/medically qualified designee should contact the PPD medical monitor or designee before breaking the mask. When the masked treatment code is broken, the date and time of unmasking, name of person doing the unmasking, and the reason for unmasking must be fully documented in the source documentation. Treatment unmasking will also be recorded on the eCRF, including whether the FAI insert was removed and if so, the removal date. In the rare event that the FAI insert is removed, the subject should continue to be followed for safety and recurrence of uveitis through Month 36.

Randomization and unmasking data, for those subjects who were unmasked during the study, will be presented in a listing.

#### 4.2.1. Masking of Study Team

Prior to the Month 6 database lock, study team members at PPD and pSivida Corp. will be masked to the treatment assignments, with the exception of the PPD randomization team. After the Month 6 database lock, the PPD team with the exception of the medical monitor and specific pSivida personnel will become unmasked. The PPD medical monitor will remain masked to subject-level treatment assignments until after the Month 36 database lock.

### 4.3. Analysis Population

#### 4.3.1. Intent-to-Treat (ITT)

The ITT population will include all randomized subjects. The ITT population will be used for the primary efficacy analysis and all efficacy endpoints.

All subjects in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, in the event there is a discrepancy. Similarly, in any ITT analysis by systemic treatment at study entry (randomization stratification factor), subjects will be analyzed by the strata to which they were randomized, not the actual strata, in the event there is a discrepancy.

#### 4.3.2. Per Protocol (PP)

Analysis on the PP population will be used as a supplement to the ITT analysis and will be performed for all efficacy endpoints. The PP population will be defined separately for the Month 6, Month 12 and Month 36 analyses and will exclude all subjects in the ITT population who meet any of the following criteria:

- Received systemic treatment for recurrence of uveitis in fellow eye
- Received an imputed endpoint at the 6 month (or the 12 month or the 36 month) endpoint of the study
- Failed screening, without exemption, but received FAI insert
- Had a major protocol deviation

Protocol deviations, both major and minor, will be identified prior to database lock and study unmasking at Month 6 and prior to database locks at Months 12 and 36. The review and identification of protocol deviations at Months 12 and 36 will be conducted in an unmasked manner since pSivida and the PPD biostatistics team are unmasked at the Month 6 database lock. All subjects who failed screening but received FAI insert will be determined at Month 6 database lock.

Additional sensitivity analyses involving alternative definitions of the PP population may be conducted, if warranted.

All subjects in the PP population will be analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event there is a discrepancy. Similarly, in any PP analysis by systemic treatment at study entry (randomization stratification factor), subjects will be analyzed by the actual strata to which they belong and not according to the strata under which they were randomized, in the event there is a discrepancy.

#### 4.3.3. Safety

The Safety population will include all randomized subjects. All subjects in the Safety population will be analyzed according to the treatment actually received and not according to the treatment they were randomized to receive, in the event there is a discrepancy. Similarly, in any Safety analysis by systemic treatment at study entry (randomization stratification factor), subjects will be analyzed by the actual strata to which they belong and not according to the strata under which they were randomized, in the event there is a discrepancy.

# 5. Subject Disposition

## 5.1. Disposition

Subject disposition will be summarized for the ITT population. A disposition of subjects includes the number and percentage of subjects for the following categories: subjects randomized, subjects who completed the study, subjects who discontinued from the study, subjects in the Safety population, subjects in the ITT population, and subjects in the Month 6, Month 12 and Month 36 PP populations. All percentages will be based on the number of subjects randomized.

The reasons for study discontinuation will also be summarized in the disposition table. The reason for study discontinuation includes the following: adverse event, lack of efficacy, lost to follow-up, death, subject voluntarily withdrew, physician decision, sponsor decision, and study cancelled.

Subject disposition data will be presented in a listing.

### 5.2. Protocol Deviations

The investigator is not to deviate from the requirements from this protocol without prior approval from pSivida Corp. unless necessitated by a medical emergency (i.e., those that impact subject safety or the validity of the study). Any deviation from the protocol, with or without prior pSivida approval, will be recorded including the following information:

- Investigator site
- Subject
- Subject visit
- Description (including associated Significant Protocol Deviation rule number, if applicable)
- Date of occurrence
- Ethics Committee notification date if known
- Significant (Yes/No)

Significant protocol deviations will be defined in the Significant Protocol Deviations Rules document. Each significant deviation will be assigned a rule number. As the study is ongoing, additional significant protocol deviations can also be spontaneously identified or defined during trending and review of protocol deviations by pSivida and/or the project team during the regularly planned study deviation review meetings and the significant Protocol Deviations Rules document will be updated.

All protocol deviations will be reviewed and assessed as to significance prior to each database lock. The list of protocol deviations (significant or minor) that are additionally considered major for the purposes of analysis (i.e. result in exclusion from the PP population) will also be identified prior to each database lock.

## 6. Demographics and Baseline Characteristics

### 6.1. Demographics

A summary of demographics and baseline information will be presented for the ITT and Safety populations. Summaries will be generated for the Safety population only if there are randomized subjects who do not receive treatment. The demographic characteristics consist of age (years), sex, race, ethnicity, and iris color. The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) ($kg/m^2$). Body mass index is calculated as (body weight in kilograms) / (height in meters)$^2$.

A subject's age in years is calculated using the date of the informed consent and date of birth. Age (years), baseline height (cm), baseline weight (kg), and baseline BMI ($kg/m^2$) will be summarized using descriptive statistics. The number and percentage of subjects by age category ($<20$, $20 - < 40$, $40 - < 60$, $\geq 60$), sex (Male, Female), race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino), and iris color (Black, Brown, Hazel, Green, Blue, Grey, and Other) will also be reported. Percentages will be based on the total number of subjects in the ITT or Safety population, as applicable.

Subject demographic and baseline characteristics will be presented in a listing.

## 6.2. Baseline Disease and Ocular Characteristics

A summary of baseline disease characteristics will be presented for the study eye and fellow eye for the ITT and Safety populations. Summaries will be generated for the Safety population only if there are randomized subjects who do not receive treatment. The baseline characteristics consist of study eye, randomization strata for systemic treatment to control uveitis, duration of uveitis (years), number of recurrences in the last 12 months, lens status, presence of cataract, history of vitrectomy procedure and history of incisional surgery to control elevated IOP.

Duration of uveitis is calculated as (Screening date – date of onset of uveitis +1)/ 365.25 and will be summarized using descriptive statistics. For partial onset dates, a missing month will be imputed as January and a missing day will be imputed as the first of the month.

The number and percentage of subjects by study eye (OD, OS), randomization strata (Not receiving systemic treatment, Receiving systemic treatment – corticosteroid therapy, Receiving systemic treatment – immunosuppressive therapy), duration of uveitis (< 2 years, 2 to 5 years, > 5 years), number or recurrences (≤2, >2), lens status (phakic, aphakic, and pseudophakic), presence of cataract for subjects with a lens status of phakic, history of vitrectomy procedure, and history of incisional surgery to control elevated IOP will also be reported. Percentages will be based on the total number of subjects in the ITT or Safety population, as applicable.

In addition, baseline ocular characteristics will be summarized. The baseline ocular characteristics consist of severity of macular edema, IOP (mmHg), BCVA (letters), vitreous haze and anterior chamber cells. Baseline IOP and BCVA will be summarized using descriptive statistics. The number and percentage of subjects by baseline vitreous haze, anterior chamber cells and severity of macular edema (central subfield thickness [CSFT] < 300 microns, CSFT ≥ 300 microns) will also be reported.

Subject baseline disease and ocular characteristics will be presented in a listing.

## 6.3. Medical History

### 6.3.1. Non-ocular Medical History

The number and percentage of subjects with any non-ocular medical history and current non-ocular conditions will be summarized overall and for each body system for the ITT population. Body systems will be included as recorded on the eCRF. Percentages will be calculated based on number of subjects in the ITT population.

