EYEPOINT
PHARMACEUTICALS

Cover Page Statistical Analysis Plan (SAP)

SAP Title:	Statistical Analysis Plan – A Controlled, Multi-center Study of the Utilization and Safety of the MK II Inserter and the Safety of the FAI Insert in Subjects with Non-infectious Uveitis Affecting the Posterior Segment of the Eye
NCT Number:	NCT02748512
Document Date:	12 APRIL 2016

pSivida Corp.

PSV-FAI-006

A Controlled, Multi-center Study of the Utilization and Safety of the MK II Inserter and the Safety of the FAI Insert in Subjects with Non-infectious Uveitis Affecting the Posterior Segment of the Eye

12 APRIL 2016

Statistical Analysis Plan

Version 1.0

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List of Abbreviations

AE	Adverse Event
BCVA	Best Corrected Visual Acuity
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
GCP	Good Clinical Practices
hpf	High power field
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operational Procedure
TEAE	Treatment-Emergent Adverse Event
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, at a nominal rate of approximately 0.2 µg FA/day. In this study, this specific drug product candidate is abbreviated as "FAI insert" (for Fluocinolone Acetonide Intravitreal insert).

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 intra-ocular 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.

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 contains the same drug product as Iluvien™, an intravitreal fluocinolone acetonide product candidate that is commercially available in the United States and Europe for the treatment of diabetic macular edema (DME) [Iluvien prescribing information (December 2014)].

Additionally, Retisert®, a larger 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. has developed the FAI insert to provide local steroid therapy with an improved benefit/risk profile. The FAI insert is currently being evaluated in PSV-FAI-001, a phase III clinical study in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

Based on information reported in the Iluvien phase 3 trials and in PSV-FAI-001, pSivida Corp. has modified the inserter used in intravitreal administration of the FAI insert. This modified inserter (the Mk II inserter) is expected to be easier to use than the Mk I inserter used in

PSVFAI-001. PSV-FAI-006 is designed to assess the utilization and safety of the Mk II inserter, compared to the Mk I inserter, and also assesses the safety of the FAI insert.

2. Objectives

To evaluate the utilization and safety of the Mk II inserter and to evaluate the safety of the FAI insert in eyes with non-infectious uveitis affecting the posterior segment of the eye.

2.1. Primary Objective

To assess the utilization and the safety of the Mk II inserter, and the safety of the FAI insert, from the day of treatment through 7 days following treatment.

2.2. Secondary Objective

To assess the safety of the FAI insert during 12 months following treatment.

3. Investigational Plan

3.1. Overall Study Design and Plan

This trial is a 12 month, phase 3, multi-center, randomized, single-masked (subject), controlled study designed to evaluate the utilization and safety of the Mk II inserter and the safety of the FAI insert, in subjects with non-infectious uveitis affecting the posterior segment of the eye. This study will be conducted in at least 3 study sites. Enrollment of approximately 25 subjects is expected. A total enrollment of approximately 30 eyes is planned for this study (20 Mk II inserter: 10 Mk I inserter) in one or both eyes in each subject.

All subjects will receive the FAI insert on Day 1 of the study, administered using either an Mk I inserter or an Mk II inserter. If both eyes in a subject with bilateral uveitis satisfy the study's inclusion/exclusion criteria, both eyes may be enrolled in the study. In this case, randomization of a subject's second eye will occur independently and will occur no earlier than the study Day 7 visit for the subject's first study eye.

At least 10 different investigators will administer the FAI insert. Each time a subject's eye is enrolled in the study, one investigator will serve as the treating investigator (Investigator); another staff member in the study site will serve as the trained observer (Observer). On study Day 1, the Investigator will administer the FAI insert, and the Observer will observe the procedure used by the Investigator to administer the FAI insert. The Investigator and the Observer will complete questionnaires related to the administration of the FAI insert on Day 1. The Investigator (or designee) will perform all subsequent study assessments. Study personnel will not disclose to the subject which inserter was used for intravitreal administration of the FAI insert.

Subjects will receive standard care in the study eye(s) and any non-study eye for 12 months following enrollment, in accord with medical need and the Investigator's standard practice. Eyes will be assessed according to the schedule of procedures and assessments (Appendix 13.1).

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

1. After all subjects have completed the Day 7 visit (or have been discontinued from the study prior to this visit). The primary utilization and safety analyses of the inserters will be conducted at Day 7 time point.
2. After all subjects have completed the Month 12 visit (or have been discontinued from the study prior to this visit). The safety analyses of the FAI insert will be conducted at Month 12 time point.

3.2. Study Endpoints

The primary utilization and safety analyses of the inserters will be conducted at Day 7; safety analyses of the FAI insert will be conducted at Day 7 and Month 12. Analyses will be based on individual eyes.

