EYEPOINT PHARMACEUTICALS

Cover Page Study Protocol

Protocol Title:	A PHASE III, MULTI-NATIONAL, MULTI-CENTER, RANDOMIZED, MASKED, 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
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FLUOCINOLONE ACETONIDE INTRAVITREAL INSERT

PROTOCOL PSV-FAI-001

A PHASE III, MULTI-NATIONAL, MULTI-CENTER, RANDOMIZED, MASKED, 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

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pSivida Corp.

480 Pleasant Street

Watertown, MA 02472 USA

CONFIDENTIALITY STATEMENT

INVESTIGATOR'S AGREEMENT

I have read the attached protocol, concur that it contains all information necessary to conduct the study, and agree to follow the study procedures as outlined in this protocol.

I agree to comply with FDA regulations (21 CFR Parts 50, 54, 56 and 312) and ICH guidelines. I will not initiate the study until I have obtained written approval by the appropriate Institutional Review Board/Ethics Committee and have complied with all financial and administrative requirements of the governing body of the clinical institution. I will obtain written informed consent from all study participants prior to performing any screening procedures.

This protocol and related information is subject to the Confidentiality Agreement between myself and pSivida Corp. and as such must be held in confidence and not disclosed to any third party for a period of seven (7) years from the date of the Confidentiality Agreement, or until said information shall become a matter of public knowledge, or until a formal written agreement for that purpose has been entered into by the parties.

_____ _____

Principal Investigator Signature Date

_____

Print Name

1. PERSONNEL CONTACT INFORMATION

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2. SYNOPSIS

Name of Sponsor/Company: pSivida Corp. **Name of Investigational Product:** Fluocinolone Acetonide Intravitreal Insert **Name of Active Ingredient:** Fluocinolone Acetonide	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(for National Authority Use only)*

Title of Study: A Phase III, Multi-National, Multi-Center, Randomized, Masked, 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

Studied Period (years): 3 years	**Phase of Development:** 3

Objectives: 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.

Methodology: A 36 month, multicenter, randomized, controlled, masked safety and efficacy study.

Number of Subjects (planned): Approximately 120 subjects (80 FAI insert: 40 sham injection) at approximately 40 to 50 sites. One eye in each subject will be designated as the study eye.

Diagnosis and Main Criteria for Inclusion:

Diagnosis:

Unilateral or bilateral chronic non-infectious uveitis affecting the posterior segment of the eye

Inclusion Criteria:

- Male or non-pregnant female at least 18 years of age at time of consent
- One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye with or without anterior uveitis ≥ 1 year duration
- During the 12 months prior to enrollment (Day 1),

  the study eye has either received treatment:
  - systemic corticosteroid or other systemic therapies given for at least 3 months, and/or
  - at least 2 intra- or peri-ocular administrations of corticosteroid for management of uveitis

  OR the study eye has experienced recurrence:
  - at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid
- At the time of enrollment (Day 1), study eye has < 10 anterior chamber cells/HPF and a vitreous haze ≤ grade 2.
- Visual acuity of study eye is at least 15 letters on the ETDRS chart
- Subject is not planning to undergo elective ocular surgery during the study
- Subject has ability to understand and sign the Informed Consent Form
- Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures

Exclusion Criteria:

- Allergy to fluocinolone acetonide or any component of the FAI insert
- History of posterior uveitis only that is not accompanied by vitritis or macular edema
- History of iritis only and no vitreous cells, anterior chamber cells or vitreous haze
- Uveitis with infectious etiology
- Vitreous hemorrhage
- Intraocular inflammation associated with a condition other than noninfectious uveitis (e.g. intraocular lymphoma)
- Ocular malignancy in either eye, including choroidal melanoma
- Toxoplasmosis scar in study eye or scar related to previous viral retinitis
- Previous viral retinitis
- Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, mycobacterial infections of the eye or fungal diseases of ocular structures
- Media opacity precluding evaluation of retina and vitreous
- Peripheral retinal detachment in area of insertion
- Diagnosis of any form of glaucoma or ocular hypertension in study eye at Screening, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
- Intraocular pressure (IOP) > 21 mmHg or concurrent therapy at screening with any IOP-lowering pharmacologic agent in the study eye
- Chronic hypotony (< 6 mmHg)
- Ocular surgery on the study eye within 3 months prior to study Day 1
- Capsulotomy in study eye within 30 days prior to study Day 1
- Prior intravitreal treatment of study eye with Retisert within 36 months prior to study Day 1
- Prior intravitreal treatment of study eye with Ozurdex within 6 months prior to study Day 1
- Prior intravitreal treatment of study eye with Triesence or Trivaris within 3 months prior to study Day 1
- Peri-ocular or subtenon steroid treatment of study eye within 3 months prior to study Day 1
- Subjects requiring chronic systemic or inhaled corticosteroid therapy (>15mg prednisone daily) or chronic systemic immunosuppressive therapy
- Excluding certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to study Day 1
- Subjects who test positive for human immune deficiency virus (HIV) or syphilis during screening
- Mycobacterial uveitis or chorio-retinal changes of either eye which, in the opinion of the Investigator, result from infectious mycobacterial uveitis
- Systemic infection within 30 days prior to study Day 1
- Any severe acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the subject inappropriate for entry into this study
- Any other systemic or ocular condition which, in the judgment of the investigator, could make the subject inappropriate for entry into this study

- Treatment with an investigational drug or device within 30 days prior to study Day 1
- Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days prior to study Day 1 until the Month 12 Visit
- Subjects unlikely to comply with the study protocol or who are likely to be lost to follow-up within three years

Treatment Assignment:
All study subjects will be randomized (2:1) to receive either a FAI insert (the test article) or a sham injection in the designated study eye. Randomization will be stratified on the basis of whether the patient is receiving systemic treatment to control uveitis at the time of study entry. For patients receiving systemic treatment at time of study entry, randomization will be stratified on the basis of the type of treatment (steroid or immunosuppressant).

Control:
Sham injection

Duration of Treatment:
36 months

Reference Therapy, Dosage and Mode of Administration:

Reference therapy: Sham injection, followed by standard of care

Test article therapy: Fluocinolone Acetonide Intravitreal insert (FAI insert). The FAI insert contains 0.18 mg FA and delivers FA into the vitreous humor for 36 months. The FAI insert will be administered to the study eye by injection through the pars plana using a pre-loaded applicator with a 25 gauge needle.

Designation/Randomization of Study Eye:
For subjects with unilateral uveitis, the study eye will be the affected eye; for subjects with bilateral uveitis, the study eye will be the more severely affected eye fitting the inclusion/exclusion criteria (i.e. the eye having suffered more recurrences in the previous year, or if equal, the eye having received more therapy in the previous year, or if equal, the eye having the worse VA or if equal, the eye clinically judged to be the more severely affected eye.) If the eyes are symmetrically affected, the study eye will be the right eye.

Study Procedures:

Screening (within 30 days prior to injection):

Eligibility determination, informed consent, demographics, medical and ophthalmic history including a detailed history of the management of their uveitis over the previous 12 months, vital signs, clinical labs, physical exam, ophthalmic exam (includes BCVA, IOP, dilated ophthalmoscopy and anterior, posterior and intermediate slit lamp examination), visual field, subjective ocular tolerability and discomfort assessment, concomitant medications and a pregnancy test, as appropriate.

Treatment Day (Day 1):

Eligibility confirmation; including meeting the entry criteria for anterior chamber cells, vitreous haze, IOP and visual acuity on study Day 1. Following randomization (via IVRS), subjects will receive the FAI insert or sham injection. Assessments on that day will include vital signs, ophthalmic exam, OCT, subjective ocular tolerability and discomfort assessment, pregnancy test, concomitant medications, and adverse events (AEs).

Follow-up Visits:

Following injection on Study Day 1, subjects will return on Study Days 7, 28 and Months 2, 3, 6, 9, 12, 18, 24, 30 and 36. Evaluations on these days include: concomitant medications, vital signs, ophthalmic

exam, OCT, subjective ocular tolerability and discomfort assessment, and AEs.
All subjects enrolled in the study will be followed for 36 months.

Masking:
To minimize bias, two investigators will participate at each site. One investigator will administer study treatments and perform study Day 1 assessments. The second investigator will be masked to the assigned treatment and will perform all study assessments after study Day 1. Study personnel will use every reasonable effort to maintain the study masking.

Concomitant Medications:
Subjects may be treated prior to entry in order to meet study inclusion criteria and obtain a relatively quiet eye prior to enrollment. If a subject is receiving a systemic treatment regimen 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 treatments may be ended immediately, while others require a period of gradual dose reduction (tapering).

If a subject experiences a recurrence of uveitis in either eye that requires treatment during the study, local (topical, periocular or intraocular) treatment will be used as the first line of therapy. Systemic immunosuppressants or systemic steroids will be used only if local therapy fails. Subjects who experience a recurrence of uveitis will continue in the study; once the subject's recurrence is controlled, the treatment regimen will be ended in a manner that follows the standard of care for ending the specific treatment regimen.

Criteria for Evaluation:

Efficacy:

Primary Efficacy Endpoint: Proportion of subjects who have a recurrence of uveitis in the study eye within 6 months after receiving study treatment. Recurrence is defined as:

- A $\geq$ 2 step increase in the number of cells in the anterior chamber per high powered field (1.6 X using a 1-mm beam), compared to any visit time point prior to Month 6

  OR

- An increase in the vitreous haze of $\geq$ 2 steps, compared to any visit time point prior to Month 6

  OR

- A deterioration in visual acuity of at least 15 letters BCVA, compared to 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 study Day 7 visit.

Exploratory Efficacy Endpoints:

- Proportion of subjects who have a recurrence of uveitis in the study eye within 12 months or 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 (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 measured by OCT imaging (at 6 months, 12 months and 36 months)

Safety:

- 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 changes; procedure related adverse events

Statistical Methods:

Sample Size:

A two group continuity corrected Chi-square test with a 0.05 two-sided significance level will have 89% 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 40 and 80, respectively (a total sample size of 120).

Study Populations:

The ITT (Intent to Treat) population will include all subjects randomized into the study; analyzed as randomized. The safety population will include all subjects randomized into the study; analyzed as treated. The per protocol (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 12 month or 36 month) endpoint of the study
- Failed screening, without exemption but received FAI insert
- Had a major protocol deviation

Efficacy Analyses:

Efficacy analyses will be performed on both the ITT population and the PP population at 6, 12 and 36 months. The primary efficacy analysis will be performed on the ITT population at 6 months and will be the difference between study groups in the proportion of subjects who have a recurrence of uveitis. The primary efficacy analysis will be conducted after all subjects in the study have completed 6 months of treatment or have discontinued. A continuity corrected Chi-square analysis will be used to assess the statistical significance of a difference between study groups in the primary efficacy analysis.

Recurrence will be imputed in the following circumstances:

- A subject who has not previously experienced a recurrence and does not complete the required eye examinations at Month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) for any reason will be considered as having a recurrence.
- A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication or a prohibited local concomitant medication in the study eye at 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.

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering) (as described in Section 9.10.1) will not be considered prohibited medications. Topical steroids administered as part of short term standard treatment following an ocular surgical procedure will also not be considered prohibited medications (as described in Section 9.10.2).

Sensitivity analyses for the primary outcome at 6, 12 and 36 months will be employed. These analyses will include an analysis where a subject imputed as having a recurrence due to missing eye examinations at Month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) will NOT be considered as having a recurrence, plus a "tipping point" analysis. Additionally, for missing data due to other reasons, sensitivity analyses will be conducted by using multiple imputation methods.

Descriptive statistics only will be used in all exploratory efficacy analyses. Exploratory efficacy outcomes will be described by treatment group.

Safety Analyses:

Safety analyses will be performed on the safety population at 6, 12 and 36 months. Descriptive statistics will be provided for all treatment emergent adverse events. Frequency counts and percentage of subjects within each treatment group will be provided by MedDRA SOC and preferred term by treatment. Vital signs will be presented using descriptive statistics by treatment by visit. Concomitant medication will be presented by treatment after coding with WHO-Drug Dictionary terms. Laboratories assessments will be presented by descriptive statistics.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AC	Anterior Chamber
ADR	Adverse Drug Reaction
AE	Adverse Event
AMD	Age Related Macular Degeneration
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
DME	Diabetic Macular Edema
eCRF	Electronic Case Report Form
ESR	Erythrocyte Sedimentation Rate
ETDRS	Early Treatment Diabetic Retinopathy Study
ExSR	Expedited Safety Report
FA	Fluocinolone Acetonide
FAI Insert	Fluocinolone Acetonide Intravitreal Insert
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug application
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent to Treat
NDA	New Drug Application
OCT	Optical Coherence Tomography
PI	Principal Investigator; the investigator who leads the study conduct at an individual study center.
PP	Per-Protocol
PVA	Polyvinyl Alcohol
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
SOC	Standard of Care
SOP	Standard Operational Procedure
VA	Visual Acuity
WOCBP	Women of Child Bearing Potential

5. 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. In this protocol, this specific drug product candidate is abbreviated as "FAI insert" (for fluocinolone acetonide intravitreal insert).