Subject non-ocular medical history data, including specific details on the condition/diagnosis and start/end dates, will be presented in a listing.

### 6.3.2. Ocular Medical History

Any clinically significant ocular conditions within the 12 months prior to Screening will be recorded on the eCRF. Subject ocular medical history data, including specific details on the

condition/diagnosis, location (OS, OD, and OU), study eye designation, treatment required, and start/end dates, will be presented in a listing.

### 6.4. Inclusion and Exclusion Criteria

Prior to randomization, the investigator will assess whether the subject fulfills all of the inclusion and exclusion criteria outlined in the protocol. If a subject does not fulfill all of the requirements, the specific inclusion criterion not met or exclusion criterion which was met will be recorded on the eCRF. This information and whether the sponsor granted a waiver will be presented in a listing.

# 7. Treatments and Medications

### 7.1. Prior and Concomitant Medications

Medications and systemic/topical treatments for uveitis at study entry will be coded using the World Health Organization (WHO) Drug Dictionary (WHO201209 version or higher).

All summaries will be provided for ocular medications and non-ocular medications, separately. Ocular medications will be presented by eye (study, fellow).

All medication and systemic/topical treatment data will be presented in listings.

#### 7.1.1 Prior Medications

Prior medications are defined as those medications with a recorded end date prior to the initiation of study treatment. The total number of prior medications and the number and percentages of subjects with at least one prior medication will be summarized by treatment group. The number and percentages of all prior medications will be summarized by treatment group and preferred term. All summaries will be performed using the Safety population.

#### 7.1.2 Concomitant Medications

Concomitant medications are defined as those medications which are taken on or after the initiation of study treatment (Day 1). This includes medications which start prior to Day 1 but continue while the subject is on treatment.

The total number of concomitant medications and the number and percentages of subjects with at least one concomitant medication will be summarized by treatment group. The number and percentages of all concomitant medications will be summarized by treatment group and by Anatomical Therapeutic Chemical (ATC) level 1 term, ATC level 2 term, and preferred term. An additional summary of the number and percentage of subjects with at least one concomitant medication for each of the specified reasons for medication (recurrence of uveitis, treatment emergent AE, increased IOP, cataract, other) will be summarized by treatment group and by ATC level 1 term, ATC level 2 term, and preferred term. All summaries will be performed using the Safety population.

##### 7.1.2.1 IOP Lowering Medication

The number and percentage of subjects requiring IOP lowering medication to control elevated IOP will be summarized by treatment group, eye (study, fellow), and time interval. Any systemic

medications will be summarized as received in both the study and fellow eyes. IOP lowering medications will be identified as those medications with a reason for medication of "Increased IOP". Incidence will be summarized overall (through 6, 12 or 36 months) and for 3 month time intervals through 6 or 12 months and 6 month time intervals from 12 to 36 months.

The number of medications (1, 2, $\geq 3$) required to achieve adequate IOP control will also be included in the summary. IOP medications will be counted at the "ingredient" level. For example, if the subject is receiving COSOPT (which contains two ingredients TIMOLOL MALEATE and DORZOLAMIDE HYDROCHLORIDE) and TIMOLOL MALEATE at the same time, the subject will be included in analysis as receiving two medications.
A single medication must be used for a minimum of 7 days. Multiple medications must be used concurrently for a minimum of 14 days. A subject does not need to be taking the same medication(s) over a given period to be counted for analysis. For example, if a subject is taking Medication A from Days 50 to day 55, then Medication B from Days 56 to 61, the patient will be counted as receiving 1 medication to control IOP, because the subject required at least one IOP medication/ingredient for 7 consecutive days, even though each medication/ingredient was used for less than 7 days. In a similar example, if a subject was receiving Medication A from Days 50 to 60, Medication B on Days 61 to 70, and Medication C on Days 52 to 70, then the subject will be counted in the analysis as receiving 2 medications, because the subject received 2 unique medications/ingredients over Days 52 to 70.

Because medications can start and stop at various times in the analysis periods (up to Month 3, Month 3 to Month 6, etc.) a medication will be counted in a given period if the start date(s) for the required number days of consecutive use (7 days for a single medication, 14 days for multiple medications) occurs within the period, even if the end of the 7 or 14 days of consecutive use falls after the end of the given analysis period. Medication(s) which begin in one analysis period and continue to the "next" analysis period will be counted in the "next" analysis period only if the medication(s) were received for at least 7 or 14 days (for single or multiple medications, respectively) in the "next" period.

A summary of IOP lowering medications will also be presented by history of incisional surgery to control elevated IOP (History of Incisional Surgery, No History of Incisional Surgery). All summaries will be performed using the Safety population.

### 7.1.3 Systemic/Topical Treatment at Study Entry

If a subject is receiving systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis prior to study enrollment, that subject will have such treatment ended within three months following study Day 1, in a manner that follows the standard of care for ending the specific treatment. For example, some systemic treatment regimens may be ended immediately, while others require a period of gradual dose reduction (tapering). Systemic medications or topical steroids administered as part of gradual dose reductions are not considered prohibited medications. Medications received as such treatments will not be recorded on the concomitant medications page but will be recorded on a separate eCRF page.

The number and percentages of subjects with at least one systemic/topical treatment medication at the time of study entry will be summarized by treatment group. The number and percentages

of all medications received as systemic/topical treatments will be summarized by treatment group and by ATC level 1 term, ATC level 2 term, and preferred term. All summaries will be performed using the Safety population.

## 7.2. Ocular Surgeries

All ocular surgeries, including cataract removal, during a subject's participation in the study will be recorded on the eCRF. The number and percentage of subjects with at least one surgery/procedure and at least one surgery/procedure for each of the specified reasons (recurrence of uveitis, treatment emergent AE, increased IOP, cataract, other) will be summarized by treatment group and eye (study, fellow). A frequency distribution for the number of surgeries/procedures during the study per subject will also be presented. All summaries will be performed using the Safety population and percentages will be based on the total number of subjects in the Safety population.

Ocular surgery data, including details on the procedure, eye, study eye designation, start date, and reason for the surgery, will be presented in a listing.

### 7.2.1 Surgical Intervention to Control Elevated IOP

The number and percentage of subjects requiring any surgical intervention to control elevated IOP will be summarized by treatment group, eye (study, fellow), and time interval. Ocular surgeries with a reason of "Increased IOP" will be included in the summary. Surgery data will be reviewed to ensure all IOP surgeries including those with "Other" indication are also identified using the specification text. Incidence will be summarized overall through 6 months and for 6-month time intervals through 12 (or 36) months.

A summary of incidence of surgical interventions to control elevated IOP will also be presented by history of incisional surgery to control elevated IOP (History of Incisional Surgery, No History of Incisional Surgery). All summaries will be performed using the Safety population.

A listing of all subjects requiring surgical interventions to control elevated IOP will be provided. This listing will include details relating to the IOP-lowering surgical intervention (procedure, eye, study eye designation, and date procedure performed), demographic and baseline ocular characteristics including BCVA and IOP, the last available BCVA and IOP values as of the data cut-off, and the date of first recurrence of uveitis, if any.

### 7.2.2 Cataract Surgeries

The number and percentage of subjects requiring cataract surgery will be summarized by treatment group, eye (study, fellow), and time interval. Only eyes which are indicated as phakic at study entry will be included for analysis. Ocular surgeries with a reason of "Cataract" will be included in the summary. Incidence will be summarized overall through 6 months and for 6-month time intervals through 12 (or 36) months. All summaries will be performed using the Safety population and percentages will be based on the total number of phakic eyes in the Safety population.

## 7.3. Study Treatments

Fluocinolone acetonide (FA) is the active ingredient in the FAI insert. The FAI insert is provided

in a sterile preloaded applicator and is administered via injection through the pars plana. The FAI insert is designed to release FA for a period of 36 months.