Evaluation of Mk II inserter and Mk I inserter

Utilization evaluation (based on individual eye):
The primary utilization endpoint is defined as the proportion of intravitreal insertion procedures that are assessed by the Investigator as satisfactory. A satisfactory procedure is defined as one receiving a score from the Investigator as either Very Easy (VE), Easy (E), or Routine (R), according to the following categories:

- Very Easy (VE)
- Easy (E)
- Routine (R)
- Difficult (D)
- Very Difficult (VD)

Secondary utilization endpoints include:

- Clarity of the Instructions for Use, as assessed by the Investigator
- Differences between observed procedure and instructions for use, as assessed by an Observer

Safety evaluation (based on individual eye):
Safety will be evaluated over one period: Day 1- Day 7, and will include:

- Ocular adverse events, including: procedure-related adverse events, IOP increase/decrease, medications/procedures required to treat adverse events, clinically significant ocular changes

Evaluation of the FAI insert

Safety will be evaluated for two periods: through Day 7 and through Month 12. Descriptive statistics will be used to present the results of all safety evaluations and will include:

- Ocular adverse events (base on individual eye), including: IOP increase/decrease, medications/procedures required to control elevated/low IOP, development or worsening of cataract, cataract-related procedures, clinically significant ocular changes
- Systemic 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 eye/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, unless otherwise specified. A subject will be assigned by the study site. The first 3 digits of the ID number will be the assigned site number, followed by a 3-digit subject number in sequential order (i.e., 201001, etc.). Within the IWRS system, at the time of randomization, a 1-digit eye identification number will be added: the subject's first eye (if eligible) to be randomized will be assigned the additional digit "1" (e.g., 201001-1); the subject's second eye (if eligible) to be randomized will be assigned the additional digit "2" (e.g., 201001-2). However all data within the clinical data base will be recorded based on the subject number (without the eye id) and eye level data will be recorded as OD or OS. For non-ocular/systemic assessments, subjects who have more than one eye randomized/treated will have data listed once for each different treatment received. (e.g., the data could be listed for both the Mk II and Mk I injectors.)

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. For by treatment summaries, the denominator for percentages will be the number of eyes in each category in that treatment within the analysis population of interest, unless otherwise specified. For summaries for all subjects for data summarized at the subject level, the denominator for percentages will be the number of subjects who have at least one eye 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. Study day for non-ocular events and assessments will be determined using the date of treatment in the first treated study eye. Study day for ocular assessments for the first treated eye will be determined using the date of treatment in the first treated study eye. If the second eye is also treated, study day for the ocular assessments in that eye will be based on the date of treatment in that eye. If the second eye is not treated, study day for ocular assessments in that eye will be based on the date of treatment in the treated study eye.

For all utilization 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	-60 to 0	Not applicable

Day 1	1	Not applicable
Day 7	7	4 to 10
Day 28	28	14 to 42
Month 3	90	69 to 111
Month 12	360	332 to 388

Only those assessments which are assigned to an analysis visit will be included in the summary tables and figures which are presented by visit. If there are multiple assessments assigned to the same visit window, the observation to be used for analysis will be determined as follows:

If there is only one observation falling into a defined visit window, then that observation will be flagged for inclusion in by-visit analyses.

If there is more than one observation falling in a defined visit window and one of the observations was made in a "scheduled " study visit (e.g., day 7, day 28, Month 3, etc.) and the other observation(s) was made in an unscheduled visit , then the observation from the scheduled study visit will be used for by-visit analyses.

If there is more than one observation falling into a defined visit window and all observations are from unscheduled visits, then the earliest observation with non-missing data for a given assessment will be used for by-visit analyses.

All assessments will be presented in the data listings.

The Day 7 analysis will include all assessments with a start day on or before the upper limit of the Day 7 visit window (study day 10). The analysis at Month 12 will include all data in the database.

Subjects may have more than one eye randomized to treatment; therefore, for summaries counting patients by treated eye, a subject may be included more than once in a given summary. The same subject may be included more than once in the same treatment group if both eyes are randomized to the same inserter. Similarly, a subject may be counted more than once in the total eyes column if both eyes are randomized.

Subjects will be counted at most once for total subject summaries even if the subject has both eyes randomized.

Eyes not receiving assigned treatment and non-study eyes will have all safety data listed and will be included in selected AE and SAE summaries only. In the listings, randomized eyes that did not receive treatment will be grouped separately by their randomized treatment assignment (i.e., Mk I inserter - Not Treated, Mk II inserter - Not Treated). Non-randomized eyes which do not receive treatment will be grouped in listings. Percentages for Safety population summaries will be based on the number of eyes that received treatment.