The clinical trial described in this protocol will be conducted in compliance with the protocol, Good Clinical Practices (GCP) as well as all applicable regulatory requirements.

5.1. Uveitis

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.

Uveitis has been estimated to be responsible for approximately 10% of blindness in the United States (Suttorp-Schulten 1996). 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.

5.2. Current Treatments for Uveitis

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 peri-ocular, intravitreal) and/or systemic administration of steroids or immunosuppressants. Immunosuppressive therapy is used for patients with severe uveitis who are unresponsive to corticosteroid therapy or for patients with severe corticosteroid-induced complications or who are otherwise intolerant of corticosteroid therapy. 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. Peri-ocular corticosteroid injections may be required frequently and have the additional potential risk for globe perforation, orbital fibrosis, endophthalmitis and ptosis.

Corticosteroids currently approved for the intravitreal treatment of posterior uveitis include Retisert®, Ozurdex®, Triesence® and Trivaris®. Despite the availability of these approved products for intravitreal therapy of uveitis of the posterior segment, systemic corticosteroids are often required to treat uveitis (MUST group 2011). However, long term use of systemic corticosteroids is associated with significant systemic side effects (Brunton 2006) and may not be a practical option for many patients.

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.

5.3. Summary of Data for Intravitreal Fluocinolone Acetonide

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 (DME), retinal vein occlusion, wet age-related macular degeneration (AMD) or dry AMD.

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)].

5.3.1. Nonclinical Data

Details of the nonclinical data summarized below can be found in the Investigator's Brochure (IB) that accompanies this protocol.

5.3.1.1. Pharmacology

The affinity of FA for the glucocorticoid receptor in vitro has been confirmed in a number of studies. In animal pharmacology studies, intravitreal FA significantly decreased the severity of proliferative vitreoretinopathy in a rabbit model, reduced ocular inflammation in a rabbit uveitis model, and showed neuroprotective effects in rodent models of retinal degeneration.

5.3.1.2. Pharmacokinetics

Nonclinical pharmacokinetic studies in rabbits demonstrated that there is no quantifiable systemic exposure of fluocinolone acetonide following intravitreal injection of FA. FA elimination from ocular tissues was very slow and was not apparently tissue or dose dependent. The estimated half-life of FA was considered the result of the controlled release of FA from the delivery system. FA exposure was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. The ocular exposure of FA in the aqueous humor was minimal at all dose levels. The observed exposure profiles are consistent with the mode of administration of FA.

5.3.1.3. Toxicology

FA-related findings in the rabbit toxicity studies were limited to the eye. Cataracts and/or lens fiber degeneration were observed by ophthalmological examination and/or histopathological evaluation in two studies (9 and 24 month duration) and may be related to pharmacologic effects of FA. The 24-month toxicity study observed dose-dependent increase in the frequency and severity of cataracts at nominal daily doses of 0.5 and 1.0 µg FA/day; however, there were no apparent ocular effects at a nominal daily dose of 0.2 µg FA/day. Other ocular findings (*e.g.,* focal retinal scarring) were considered likely related to experimental procedures, rather than FA itself.

No systemic toxicity was observed in either study. The absence of characteristic systemic effects of glucocorticoids such as body weight gain, Cushingoid syndrome, reductions in lymphocytes and lymphoid organ weights, and hepatic glycogen deposition and fatty liver changes (Brunton 2006) was most likely due to the minimal systemic exposure resulting from the intravitreal route of administration. FA was not genotoxic in a core battery of *in vitro* and *in vivo* tests. Carcinogenicity and developmental/reproductive studies have not been conducted because FA systemic exposure is very low following intravitreal administration. FA has been previously shown to be teratogenic and an abortifacient in rats and rabbits (Kihlstrom 1987; Casilli 1977). However, the doses of FA that produced these developmental and reproductive effects are several thousand-fold higher than the amount of FA per day released by the FAI insert.

5.3.2. Clinical Data

Details of the clinical data summarized below can be found in the Investigator's Brochure (IB) that accompanies this protocol. There are two products related to the FAI insert (Retisert® and Iluvien®) for which there is considerable previous human experience that is relevant to the clinical evaluation of the FAI insert.

5.3.2.1. Previous Human Experience with Retisert

Retisert is a sustained release intravitreal product indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye [Retisert® Prescribing Information (June 2011)]. Retisert contains 0.59 mg FA and is surgically inserted into the affected eye through a pars plana incision. Retisert is designed to release FA at a nominal initial rate of 0.6 µg FA/day decreasing over the first month to a steady state between 0.3-0.4 µg FA/day over approximately 30 months. Because Retisert and the FAI insert both utilize FA as the active ingredient, previous human experience with Retisert identifies potential FA-related safety issues that are relevant to the clinical studies proposed for the FAI insert.

5.3.2.1.1. Chronic Non-infectious Uveitis Affecting the Posterior Segment of the Eye

FDA approval of Retisert was based on two randomized, double-masked multicenter controlled clinical trials that enrolled 224 patients with chronic non-infectious uveitis affecting the posterior segment of one or both eyes.

Efficacy

The primary efficacy endpoint in both trials was the rate of recurrence of uveitis affecting the posterior segment of the study eye in the 34 week pre-implantation period compared to the

rate of recurrence at the 34 week post-implantation period. Both studies demonstrated that recurrences occurred significantly less frequently in the Retisert treatment group compared to historic control (Study 1: 1.8% vs. 53.7%; Study 2: 12.9% vs. 39.7%, respectively).

Safety

Nearly all phakic eyes treated with Retisert developed cataracts and required cataract surgery over a three year period. Additionally, over a three year period, approximately 77% of patients receiving Retisert required medication to control elevated IOP and 37% required filtering operations to control elevated IOP. Note: these trials included patients who at baseline had an IOP as high as 25 mmHg while receiving as many as two medications to control IOP.

The above risks are consistent with risks generally associated with intraocular corticosteroid administration, which have also been previously shown to be associated with posterior subcapsular cataract formation and elevated IOP and/or glaucoma.

Cases of late onset endophthalmitis were also observed in these trials, often related to the integrity of the wound site. Other surgical complications include choroidal detachment, hypotony, increased intraocular IOP, retinal detachment, vitreous hemorrhage, wound dehiscence, and exacerbation of ocular inflammation.

5.3.2.1.2. Diabetic Macular Edema (DME)

Retisert has been evaluated in a clinical study of 198 patients with DME (Pearson 2011).

Efficacy

Two years after enrollment, 31.8% of Retisert-treated patients experienced an improvement in BCVA of at least 15 letters, versus 9.3% of SOC-treated patients. This difference was statistically significant ($p = 0.0016$). Three years after enrollment 31.1 % of Retisert-treated patients experienced an improvement in BCVA of at least 15 letters, versus 20.0% of SOC-treated patients. This difference was not statistically significant.

Safety

Nearly all phakic eyes treated with Retisert developed cataracts and required cataract surgery over a four year period. Additionally, 61.4% of patients receiving Retisert experienced IOP $\geq$ 30 mmHg and 33.8% required surgical intervention to control IOP. Surgery-related adverse events reported in this trial were similar to those reported in the uveitis studies described in Section 5.3.2.1.1. Note: this trial included patients who at baseline had an IOP < 21mmHg while receiving no more than one IOP lowering medication.

The types and incidences of adverse events associated with Retisert in this DME clinical trial were highly similar to those reported for Retisert in the uveitis clinical trials described in Section 5.3.2.1.1.

5.3.2.2. Previous Human Experience with Iluvien

Iluvien is an intravitreal product candidate that is designed to provide long term delivery of FA and is administered by injection. Iluvien was invented by pSivida and licensed to Alimera Sciences, Inc. for certain ophthalmic indications, excluding uveitis. Two Iluvien product

candidates were evaluated in clinical trials under IND 072056; both contained 0.18 mg FA. A "high dose" Iluvien insert was designed to provide a nominal initial release rate of 0.5 µg FA/day slowing to 0.2 µg FA/day. A "low dose" Iluvien insert was designed to provide a constant nominal release rate of 0.2 µg FA/day for 36 months. Both inserts were administered by intravitreal injection. Due to similar efficacy and a better safety profile the low dose Iluvien insert has been selected for further development by Alimera Sciences.

The "low dose" Iluvien insert and the FAI insert are virtually the same:

- The composition of the FAI insert is the same as the composition of the Iluvien insert, with respect to active ingredient (FA), excipients (PVA and WFI) and insert components (polyimide tubing, silicone adhesive and PVA membrane).
- The FA release rates of the FAI insert and the "low dose" Iluvien insert are the same; both drug products are designed to release FA for 36 months.

Consequently, previous human experience with Iluvien is highly relevant to the clinical studies that evaluate the FAI insert.

5.3.2.2.1. Pharmacokinetics

The pharmacokinetics of FA release from high dose or low dose Iluvien inserts in human subjects with DME was assessed using plasma and aqueous humor sampling (Campochiaro 2012). This three year study demonstrated that Iluvien inserts release FA continuously within the eye for 36 months, and that FA is not measurable in the plasma at any time through 36 months.

FA levels in the aqueous humor of subjects receiving a low dose Iluvien insert (the same drug product as the FAI insert) were initially 2 ng/mL (month 1), gradually decreasing to 0.5 ng/mL (month 36).

Systemic FA levels were below the level of detection at all time points. This observation is consistent with the low systemic bioavailability of FA associated with an intraocular route of administration and the low intraocular daily dose released by the Iluvien inserts.

These clinical findings are generally consistent with the results of a rabbit pharmacokinetics study (see Section 5.3.1.2 above). One difference observed between rabbit and human data concerns the concentrations of FA detected in the aqueous humor. In rabbits, FA was typically not detected in the aqueous humor; in humans, FA was detected in the aqueous humor at every time point through Month 36. This difference may be due to species differences in ocular clearance.

5.3.2.2.2. Diabetic Macular Edema (DME)

Two large studies in DME patients (FAME A and B) were performed as randomized, double-masked, sham injection-controlled, parallel-group, multi-center studies of 36-month duration. The studies enrolled patients with DME who had received prior laser photocoagulation and who, at baseline, had a retinal thickness ≥ 250 microns.

The studies both evaluated the "high dose" and "low dose" Iluvien inserts, which were administered by intravitreal injection.

The entry criteria for the FAME studies were similar to those used in the Retisert DME study (Section 5.3.2.1.2), with one notable difference. In the Retisert DME study, a patient could be enrolled if baseline IOP was < 21mmHg while receiving no more than one IOP lowering medication. In the Iluvien DME studies, a patient could be enrolled if baseline IOP was below 21mm Hg while receiving no IOP-lowering medication. (Note: Protocol PSV-FAI-001uses this same inclusion criterion.)

Efficacy

The studies' primary efficacy endpoint was the proportion of subjects with ≥ 15-letter improvement in BCVA at Month 24; the primary efficacy endpoint was also assessed at Month 36. Statistically significant differences (vs. sham) were demonstrated in both treatment groups in both studies at 24 months. The efficacy of the 0.2 µg FA/day dose was similar to that of the 0.5 µg FA/day dose.

Safety

Systemic Adverse Events

Since FA released from Iluvien is not measurable in the plasma of humans or rabbits at any time following administration, systemic effects related to study drug were not expected. This expectation was consistent with the adverse events collected in the FAME studies: of the 1524 treatment emergent adverse events (TEAEs) reported overall in these two studies that were considered by the investigator to be drug-related, only 3 events were systemic in nature (3 cases of headache).

A higher incidence of anemia (irrespective of relationship to drug) was observed in subjects who received Iluvien compared to sham (3%, sham; 7%, 0.2 µg FA /day; 9%, 0.5 µg FA /day). The cause of this increase is not known and was not considered by the Data Monitoring Safety Board to be related to FA. It has been hypothesized that the increase may be due to the use of oral carbonic anhydrase inhibitors (CAIs) (which occurred more frequently in the active treatment groups). This class of IOP-lowering drugs is known to exacerbate renal dysfunction and possibly compromise erythropoietin production. A post-hoc analysis was performed in which all subjects were categorized with or without anemia and with or without a systemic CAI (administered during or within 90 days of anemia). Based on a Pearson chi-square test, there was a relationship between the use of a CAI and anemia in the 0.2 µg FA /day group (p-value <0.0001, and in the 0.5 µg FA /day group (p=0.0073).