The Sham applicator is an empty 1 mL syringe attached to a blunt needle; it does not contain a FAI insert.

Data related to the study treatment procedure will be presented in a listing.

### 7.3.1. Extent of Exposure

For subjects in the FAI insert group, overall duration of exposure is defined as the total number of days a subject is exposed to any study drug and will be presented as the total number of days from the injection date (Day 1) to either the FAI insert removal date, for those subjects who have the insert removed while in the study, or the last visit date (date of insert removal or last visit - the date of injection + 1) as recorded on the End of Study/Early Termination page. If the last visit date on the End of Study/Early Termination page is missing, or if a subject is lost to follow-up, the latest available visit date will be used. Duration of exposure at Month 6 is defined similarly to overall exposure, using either the FAI insert removal date, if removal occurred prior to Month 6 visit date, or the Month 6 visit date as the cut off date. If a subject's Month 6 visit date occurs later than the data cut off for the Month 6 analysis (upper limit of Month 6 visit window) then the upper limit of the Month 6 visit date will be used as the end date of exposure. A similar approach will be used to define duration of exposure at Month 12.

The duration of study participation will be summarized for all subjects. The duration of study participation (days) is calculated as date of last visit as recorded on the End of Study/Early Termination page – date of Day 1 visit + 1. If the last visit date on the End of Study/Early Termination page is missing, or if a subject is lost to follow-up, the latest available visit date will be used. Duration of study participation at Month 6 is calculated as the date of Month 6 visit – date of Day 1 visit + 1. If a subject's Month 6 visit date occurs later than the data cut off for the Month 6 analysis (upper limit of Month 6 visit window) then the upper limit of the Month 6 visit date will be used as the end date of participation. A similar approach will be used to define duration of study participation at Month 12.

The duration of exposure to study drug and duration of study participation up to Month 6 (or 12 or 36) will be summarized by treatment for all subjects in the Safety population and will be presented in a table by summary statistics. The durations of exposure and study participation will then be classified into one of the following categories: ≤ 28 days, 29 to 60 days, 61 to 90 days, 91 to 180 days, 181 to 270 days, 271 to 360 days, 361 to 540 days, 541 to 720 days, 721 to 900 days, 901 to 1080 days, and ≥ 1081 days and will be presented as the number and percentage of subjects in each duration category. Percentages will be computed from the number of subjects in the Safety population.

A summary of each subject's exposure and duration of study participation will be presented in a listing.

# 8. Efficacy Analysis

PSV-FAI-005 is intended to support submissions to the US/FDA and submissions to other regulatory authorities in the rest of the world (ROW). The FDA has requested a definition of

recurrence for the primary efficacy analyses that differs from the ROW definition of recurrence in PSV-FAI-005. The recurrence definition to be used for the US/FDA is outlined in Section 8.1 below. The FDA definition of recurrence will also be used for all supporting sensitivity analyses, subgroup analyses, and exploratory analyses on recurrence of uveitis endpoints for the FDA submission.

Efficacy analyses will be performed on both the ITT and PP populations at 6, 12 and 36 months. All primary and exploratory efficacy endpoints will be analyzed using the ITT and PP populations. The ITT analyses will be considered primary; the PP analyses will be considered supportive of the primary analyses on the ITT population.

### 8.1. Primary Efficacy Endpoint

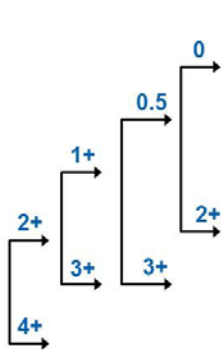
The primary efficacy endpoint is defined as the proportion of subjects who have a recurrence of uveitis in the study eye within 6 months following treatment. As noted in section 4, all recurrence assessments (including unscheduled visits) on or before the upper limit of the 6 month visit window (Day 208) will be considered. Recurrence is captured on the Recurrence of Uveitis eCRF page and, for the US/FDA, is defined as:

- An increase in the vitreous haze of $\geq$ 2 steps (Nussenblatt 1985), compared to baseline or any visit time point prior to Month 6
  OR
- A deterioration in visual acuity of at least 15 letters BCVA associated with recurrence of uveitis, compared to baseline or any visit time point prior to Month 6

Any criterion used to define recurrence must be attributable only to non-infectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis will begin after the study Day 7 visit.

The definition of a $\geq$ 2 step increase in vitreous haze is detailed in the diagram below.

Vitreous Haze: $\geq$ 2 step increase




| Score* | Characteristics* |
|---|---|
| Absent [ 0 ] | Clear view of optic disc, retinal vessels and nerve fiber layer |
| Trace [ 0.5 ] | Slight blurring of optic disc margin and of normal striations and reflex of nerve fiber layer |
| 1+ | Mild blurring of optic disc margin and slight loss of retinal vessel definition |
| 2+ | Moderate blurring of optic disc margin and loss of retinal vessel definition |
| 3+ | Optic nerve head and large vessels visible but borders quite (very) blurry |
| 4+ | Optic nerve head obscured |

* Nussenblatt et al 1985

### 8.1.1. Primary Analysis

The primary efficacy analysis will be performed on the ITT population at 6 months and will compare the proportion of subjects, in the treatment and control groups, who do not have a recurrence of uveitis in the study eye (as defined above) in the 6 months following Day 1.

The primary efficacy analysis will be conducted after all subjects in the study have completed 6 months of treatment or have discontinued study participation.

The number and percentage of subjects with no recurrence of uveitis in the study eye will be presented by treatment group. A continuity-corrected Chi-square test will be used to assess the statistical significance of a difference between treatment groups in the primary efficacy analysis. Mathematically stated:

$H_0$: 6 Month Recurrence Free Rate $_{FAI}$ = 6 Month Recurrence Free Rate $_{Sham}$
$H_1$: 6 Month Recurrence Free Rate $_{FAI} \neq$ 6 Month Recurrence Free Rate $_{Sham}$

The odds ratio for no recurrence (FAI insert/Sham) and 95% confidence interval will also be presented.

Although the primary analysis will be performed on both the FDA and ROW definitions of recurrence, no adjustment of type I error will be performed as the FDA and ROW primary efficacy endpoint analyses will be independently evaluated.

The same inferential analysis employing the same methods as for the primary analysis will be performed for the PP population to assess recurrence at Month 6. Additionally, the same analysis will be performed for both the ITT and PP populations to assess recurrence in the exploratory analyses conducted at Months 12 and Month 36. For Month 12, any recurrence at or before the end of the 12 month visit window (Day 388) will be counted. For Month 36, any recurrence at or before the end of the 36 month visit window (Day 1108) will be counted. No adjustment of type I error will be performed as these analyses are considered supportive to the primary analysis.

### 8.1.2. Data Imputation

Data for the primary outcome only (recurrence of uveitis) will be imputed using a straightforward method:

- A subject who has not previously experienced a recurrence and does not have the required eye examination data for assessing recurrence at Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason will be considered as having a recurrence. If one or more of the required eye examinations, including BCVA and vitreous haze, is not completed at Month 6 (or Month 12 or Month 36), the subject will be considered as having a recurrence. Reasons for missing recurrence data at Month 6 (or 12 or 36) include, but are not limited to: discontinuation from the study prior to visit, visit occurred outside of the visit window, and missed visit.
- A subject who has not previously experienced a recurrence and receives a rescue concomitant medication for uveitis as described in section 9.11of the protocol any time during the study prior to month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.

- A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.
- A subject who has not previously experienced a recurrence and takes a prohibited local concomitant medication in the study eye as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.

Systemic medications administered as part of a gradual dose reduction (tapering) (as described in Section 9.14.1 of the protocol) will not be considered prohibited medications for the analysis of the primary endpoint. For the analysis of the primary endpoint for US/FDA, topical steroids will not be considered a prohibited or rescue medication.