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

4.1. Sample Size

This study is not statistically powered to detect a difference between the Mk I and Mk II inserters for the proportion of satisfactory procedures.

With a sample size of 20 eyes in the Mk II inserter group, the 95%, two-sided confidence interval of satisfactory procedures in the Mk II inserter group will be no larger than 27.2% - 72.8% when the exact binomial method and a proportion of 10 satisfactory procedures out of 20 Mk II inserter procedures are employed. All other satisfactory procedure proportions for the Mk II inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

With a sample size of 10 eyes in the Mk I inserter group, the 95%, two-sided confidence interval of the satisfactory procedures proportion will be no larger than 18.7% - 81.3% when the exact binomial method and a satisfactory procedures proportion of 5 out of 10 are employed. All other satisfactory procedures proportions for the Mk I inserter will result in two-sided, 95% confidence bounds that are narrower than that described above.

These confidence bounds, based on eye, are thought to adequately characterize the ease of use and other performance characteristics of the two inserters being studied.

4.2. Designation of Study Eye(s) and Randomization

For subjects with unilateral uveitis, the study eye will be the affected eye. For subjects with bilateral uveitis, the study eye(s) will be the eye(s) meeting eligibility criteria. If both eyes satisfy eligibility criteria, both eyes may be enrolled in the study. In a subject with both eyes eligible for enrollment, randomization of the subject's second study eye may occur no sooner than study Day 7 of that subject's first study eye.

Following confirmation of eligibility at Day 1, eyes will be randomly assigned (2:1) to receive the FAI insert using either the Mk II inserter or the Mk I inserter, respectively. Randomization assignments will be administered through a central Interactive Web Response System (IWRS). Randomization will be stratified on the basis of the investigator administering the treatment. The randomization schedule will be prepared using a blocked randomization and will be generated by an independent statistician. Only those subjects who have been enrolled in the study will have data recorded on the electronic case report forms (eCRF).

4.3. Masking of Study Subjects

Treatment assignments will be masked to study subjects. Any non-study eye may receive any standard treatment at the discretion of the Investigator.

4.4. Analysis Population

4.4.1. Intent-to-Treat (ITT) Population

The ITT population will include all eyes randomized into the study; analyzed as randomized. A given subject may have more than one eye included in the ITT population. All eyes 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.

4.4.2. Safety Population

The safety population will include all eyes randomized into the study; analyzed as treated. A given subject may have more than one eye included in the Safety population. All eyes 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.

5. Subject Disposition

5.1. Disposition

Disposition will be summarized for the ITT population at the subject level and at the eye level.

Disposition summarized at the subject level will include the number and percentage of subjects for the following categories: number of eyes randomized (one, two), subject randomization (one eye randomized to the MK I Inserter, one eye randomized to the MK II Inserter, both eyes randomized to the MK I inserter, both eyes randomized to the MK II Inserter, and one eye randomized to the MK I inserter and one eye randomized to the MK II Inserter),subjects who completed the study, subjects who discontinued from the study, and reasons for study discontinuation. The reason includes the following: adverse event, lack of efficacy, lost to follow-up, death, subject voluntarily withdrew, physician decision, sponsor decision, and study cancelled. Percentages will be based on the number of subjects who have at least one eye randomized.

Disposition will also be summarized at the eye level for the ITT population, summarizing eyes in the Safety population, eyes that completed the study, eyes that discontinued the study, and the reason for premature study termination by treatment group and for all treated eyes. Percentages will be based on the number of eyes randomized.

All disposition data will be presented in a listing.

5.2. Protocol Deviations

All protocol deviations will be reviewed and assessed as to significance prior to each database lock. The protocol deviations will be summarized by treatment group for the ITT population.

Protocol deviations will be presented in a listing for the ITT population.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographics will be summarized by treatment group and at the subject level for all subjects for the ITT population and Safety populations. Summaries will be generated for the Safety population only if there are randomized eyes that do not receive treatment. Summaries by treatment group will be based on the number of randomized (ITT) or treated eyes (Safety); therefore a subject who has both eyes randomized (treated) will be counted more than once, “repeating” the subject level demographics information once for each treated eye. Percentage for the by treatment summaries will be based on the number of randomized eyes and percentages

for the total subjects summary will be based on the number of subjects who have at least one eye randomized (treated).

The demographics data consist:

- Age (years) calculated using the date of the informed consent and date of birth
- Sex
- Race
- Ethnicity
- Iris color
- Height (cm)
- Weight (kg)
- Body Mass Index (BMI) (kg/m^2) calculated as (body weight in kilograms) / (height in meters)^2

Age (years), height (cm), weight (kg), and BMI (kg/m^2) will be summarized as continuous variables. The number and percentage of eyes/subjects by age category (<=20, 20 - < 40, 40 - < 60, >= 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.