Deaths and Serious Adverse Events

A total of 56 (6%) deaths were reported in the FAME studies. None of the deaths were attributed to study drug or unexpected in the patient population.

A total of 401 (42%) subjects had at least 1 drug-related serious adverse event (SAE), all of which were ocular in nature. The overall incidence of drug-related SAEs was several-fold higher in the Iluvien insert groups relative to sham.

Ocular Adverse Events

In the FAME Studies, the most common drug-related TEAEs were cataract operation (39% of subjects), cataract (36%), increased intraocular pressure (25%), and myodesopsia (8%).

Cataract-Related Events in Phakic Subjects

The FAME studies enrolled 621 subjects with phakic study eyes at baseline; the remaining 335 study eyes were pseudophakic at baseline. The incidence of cataract in the study eye was higher in the active treatment groups [80% (low dose), 88% (high dose)] than in the sham group (46%). The most common types of cataracts in the study eye were cataract (NOS) and posterior subcapsular cataract, both of which were reported more frequently in the active treatment groups than in the sham group. The percentage of phakic subjects who had a cataract operation in the study eye was also higher in the active treatment groups [75% (low dose), 85% (high dose)] than in the sham group (23%).

IOP-Related Events and Procedures

In the study eye, elevated intraocular pressure was reported as a TEAE more frequently in the active treatment groups than in the sham group, for the following parameters:

- IOP increase from baseline ≥ 12 mmHg
- IOP value >25 mmHg
- IOP value >30 mmHg
- Surgical intervention to control elevated IOP

The most common IOP-related procedure in the study eye was trabeculectomy, which occurred in 3% of subjects overall. Other procedures were performed in less than 2% of all subjects and included vitrectomy for elevated IOP or device removal, or trabeculoplasty in the study eye.

5.3.2.2.3. Other Patient Populations

Iluvien is also being evaluated in subjects with age-related macular degeneration, geographic atrophy or retinal vein occlusion.

The interim safety data from these studies are consistent with the safety profile observed for Iluvien in DME subjects and do not provide any new safety signal.

5.4. Study Rationale

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. Specifically, the FAI insert has been designed to:

Eliminate the need for surgical implantation:
The FAI insert to be used in the present study is inserted into the eye by injection, using a pre-loaded applicator with a 25 g needle. In contrast, Retisert® devices are surgically placed via a 3-4 mm incision.

Eliminate the side effects associated with the use of systemic corticosteroids or immunomodulating drugs:

Systemic corticosteroids and non-steroidal immunosuppressive agents are currently used for treating posterior uveitis. These therapies often fail because sufficient drug does not reach the uveal tissues due to the presence of a "blood-eye" barrier. Systemic toxicities are dose limiting for those medications. The FAI insert can be injected into the vitreous cavity of the eye, where it slowly releases FA over a period of 36 months. Intravitreal delivery of FA minimizes systemic exposure and thereby reduces systemic side effects.

Yield efficacy comparable to Retisert (recurrence of uveitis):

Although the FA dose delivered by the FAI insert (0.2 µg/day) is lower than the FA dose delivered by Retisert (0.5-0.6 µg/day), it is anticipated that the FAI insert will prevent the recurrence of uveitis as effectively as Retisert. This expectation is based upon nonclinical and clinical observations:

Nonclinical studies of FA intravitreal administration have demonstrated that FA levels in the vitreous humor are 10- to 80-fold higher than FA levels in the aqueous humor, and that an FA dose as low as 0.1 µg FA /day controlled inflammation in the posterior segment. In clinical studies, FA concentrations were consistently detected in the aqueous humor at levels of 0.5 – 1.0 ng/ml in patients who had received an Iluvien insert delivering 0.2 µg/day. If one applies the nonclinical study findings to these data, then FA concentrations in the vitreous humor of these patients should have ranged from 5-80 ng/ml. These concentrations are predicted to be sufficiently high to achieve pharmacologic activity in the posterior tissues of the eye, given the potency of FA for glucocorticoid receptor transactivation in vitro [IC50 ≈ 1 nM (0.45 ng/ml); Nehmé 2009)].

Clinical study results are consistent with this prediction: low dose Iluvien (0.2 µg FA/day) and Retisert demonstrated comparable efficacy in DME patients (Table 2).

Yield an improved safety profile compared to Retisert, with respect to elevated IOP

The use of the FAI insert in uveitis patients is anticipated to result in fewer adverse events associated with elevated IOP than have been previously observed with Retisert. This expectation is based on a comparison of the safety observed in DME patients of low dose Iluvien versus Retisert (Table 2).

Table 2: Efficacy and Safety of Iluvien and Retisert in DME trials

Treatment [data source]	Outcome		
	Efficacy	Safety	
	BCVA ≥ 15 letters	IOP ≥ 30 mmHg	IOP lowering surgical interventions
Retisert [Pearson 2011]	31% (vs. 9% SOC) @ 24 months	61.4% (vs. 5.8% SOC) @ 48 months	33.8% (vs. 0% SOC) @ 48 months
"Low dose" Iluvien (0.2 µg FA/day)[2] [Alimera Biosciences 2011]	28.7% (vs. 16.2% sham) @ 24 months	18.4% (vs. 4.3% sham) @ 36 months	4.8% (vs. 0.5% sham) @ 36 months

pSivida expects that the IOP-related safety profile of the FAI insert in uveitis patients will be comparable to that of low dose Iluvien in DME patients.

This expectation is predicated on observations from previous clinical trials with Retisert: the IOP-related safety profile of Retisert is similar in both DME and uveitis patients (Table 3).

Table 3: IOP-Related Adverse Events Observed in Retisert Clinical Trials

Study	Safety Outcome	
	Elevated IOP (AE description)	IOP lowering surgical interventions
Diabetic macular edema [Pearson 2011]	61.4% (≥30mmHg) @ 48 months	33.8% @ 48 months
Chronic non-infectious uveitis affecting the posterior segment [Retisert Prescribing Information (June 2011)]	77% (require medication to lower IOP) @ 36 months	37% @ 36 months

5.5. Description of the FAI insert (Test Article)

5.5.1. Drug Name

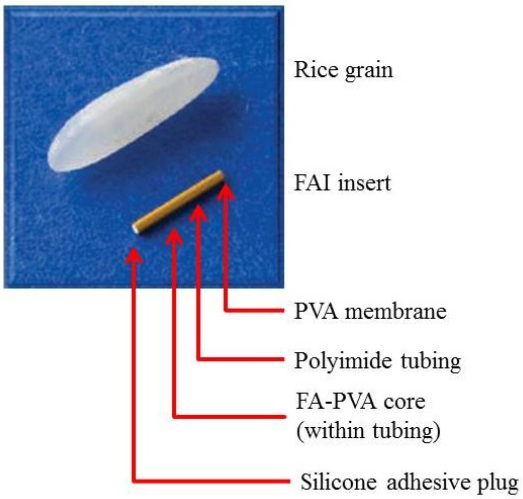
Fluocinolone acetonide is the active ingredient in the FAI insert.

Fluocinolone acetonide is a member of a class of fluorinated synthetic corticosteroids that includes dexamethasone, triamcinolone acetonide and fluocinolone acetonide.

5.5.2. Drug Formulation

FA is combined with one excipient, polyvinyl alcohol (PVA), to form a FA-PVA core (3.5 mm length x 0.34 mm diameter) that is contained within a polyimide tube. The polyimide tube has a permeable PVA membrane at one end and an impermeable silicone adhesive plug on the other end. Figure 1 shows the FAI insert adjacent to a grain of rice.

Figure 1: FAI Insert



5.5.3. Route of Administration

The FAI insert is administered as an intravitreal injection. The FAI insert is provided in a sterile preloaded applicator with a 25 g needle and is administered via injection through the pars plana.

5.5.4. Dose and Duration

The FAI insert contains 0.18 mg FA and delivers FA into the vitreous humor for 36 months, as demonstrated in a clinical pharmacokinetics study of Iluvien (Campochiaro 2012). In vitro data demonstrate that initial FA release occurs at a rate of approximately 0.2 µg FA/day, gradually decreasing over three years to a rate of approximately 0.1 µg FA/day.

6. TRIAL OBJECTIVES AND PURPOSE

6.1. Primary Objective

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.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This trial is a 36 month, Phase 3, multi-national, multi-center, randomized, masked, controlled, safety and efficacy study of FAI inserts in subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

As depicted in Figure 2, subjects will receive either a FAI insert or sham injection on Day 1 of the study; subjects will be assessed according to the schedule presented in Table 4.

7.2. Number of Subjects

A total enrollment of approximately 120 subjects is planned for this study.

7.3. Control

Sham injection

7.4. Measures Taken to Minimize Bias

To minimize bias, two investigators will be used at each study site. One investigator will serve as the unmasked treating investigator (Investigator 1) and the other investigator will serve as the masked assessing investigator (Investigator 2). On study Day 1, Investigator 1 will inject the FAI insert or perform a sham injection, and will perform all study Day 1 assessments. All other study assessments will be performed by Investigator 2. Only Investigator 1 will know the assigned treatment. Study personnel will use every reasonable effort to maintain the study mask.

7.5. Number of Study Centers

This study will be conducted at approximately 40 to 50 study sites.

7.6. Study Duration

All subjects will be followed for 36 months after treatment.

Figure 2: Study Design

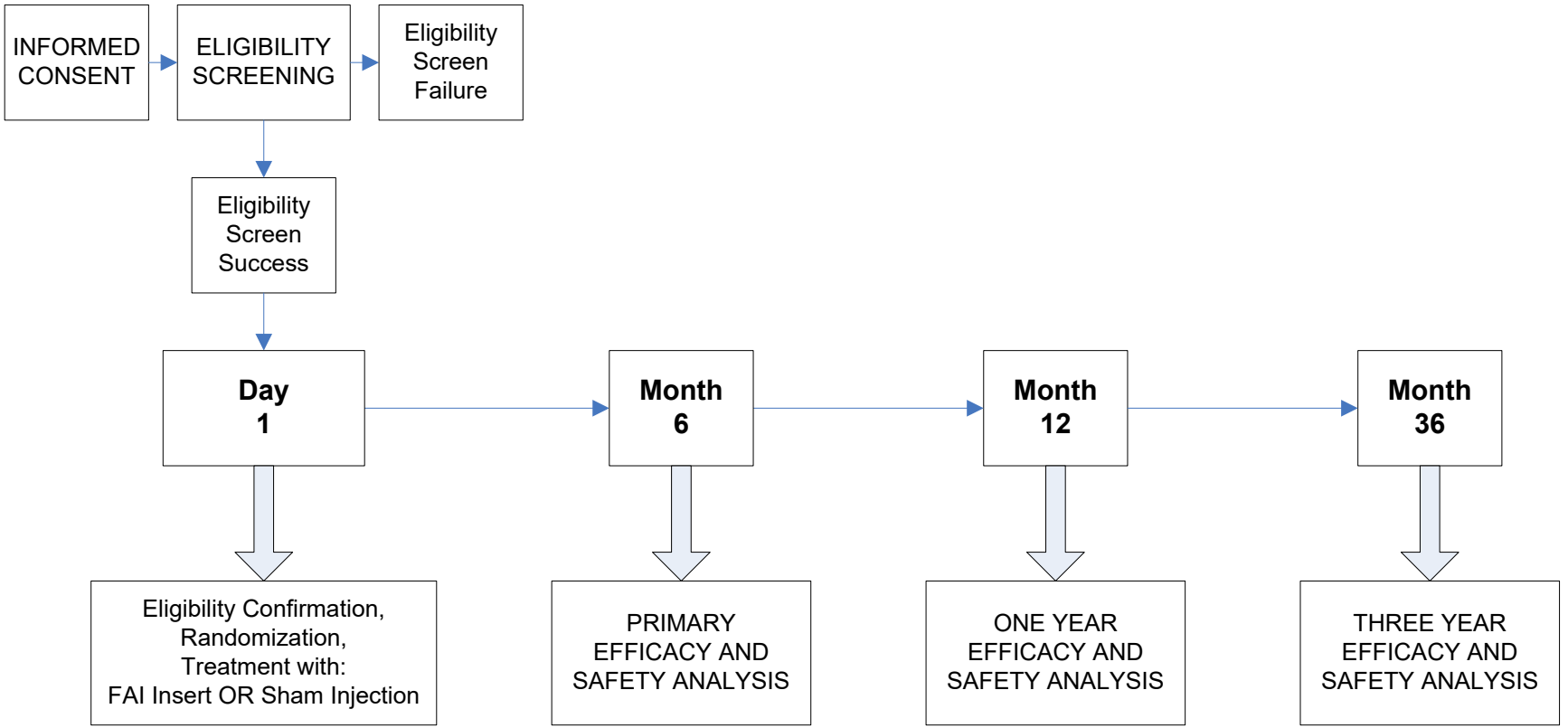


Table 4: Schedule of Procedures and Assessments

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[a]
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[e]
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

[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; ESR; serum chemistry; urinalysis; HIV and syphilis serology testing; TB 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.