The prohibited and rescue medication data (based on preferred terms and/or ATC codes) will be reviewed and medications will be categorized as either having a potential impact on the efficacy assessments (consistent with the US/FDA definition of the primary endpoint) or no impact on the efficacy assessments. Only prohibited and rescue medications determined to have a potential impact on efficacy assessments will be taken into consideration for data imputation. The list of prohibited and rescue medications which will result in an imputed recurrence of uveitis value, for either eye, will be identified prior to each database lock. Note: although local medications are permitted in the fellow eye, in order to ensure consistency in analysis between the study eye and fellow eye, the same list of medications considered prohibited or rescue in the study eye, including local medications, will be considered "prohibited" or "rescue"for the fellow eye for the purposes of recurrence imputation.

A listing of subjects with missing recurrence information at Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be provided. All available recurrence data for these subjects will be included in the listing.

### 8.1.3. Sensitivity Analyses

In addition to the conservative imputation for the US/FDA primary efficacy endpoint detailed in Section 8.1.2, the following sensitivity analyses of the primary efficacy endpoint will be performed separately at 6, 12 and 36 months for the ITT population only.

- The primary outcome will be imputed exactly as in Section 8.1.2 except that a subject imputed as having a recurrence because of missing data at Month 6 (or Month 12 or Month 36) for any reason will be considered as NOT having a recurrence. Inferential analysis employing the same methods as for the primary analysis will be performed.
- A "tipping point" analysis will be performed. This analysis will begin by using the following imputations associated with missing data at Month 6 (or Month 12 or Month 36) for any reason: FAI insert treated subjects will be considered as having a recurrence, and Sham treated subjects will be considered as NOT having a recurrence. The analysis will proceed one imputed FAI insert treated subject at a time, assuming that this given subject will be considered as NOT having a recurrence. All other imputations stated in Section 8.1.2 will be performed during this "tipping point"

analysis. Inferential analysis employing the same methods as for the primary analysis will be performed at each step of the "tipping point" assessment.

Additionally, for missing data due to any reason, sensitivity analyses will be conducted by using multiple imputation (MI) methods. The list of subjects who will have their Month 6 (or 12 or 36) value imputed using MI methods will be determined prior to each database lock. A fully conditional specification imputation method will be used to impute missing recurrence values. Five imputations will be performed to obtain five complete data sets. The volume of missing data will be assessed prior to unmasking at Month 6 and the number of imputations may be increased, if necessary. The SAS procedure MI will be used to generate the imputed data sets. The following variables will be included in the imputation model: recurrence, age, gender, treatment group, systemic treatment at study entry (stratification factor), duration of disease (years) in the study eye, number of recurrences in study eye within the 12 months prior to screening, and bilateral uveitis history (yes/no). The imputed datasets will be analyzed by a logistic regression model with recurrence as the dependent term and treatment as the independent term. Using the SAS procedure MIANALYZE, results from the logistic regression analysis of the five imputed data sets will be combined to obtain overall estimates [SAS/STAT User Guide, version 9.3]. Additional details are provided in Appendix 13.2. Note: for this sensitivity analysis, subjects who have not previously experienced a recurrence and who take prohibited or rescue medications prior to the time point of interest will have their Month 6 (or 12 or 36) value imputed as a recurrence as described in Section 8.1.2.

The primary efficacy endpoint will be also analyzed with logistic regression with recurrence as the dependent term and treatment as the independent term, and including systemic treatment at study entry (stratification factor) as a covariate.

### 8.1.4. Subgroup Analyses

Subgroup analyses, using descriptive statistics only, will be performed on the US/FDA primary efficacy endpoint for the ITT population at Month 6. Analyses will be performed to determine the treatment effect within specific subgroups of interest, and to determine if the treatment effect is consistent across different subgroup levels. Subgroups will be defined on the basis of study eye baseline characteristics, including:

- Severity of macular edema [CSFT < 300 microns, CSFT ≥ 300 microns]
- Duration of disease [< 2 years, 2 to 5 years, > 5 years]
- Lens status [Phakic, Aphakic, Pseudophakic]
- Intraocular pressure [< 10 mmHg, 10 to 15 mmHg, > 15 to 21 mmHg]
- History of incisional surgery to control elevated IOP [History, No History]
- Presence/absence of vitrectomy
- BCVA [≤ 49 letters, > 49 letters]
- Randomization strata [Not receiving systemic treatment, Receiving systemic treatment – corticosteroid therapy, Receiving systemic treatment – immunosuppressive therapy]
- Age category (<20, 20 - < 40, 40 - < 60, ≥ 60)
- Gender (Male, Female)

Subgroup analyses will also be performed based on study site.

Additionally, subgroups will be defined based on IOP lowering medication or surgery received in the study eye, as follows:

- Use of IOP lowering medication [No IOP lowering medication, Required IOP lowering medication]
- Surgical Intervention to Control Elevated IOP [No surgical intervention, Required surgical intervention]

IOP lowering medication status will be based on a subject's use of any IOP lowering medication in the study eye up to the time point of interest (Month 6, 12 or 36). Surgical intervention status will be defined in a similar manner.

### 8.2. Exploratory Efficacy Endpoints

The proportion of subjects with recurrence in the study eye within 12 and 36 months will be analyzed using the same inferential analysis employing the same methods as for the primary analysis as noted in Section 8.1.1. Sensitivity analysis will also be performed for the proportion of subjects with recurrence in the study eye within 12 and 36 months as noted in section 8.1.3.

The following endpoints will be analyzed for the ITT and PP populations employing descriptive statistics:

- Proportion of subjects in each treatment group who have a recurrence of uveitis in the fellow eye (within 6 months, within 12 months and within 36 months)
- Mean change from baseline in BCVA letter score in the study eye in each treatment group (at 6 months, 12 months and 36 months)
- Number of recurrences of uveitis in each treatment group (within 6 months, within 12 months and within 36 months)
- Time to recurrence of uveitis in study eye in each treatment group (within 6 months, within 12 months and within 36 months)
- Number of adjunctive treatments required to treat recurrences of uveitis in each treatment group (within 6 months, within 12 months and within 36 months)
- Resolution of macular edema, as measured by OCT imaging (at 6 months, 12 months and 36 months)

Exploratory analyses will use the US/FDA definition of recurrence of uveitis. No missing data will be imputed other than as noted in Section 8.1.2. The data imputation method will be applied to recurrence of uveitis in the fellow eye values in the same manner as the study eye, with the criteria revised to consider use of prohibited or rescue local medications in the fellow eye, instead of the study eye.

The number and percentage of subjects with a recurrence of uveitis in the fellow eye within 6 months, within 12 months and within 36 months will be presented by treatment group.

BCVA (letters) absolute value and change from baseline at Month 6 (and 12 and 36) will be described for each treatment group using descriptive statistics.

For each subject and eye (study, fellow), the number of recurrences through Month 6, 12 and 36 will be calculated. Recurrences imputed at Month 6, 12 or 36 due to missing data as per Section 8.1.2 will be considered a recurrence for this calculation. The number of recurrences per subject and eye (study, fellow) will be described using descriptive statistics as well as the number and percentage of subjects by category (0, 1, 2, 3, 4, 5, >5). Additionally, the total number of recurrences summed across all subjects, all study eyes and all fellow eyes will be presented by treatment group.

The time to first recurrence of uveitis within 6 months is calculated as the number of days between the date of injection (Day 1) and the visit date of the first reported recurrence of uveitis in the study eye. Subjects who do not experience a recurrence of uveitis within 6 months will be censored at the date of their Month 6 visit. The time to first recurrence of uveitis within 12 (or 36) months will be calculated in a similar manner, censoring at the date of a subject's Month 12 (or 36) visit if the subject does not experience a recurrence of uveitis within 12 (or 36) months. Recurrences imputed at Month 6 (or Month 12 or Month 36) due to missing data as per Section 8.1.2 will be considered a recurrence in the time to recurrence analysis. Median time to recurrence and the 95% confidence interval for the median will be summarized by treatment group and randomization strata. The Kaplan-Meier estimated probabilities of recurrence will also be presented for monthly intervals through 36 months. Since time to recurrence is calculated in days, the monthly intervals will be defined based on 30 days = 1 month. Kaplan-Meier plots for time to first recurrence of uveitis will also be presented.