Demographics data will be presented in a listing for the ITT population.

6.2. Baseline Ocular Characteristics

Baseline ocular characteristics will be summarized by treatment group and for all treated eyes for the ITT and Safety populations. Summaries will be generated for the Safety population only if there are randomized eyes that do not receive treatment.

The baseline ocular characteristics to be summarized include:

- Treated Eyes (OD, OS)
- Duration of uveitis (years) calculated as (screening date – date of onset of uveitis +1)/ 365.25
- Number of recurrences in the last 12 months
- Lens status
- Presence of cataract (if with lens status of phakic)
- History of vitrectomy procedure(s)
- Prior incisional anti-glaucoma surgeries
- Baseline BCVA (letters)
- Baseline IOP (mmHg)

Duration of uveitis, baseline BCVA (letters), and baseline IOP (mmHg) will be summarized as continuous variables. For partial uveitis 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 eyes by duration of uveitis (< 2 years, 2 to 5 years, > 5 years), number or recurrences in the last 12

months (<= 2, >2), lens status (phakic, aphakic, and pseudophakic), presence of cataract (if with lens status of phakic), and history of related procedure(s) and surgeries will also be reported.

Baseline ocular characteristics will be summarized for randomized eyes only. Summaries will be presented at the eye level. Percentage will be based on the number of randomized eyes (ITT) or treated eyes (Safety).

All collected baseline ocular characteristics data for all eyes will be presented in a listing for the ITT population.

6.3. Medical History

6.3.1. Non-ocular Medical History

Non-ocular medical history and current non-ocular conditions will be summarized by treatment group for each body system for the ITT population. Body systems will be included as recorded on the eCRF. The non-ocular medical history data will be also summarized for all subjects at the subject level. Summaries by treatment group will be based on the number of randomized eyes; therefore a subject who has both eyes randomized will be counted more than once, "repeating" and counting the non-ocular history once for each treated eye. Percentage for the by treatment summaries will be based on the number of randomized eyes and percentage for the total subjects summary will be based on the number of subjects who have at least one eye randomized.

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

6.3.2. Ocular Medical History

Any clinically significant ocular conditions within the past 12 months prior to Screening will be recorded on the eCRF. Ocular medical history data, including specific details on the condition/diagnosis, location (OS, OD, and OU), study eye(s) designation, treatment required, and start/end dates, will be presented in a listing for the ITT populations.

6.4. Inclusion and Exclusion Criteria

Prior to randomization, the investigator will assess whether the eye fulfills all the requirements of the inclusion and exclusion criteria outlined in the protocol. If an eye 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

Prior and concomitant medication will be summarized by drug class and preferred term after coding with WHO Drug (WHO201209 version or higher) Dictionary terms.

All summaries will be provided for ocular medications and non-ocular medications, separately. Systemic steroids and immunosuppressants that have been prescribed for uveitis will be

summarized as ocular medications, but are not considered prohibited in this study. Summaries will include the total number of medications, the number and percentage of eyes or subjects receiving at least one medication, and the number and percentage of eyes or subjects receiving a medication summarized at the summarized by ATC level 1 term, ATC level 2 term, and preferred term. Eyes and/or subjects may receive more than one medication per ATC level 1 category, ATC level 2 category, and preferred term. At each level of summarization, an eye or subject is counted once if the eye or subject received one or more medications.

All prior and concomitant medication, including pre- and post-ocular procedure medications will be presented in listings for the Safety population.

7.1.1 Prior Medications

Prior medications are defined as those medications with a recorded end date prior to the initiation of study treatment.

Prior non-ocular medication will be summarized by treatment group for each drug class and preferred term for the Safety population. The prior non-ocular medication data will be also summarized for all subjects at subject level. Summaries by treatment group will be based on the number of treated eyes; therefore a subject who has both eyes treated will be counted more than once, "repeating" the non-ocular medication and counting once for each treated eye. Percentages for the by treatment summaries will be based on the number of treated eyes and percentages for the total subjects summary will be based on the number of subjects who have at least one eye treated.

Prior ocular medication will be summarized by treatment group and for all treated eyes for each drug class and preferred term for the Safety population. Percentages will be based on the number of treated eyes.

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.

Concomitant non-ocular medication will be summarized by treatment group for ATC level 1 term, ATC level 2 term and preferred term for the Safety population. The concomitant non-ocular medication data will be also summarized for all subjects at the subject level. Summaries by treatment group will be based on the number of treated eyes; therefore a subject who has both eyes treated will be counted more than once, "repeating" and counting the non-ocular medication once for each treated eye. Percentages for the by treatment summaries will be based on the number of treated eyes and percentages for the total subjects summary will be based on the number of subjects who have at least one eye treated.