8. SELECTION AND WITHDRAWAL OF SUBJECTS

8.1. Subject Inclusion Criteria

- Male or non-pregnant female at least 18 years of age at time of consent
- One or both eyes having a history of recurrent non-infectious uveitis affecting the posterior segment of the eye with or without anterior uveitis ≥ 1 year duration.
- During the 12 months prior to enrollment (Day 1),

  the study eye has either received treatment:

  - systemic corticosteroid or other systemic therapies given for at least 3 months, and/or
  - at least 2 intra- or peri-ocular injections of corticosteroid for management of uveitis

  OR the study eye has experienced recurrence:

  - at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid
- At the time of enrollment (Day 1), study eye has < 10 anterior chamber cells/HPF and a vitreous haze ≤ grade 2.
- Visual acuity of study eye is at least 15 letters on the ETDRS chart
- Subject is not planning to undergo elective ocular surgery during the study
- Subject has ability to understand and sign the Informed Consent Form
- Subject is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

8.2. Subject Exclusion Criteria

- Allergy to fluocinolone acetonide or any component of the FAI insert
- History of posterior uveitis only that is not accompanied by vitritis or macular edema
- History of iritis only and no vitreous cells, anterior chamber cells or vitreous haze
- Uveitis with infectious etiology
- Vitreous hemorrhage
- Intraocular inflammation associated with a condition other than noninfectious uveitis (e.g. intraocular lymphoma)
- Ocular malignancy in either eye, including choroidal melanoma
- Toxoplasmosis scar in study eye; or scar related to previous viral retinitis
- Previous viral retinitis

- Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, mycobacterial infections of the eye or fungal diseases of ocular structure
- Media opacity precluding evaluation of retina and vitreous
- Peripheral retinal detachment in area of insertion
- Diagnosis of any form of glaucoma or ocular hypertension in study eye at Screening, unless study eye has been previously treated with an incisional surgery procedure that has resulted in stable IOP in the normal range (10-21 mmHg)
- Intraocular pressure (IOP) > 21 mmHg or concurrent therapy at screening with any IOP-lowering pharmacologic agent in the study eye
- Chronic hypotony (< 6 mmHg)
- Ocular surgery on the study eye within 3 months prior to study Day 1
- Capsulotomy in study eye within 30 days prior to study Day 1
- Prior intravitreal treatment of study eye with Retisert within 36 months prior to study Day 1
- Prior intravitreal treatment of study eye with Ozurdex within 6 months prior to study Day 1
- Prior intravitreal treatment of study eye with Triesence or Trivaris within 3 months prior to study Day 1
- Prior peri-ocular or subtenon steroid treatment of study eye within 3 months prior to study Day 1
- Subjects requiring chronic systemic or inhaled corticosteroid therapy (>15mg prednisone daily) or chronic systemic immunosuppressive therapy
- Excluding certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to study Day 1
- Subjects who test positive for human immune deficiency virus (HIV)or syphilis during screening
- Mycobacterial uveitis or chorio-retinal changes of either eye which, in the opinion of the Investigator, result from infectious mycobacterial uveitis
- Systemic infection within 30 days prior to study Day 1
- Any severe acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or could interfere with the interpretation of study results and, in the judgment of the investigator, could make the subject inappropriate for entry into this study
- Any other systemic or ocular condition which, in the judgment of the investigator, could make the subject inappropriate for entry into this study

- Treatment with an investigational drug or device within 30 days prior to study Day 1
- Pregnant or nursing females; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception as outlined in this protocol from at least 14 days prior to study Day 1 until the Month 12 Visit
- Subjects unlikely to comply with the study protocol or who are likely to be lost to follow-up within three years

9. STUDY PROCEDURES

9.1. Subject Screening and Informed Consent

The investigator will obtain written informed consent from each subject as a condition of enrollment in the study. Informed consent will be obtained after providing the prospective study participant with an adequate explanation of the protocol procedures and prior to the subject's participation in the study (including screening procedures).

The content of the informed consent form (ICF) will conform to FDA regulations as defined in 21 CFR Part 50, other necessary Regulations, and must have current Institutional Review Board (IRB)/ Ethics Committee (EC) approval.

The subject will sign the ICF before any study procedures are initiated. The subject or guardian will sign and date one or two copies of the ICF in the presence of the investigator or designee, in accordance with applicable local requirements. A signed original copy will be retained with the subject records, and either a copy of the signed original or another signed original of the ICF will be given to the subject, in accordance with applicable local requirements. .

9.2. Assignment of Subject Identification Number

Once a subject has provided written informed consent, and it has been determined that the subject will undergo screening, a Subject Identification (PtID) Number will be assigned by the study site. The first 2 digits of the PtID number will be the assigned site number as followed by a 3-digit number in sequential order (i.e., 01-001, 01-002, etc.).

The PtID number and subject initials (where permitted by local authorities) are to be recorded on all study documents and will link the documents to the subject's medical record. To maintain confidentiality, the subject's name should not be recorded on any study document other than the ICF.

Only those patients who have been randomized will have Exclusion/Inclusion data recorded on the electronic case report forms (eCRF).

9.3. Randomization

Following confirmation of eligibility at Day 1, 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). Randomization will be stratified on the basis of whether the patient is receiving systemic treatment to control uveitis at the time of study entry.

The randomization schedule will be prepared using a blocked randomization and will be generated by an independent statistician.

The treatment assignment will be revealed to the assessing investigator only in emergency situations when medical/supportive care cannot be provided without determining if the subject received the FAI insert.

9.3.1. Unmasking

Unmasking a subject's treatment to the assessing investigator should only be done in emergency situations for reasons of subject safety.

At the initiation of the study, the clinical sites will receive instructions for unmasking a subject.

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 back-up 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.

9.4. Screen Failures

Study centers will document all screen failures on the Subject Screening/Enrollment Log with the reason for the failure to be enrolled. Subjects who fail to meet inclusion/exclusion criteria during the screening period or on study Day 1 may be rescreened.

9.5. Study Schedule

See Table 4 for the schedule of visits and assessments. The screening visit and Day 1 (administration of study treatment) are to be within a 30-day period. The windows for the follow-up visits are Day 7: +/- 2 days; Day 28: +/- 3 days; Months 2, 3: +/- 7 days; Months 6, 9, 12, 18, 24, 30 & 36: +/- 28 days.

9.6. Screening

All study data will be collected for the study and fellow eye.

After obtaining informed consent, the following assessments will be performed:

- Demographic information, medical history and ophthalmic history including a detailed history of the subject's posterior uveitis and its management over the previous 12 months
- Physical exam including height, weight and vital signs (includes systolic/diastolic blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Obtain blood samples for routine clinical laboratory tests (hematology, ESR, serum chemistry)

- HIV and syphilis serology testing
- TB testing
- Ophthalmic exam (including BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations)
- Visual field
- Collect urine for Urinalysis and for Urine pregnancy test (females of childbearing potential)
- Subjective Ocular Tolerability and Discomfort Assessment
- Concomitant medications
- Verification that the subject satisfies all inclusion and exclusion criteria. Do not continue screening any subject who does not meet the screening eligibility requirements.

9.7. Procedures on Day of Treatment

9.7.1. Designation of Study Eye and Randomization

For subjects with unilateral uveitis, the study eye will be the affected eye. For subjects with bilateral uveitis, the study eye will be the worse eye meeting the inclusion/exclusion criteria. For subjects with symmetrical uveitis the study eye will be the right eye. The non-study eye may receive any local ocular treatment at the discretion of the investigator.

If the subject meets the inclusion and exclusion criteria at Screening and Day 1, the randomization to the FAI insert or sham injection will be performed via the IVRS. Randomization will be stratified on the basis of whether the patient is receiving systemic treatment to control uveitis at the time of study entry. For patients receiving systemic treatment at time of study entry, randomization will be stratified on the basis of the type of treatment (steroid or immunosuppressant).

To preserve study masking as much as possible within the imposed ethical constraints, the study personnel who administer the assigned treatment will refrain from performing any subject assessments after study Day 1. Treatment assignments will be masked to the subjects and to those involved in administering routine follow-up care to the subjects. Follow-up assessments will only be performed by study personnel at the site who are masked to the assigned treatment.

9.7.2. Data Collection Prior to Injection of FAI Insert or Sham Injection

- Vital signs (blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes)
- Ophthalmic exam (including BCVA, IOP [recorded as the mean of three measurements], dilated indirect ophthalmoscopy and slit lamp examinations)
- Determination of < 10 anterior chamber cells/HPF and a vitreous haze ≤ grade 2 for study eye

- OCT
- Urine Pregnancy test
- Concomitant medications
- Subjective tolerability and discomfort assessment
- Verification that the subject satisfies all other inclusion and exclusion criteria

9.7.3. FAI Insert Injection Procedure

1. Administer a topical antibiotic at the rate of one drop every 5 minutes for a total of 3 drops prior to the injection of the FAI insert.
2. Just prior to the insert injection, administer additional topical anesthesia over the injection site as one- two drops followed by either a cotton-tipped applicator soaked in anesthetic or as subconjunctival administration of lidocaine.
3. Administer 2-3 drops of 5% Betadine topically into the lower fornix. The lids may be scrubbed (if necessary) with cotton-tipped applicators soaked in 5% Betadine. Place a sterile lid speculum. Have the subject look up and apply a cotton-tipped applicator soaked in Betadine to the injection site. Allow 30-60 seconds for the Betadine to dry prior to insert injection.
4. Mark the injection site 3.5-4.0 mm posterior to the limbus in inferior quadrant with either calipers or the blunt end of a sterile tuberculin syringe.
5. Open the foil pouch containing the applicator. Retain the foil pouch with the patient's source documents. Prior to inserting the needle, the conjunctiva should be gently displaced so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Insert the needle at the marked site up to the hub. Once plunger is depressed fully and the insert has been delivered, remove the applicator.
6. Administer 1-2 drops of topical antibiotic. Remove the lid speculum.
7. Perform indirect ophthalmoscopy to verify adequate central retinal artery perfusion, absence of any other complications, and to verify the placement of the insert.
    a. If the FAI insert is observed to be misplaced within the eye, please contact the unmasked monitor and sponsor immediately. Administration of a second FAI insert within the study eye is not permitted.
8. Discard the used applicator.
9. Determine IOP [recorded as a mean of three measurements within 10 minutes of injection and at 60 minutes following the injection]
10. For post-administration follow-up, prescribe a topical antibiotic for the subject to self-administer 4 times per day for 3-5 days
11. Contact the subject on the next day to follow up on the subject's ocular condition and to identify any complaint and/or adverse event.

9.7.4. Sham Injection Procedure

Subjects assigned to the sham injection control group will be prepared for injection in the same manner as the subjects in the FAI insert treatment group (steps 1-4 above) and will receive the same post-treatment evaluations and medications as the FAI insert group (steps 6-11 above). Only step 5 is different. When the investigator opens the treatment packaging for a subject assigned to the sham injection control group, the package will contain a syringe with a blunt needle attached. The sham injection will consist of pressing the blunt needle against the sclera of the eye with approximately the same pressure as would be used during the injection of a FAI insert.

9.8. Criteria for FAI Insert Removal

Investigators should consider removing the FAI insert if any of the following events occur:

- Apparent intolerance to insert
- Endophthalmitis
- Partial extrusion or exposure of insert

Based on prior human experience with Iluvien, a product virtually identical to the FAI insert (refer to the Investigator's Brochure for more details), the likelihood that insert removal will become necessary is very small.

9.9. Post-Treatment Visits and Long Term Follow-up

Investigator 2 (masked investigator) will be responsible for all safety and efficacy procedures and assessments following Day 1.

The subject will return to the study site on Day 7, 28 and Months 2, 3, 6, 9, 12, 18, 24, 30, and 36, for a total duration of 36 months. Subjects may be seen more frequently if medically indicated. Table 4 provides descriptions of the ophthalmic assessment procedures to be performed, as indicated, at the scheduled visits. All assessments are made for both eyes of all subjects.