The number of adjunctive treatments, including systemic steroids or immunosuppressants, intra/peri-ocular steroids, and topical steroids, will be determined using medications/therapies recorded on the Concomitant Medications page with start/end dates within the given time period (6, 12 or 36 months). The number and percentage of subjects by number of adjunctive treatments will be presented by treatment group and category of adjunctive treatment. The intra/peri-ocular steroids and topical steroids will also be presented by eye (study, fellow). Multiple doses of the same medication which are part of one treatment regimen will be counted as one adjunctive treatment for the purposes of analysis.

Resolution of macular edema will be summarized using a shift table comparing the presence (Yes, No, Not Evaluable) of macular edema at Month 6 (and 12 and 36) to the baseline response by eye (study, fellow) and treatment group.

# 9. Safety Analysis

Safety analyses will be performed on the Safety population at 6, 12 and 36 months. Subjects who are randomized but do not receive treatment will not be included in safety tabulations but will have all safety data listed only. Percentages for safety summaries based on the number of subjects with a given event or attribute will be based on the number of subjects who were treated (including Sham treatment).

## 9.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the date of injection (Day 1);

- begins before the date of injection (Day 1) and worsens in severity on or after the date of injection (Day 1);
- is completely missing a start date and end date;
- is completely missing a start date and the end date is on or after the date of injection (Day 1).

For the purpose of inclusion in TEAE tables, incomplete AE start and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of injection, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of injection, and the end date (after any imputation) is on or after the date of injection, then assume the date of injection (Day 1). If the month and year are the same as the date of injection, and the end date (after any imputation) is prior to the date of injection, then assume the end date for the start date.
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of the date of injection, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of injection year, and the end date (after any imputation) is on or after the date of injection, then assume the date of injection (Day 1). If the year is the same as the date of injection, and the end date (after any imputation) is prior to the date of injection, then assume the end date for the start date.

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

All adverse events will be classified by System Organ Class and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0 or higher).

An overview summary of the number and percentage of subjects with any TEAE, serious TEAE, treatment-related TEAE, treatment-related serious TEAE, TEAE leading to FAI insert removal, TEAE leading to study discontinuation, and AE leading to death will be provided by treatment group.

All AE summaries will be provided for ocular events and non-ocular events, separately. Ocular event tables will be presented by eye (study, fellow).

All AEs will be presented in a listing.

### 9.1.1. Incidence of Adverse Events

Summaries of the total number of TEAEs and the number and percentage of subjects with at least one TEAE will be provided by treatment group and overall. TEAEs will be presented by System Organ Class and PT. At each level of subject summarization, a subject is counted once if

the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety population.

The summary of TEAEs will be presented in descending order from the System Organ Class with the highest total incidence (that is, summed across all treatment groups) to the System Organ Class with the lowest total incidence. If the total incidence for any two or more System Organ Classes is equal, the System Organ Classes will be presented in alphabetical order. Within each System Organ Class, the PTs will be presented in alphabetical order.

A separate summary of protocol defined ocular AEs, overall and by criteria, will be provided. This summary will include the following ocular events, as reported on the AE eCRF page:

- decrease in visual acuity of at least ≥ 15 letters or ≥ 3 lines from the previous measurement of visual acuity
- moderate or severe (grade 3 or 4) ocular findings compared to the last ophthalmic examination
- worsening of ≥ 2 steps in anterior chamber cell count or vitreous haze, compared to the last ophthalmic examination
- increase in IOP of ≥ 10 mmHg at two visits at least 1 week apart or an increase in IOP to ≥ 25 mmHg

### 9.1.2. Relationship of Adverse Events to Study Treatment

A summary of TEAEs by relationship to study treatment will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are “Unrelated”, “Possibly Related”, and “Probably Related”. In the TEAE relationship table, if a subject reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. TEAEs that are missing a relationship will be presented in the summary table as “Probably Related” but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of subjects in the Safety population.

The TEAE data will be categorized and presented by System Organ Class, PT, and relationship in a manner similar to that described in Section 9.1.1.

### 9.1.3. Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are “Mild,” “Moderate,” and “Severe.” In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. TEAEs that are missing severity will be presented in tables as “Severe” but will be presented in the data listing with a missing severity. Percentages will be calculated out of the number of subjects in the Safety population.

A summary of TEAEs related to study treatment by severity will be presented in a table. Events with a relationship if “Possibly Related” and “Probably Related” will be considered related to study treatment and included in this summary.

The TEAE data will be categorized and presented by System Organ Class, PT, and severity in a manner similar to that described in Section 9.1.1.

### 9.1.4. Serious Adverse Events

Serious treatment-emergent adverse events (SAEs) will be presented in a table. Treatment-emergent SAEs by severity will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety population.

The treatment-emergent SAE data will be categorized and presented by System Organ Class and PT in a manner similar to that described in Section 9.1.1 and by severity as described in Section 9.1.3.

A separate summary of protocol defined SAEs, overall and by criteria, will be provided. This summary will include the following sight-threatening ocular events, as reported on the AE/SAE eCRF page:

- An AE which causes a decrease in visual acuity of ≥ 30 letters or ≥ 6 lines from the most recent previous measurement of visual acuity, lasting more than 1 hour
- An AE which causes a decrease in visual acuity to light perception or worse, lasting more than 1 hour
- An AE which requires surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infective, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- An AE which is associated with severe intraocular inflammation (i.e., 4.0 anterior chamber cell score, 4+ flare or 4+ vitritis)
- Two consecutive IOP measurements of 30 mmHg or higher taken at least 72 hours apart when a subject is already being treated with two glaucoma medications
- An IOP < 6 mmHg requiring medical intervention
- An AE which in the opinion of the investigator requires medical or surgical intervention to prevent permanent loss of sight

### 9.1.5. Adverse Events Leading to FAI Insert Removal

A summary of TEAEs with an action taken with study treatment of "FAI Insert Removal" will be presented in a table. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of FAI insert subjects in the Safety population.

The summary of TEAEs with an action taken with study treatment of "FAI Insert Removal" will be presented in descending order of frequency from the System Organ Class with the highest total incidence (that is, summed across all treatment groups) to the System Organ Class with the lowest total incidence. Within each System Organ Class, the PTs will be presented in alphabetical order.

### 9.1.6. Adverse Events Leading to Study Discontinuation

All subjects who have an AE where the answer to "Was Subject Terminated from study due to this AE?" is "Yes" will be presented in a listing.

#### 9.1.7. Death

All subjects who have an AE with an outcome of "Fatal" will be presented in a listing.

#### 9.1.8. Adverse Events of Special Interest

A summary of TEAEs of cataract and elevated IOP will be presented in a table by treatment group and overall. Events will be included in the summary based on a list of preferred terms for each event category. Cataract events will include any event whose MedDRA coded high-level term (HLT) is "CATARACT CONDITIONS". IOP elevations will be based on the specific preferred term "INTRAOCULAR PRESSURE INCREASED" or if the preferred term contains the phrase "GLAUCOMA". At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the Safety population. Within each event category, the PTs will be presented in alphabetical order.

A summary of ocular TEAEs which are considered complications of IOP lowering medications to control IOP will be presented by treatment group and overall. Events will be included in the summary based on manual review of AEs with an onset date on or after the date of first use of any IOP lowering medication. The list of PTs will be generated based on the most common adverse events associated with the IOP lowering medications used.