Concomitant ocular medication will be summarized by treatment group and for all treated eyes for each drug class and preferred term for the Safety population. Percentages will be based on the number of treated eyes.

An additional summary of concomitant medication for each of the specified reasons for medication (recurrence of uveitis, treatment emergent AE, increased IOP, cataract, other) will be reported as well.

7.1.3 IOP Lowering Medications

The number and percentage of eyes requiring IOP lowering medication to control elevated IOP will be summarized by treatment group and for all treated eyes. Any systemic medications will be summarized as received in both eyes. IOP lowering medications will be identified as those medications with a reason for medication of "Increased IOP". Incidence will be summarized through 12 months and for 3 month time intervals through 12 months.

The number of medications (one, two, ≥ three) 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 62, 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 two 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 for the final analysis at Month 12 only.

7.2. Ocular Surgeries

All ocular surgeries during a subject's participation in the study will be recorded on the eCRF.

A summary of surgery/procedure for each of the specified reasons (recurrence of uveitis, treatment emergent AE, increased IOP, cataract, other) will be reported. Summaries will be provided by treatment group and for all treated eyes for the Safety population.

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

7.2.1 Surgical Intervention to Control Elevated IOP

The number and percentage of eyes requiring any surgical intervention to control elevated IOP will be summarized by treatment group and for all treated eyes. 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 12 months and for 6 month time intervals through 12.

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 for the final analysis at Month 12 only.

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, and the last available BCVA and IOP values as of the data cut-off.

7.2.2 Cataract Surgeries

The number and percentage of eyes requiring cataract surgery will be summarized by treatment group and for all treated eyes. 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 12 months and for 6 month time intervals through 12 months. All summaries will be performed using the Safety population and percentages will be based on the number of phakic eyes in the Safety population. Analysis will be performed for the final analysis at Month 12 only.

7.3. Study Treatments

Fluocinolone acetonide (FA) is the active ingredient in the FAI insert. The FAI insert is an injectable intravitreal sustained-release FA delivery system pre-loaded into an injection device and is administered as an intravitreal injection through the pars plana. For this study, the FAI insert will be provided in one of two sterile preloaded inserters: the Mk I inserter or the Mk II inserter. The FAI insert is designed to release FA for a period of 36 months at a nominal rate of approximately 0.2 μg FA/day.

The Mk I inserter is a sterile, pre-loaded, modified syringe that uses a 25 gauge XX-thin wall

needle to penetrate the conjunctiva and sclera; the needle is not retracted after intravitreal injection has been completed. The Mk I inserter has been used previously in clinical study PSVFAI-001.

The Mk II inserter is a sterile, pre-loaded applicator that uses a 27 gauge standard wall needle to penetrate the conjunctiva and sclera; the needle is retracted during intravitreal injection.

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

7.3.1. Extent of Exposure

Duration of insert (days) is defined as the total number of days a study eye is exposed to 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 eyes which 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 insert at Day 7 is defined similarly to overall insert duration, using either the FAI insert removal date, if removal occurred prior to Day 7 visit date, or the Day 7 visit date as the cut-off date. If a subject's Day 7 visit date occurs later than the data cut off for the Day 7 analysis (upper limit of Day 7 visit window) then the upper limit of the Day 7 visit date will be used as the end date of the insert duration.

Duration of insert up to Day 7 (or Month 12) will be summarized by treatment group and for all treated eyes for the Safety population. The duration of insert will be classified into following categories: <= 7 days, 8 to 28 days, 29 to 90 days, 91 to 360 days, and >= 360 days and the number and percentage of eyes in each duration category will be presented for the Safety population.

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 Day 7 is calculated as the date of Day 7 visit – date of Day 1 visit + 1. If a subject's Day 7 visit date occurs later than the data cut-off for the Day 7 analysis (upper limit of Day 7 visit window), then the upper limit of the Day 7 visit date will be used as the end date of participation.

Duration of study participation up to Day 7 (or Month 12) will be summarized by treatment group and for all subjects at the subject level for the Safety population. The durations of study participation will be classified into one of the following categories: <= 7 days, 8 to 28 days, 29 to 90 days, 91 to 360 days, and >= 360 days and the number and percentage of eyes or subjects in each duration category will be presented for the Safety population. Summaries by treatment group will be based on the number of treated eyes; therefore a subject who has both eyes treated will be counted more than once, "repeating" and including the duration of subject participation once for each treated eye. Percentages for the by treatment summaries will be based on the

number of treated eyes and percentage for the total subjects summaries will be based on the number of subjects who have at least one eye treated.

Duration of insert and duration of study participation will be presented in a listing for the Safety population.

8. Utilization Analysis

Utilization analyses will be performed by treatment group, at Day 1 based on the questionnaires from Investigator and the Observer (Appendix 13.2).