9.9.1. Post-Treatment Follow-up (Days 7 & 28)

Assessments include: Vital signs (blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes); Ophthalmic exam (BCVA, IOP, dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations); OCT (Day 28); subjective ocular tolerability and discomfort assessment; concomitant meds and AEs.

9.9.2. Long-Term Follow-up (Months 2, 3, 6, 9, 12, 18, 24, 30, & 36)

Assessments include: Vital signs (blood pressure and pulse rate after subject is in the sitting position for at least 5 minutes); Ophthalmic exam (BCVA, IOP, dilated indirect ophthalmoscopy and anterior, posterior and intermediate slit lamp examinations); subjective ocular tolerability and discomfort assessment; visual field (Months 12, 24 and 36); OCT, pregnancy test (Months 12, 24 and 36) and concomitant Meds and AEs.

9.10. Concomitant Medications/Procedures

9.10.1. Tapering/Ending Systemic or Topical Uveitis Treatment Following Day1

Subjects may be treated prior to entry in order to meet study inclusion criteria. The objective of prior treatment is to obtain a relatively quiet eye prior to enrollment. 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 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 reduction are not considered prohibited medications.

9.10.2. Prohibited Medications

Other than the exceptions described in Section 9.10.1, Section 9.12 or in this section below, the following concomitant medications are not permitted during the study:

- Oral, systemic, injectable, or topical steroids
- Systemic immunosuppressants

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering), as described in Section 9.10.1, are not considered prohibited medications. Additionally, topical steroids administered as short term standard treatment following an ocular surgical procedure are not considered prohibited medications.

It is advisable for the PI to discuss treatment with the Medical Monitor before administering any prohibited medication unless it is an emergency.

9.10.3. IOP Reduction Therapy

Pharmacologic treatment (eyedrops) of elevated IOP must be instituted whenever the IOP is >30 mmHg, and may be instituted at lower IOP levels, at the discretion of investigator 2 and in accordance with the investigator's standard of care. Treatment may include referral to another ophthalmologist. If IOP does not adequately respond to pharmacologic treatment, alternative treatment should be considered (laser, trabeculectomy). The investigator should obtain information on the treatment administered by non-study ophthalmologists for inclusion in the study records.

9.10.4. Cataract Removal and Other Elective Ocular Surgery

Cataracts are recommended to be removed by extra-capsular extraction with phacoemulsification. A cataract may be removed prior to a subject's enrollment.
Because of the importance of VA evaluations in this study, the timing of cataract removal or any elective surgery during the post-treatment follow-up period should be scheduled at least 4 weeks prior to any study visit involving VA assessment.

9.11. Unscheduled Follow-up Visits

Additional examinations may be conducted as necessary to ensure the safety and well-being of subjects during the study period. Electronic case report forms (eCRFs) should be completed for each unscheduled visit or test that the subject completes.

9.12. Treatment of Recurrences of Uveitis

In the event of a uveitis recurrence in either eye (defined as an "Endpoint"), peri-ocular or intraocular corticosteroid injections, or topical medications should be administered as first line local therapy, in accordance with the protocol. Investigators should consider treatment with topical steroids as first line therapy for a recurrence that involves only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic immunosuppressants or systemic steroids should be used only if local therapy fails.

Subjects who experience a recurrence of uveitis will continue participation in the study. Once the subject's recurrence is controlled, the treatment regimen (local or systemic therapy) will be ended in a manner that follows the standard of care for ending the specific treatment regimen.

Details of each recurrence and its treatment will be documented in the eCRF.

9.13. Description of Procedures

Refer to Table 4 and the appendices (Sections 18, 19, and 20) for more details.

9.13.1. Slit Lamp Examination

Slit lamp examination should be performed using the investigator's standard procedure. This procedure should be the same for all subjects examined at the site and use the same equipment. Observations should be made to indicate the absence or presence of findings for conjunctiva, cornea, iris, and anterior and posterior chambers. All findings are to be documented in the source documentation and the appropriate eCRF.

9.13.2. Dilated Indirect Ophthalmoscopy

Dilated indirect ophthalmoscopy should be performed as part of each ophthalmic examination. This procedure should be the same for all subjects examined at the site and use the same equipment. All findings are to be documented in the source documentation and the appropriate eCRF.

9.13.3. Visual Acuity

BCVA will be measured according to the standard procedure developed for ETDRS at 4 meters or 3 meters if the electronic (E)-ETDRS system is employed. Corrected-distance VA is to be reported as number of letters read correctly by the subject. The details of refraction and VA determination procedures are provided in Section 18.

9.13.4. OCT

Optical coherence tomography (OCT) will be performed; Cirrus or Spectralis instruments are preferred.

9.13.5. Intraocular Pressure

Applanation tonometry (preferably Goldmann) will be used for IOP measurements where an average of 3 measurements will be recorded using the investigator's standard procedure.

9.13.6. Subjective Ocular Tolerability and Discomfort Assessment

Refer to Appendix 3 (Section 20) for details:

- Subjective ocular discomfort grading
- Subjective tolerability using visual analog scale for pain

9.14. Laboratory Testing

Clinical laboratory testing will include:

- Hematology (standard tests)
- ESR
- electrolytes: sodium; potassium; chloride; calcium; bicarbonate/CO_2
- renal function: serum creatinine, BUN
- hepatic function: serum bilirubin, alkaline phosphatase, SGOT/AST, SGPT/ALT, total albumin, total protein
- HIV and syphilis serology testing
- Screening test for latent mycobacterium tuberculosis (TB) infection
- Urinalysis (standard tests)
- Urine pregnancy test (for females of childbearing potential)

9.15. Protocol Deviations

The investigator will not 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). All other significant changes to the protocol will be made by pSivida Corp. as a protocol amendment and approved by IRB/EC and the appropriate regulatory authority prior to implementation.

9.16. Study Termination or Suspension

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority.

In addition, if the investigator terminates or suspends a trial without prior agreement of pSivida, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform pSivida and the IRB/IEC, and should provide pSivida and the IRB/IEC a detailed written explanation of the termination or suspension.

If pSivida terminates or suspends this trial, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

If the IRB/IEC terminates or suspends its approval/favorable opinion of this trial, the investigator should inform the institution where applicable and the investigator/institution should promptly notify pSivida and provide pSivida with a detailed written explanation of the termination or suspension.

9.17. Subject Withdrawal Criteria

Subjects have the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. The following are examples of criteria for considering withdrawal from this study:

- Withdrawal of subject consent; or
- Intercurrent illness including death that prevents continuation of regular follow-up visits

All subjects will be followed for safety through their final visit unless withdrawn from the study for the above reasons.

The investigator, IRB/EC and pSivida Corp. also have the right to withdraw subjects from the study for the following reasons: when continuation may jeopardize the health of the subject, protocol violations, AEs or concurrent conditions, administrative or other reasons.

Subjects who withdraw for any reason from the study following randomization and administration of study treatment (FAI insert or sham injection) will not be replaced. All randomized subjects will be followed for as long as they agree to return for visits.

10. INVESTIGATIONAL MATERIALS

10.1. Test Article

10.1.1. Description

The FAI insert is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contains a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5 mm long with an external diameter of 0.37 mm. One end of the tube is capped with an impermeable polymer (silicone adhesive); the other end is capped with a permeable polyvinyl alcohol membrane. FA release occurs through the permeable end of the cylinder. Each FAI insert contains 0.18 mg FA and delivers FA into the vitreous humor for 36 months, as demonstrated in a clinical pharmacokinetics study of Iluvien (Campochiaro 2012). In vitro data demonstrate that initial FA release occurs at a rate of approximately 0.2 µg FA/day, gradually decreasing over three years to a rate of approximately 0.1 µg FA/day. The FAI insert is designed to be injected through the pars plana into the vitreous.

10.1.2. FAI Insert Packaging and Labeling

FAI inserts will be supplied as individual finished products in primary, secondary and tertiary packaging. The primary packaging is the applicator, which includes a 25 g needle that is attached to the applicator. The FAI insert is pre-loaded in the applicator, which is designed to facilitate precise placement of the FAI insert to an exact depth in the vitreous. The pre-loaded applicator is placed into the secondary packaging, a 2.5" x 15" foil chevron pouch and heat-sealed. Lastly, the foil pouch is placed into a 3.5" x 18" Tyvek chevron pouch. The outer chevron pouch will be labeled as investigational drug in accordance with applicable regulations. The assembled units are subsequently sterilized by gamma irradiation, resulting in the FAI insert Finished Product, a sterile, single-use product.

10.1.3. Investigational Product Storage

Investigational product must be stored at controlled room temperature in a secured location accessible only to study personnel.

10.2. Sham Injector

10.2.1. Description

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

10.2.2. Sham Injector Packaging and Labeling

Sham injectors will be supplied as individual finished products in primary, secondary and tertiary packaging. The primary packaging is the sham applicator, which includes a blunt needle. The sham applicator is placed into the secondary packaging, a 2.5" x 15" foil chevron pouch and heat-sealed. Lastly, the foil pouch is placed into a 3.5" x 18" Tyvek chevron pouch. The outer chevron pouch will be labeled for investigational use in accordance with applicable regulations. The assembled units are subsequently sterilized by gamma irradiation, resulting in the sham injector, a sterile, single-use product.

10.2.3. Sham Injector / Finished Product Storage

Sham injector / Finished Product units must be stored in a secure, locked location accessible only to authorized study personnel, and maintained at controlled room temperature of 15°-25ºC (59-77ºF).

10.3. Supply and Accountability of Materials

pSivida Corp. will supply the Finished Product units (FAI insert or sham injector) for this study. A log will be maintained at each study site, showing the ID number of the subject to whom each unit is dispensed, the date and who dispensed the Finished Product unit. Sufficient Finished Product units will be supplied to each investigative site to allow replacement, as necessary, of any damaged unit. The investigator must maintain records of all shipments of study materials and account for all used and unused materials. All unused and damaged study materials must be returned to pSivida Corp. or destroyed on site, with an accounting of all materials supplied, used, and returned, and an explanation for any discrepancies.

11. ASSESSMENT OF SAFETY

11.1. Adverse and Serious Adverse Events

The following are specific definitions of terms guided by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and the U.S. Code of Federal Regulations (CFR) that apply to this section.

11.1.1. Adverse Events (AE)

An *Adverse Event (AE)* is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that 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.

11.1.2. Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (The term “life-threatening” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more intense.)
- Requires in subject hospitalization or prolongs existing hospitalization
- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect
- May jeopardize the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgment should be exercised in deciding if these events should be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or life threatening event)
- Elective surgery, planned prior to signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

11.1.3. Ocular Events

11.1.3.1. Ocular adverse events

The following ocular events will be considered adverse events for the purposes of this trial:

- 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

11.1.3.2. Sight-Threatening Ocular Events Defined as SAEs in This Study

In addition to the standard SAE categories described above, this study defines these additional ocular events as SAEs:

- 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-infectives, 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

11.1.4. Laboratory Test Abnormalities

All laboratory test values captured as part of the study, including screening, should be recorded on the appropriate laboratory test results pages of the eCRF.

In addition, the following laboratory abnormalities should also be captured on the nonserious AE CRF page (paper or electronic) or SAE paper CRF page as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

11.1.4.1. Pregnancy

Sexually active women of child bearing potential (WOCBP) must be encouraged to use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

All WOCBP MUST have a **negative urine** pregnancy test within 48 hours **prior** to receiving the investigational product. If the pregnancy test is positive, the subject must not receive the investigational product and must not be enrolled in the study.

Pregnancy testing must also be performed on all WOCBP throughout the study as specified and the results of all pregnancy tests (positive or negative) recorded on the eCRF.

In addition, all WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

11.2. Adverse Event Assessment

11.2.1. Relationship to Study Treatment

The study treatment relationship to each AE should be determined by the investigator using these explanations:

Unrelated: Evidence indicates no plausible direct relationship to the study medication, device or procedure, or there is a reasonable causal relationship between noninvestigational product, concurrent disease, or circumstance and the AE.

Possibly Related: There is reasonable causal relationship between the investigational product, device or procedure and the AE. Suggests that the association of the event with the study medication, device, or procedure is unknown; however, the adverse event is not reasonably supported by other conditions.

Probably Related: Suggests that a reasonable temporal sequence of the event with medication administration, device usage or the index procedure exists and, based upon the

investigator's clinical experience, the association of the event with study medication, device or procedure is likely.

The Investigator will make the determination of relationship to the investigational product for each AE (Unrelated, Possibly Related or Probably Related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product, device or procedure. If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated."

If there is any valid reason, even if undetermined, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered as related.