A summary of ocular TEAEs which are considered complications of surgical interventions to control IOP will be presented by treatment group and overall. Events will be included in the summary based on manual review of AEs with an onset date on or after the first date of surgical intervention. The list of PTs will be generated based on the most common adverse events associated with surgical interventions.

A summary of ocular TEAEs which are considered complications of cataract surgeries will be presented by treatment group and overall. Events will be included in the summary based on manual review of AEs with an onset date on or after the first date of cataract surgery. The list of PTs will be generated based on the most common adverse events associated with cataract surgeries.

A manual data review memo will be written at the time the manual data reviews are performed. Because investigators may report similar events differently, the memo will be written at the time of the manual review to document the specific details on the preferred terms and other text specifications that are used to identify IOP lowering medications, IOP surgeries, and Cataract surgeries.

### 9.2. Ophthalmic Examination

All ophthalmic examinations are performed on both eyes.

#### 9.2.1. Best-corrected Visual Acuity (BCVA)

Best-Corrected Visual Acuity will be measured according to the standard procedure developed for Early Treatment Diabetic Retinopathy Study (ETDRS) at 4 meters or 3 meters if the electronic (E)-ETDRS system is employed. For patients who are illiterate or not familiar with the English alphabet, BCVA will be determined using the Tumbling E ETDRS charts. Corrected-

distance VA is reported as the number of letters read correctly by the subject. The Snellen Fraction will also be recorded. If the subject is unable to read any letters at 4 meters or 1 meter, the investigator will assess the subject's ability to count fingers, recognize hand motion, or light perception.

A summary table presenting the observed values and changes from baseline in BCVA (letters) will be presented by eye (study, fellow), treatment group and overall for subjects in the Safety population. Changes from baseline to each scheduled post-baseline visit will be presented. In addition, a categorical summary of change from baseline in BCVA will present the letter change at Month 6 (or Month 12 or Month 36) and the maximum letter change at any time point up to Month 6 (or Month 12 or Month 36), including categories of ≥ 15 letters lost, ≥ 10 letters lost, ≥ 5 letters lost, no change, ≥ 5 letters gained, ≥10 letters gained, and ≥ 15 letters gained.

The BCVA summaries will also be presented by eye for the following subgroups:

- IOP lowering medication [No IOP lowering medication, Required IOP lowering medication]
- Surgical Intervention to Control Elevated IOP [No surgical intervention, Required surgical intervention]
- Lens status at Baseline [Phakic, Aphakic, Pseudophakic]

IOP lowering medication status will be based on a subject's use of any IOP lowering medication up to the time point of interest (Month 6, 12 or 36). Surgical intervention status will be defined in a similar manner. Subgroups will be defined per eye and a subject's study eye may belong to a different subgroup than the fellow eye.

For subjects with phakic lens status at study entry who undergo cataract surgery while in the study, the change in BCVA (letters) from the last BCVA measurement prior to surgery to the first BCVA measurement after surgery will be summarized by treatment and eye. In addition, a summary of change from baseline in BCVA (letters) at Month 6 (or 12 or 36) will be presented by treatment for subjects with phakic eyes at study entry who undergo cataract surgery prior to Month 6 (or 12 or 36) vs. subjects with a lens status of pseudophakic at study entry.

BCVA data will be presented in a listing.

### 9.2.2. Intraocular Pressure (IOP)

Applanation tonometry (preferably Goldmann) will be used for IOP measurements, where the value recorded on the eCRF is an average of 3 measurements. On Day 1, this assessment will be performed pre- and post-administration of study treatment.

A summary table presenting the observed values and changes from baseline in IOP (mmHg) will be presented by eye (study, fellow), treatment group and overall for subjects in the Safety population who received treatment. Changes from baseline to each scheduled post-baseline visit, as well as the Day 1 post-administration of study treatment, will be presented.

The number and percentage of patients with an IOP measurement > 21 mmHg at any post-administration assessment will be presented for each treatment group and overall by eye (study,

fellow). Incidence will be summarized overall (through 6, 12 or 36 months) and for 3-month time intervals through Month 6. For Month 12 analysis, the incidence will be summarized for 3-month intervals through Month 12. For Month 36 analysis, the incidence will also be summarized for 6-month time intervals from Month 12 through Month 36.

Additionally, the number and percentage of patients with an IOP measurement meeting any of the IOP elevation criteria at any post-administration assessment and by visit will be presented for each treatment group and overall by eye (study, fellow). The IOP elevation criteria include:

- Increase in IOP from baseline of > 5 mmHg
- Increase in IOP from baseline of ≥ 12 mmHg
- IOP measurement > 25 mmHg
- IOP measurement > 30 mmHg

IOP data will be presented in a listing.

### 9.2.3. Dilated Indirect Ophthalmoscopy

The investigator will assess the status (Normal, Abnormal – Clinically Significant, Abnormal – Not Clinically Significant) of the vitreous, macula, retina, optic nerve, choroid, and retinal periphery. On Day 1, this assessment will be performed pre- and post-administration of study treatment. Post-administration of study treatment, the investigator will assess the adequacy of the central retinal artery perfusion and indicate the presence of any complications. Data from the indirect ophthalmoscopy examination will be presented in a listing.

### 9.2.4. Slit Lamp Examination

The investigator will assess any changes in lens or cataract status and the status (Normal, Abnormal – Clinically Significant, Abnormal – Not Clinically Significant) of the conjunctiva, cornea, iris, anterior chamber, and posterior chamber.

A summary table presenting the number and percentage of subjects with a change in lens/cataract status since screening or a worsening of an existing cataract since the previous visit will be presented by eye (study, fellow), baseline lens status, treatment group and overall for subjects in the Safety population with a phakic or pseudophakic lens status at study entry for the given eye.

Data from the slit lamp examination will be presented in a listing.

### 9.2.5. Vitreous Haze and Anterior Chamber Cells

Indirect ophthalmoscopy will be performed for each eye with pupil dilation. The following scale (Nussenblatt 1985) will be used to define the extent of vitreous haze:

| | |
|---|---|
| Absent | Clear view of optic disc, retinal vessels and nerve fiber layer |
| Trace | Slight blurring of optic disc margin and of normal striations and reflex of nerve fiber layer |
| 1+ | Mild blurring of optic disc margin and slight loss of retinal vessel definition |
| 2+ | Moderate blurring of optic disc margin and loss of retinal vessel definition |

| | |
|---|---|
| 3+ | Optic nerve head and large vessels visible but borders quite (very) blurry |
| 4+ | Optic nerve head obscured |

Anterior chamber cells will be measured using a Haag/Streit or similar slit lamp at high magnification (1.6 X) 1-mm beam. Assessment will be made using the following scale (Jabs 2005).

Field size: 1 mm by 1 mm slit beam

| | |
|---|---|
| 0 | <1 cells/hpf |
| 0.5+ | 1-5 cells/hpf |
| 1+ | 6-15 cells/hpf |
| 2+ | 16-25 cells/hpf |
| 3+ | 26-50 cells/hpf |
| 4+ | >50 cells/hpf |

Frequency distributions of the vitreous haze and anterior chamber cells grading at each scheduled visit will be summarized in a table by eye (study, fellow), treatment group, and overall for subjects in the Safety population.

All vitreous haze and anterior chamber cell data will be presented in a listing.

### 9.3. Humphrey 24-2 Visual Field Test

A summary table presenting the observed values and changes from baseline will be presented for mean deviation (dB) by eye (study, fellow), treatment group and overall for subjects in the Safety population who received treatment. Changes from baseline to each scheduled post-baseline visit will be presented. Visual field test data will be presented in a listing.

### 9.4. Optical Coherence Tomography (OCT)

The OCT assessments will evaluate the central foveal thickness (CFT), CSFT, total volume of the central subfield, and the presence of macular edema, cysts, intra-retinal fluid, sub-retinal fluid, and fibrosis for both eyes.