All primary and secondary utilization endpoints will be analyzed using the ITT population.

Data related to the utilization will be presented in a listing for the ITT population.

8.1. Primary Utilization Endpoint

The primary utilization endpoint is defined as the proportion of intravitreal insertion procedures that are assessed by the Investigator as satisfactory. A satisfactory procedure is defined as one receiving a score from the Investigator as either Very Easy (VE), Easy (E), or Routine (R), according to the following categories:

- Very Easy (VE)
- Easy (E)
- Routine (R)
- Difficult (D)
- Very Difficult (VD)

If more than one inserter is used for the same eye, the results from the first inserter will be used for completing the questionnaires and analysis. Comments related to the second inserter will be presented in a listing. Any injector which penetrates the eye but does not deliver the FAI insert into the eye will be scored as Very Difficult for analysis.

8.1.1. Primary Utilization Analysis

The primary utilization analysis will compare the proportion of intravitreal insertion procedures that are assessed by the Investigator as satisfactory (i.e., VE, E or R), in the Mk I inserter and the Mk II inserter groups.

The number and percentage of eyes with satisfactory intravitreal insertion procedures will be presented, for the Mk I inserter and the Mk II inserter groups of eyes employing descriptive statistics including 95% confidence intervals using the exact binomial methodology. The difference in proportions, the 95% exact unconditional confidence interval for the treatment difference (Mk II vs Mk I) in proportions, and the Fisher's exact test p-value will also be provided, however this comparison is considered exploratory only as the study is not powered to detect a difference between the inserters.

The primary utilization analysis will be conducted after all eyes in the study have completed study Day 7 or have discontinued study participation.

The study will be deemed a success for the Mk II inserter if the following condition is met: The proportion of Mk II procedures scored as satisfactory is not numerically lower than the corresponding proportion of Mk I procedures.

8.2. Secondary Utilization Endpoints and Analysis

Secondary endpoints include:

- Clarity of the instructions for use, as assessed by the Investigator (yes, no)
- Differences between observed procedure and instructions for use, as assessed by an Observer (yes, no)

These secondary utilization endpoints will be analyzed employing descriptive statistics. Additionally descriptive statistics for other items on the investigator and observer questionnaires will be presented.

9. Safety Analysis

Safety analyses will be performed by treatment group for the Safety population at Day 7 and Month 12. Descriptive statistics will be used in safety analyses. Summary at the subject level will also be provided.

Non-treated randomized eyes and non-study eyes will only have all safety data listed. Adverse events will be summarized for these eyes, but otherwise they will not be included in safety tabulations.

9.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject administered an investigational product; an AE does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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 (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1 or higher).

An overview summary of 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.

All TEAE summaries will be provided for ocular events and non-ocular events, separately. All adverse events starting on or after the date of treatment in the first study eye are considered TEAE, however ocular events occurring in non-treated eyes and events occurring in the second treated eye between the date of treatment in the first treated eye and the date of treatment in the second treated eye will be summarized separately from ocular events that occur in treated eyes after the date of treatment within the respective eye.

All AEs will be presented in a listing.

9.1.1. Incidence of Adverse Events

Summaries of the total number of ocular TEAEs and the number and percentage of eyes having at least one ocular TEAE will be provided by treatment group and for all treated eyes. Similarly, summaries of the total number of non-ocular TEAEs and the number and percentage of subjects having at least one non-ocular TEAE will be provided by treatment group. Ocular events and non-ocular events will be also summarized at the subject level for all subjects. Ocular events which occur in non-treated eyes and ocular events which occur in the second treated eye with a start date on or after the date of treatment in the first study eye but before the date of treatment in the second eye will be summarized separately as noted in section 9.1.10.

Ocular and non-ocular TEAEs will be summarized by SOC and PT. At each level of summarization, eye or subject level, an eye or subject is counted once for multiple events within PT/SOC.

Summaries by treatment group and for all treated eyes will be based on the number of treated eyes; therefore non-ocular events for subjects who have both eyes treated may be counted more

than once, "repeating" and counting the adverse event once for each treated eye. A non-ocular event will be counted for a given eye if the event start date is on or after the treatment date in the given eye. (i.e., non-ocular events which occur on or after the date of treatment in the first treated eye but before the date of treatment in the second eye will be counted once for the first eye only. If the event start date was on or after the treatment date in the second treated eye, the event would be counted twice, once for each eye.) Ocular events will be counted for a given study eye/treatment if the event start date is on or after treatment date within the given treated eye. Percentages will be calculated out of the number of treated eyes in the Safety Population.

Subject level summaries for all subjects will be based on the number of subjects who have at least one treated eye and a subject will be counted as having an event in the total subject summary if the subject has an event in at least one treated eye. Percentages will be calculated out of the number of subjects in the Safety Population with at least one treated eye.