If the relationship between the AE/SAE and the investigational product is determined to be "possible" or "probable" the event will be considered to be related to the investigational product for the purposes of expedited regulatory reporting.

11.2.2. Severity

AE severity is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article relationship or seriousness of the event and should be evaluated according of the following scale:

Mild: Awareness of event but easily tolerated. Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.

Moderate: Discomfort enough to cause some interference with usual activity. Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually relieved by simple therapeutic measures.

Severe: Causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment.

11.3. Recording of Adverse Events

Changes in a chronic condition or disease, part of the medical history of the patient, that are consistent with natural disease progression are not to be considered as AEs and should not be recorded as such. Medical conditions or diseases present before a subject starts study treatment are only considered AEs if they worsen after the start of the study treatment.

Adverse events can be spontaneously reported or elicited at each study visit through open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs).

The investigator will record all AEs in eCRF. If known, the diagnosis of the underlying illness or disorder should be recorded, rather than its individual symptoms.

The following information should be captured for all AEs: onset and end date, severity, seriousness, relationship to investigational product, action taken and treatment required and outcome. If treatment for the AE was administered, it should be recorded on the appropriate eCRF page.

Completion of supplemental eCRF pages may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

The investigator will take or organize all appropriate and necessary therapeutic measures required for resolution of the adverse event. Any medication necessary for the treatment of an adverse event must be recorded on the concomitant medication case report form. If more than one distinct AE occurs, each event should be recorded separately.

11.4. Adverse Event Reporting

All subjects enrolled in the study will be evaluated for adverse events. For the individual subjects, adverse events will be collected from Day 1 until study completion.

All AEs will be evaluated from their onset until resolution, stabilization, last day of participation in the study of the patient or the last day of the study, whichever is first.

Adverse events that continue after the subject's discontinuation or completion of the study will be followed until their medical outcomes are determined or until no further change in the condition is expected. The event and outcome will be reported in writing by the investigator to pSivida. The investigator shall supply the sponsor and IRB/EC with any additional requested information, notably for reported deaths of subjects.

11.4.1. Reporting of Serious Adverse Event

All SAEs that occur during the course of the study, including death, ***must be reported within 24 hours following the site's knowledge of the SAE*** and recorded on the Serious Adverse Event Page of the eCRF (or use a back-up paper form if electronic system is not functioning).

Minimal information to be provided includes:

- Identification of the study
- Identification of the initial reporter
- Patient identification number
- Event term
- Date of onset of the event
- Severity criteria of the event
- Reporting criteria
- Narrative description of the event
- Outcome if known
- Causal relationship to the investigational medication, device and procedure
- Additional and follow-up information as requested by the medical monitor

11.4.2. Reporting of Pregnancy

To ensure patient safety, each pregnancy in a female patient must be reported by the investigator to pSivida Corp., within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal or newborn complications.

Pregnancy should be recorded on a Pregnancy Report Page of the eCRF. Pregnancy follow-up should be recorded on the paper Pregnancy Report form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported as appropriate.

If any male subject's partner becomes or is found to be pregnant during the male subject's treatment with the investigational product, the investigator must submit this information to pSivida on a Pregnancy Report Form as described above.

11.4.3. Other Safety Considerations

Any significant changes noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded on the appropriate nonserious AE page of the eCRF or SAE eCRF page.

The SAE(s) is to be reported by the Investigator within 24 hours of awareness of the event via eCRF.

Sites in Europe, Asia-Pacific, Africa, and the Middle East will contact:
PPD Medical Support Center
Telephone: +44 1223 374 240
Telefax: +44 1223 374 102

Sites in North America will contact:
PPD Medical Support Center
Telephone: 800-201-8725
Telefax: 888-529-3580

11.5. Expedited Safety Reporting

Adverse drug reactions (ADRs) that are suspected, serious, and unexpected are subject to expedited reporting. Reports which add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the protocol under safety assessments would be considered "unexpected". Specific examples would be (a) acute renal failure as a labeled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

The purpose of expedited reporting is to make regulators, investigators, and other appropriate people aware of new, important information about serious adverse product reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented.

Accordingly, expedited reporting will ordinarily be inappropriate for adverse drug reactions that are serious but expected.

In accordance with local regulations, pSivida will notify investigators of all SAEs that are suspected (probably or possibly related to the investigational product) and unexpected (i.e., not previously described in the Investigator Brochure).

Investigator notification of these events will be in the form of an expedited safety report (ExSR).

Other important findings which may be reported by the sponsor as an ExSR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ExSR from pSivida, the investigator must review and retain the ExSR with the Investigator Brochure. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ExSR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

12. REPORTING OF TECHNICAL COMPLAINTS

Technical complaints include quality complaints reported in writing, electronically, or orally involving the use or attempted use of this product that identify any defects in the product (e.g., failure of the applicator to deliver the FAI insert), or dissatisfaction with any other characteristic(s) of the drug product (labeling, packaging, etc.).

Any technical complaint should be reported by telefax to pSivida Corp. (1-617-926-5050), Attention: Marty Nazzaro, within 24 hours.

The complaint report should include the following information:

- Product identification number
- Investigator name, study center name, and contact number
- Date the complaint occurred
- Brief description of the complaint
- Subject involved? (yes or no); if yes, were any AEs associated with the complaint? (yes or no), (If an AE is associated with the complaint, refer to Section 11.)

The drug container which initiated the complaint should be returned to pSivida Corp. (address below) for analysis.

Attention: Marty Nazzaro or Gerard Riedel

pSivida Corp.

480 Pleasant Street

Watertown, MA 02472 USA

Any complaint about an investigational product must be reported regardless of whether the defect or deficiency had any effect on a subject or on study personnel.

13. ASSESSMENT OF EFFICACY

13.1. 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. Recurrence is defined as:

- 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

  OR

- An increase in the vitreous haze of ≥ 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, 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 study Day 7 visit.

Refer to Appendix 2 (Section 19) for additional information.

13.2. Exploratory Efficacy Endpoints:

Exploratory endpoints include:

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

14. DATA ANALYSES

14.1. Sample Size

A two group continuity corrected Chi-square test with a 0.05 two-sided significance level will have 89% 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 40 and 80, respectively (a total sample size of 120).

14.2. Study Populations

14.2.1. Intent to Treat (ITT) Population

The ITT population will include all subjects randomized into the study; analyzed as randomized.

14.2.2. Safety Population

The safety population will include all subjects randomized into the study; analyzed as treated.

14.2.3. Per Protocol (PP) Population

The per protocol (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 defined prior to database lock)

14.3. Analyses

14.3.1. Analyses of Demographic and Baseline Data

Demographic and baseline characteristics of the ITT population will be presented in tabular summaries by treatment group. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum; categorical variables will be summarized using counts and percentages of subjects in each category.

14.3.2. Subject Disposition and Exposure

Tabulation of study completion and premature study termination along with reasons for termination will be provided by treatment group. Duration of study participation and insert duration will also be tabulated.

14.3.3. Schedule of Analyses of Efficacy and Safety

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).

14.3.4. Analyses of Efficacy

Efficacy analyses will be performed on both the ITT population and the PP population, at 6, 12 and 36 months. All primary and exploratory efficacy endpoints will be analyzed using the ITT population and the PP population. Descriptive statistics will be used in all exploratory efficacy analyses. The ITT data set analyses will be considered primary; the PP data set analyses will be considered supportive of the primary analyses.

14.3.4.1. Primary Efficacy Variable and 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 in the protocol) in the 6 months following Day 1. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis will begin after study Day 7 visit.

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

A continuity corrected Chi-square analysis will be used to assess the statistical significance of a difference between study groups in the primary efficacy analysis.

Mathematically stated:

$$H0: \text{6 Month Recurrence Free Rate}_{FAI} = \text{6 Month Recurrence Free Rate}_{Sham}$$

$$H1: \text{6 Month Recurrence Free Rate}_{FAI} \neq \text{6 Month Recurrence Free Rate}_{Sham}$$

14.3.4.2. Data Imputation

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

- A subject who has not previously experienced a recurrence and does not complete the required eye examinations at Month 6 (or Month 12 or 36 for the Month 12 or 36 analyses, respectively) for any reason 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 9.10.2 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 local concomitant medication in the study eye as defined in Section 9.10.2 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.

Systemic medications and topical steroids administered as part of gradual dose reduction (tapering) (as described in Section 9.10.1) will not be considered prohibited medications. Additionally, topical steroids administered as short term standard treatment following an ocular surgical procedure will not be considered prohibited medications (as described in Section 9.10.2).

14.3.4.3. Sensitivity Analyses for the Primary Outcome at 6, 12 and 36 Months

In addition to the conservative imputation for the primary efficacy outcome detailed in Section 14.3.4.2, the following sensitivity analyses of the primary efficacy outcome will be separately performed at 6, 12 and 36 months.

- The primary outcome will be imputed exactly as in Section 14.3.4.2 except that a subject imputed as having a recurrence because of missing eye examinations at Month 6 (or Month 12 or Month 36) for any reason will be considered as NOT having a recurrence.
- A "tipping point" analysis will be performed. This analysis will begin by using the following imputations associated with missing required eye examinations 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 14.3.4.2 will be performed during this "tipping point" analysis. Inferential analysis employing the primary analysis will be performed at each step of the "tipping point" assessment.

Additionally, for missing data due to other reasons, sensitivity analyses will be conducted by using multiple imputation methods. Further details will be provided in the statistical analyses plan (SAP).

14.3.4.4. Exploratory Analyses

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

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

14.3.4.5. Subgroup Analyses

Subgroup analyses will be performed on the primary efficacy variable. 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 baseline characteristics, including severity of edema, duration of disease, lens status, intraocular pressure, presence/absence of vitrectomy, and BCVA. Further details will be provided in the statistical analyses plan (SAP).

14.3.5. Analyses of Safety

Safety analyses will be performed on the safety population at 6, 12 and 36 months. Subjects randomized but not receiving treatment will have all safety data listed only but will not be included in safety tabulations. Descriptive statistics will be provided for all adverse events. Frequency counts and percentage of subjects within each category will be provided for categorical data. Treatment Emergent Adverse Events (TEAEs; those that occurred on the day or after treatment) will be coded to a corresponding preferred term from the MedDRA coding dictionary.

Ocular safety will be assessed by evaluating ocular TEAEs, visual acuity, IOP, concomitant medications, and slit lamp / dilated indirect ophthalmoscopy exams. Systemic safety will be assessed by evaluating all TEAEs, vital signs, concomitant medications and clinical laboratory tests by treatment group.

Adverse events will be summarized by presenting the number and percentage of subjects having at least one occurrence of any TEAE during the study, having at least one occurrence of an TEAE within each system organ class, and having at least one occurrence of each individual TEAE (preferred term) in each treatment group. Occurrence of TEAEs using MedDRA preferred term, SOC, by severity and relationship will be provided by treatment group. If a patient experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relation to the investigational product will be assigned to the SOC and preferred term for the appropriate summaries.

Treatment-emergent serious adverse events (SAEs) and TEAEs related to FAI treatment will be provided by preferred term, SOC and severity for each treatment group. Again, if a patient experiences multiple events that map to a single preferred term, the greatest severity and strongest investigator assessment of relation to the investigational product will be assigned to the

SOC and preferred term for the appropriate summaries. Adverse events leading to study discontinuation and any deaths will be listed.

Vital signs will be presented using descriptive statistics by visit in each treatment group. Concomitant medication will be summarized by presenting the number and percentage of patients receiving each medication by term and treatment after coding with WHO-Drug Dictionary terms. Laboratories assessments will be presented by descriptive statistics.

15. ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

15.1. Quality Control and Quality Assurance

pSivida Corp. employees and/or their contracted representatives utilize SOPs designed to ensure that research procedures and documentation are consistently conducted/prepared to the highest quality standards. These SOPs also require compliance with Health Authority regulations and GCP guidance.

A Quality Assurance audit may be conducted by pSivida Corp. or a designee at any time during or after completion of this study. The investigator will be given adequate notice if he/she is selected for an audit. The audit will include, but is not limited to, a review of all ICFs, a review of eCRFs, associated source documents and medical records, a review of regulatory documentation, an assessment of study conduct and protocol compliance, and a review of the investigational drug accountability. At the conclusion of an audit, the auditor will conduct a brief meeting with the investigator to review the audit findings.