A summary table presenting the observed values and changes from baseline will be presented for CFT (microns), CSFT (microns), and total volume of the central subfield ($mm^3$) by eye (study, fellow), treatment group and overall for subjects in the Safety population. Changes from baseline to each scheduled post-baseline visit will be presented.

The categorical data from the OCT assessment will be summarized in a shift table comparing the presence (Yes, No, Not Evaluable) of each symptom noted above at each post-baseline visit to the baseline response by eye (study, fellow), treatment group, and overall for subjects in the Safety population. Shifts from baseline to each scheduled post-baseline visit will be presented.

All OCT data will be presented in a listing.

### 9.5. Subjective Ocular Tolerability and Discomfort Assessment

Subjects will assess ocular tolerability using a subjective scale (Scoville 1985). A visual analogue scale is performed by asking subjects to indicate on an unmarked 100 mm line the intensity of their irritation. A mark of '0' represents no sensation while '100' indicates the worst imaginable irritation. The location of the mark on the line then is measured with an mm ruler to provide a numeric score. A summary table presenting the observed values and changes from baseline in irritation intensity (mm) will be presented by eye (study, fellow), treatment group and overall for subjects in the Safety population. Changes from baseline to each scheduled post-baseline visit will be presented. As part of the ocular tolerability assessment, subjects will be asked to indicate which eye feels more uncomfortable. The responses (no difference, study eye, fellow eye) will be summarized by visit, treatment group and overall for subjects in the Safety population.

Subjects will also assess discomfort using the following subjective scale (Maca 2010). This parameter will consist of a single overall assessment of the subject's discomfort considering superficial pain, foreign body, or gritty sensation, itching, burning, and other forms of non-specific discomfort.

Grade 0: Absent
Grade 0.5: Very mild
Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Intolerable

The categorical data from the discomfort assessment will be summarized in a shift table comparing the grade at each post-baseline visit to the baseline grade of discomfort by eye (study, fellow) and treatment group for subjects in the Safety population who received treatment. Shifts from baseline to each scheduled post-baseline visit will be presented.

All subjective ocular tolerability and discomfort data will be presented in a listing.

### 9.6. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a local laboratory at the Screening visit only. Laboratory results will not be included in the clinical database. Any clinically significant laboratory values at Screening will be entered into the subject's medical history.

The laboratory testing eCRF data, including confirmation that the lab tests were performed, an explanation if they were not performed, and whether there were any clinically significant values, will be presented in a listing.

Female subjects of child-bearing potential will have urine pregnancy tests conducted throughout the study. Any subjects with positive pregnancy test results at any time during the study will be presented in a listing. The listing will also include the subject's fertility status collected at the Screening visit.

### 9.7. Vital Sign Measurements

Summary tables will be presented for vital sign data, including sitting systolic blood pressure (mmHg), sitting diastolic blood pressure (mmHg) and pulse (bpm), by treatment group and overall for subjects in the Safety population. Observed results at each visit and changes from baseline to each scheduled post-baseline visit will be presented. All vital sign data by subject will be presented in a listing.

### 9.8. Physical Examination

Any abnormalities noted during the physical examination will be presented in a listing for all subjects.

# 10. Interim Analysis

No interim analysis is planned for this study. The primary analysis and all other efficacy and safety analyses will be conducted at the Month 6 database lock; i.e., after all subjects have completed the Month 6 visit or have been discontinued from the study prior to this visit. Analysis of the study data through Month 12 and the complete study data (through Month 36) will be performed after all subjects have either completed the Month 12 or Month 36 visit, or have been discontinued from the study prior to the respective visit, Month 12 or Month 36.

# 11. Changes in the Planned Analysis

Laboratory assessments will not be presented by descriptive statistics as stated in the protocol.

The primary efficacy analysis will be performed using the US/FDA definition of recurrence and not the definition in the protocol. For data imputation of the US/FDA primary endpoint, topical steroids will not be considered a prohibited or rescue medication that would result in imputation of recurrence of uveitis.

# 12. References

Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (**SUN**) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop, Am J Ophthalmol 2005; 140: 509-16.

Maca SM, Amon M, Findl O, Kahraman G, Barisani-Asenbauer T. Efficacy and tolerability of preservative-free and preserved diclofenac and preserved ketorolac eye drops after cataract surgery. Am J Ophthalmol. 2010; 149: 777-784.

Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology 1985; 92: 467–71.

Retisert Prescribing Information (June 2011).

SAS/STAT User's Guide, version 9.2., SAS Institute, Inc., Cary, North Carolina.

Scoville B, Krieglstein GK, Then E, Yokoyama S, Yokoyama T. Measuring drug-induced eye irritation: a simple new clinical assay. J Clin Pharmacol 1985; 25: 210–218.

# 13. Appendices

## 13.1. Schedule of Study Procedures and Assessments

| Assessments | Screening | Day 1 | Day 7 | Day 28 | Months 2, 3 | Months 6, 9, 12, 18, 24, 30, 36 |
|---|---|---|---|---|---|---|
| Timing/Interval | -30 to 0 | 1 | ±2D | ±3D | ±7D | ±28D |
| Medical/Ophthalmic History | X | | | | | |
| Demographics | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Randomization | | X | | | | |
| Pregnancy Test[a] | X | X | | | | X |
| Vital Signs[b] | X | X | X | X | X | X |
| Clinical Labs[c] | X | | | | | |
| Ophthalmic Examination[d] | X | X | X | X | X | X |
| Visual Field[e] | X | | | | | X |

[a] Females of child-bearing potential only: urine test conducted only at Screening, Day 1, Month 12, Month 24 and Month 36.
[b] Includes systolic/diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes. Height and weight at Screening only.
[c] Hematology; erythrocyte sedimentation rate; serum chemistry; urinalysis; human immunodeficiency virus and syphilis serology testing; tuberculosis testing.
[d] Ophthalmic examination includes BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy, and anterior, posterior, and intermediate slit lamp examinations.
[e] Conducted only at Months 12, 24 and 36.

| **Assessments** | **Screening** | **Day 1** | **Day 7** | **Day 28** | **Months 2, 3** | **Months 6, 9, 12, 18, 24, 30, 36** |
|---|---|---|---|---|---|---|
| OCT | | X | | X | X | X |
| Physical Exam | X | | | | | |
| Subjective Ocular Tolerability & Discomfort Assessment | X | X | X | X | X | X |
| FAI Insert Placement or Sham Injection | | X | | | | |
| Concomitant Meds | X | X | X | X | X | X |
| AEs | | X | X | X | X | X |

### 13.2 SAS Code for Multiple Imputation Method

A fully conditional specification imputation method will be used to impute missing recurrence values at Month 6 (or 12 or 36). The following SAS code will be used to generate the imputed data sets:

```
PROC MI DATA = <derived dataset> SEED = xxxxxx NIMPUTE = 5;
        CLASS NoRecurrence Gender TrtGroup StratFactor BilateralUveitis;
        FCS DISCRIM (NoRecurrence Gender BilateralUveitis TrtGroup)
            LOGISTIC (StratFactor/ ORDER=INTERNAL)
            REG (Age DurDisease NumRecur);
        VAR Age Gender DurDisease StratFactor NumRecur BilateralUveitis TrtGroup
             NoRecurrence;
RUN;
```

where

*NoRecurrence* indicates whether the subject completed through Month 6 (or 12 or 36) without a recurrence of uveitis in the study eye (1 = Yes, 0 = No),

*Age* is the subject's age in years,

*BilateralUveitis* indicates whether the subject has a history of bilateral uveitis (1 = Yes, 0 = No).

*DurDisease* is the duration of disease (years) in the study eye,

*Gender* (1 = Male, 2 = Female),

*NumRecur* is the number of recurrences in the study eye within the 12 months prior to Screening,

*StratFactor* indicates the use of systemic treatment at study entry (1 = Not receiving systemic treatment, 2 = Receiving systemic treatment – corticosteroid therapy, 3 = Receiving systemic treatment – immunosuppressive therapy),

*TrtGroup* is the treatment variable.