The summary of TEAEs will be presented in descending order from the SOC with the highest subject incidence to the SOC with the lowest subject incidence. If the incidence for any two or more SOC is equal, the SOC will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

A separate summary of protocol defined ocular TEAEs, 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 ≥ 15 letters, compared to the most recent 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 by treatment group. 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". 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.

The TEAE data will be categorized and presented by SOC, 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 by incidence of occurrence by treatment group. The severity will be captured on the eCRF page. The possible severities are "Mild," "Moderate," and "Severe." TEAEs that are missing severity will be presented in tables as "Severe" but will be presented in the data listing with a missing severity.

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 SOC, 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) as below will be presented in a table by incidence of occurrence by treatment group.

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect
- Is a medically important event or reaction

The SAE data will be categorized and presented by SOC 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 $\geq$ 30 letters, compared to 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 by treatment group and all treated eyes. These TEAEs will be also summarized for subject level.

The summary of TEAEs with an action taken with study treatment of "FAI Insert Removal" will be presented by SOC and PT in a manner similar to that described in Section 9.1.1.

9.1.6. Adverse Events Leading to Study Discontinuation

All eyes having an AE where the answer to "Was eye terminated from study due to this AE?" is "Yes" will be presented in a listing.

9.1.7. Adverse Events Leading to 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 all treated eyes. These TEAEs will be also summarized for subject level. Events will be included in the summary based on a list of PTs for each event category. Cataract events will include any event whose MedDRA higher lever coded term is "CATARACT CONDITIONS" is contained in the preferred term. IOP elevations will be based on the specific preferred term "INTRAOCULAR PRESSURE INCREASED" or if the preferred term contains the phrase "GLAUCOMA".

A summary of ocular TEAEs which are considered complications of IOP lowering medications to control IOP will be presented by treatment group and all treated eyes. These TEAEs will be also summarized for subject level. 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.

A summary of ocular TEAEs which are considered complications of surgical interventions to control IOP will be presented by treatment group and all treated eyes. These TEAEs will be also summarized for subject level. Events will be included in the summary based on manual review of all AEs with an onset date on or after the date of surgical intervention. A similar summary will be presented for complications of cataract surgeries.

At each level of eye summarization, an eye is counted once for multiple events within PT. Percentages will be calculated out of the number of eyes in the Safety population. At each level of subject summarization, a subject is counted once for multiple events within PT. Percentages will be calculated out of the number of subjects in the Safety population. The summary will be sorted by PT in alphabetical order. Adverse events of special interest will be summarized at Day 7 and Month 12.

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 a 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.

9.1.9. Procedure Related Adverse Events

Adverse events with an onset date within 7 days of the insert procedure will be clinically reviewed to assess the relationship to the injection procedure. Events that could be considered related to the injection procedure could include but is not limited to events such as decreased IOP, increased IOP, eye pain, eye erythema, etc. The process by which the manual review is conducted will be summarized in a manual data review memo. Events which are deemed related to the injection will be summarized in similar manner as incidence of adverse events detailed in section 9.1.1.

9.1.10 Other Meaningful Adverse Events

Ocular events which occur in non-treated eyes and ocular events which occur in the second treated eye with a start date on or after the date of treatment in the first study eye but before the date of treatment in the second eye will be summarized by SOC and PT. At each level of summarization, an eye is counted once for multiple events within PT/SOC. Summaries will be for total eyes and not by randomized treatment group(s) for the first/second eye. Percentages will be based on the number of non-treated eyes or the number of second treated eyes, respectively. A similar summary of serious adverse events will also be provided. Ocular events in non-treated eyes will be presented. Events in the second study eye prior to date of treatment in the second study eye will be presented in data listings under the treatment of the second treated eye.

9.2. Ophthalmic Examination

All ophthalmic examinations are performed on both eyes.

9.2.1. Best-corrected Visual Acuity (BCVA)

BCVA will be measured according to the standard procedure developed for ETDRS at 4 meters (or at 3 meters if the electronic ETDRS system is employed). Corrected-distance VA is to be reported as 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 treatment group for 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 Day 7 (or Month 12) and the maximum letter change at any time point up to Day 7 (or Month 12), 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 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 (Day 7 and Month 12). Surgical intervention status will be defined in a similar manner.

For eyes 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 group for the Safety population. In addition, a summary of change from baseline in BCVA (letters) will be presented by treatment group with phakic eyes at study entry who undergo cataract surgery while in the study vs. eyes 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 (preferable Goldman) 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 treatment group for the Safety population. 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 eyes with an IOP measurement > 21 mmHg at any post-administration assessment will be presented for each treatment group. Incidence will be summarized through Day 7 and month 12.