15.2. Institutional Review Boards / Independent Ethics Committee

Prior to the initiation of the study, the protocol, the ICF and the Investigator's Brochure will be submitted to the IRB/EC for approval. By signing the "Statement of Investigator" form (FDA form 1572), the investigator is assuring that an IRB/EC which complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review of the proposed clinical study. A copy of the IRB/EC approval letter for the protocol, and the informed consent, as well as the protocol signature page must be submitted to pSivida Corp. or its designee prior to release of investigational supplies to the study site. The approval letter must refer to the specific protocol and informed consent form. The study site must maintain an accurate and complete record of all reports, documents and other submissions made to the IRB/EC concerning this protocol. A list of the IRB/EC members, their titles or occupations, and their institutional affiliation, or an IRB/EC assurance number must be provided to pSivida Corp. or its designee prior to release of study supplies.

FDA/relevant health authority regulations require that all advertisements for subject recruitment be approved by an IRB/EC prior to implementation. The complete text and format must be submitted to pSivida Corp. or designee for approval prior to IRB/EC submission.

The investigator is responsible for notifying the IRB/EC of any SAEs. A copy of the notification must be forwarded to pSivida Corp. or its designee.

Status reports must be submitted to the IRB/EC at least once a year (or more frequently as required by the IRB/EC) and the IRB/EC must be notified of study completion or termination.

A final report must be provided to the IRB/EC and pSivida Corp. within 6 months of study completion or termination. This report should include: any protocol deviations, the number of subjects evaluated, the number of subjects who withdrew or were withdrawn and the reasons for withdrawal, any significant AEs and the investigator's summation of the study.

15.3. Informed Consent Process

It is the responsibility of the investigator to inform each subject, prior to the screening evaluation, of the purpose of this clinical trial, including possible risks and benefits and document the informed consent process in the subject's chart. Prior to entry into the study or initiation of any study-related procedures, the subject must read, sign and date the IRB/EC approved ICF. The person executing the consent must also sign and date the final consent form page. . One or two signed originals of the ICF will be prepared, in accordance with applicable local requirements. A signed original copy will be retained with the subject records, and either a copy of the signed original or the other signed original of the ICF will be given to the subject, in accordance with applicable local requirements.

15.4. Source Documentation

The investigator must maintain adequate and accurate source documents upon which eCRFs for each subject are based. These documents are to be separate and distinct from eCRFs, except for cases in which pSivida Corp. has predetermined that direct data entry into specified pages of the subject's eCRF is appropriate. The investigator must allow access to the source documents by representatives of pSivida Corp. and regulatory authorities as needed. These records should include detailed notes on:

- The date the subject entered the study, study protocol number and name of the sponsor.
- The oral and written communication with the subject regarding the study treatment (including the risks and benefits of the study). The date of informed consent must be recorded in the source documentation.
- The subject's medical history prior to participation in the study and evidence that the subject meets study eligibility requirements
- The subject's basic identifying information, such as demographics, that links the subject's source documents with the eCRFs
- The dates of all study related subject visits.
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The subject's exposure to study treatment, documentation of study treatment accountability
- All AEs
- The subject's exposure to any concomitant therapy (including start and stop dates, route of administration, and dosage)

- All relevant observations and data on the condition of the subject throughout the study
- The date when subject exited the study and a notation as whether the subject competed the study or was discontinued, included the reason for discontinuation.

15.5. Electronic Case Report Forms

All study data must be incorporated in the corresponding electronic case report forms. The investigator will be responsible for recording all data in the eCRFs.

Data from clinical laboratory reports, etc. will be incorporated into the eCRFs either by direct transcription into appropriate eCRF pages or by inclusion of photocopies of these reports with printouts of the appropriate eCRF pages and stored in the site's Study Binder.

This study will be conducted in compliance with the regulations contained within CFR Part 11, electronic records/electronic signatures regulations.

15.6. Retention of Study Records

GCP regulations require that the investigator retain all documentation related to this clinical trial for a period of 2 years after the approval of the NDA in the U.S. (or Product License outside the U.S.) for this drug or 2 years after the withdrawal of the IND. These records include the protocol and copies of all documents submitted to pSivida Corp., or to government authorities, subject records (including signed informed consent forms, subject charts, eCRFs, and other source documents), IRB/EC approvals and correspondence, records of drug accountability, and all study communications, whether written, telephonic, or electronic. None of the required documents will be destroyed or transferred to the control of another party without the written approval of pSivida Corp.

15.7. Monitoring of the Study

Representatives or affiliates of pSivida Corp. will contact the investigator and his/her staff prior to the start of the trial to review the procedures to be followed in conducting the study and recording the findings, and to confirm the facility's readiness to conduct the trial.

Monitors may observe all aspects of subject treatment as frequently as necessary to ensure adherence to the protocol. The investigator and his staff will cooperate with pSivida Corp. representatives and will provide any missing information and grant access to all study documentation.

Representatives of pSivida Corp. may audit the study periodically to ensure that all records are correct and complete.

15.8. Discontinuation of the Study

pSivida Corp. reserves the right to discontinue this study for administrative reasons at any time.

The trial may also be terminated prematurely if unexpected adverse events occur or if the investigator does not adhere to the protocol.

15.9. Policy for Publications

The detailed procedures for the review of publications are set out in the clinical trial agreement entered into with pSivida Corp. in connection with this study.

16. ETHICS

16.1. Ethics Review

The final study protocol, including the final version of the ICF, must be approved or given a favorable opinion in writing by an IRB/EC as appropriate. The investigator must submit written approval from an IRB/EC to pSivida Corp. or the CRO before the investigator may initiate this study.

The Principal Investigator is responsible for informing the IRB/EC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/EC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB/EC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. pSivida Corp. or the CRO will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/EC according to local regulations and guidelines.

16.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

16.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The subject must have a copy of the signed and dated ICF, which will be either a copy of the signed original or another signed original, in accordance with applicable local requirements.

A signed original copy of the ICF must be retained by the study site.

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18. APPENDIX I: MEASUREMENT OF BCVA BY ETDRS

Introduction:

The procedure for carrying out the testing of best-corrected distance visual acuity will be covered in this appendix. Visual acuity is always tested with the subject's best correction. Visual acuity should be measured without the pupils being dilated and before slit lamp biomicroscopy examination or any drops or ointments are used.

Equipment and Facilities:

The best-corrected visual acuity (BCVA) of participants will be measured according to the standard procedure originally developed for Early Treatment Diabetic Retinopathy Study (ETDRS) and adapted for the AREDS protocol. To ensure best-corrected visual acuity measurement, manifest refraction must be completed prior to visual acuity testing. The study requires a set of three Lighthouse Distance Visual Acuity Test Charts (Lighthouse 2nd edition or Precision Vision "ETDRS") and a retro illuminated box providing standardized chart illumination. For patients who are illiterate or not familiar with the English alphabet, BCVA will be determined using the Tumbling E ETDRS charts.

The charts and the box are manufactured by: Lighthouse Low Vision Products

36-02 Northern Boulevard

Long Island City, New York 11101

Telephone: (718) 937-6959

Or

Precision Vision

745 North Harvard Ave.

Villa Park, IL 60181

Telephone: (630) 833-1454

Visual acuity testing in this study is required at a distance of 4 meters and for participants with reduced vision, at 1 (one) meter. The 4-meter distance should be clearly and permanently marked. The 1-meter distance is to be measured with a 1-meter stick with the participant seated in a chair.

Visual acuity charts:

Chart R is used for refraction. Chart 1 is used for testing visual acuity of the right eye. Chart 2 is used to test visual acuity of the left eye. The features of the charts are 5 high-contrast Sloan letters in each of the 14 lines. Lines are of equal difficulty, and follow a geometric progression of letter size from line to line. Further, charts 1, 2 and R have different letter sequences to avoid memorization by the participants. Participants should be prevented from seeing Chart 1 and Chart 2 until refraction has been completed, and the visual acuity testing is to begin.

Retro-illumination box:

The dimensions of the light box are 24 ¾ inches by 25 ¾ inches by 7 inches. The box can be mounted on a wall or on a 5-pronged wheel-based stand, manufactured by Lighthouse Low Vision Products. Each prong is about 14 inches long, and 2 of the 5 wheels are lockable. When the box is mounted on the stand, the height can be varied. The charts are stored in the back of the light box.

Room lights should be off during refraction and visual acuity testing. The box itself provides sufficient illumination for the examiner to record the test results. Additional light can have an adverse effect. If absolutely necessary, a small desk type light may remain on; however, the light beam should be directed away from the light box and the subject. The light box is equipped with two General Electric Cool Daylight 20-watt fluorescent tubes and ballast. As the illumination of fluorescent tubes diminishes by 5% during the first 100 hours and by another 5% during the next 2,000 hours, the following should be done:

- New tubes should be kept on for about four days (approx. 96 hours) to "warm-up", time "on" does not have to be continuous.
- All tubes should be replaced once a year.
- It is advisable to periodically check the fluorescent tubes for proper function. Replacement tubes can be purchased at a local hardware store or Lighthouse Low Vision Product.

Visual acuity lanes: 4 meter and 1 meter:

A distance of exactly 4 meters (13 feet, 1 ½ inches, or 157 ½ inches) is required between the participant's eye and the visual acuity chart for the 4-meter test. A distance of exactly 1 meter (39 3/8 inches) is required for the 1-meter test.

The room for visual acuity testing must have enough room for the 4-meter lane as well as the light box and the participant.

Mounting the light box:

The light box should be mounted at such a height that the top of the third row of letters (0.8 Log MAR) is 49 ± 2 inches from the floor.

Wall mounting: In addition to the 4-meter lane, 7 inches must be allowed for the depth of the box, plus space for the participant to sit or stand.

Stand mounted box: In addition to the 4-meter lane, 13 inches must be allowed for two of the stand's casters to touch the rear wall or a line marked on the floor if there is no wall, plus space for the participant to sit or stand.

Marking the distance: 4 meters

If the chair and visual acuity box are permanently affixed, distance measurements need only to be made once. If the box is mounted on the wall, but the participant's chair is not permanently affixed, the 4-meter distance from the participant's eye to the chart must be clearly and permanently marked.

If the box is mounted on a movable stand, the 4-meter distance must be clearly and permanently marked on the floor. The location of the box must also be clearly and permanently marked on

the floor and placement should be checked between participants. When the stand touches the rear wall, two of the casters should touch the wall.

Marking the distance: 1 meter

The 1-meter distance is measured from the eye of the participant, with his or her back firmly against the back of the chair, to the second or fourth letter of the third line of the eye chart. A 1-meter measuring stick should be used.

18.1. Refraction Technique

All visual acuity will be measured with the participant's best-corrected vision. No pinhole testing will be done. It is strongly advised that the refraction be done with the 4-meter distance. If for practical reasons, the 10-foot distance must be used, the same refraction procedure should be performed as for the 4-meter distance (visual acuity scores will be adjusted accordingly). The right eye should be refracted first, then the left eye.

If the participant wears contact lenses and has glasses, they should be reminded that they would be unable to wear their contact lenses for the duration of the study. At the screening visit, if the subject is wearing contact lenses, they should be removed and refraction and visual acuity should not be done for at least half an hour for soft lenses and one hour for hard lenses.

18.1.1. Approximate Refraction

If results of a previous subjective refraction are available, they can be used as the beginning of approximate refraction. Otherwise the following procedures should be used:

- If the participant's uncorrected visual acuity is 20/200 or better, and the participant does not have glasses for distance vision, the beginning approximate refraction is no lens correction (plano).
- If the participant's uncorrected visual acuity is less than 20/200 in either eye with their present distance glasses, or without correction if the subject does not have glasses, retinoscopy should be performed by an examiner proficient in this procedure. An acceptable alternative is to conduct an arbitrary trial with any lens to bring visual acuity to 20/200 or better. The lens corrections obtained are used as the beginning approximate refraction for determining best-corrected acuity.
- If the participant's visual acuity is 20/200 or better with participant's current distance glasses, the glasses are measured with a lensometer, and these measurements are to be used as the beginning approximate refraction.

18.1.2. Subjective Refraction

The trial frame is placed and adjusted on the subject's face so that the lens cells are parallel to the anterior plane of the orbits and centered in front of the pupil. The left eye is occluded and the beginning approximate refraction, as previously determined, is placed in the right lens cells with the cylindrical correction anterior.

- It is permissible to use a Phoropter for subjective refraction. However, for testing visual acuity, the lenses from the last Phoropter refraction must be placed in trial frames and the

final sphere must be rechecked as described in "Refining Final Spherical Power" (Section 18.1.5).

- If the participant's visual acuity is too poor to see the largest letters on the chart at the 4-meter distance, refer to "Refraction for Participants with Poor Visual Acuity" (Section 18.1.7).

18.1.3. Determination of Spherical Refraction

With the beginning refraction in place, the visual acuity of the right eye is assessed and noted. A +0.50 sphere is then held in front of the right eye and the participants are asked if the vision is "better", "worse", or "no different", while they are looking at the smallest line they can read well.