The following model will be fit in the SAS procedure LOGISTIC to analysis the imputed datasets:

```
Ods Output ParameterEstimates = parms CovB = covb;
PROC LOGISTIC DATA = < MI dataset >
        BY _IMPUTATION_;
        CLASS NoRecurrence TrtGroup (REF=last) \ PARAM=ref;
        MODEL NoRecurrence (event = '1') = TrtGroup/ covb;
RUN;
```

Then the SAS procedure MIANALYZE will be used to obtain the overall estimates, using the ParameterEstimates and CovB ods output datasets from the LOGISTIC procedure. The following code will be used:

```
Ods Output ParameterEstimates = MIparms;
PROC MIANALYZE PARMS(classvar=classval)= parms
                        COVB (effectvar=stacking)= covb;
        CLASS TrtGroup;
        MODELEFFECTS intercept TrtGroup;
RUN;
```

The odds ratio and 95% confidence interval will be calculated by taking the exponentiation of the ESTIMATE, LCLMean and UCLMean variables where PARM = 'TrtGroup' in the MIparms dataset. Variable Probt from the same observation will be used for the p-value.

### 13.3 Note for FDA Reviewers

The statistical analysis plan (SAP) for PSV-FAI-005 has been written in accordance with guidance provided by FDA to pSivida regarding: 1) the definition of the primary endpoint; 2) the use of different SAPs for different regions in the world.

Specifically, FDA provided the following guidance to pSivida:

1. **Definition of primary endpoint**:

| | |
|---|---|
| ***FDA Response to Question 1b:***<br>*No; the Agency considers anterior and posterior uveitis to be separate indications. While the inclusion criteria for study eye enrollment may include eyes with a "history of noninfectious uveitis affecting the posterior segment of the eye with or without anterior uveitis ≥ 1 year duration;" the efficacy endpoint of "a ≥ 2 step increase in the number of cells in anterior chamber" at 12 months would not be acceptable.* | |
| Source: | This excerpt is derived from FDA correspondence [titled *MEMORANDUM OF MEETING MINUTES*] dated April 10, 2015, providing FDA's minutes of a Type C meeting convened on March 10, 2015 between FDA and pSivida. |

In response to FDA's guidance, pSivida committed to using a revised definition of the primary efficacy endpoint that will NOT include "a ≥2 step increase the number of cells in the anterior chamber".

2. **Statistical analysis plans for different regions in the world**:

| | |
|---|---|
| *The Agency stated that the protocol can have different statistical analysis plans for the different regions of the world.* | |
| Source: | This excerpt is derived from FDA correspondence [titled *MEMORANDUM OF MEETING MINUTES*] dated June 5, 2015, providing FDA's minutes of a Type C meeting convened on May 7, 2015 between FDA and pSivida |

In response to FDA's guidance, pSivida has prepared US-specific statistical analysis plan using the revised definition of the primary efficacy endpoint that aligns with FDA's guidance from the March 10, 2015 type C meeting.

Note: pSivida has not revised the primary efficacy endpoint in protocol PSV-FAI-005, because regulatory authorities in other regions in which the study is being conducted have not requested the same change as has been recommended by FDA.

Consequently, pSivida has prepared two SAPs associated with PSV-FAI-005: one for the US and one for rest of world (ROW). If requested by FDA, pSivida will submit the ROW SAP for FDA's review.

The major differences between the two SAPs are presented in the following table:

| Parameter | SAP v2.0 | |
|---|---|---|
| | ROW | US/FDA |
| Primary efficacy endpoint | The primary efficacy endpoint is defined as the proportion of subjects who have a recurrence of uveitis in the study eye within 6 months following treatment. Recurrence is captured on the Recurrence of Uveitis eCRF page and is defined as:<br>• A ≥ 2 step increase in the number of cells in the anterior chamber per high powered field (1.6 X using a 1-mm beam) (Hogan 1959), compared to baseline or any visit time point prior to Month 6<br>OR<br>• An increase in the vitreous haze of ≥ 2 steps (Nussenblatt 1985), compared to baseline or any visit time point prior to Month 6<br>OR<br>• A deterioration in visual acuity of at least 15 letters BCVA associated with recurrence of uveitis, compared to baseline or any visit time point prior to Month 6<br>Any criterion used to define recurrence must be attributable only to non-infectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis will begin after the study Day 7 visit. | The primary efficacy endpoint is defined as the proportion of subjects who have a recurrence of uveitis in the study eye within 6 months following treatment. Recurrence is captured on the Recurrence of Uveitis eCRF page and is defined as:<br>• ~~A ≥ 2 step increase in the number of cells in the anterior chamber per high powered field (1.6 X using a 1-mm beam) (Hogan 1959), compared to baseline or any visit time point prior to Month 6~~<br>• An increase in the vitreous haze of ≥ 2 steps (Nussenblatt 1985), compared to baseline or any visit time point prior to Month 6<br>OR<br>• A deterioration in visual acuity of at least 15 letters BCVA associated with recurrence of uveitis, compared to baseline or any visit time point prior to Month 6<br>Any criterion used to define recurrence must be attributable only to non-infectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis will begin after the study Day 7 visit. |

| Parameter | SAP v2.0 | |
|---|---|---|
| | ROW | US/FDA |
| Imputed recurrence | Data for the primary outcome only (recurrence of uveitis) will be imputed using a straightforward method:<br>• A subject who has not previously experienced a recurrence and does not have the required eye examination data for assessing recurrence at Month 6 ( or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason will be considered as having a recurrence. If one or more of the required eye examinations, including BCVA, vitreous haze, and anterior chamber cells, is not completed at Month 6 (or Month 12 or Month 36), the subject will be considered as having a recurrence. Reasons for missing recurrence data at Month 6 (or 12 or 36) include, but are not limited to: discontinuation from the study prior to visit, visit occurred outside of the visit window, and missed visit.<br>• A subject who has not previously experienced a recurrence and receives a rescue concomitant medication for uveitis as described in section 9.11 of the protocol any time during the study prior to month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br>• A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br>• A subject who has not previously experienced a recurrence and takes a prohibited local concomitant medication in the study eye as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br><br>Systemic medications and topical steroids administered as part of a gradual dose reduction (tapering) (as described in Section 9.14.1 of the protocol) will not be considered prohibited medications. Additionally, topical steroids administered as part of short term standard treatment following an ocular surgical procedure (as described in Section 9.14.2 of the protocol) will not be considered prohibited medications. | Data for the primary outcome only (recurrence of uveitis) will be imputed using a straightforward method:<br>• A subject who has not previously experienced a recurrence and does not have the required eye examination data for assessing recurrence at Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason will be considered as having a recurrence. If one or more of the required eye examinations, including BCVA and vitreous haz~~end anterior chamber cells~~, is not completed at Month 6 (or Month 12 or Month 36), the subject will be considered as having a recurrence. Reasons for missing recurrence data at Month 6 (or 12 or 36) include, but are not limited to: discontinuation from the study prior to visit, visit occurred outside of the visit window, and missed visit.<br>• A subject who has not previously experienced a recurrence and receives a rescue concomitant medication for uveitis as described in section 9.11 of the protocol any time during the study prior to month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br>• A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br>• A subject who has not previously experienced a recurrence and takes a prohibited local concomitant medication in the study eye as defined in Section 9.14.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.<br><br>Systemic medications ~~and topical steroids~~ administered as part of a gradual dose reduction (tapering) (as described in Section 9.14.1 of the protocol) will not be considered prohibited medications for the analysis of the primary endpoint. For the analysis of the primary endpoint, a topical steroid will not be considered a prohibited or rescue medication. ~~Additionally, topical steroids administered as part of short term standard treatment following an ocular surgical procedure (as described in Section 9.14.2 of the protocol) will not be considered prohibited medications.~~ |