Additionally, the number and percentage of eyes with an IOP measurement meeting any of the IOP elevation criteria at any post-administration assessment and by visit will be presented by treatment group for the Safety population. 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 eyes with a change in lens/cataract status since screening or a worsening of an existing cataract since the previous visit will be presented by baseline lens status, treatment group for 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:

Grade	Description
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

Grade	Description
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 treatment group 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 treatment group for the Safety population. Changes from baseline to each scheduled post-baseline visit will be presented.

Visual field test data will be presented in a listing.

9.4. 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 eCRF data of laboratory testing (HIV and syphilis serology), 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.

9.5. 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 rate (bpm), by treatment group and all subjects for the Safety population. Observed results at each visit and changes from baseline to each scheduled post-baseline visit will be presented.

Summaries by treatment group will be based on the number of treated eyes; therefore non-ocular vital sign assessments for subjects who have both eyes treated will be included more than once, "repeating" and including the assessments once for each treated eye.

All vital sign data will be presented in a listing.

9.6. 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 utilization analysis and safety analyses will be conducted at the Day 7; i.e., after all subjects have completed the Day 7 visit or have been discontinued from the study prior to this visit. Analysis of the study data through Month 12 (the complete study data) will be performed after all subjects have either completed the Month 12 visit, or have been discontinued from the study prior to the Month 12.

11. Changes in the Planned Analysis

No changes in the planned analysis at present.

12. References

Iluvien Prescribing Information (December 2014).

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.

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).

13. Appendices

13.1. Schedule of Study Procedures and Assessments

Assessments	Screening	Day 1	Day 7	Day 28	Month 3	Month 12
Timing/Interval	-60	1	±3D	±14D	±21D	±28D
Medical/Ophthalmic History	X					
Demographics	X					
Inclusion/Exclusion Criteria	X	X				
Vital Signs[a]	X	X	X	X	X	X
Clinical Labs[b]	X					
Ophthalmic Examination[c]	X	X	X	X	X	X
Visual Field	X					X
Pregnancy[d]	X	X				X
Randomization		X				
FAI Insert Administration		X				
Post-Administration Assessment[e]		X				
Questionnaire[f]		X				
Concomitant Medications	X	X	X	X	X	X
Adverse Event (AEs)		X	X	X	X	X

[a] Include systolic/diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes. Height and weight at Screening visit only.
[b] HIV and syphilis serology testing.
[c] Ophthalmic examination includes: BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy, and anterior, posterior, and intermediate slit lamp examinations.
[d] Females of child-bearing potential only: urine test conducted only at Screening, Day 1 and Month 12
[e] includes indirect ophthalmoscopy to verify adequate central retinal artery perfusion, absence of any other complications, verification of insert placement; IOP [recorded as the mean of three measurements]; follow-up contact with the subject the day following Study Day 1 regarding the subject's ocular condition, and any complaint and/or adverse event.
[f] Following each administration of the FAI insert, the Investigator and the Observer will each complete a questionnaire related to the administration procedure.

13.2. QUESTIONNAIRES

13.2.1. Mk I Questionnaires

Investigator Questionnaire

1. Were the instructions for the use of the **Mk I inserter** clear and understandable?
   If not, please explain.

2. The ease of intravitreal administration using the **Mk I inserter** was:
   a. Very easy
   b. Easy
   c. Routine
   d. Difficult
   e. Very difficult

3. Were you able to deliver the insert into the vitreous using the **Mk I inserter**?
   If not, please explain.

Observer Questionnaire

1. Was sterile technique used to remove the **Mk I inserter** from the pouch?
   If not, please explain.

2. Did the Investigator follow the **Mk I inserter** instructions for use?
   If not, please explain.

3. Did you observe any difficulty experienced by the Investigator during use of the **Mk I inserter**?
   If yes, please explain.

4. Do you have any other observations to report?
   If yes, please explain.

13.2.2. Mk II Inserter Questionnaires

Investigator Questionnaire

1. Were the instructions for the use of the **Mk II inserter** clear and understandable?
   If not, please explain.

2. The ease of intravitreal administration using the **Mk II inserter** was:
   a. Very easy
   b. Easy
   c. Routine
   d. Difficult
   e. Very difficult

3. Were you able to deliver the insert into the vitreous using the **Mk II inserter**?
   If not, please explain.

Observer Questionnaire

1. Was sterile technique used to remove the **Mk II inserter** from the tray?
   If not, please explain.

2. Did the Investigator follow the **Mk II inserter** instructions for use?
   If not, please explain.

3. Did you observe any difficulty experienced by the Investigator during use of the **Mk II inserter**?
   If yes, please explain.

4. Do you have any other observations to report?
   If yes, please explain.