- If vision is improved, or there is no change, the sphere in the trial frame is replaced with one that is one-half diopter more plus. The +0.50 sphere is held in front of the study eye and participant is asked again if the vision is "better", "worse", or "no different." This process is repeated until the participant says that the additional +0.50 sphere make the vision worse. The lens should be left in place for 10 to 15 seconds in an attempt to evaluate whether the participant is accommodating. If the vision clears during this period, the +0.50 sphere may be added again. Successive attempts to evaluate additional plus lenses should be made with the 10 to 15 second delay. If there is no evidence of unrelaxed accommodation, the delay period is no longer necessary.
- Whenever the participant says that the vision is worse and no longer improves, the +0.50 sphere is removed from the front of the trial frame. By this process, the highest plus sphere that is tolerated without blurring the participant's vision has been determined.
- Next, a –0.37 sphere is held in front of the trial frame and the participant is asked if vision is better, worse, or no different. If vision is improved, the participant is requested to read the chart, and if at least one more letter is read on the smallest line noted previously or the next smaller line, the sphere in the trial is replaced by a sphere that is 0.25 diopter less plus. In certain situations, the participant is unable to read more letters, but is convinced that the vision is actually improved. If the examiner believes that this is the case, the additional minus sphere lens can be added. At any stage in the examination, no more than 0.25 diopters of minus sphere should be added without an increase in the number of letters read correctly. The additional minus sphere lens should not be added if the participant reads fewer letters but states that visual acuity is better.
- If the participant says the vision is "no different" or "worse", no minus power should be added and the determination of the sphere correction is complete.

18.1.4. Determination of Cylindrical Refraction

- Cylinder Axis Determination

  If the beginning approximate refraction contains a cylinder correction, changes in cylindrical axis are tested by adding a 0.25, 0.37 or 0.50 diopter cross-cylinder axis, first with the positive axis at 45 degrees to one side of the cylinder axis and then with the positive axis 45 degrees to the opposite side of the cylinder axis. Since neither position

may produce a clear image, the participant is encouraged to select the position producing less blur while focusing on a single round letter on the line above the lowest line on the chart they can read when the cross cylinder is not held up before the trial frame. If the participant cannot choose between the two positions of the cross-cylinder at the beginning of this test, the axis is moved 5 to 15 degrees, first in one direction and then in the other, with the cross-cylinder being checked in each position to confirm that the original axis was correct. If the participant prefers one position of the cross-cylinder to the other and the cylinder in the trial frame is plus, the axis of the cylinder is moved 5 to 15 degrees toward the positive axis of the cross-cylinder when it is in the position found to be less blurry by the participant.

When the power of the cylinder is low or the participant's discrimination is poor, larger shifts will produce more clear-cut answers. The cross-cylinder is held again with the positive axis 45 degrees, first to one side, then to the opposite of the new cylinder axis, to determine which position produces less blur.

- Cylinder Power Determination

Change in cylinder power is tested by adding the cross-cylinder, first with the positive axis and then with the negative axis coincident with the cylinder axis. The participant is requested to focus on a round letter on the lowest line of the chart they can read. If the participant prefers the positive axis coincident with the cylinder axis, the power of the correcting plus cylinder is increased by a +0.25 diopter. If the participant prefers the negative axis coincident with the cylinder axis, the total power of the correcting plus cylinder is reduced by 0.25 diopter. This process is repeated until the participant finds neither position is better than the other. As the plus cylinder is added, the examiner should notice that the spherical equivalent of the refraction is changed. More minus sphere may be needed as the plus cylinder is added. For every 0.50 diopter of cylinder power added, the sphere changes by –0.25 diopter. If the beginning refraction is a pure sphere, the presence of an astigmatism is tested by arbitrarily placing a +0.25 cylinder at 180 degrees in the trial frame, after having determined the highest-plus or least-minus sphere producing minimal blurring of vision, as described previously in Section 18.1.3. The refraction is continued by using the cross-cylinder to test for the axis and the cylinder power using the cross-cylinder technique outlined above.

18.1.5. Refining Final Spherical Power

When neither the power nor the axis of the cylinder can be improved, the power of the sphere is refined by testing with +0.25 sphere and –0.37 sphere and changing the spherical power as indicated previously in Section 18.1.3. If the sphere is changed at this point, the cylinder should be rechecked.

This process is repeated until no further significant lens changes are made.

18.1.6. Summary of Refraction Protocol

At the end of the refraction, the sphere is checked and the participant neither tolerates increased plus nor improves with increased minus spheres. Then the axis is checked and no change in this is indicated. At this point, the refraction is considered complete.

If, at the time of the refraction, the subject's pupil is dilated it must be noted on the visual acuity worksheet.

18.1.7. Refraction for Participants with Poor Visual Acuity

If it is not possible to perform a subjective refraction at 10 feet or 4 meters because visual acuity is too poor for the participant to see the largest letters on the chart at this distance, the refraction should be attempted at 1 meter. The procedure at 1 meter is the same as the procedure for 4 meters. However, the increments of lens power can be larger. For the sphere, ± 1.00 diopter or more can be tested. Cylindrical refraction can be assessed with the 0.5 or 1.00 than 0.25 diopter. If subjective refraction can be performed successfully at 1 meter, a +0.75 sphere should be subtracted from the 1-meter refraction to make the correction appropriate for the 4-meter distance.

18.2. 4-Meter Test and 1-Meter Test

18.2.1. 4-MeterTest:

The distance from the participant's eyes to the visual acuity chart must be exactly 4 meters (13 feet and 1.5 inches).

- The examiner should insure that the participant is sitting or standing comfortably, and that the head does not move back and forth during the test. The participant's eyes should always remain at the 4-meter distance.
- The participant should be told the chart contains only letters and no numbers. Should the participant forget these instructions and read a number, the examiner will remind the participant that the chart contains letters only and request a letter response in lieu of a number.
- The examiner should ask the participant to read slowly.
- The examiner should never point to the chart or to specific letters on the chart or read any letters during the test.
- Each letter is scored as correct or wrong. If the participant changes a response aloud before he or she has read the next letter aloud, that response is acceptable. If the participant changes the response after the next letter has been read aloud, that next response is unacceptable.
- Participants should be encouraged to guess. The reasons are: a) it will help maximize their effort and help ensure uniformity among different clinical sites; b) it will help prevent bias if the participant has become unmasked.
- The participant should be requested to give only one letter as a response.

- The participant can turn or shake his or her head if this improves visual acuity while the fellow eye remains securely covered.

18.2.2. 1-Meter Test:

Eyes reading less than 20 letters correctly at 4 meters will be tested at 1 meter.

- Before testing at one meter, a +0.75 sphere should be added to the 4-meter correction already in the trial frame to compensate for the closer distance.
- The participant will be asked to read only the first six lines at 1 meter, making 30 the highest possible score at this distance.
- After the test of the right eye with chart 1 is completed, repeat the test for the left eye with chart 2, starting at 4 meters. When testing of the left eye is completed, chart 1 and 2 should be removed from view and chart R mounted. At this time refraction used for the right and left eyes should be introduced to the trial frame or the Phoropter and binocular visual acuity should be assessed using the same protocol as noted above.

18.2.3. Scoring Best Corrected Visual Acuity:

The examiner will record each letter correctly identified by circling the corresponding letter on the Visual Acuity Worksheet. Letters read incorrectly or for which there was no guess will be marked with a slash mark through the corresponding letter.

- Each letter read correctly is scored as one point.
- The score of each line (which is zero if no letter was read) is recorded on the Visual Acuity Worksheet.
- If testing at 1 meter is not required, 30 points are automatically added to the total number of letters read correctly.
- If testing at 1 meter is done the score is determined by adding the total number of letters read at 4 meters to the total number read correctly at 1 meter.

The total combined score (sum of the 4-meter and 1-meter test scores) is recorded on the Visual Acuity Worksheet. Snellen-equivalent is calculated from the lowest line read with ≤ 2 letter errors (≥ 3 letters correct).

18.2.4. Visual Acuity Grading Scale

Measurement of best corrected visual acuity is measured with logarithmic visual acuity charts at a distance of 4 meters, and at 1 meter if visual acuity is worse than 20/100. Participants are encouraged to make a maximum effort to read as many lines as possible.

19. APPENDIX 2: METHODS OF CLINICAL EVALUATION

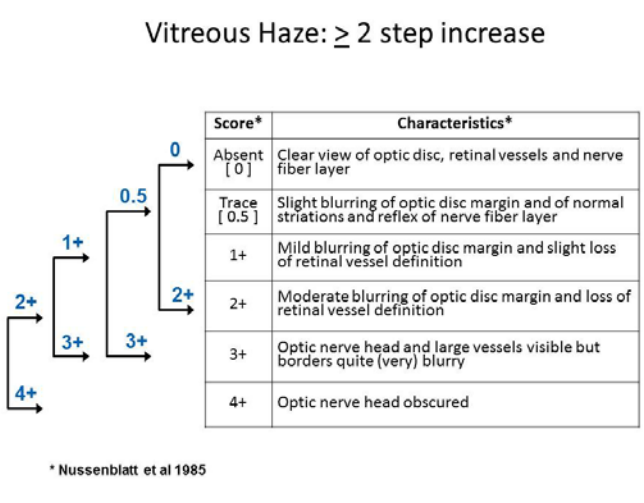
19.1. Ophthalmoscopy and Grading of Vitreous Haze

Ophthalmoscopy will be performed to assess retinal and choroid appearances and vitreous haze (Nussenblatt 1985). Indirect ophthalmoscopy will be performed for each eye with pupil dilation and should be completed after IOP measurement has been completed.

Vitreous Haze Grading Scale
The following scale 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

Figure 3: Vitreous Haze Scoring Convention

The diagram on the right presents the scoring convention that will be used to identify a minimum of "≥ 2 step increase" of vitreous haze for the primary efficacy endpoint.	

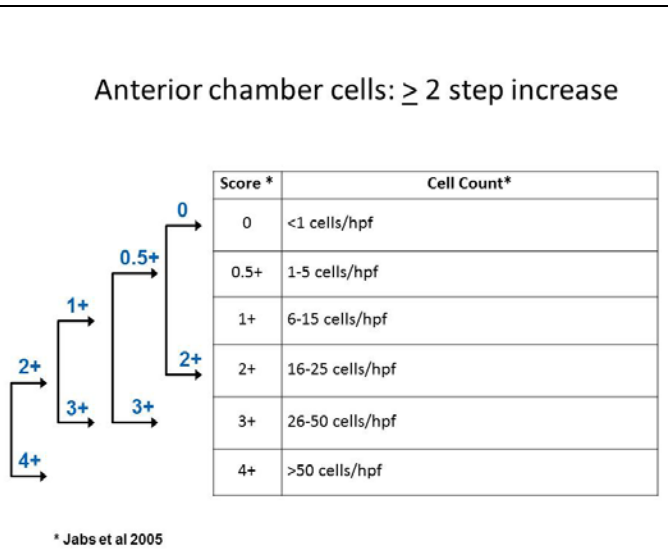
Anterior Chamber Cells Grading Scale

Anterior chamber cells will be measured using a Haag/Streit or similar slit lamp at high magnification (1.6 X) 1-mm beam. The same instrument, and when possible the same examiner should be used on each patient throughout the study. 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

Figure 4: Anterior Chamber Cell Scoring Convention

The diagram on the right presents the scoring convention that will be used to identify a minimum of "≥ 2 step increase" of anterior chamber cells for the primary efficacy endpoint.	

Fundus Examination

The fundus assessments should be conducted using indirect ophthalmoscopy with a 20 diopter, 28 diopter, or 30 diopter condensing lens. In order to minimize variability, every effort should be made to have a single examiner conduct all assessments on a given subject.

19.2. Intraocular Pressure

Intraocular pressure will be assessed by applanation tonometry (preferably, Goldmann) and should be measured only after slit lamp examination has been completed. The mean of 3 measurements per eye will be recorded as the IOP. All reasonable efforts should be made to have the same examiner obtain all IOP measurement for a given subject. Measurement should be performed before dilated ophthalmoscopy.

19.3. Humphrey Visual Field Measurement

The 24-2 program will be used. Measurement should be performed before ophthalmoscopy.

20. APPENDIX 3: SUBJECTIVE OCULAR TOLERABILITY AND DISCOMFORT ASSESSMENT

Subjects will be asked to grade ocular tolerability and discomfort in both eyes at all study visits.

Subjective ocular discomfort grading

Subjects will assess discomfort using the following subjective scale (Maca 2010). This parameter will consist of questioning about 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

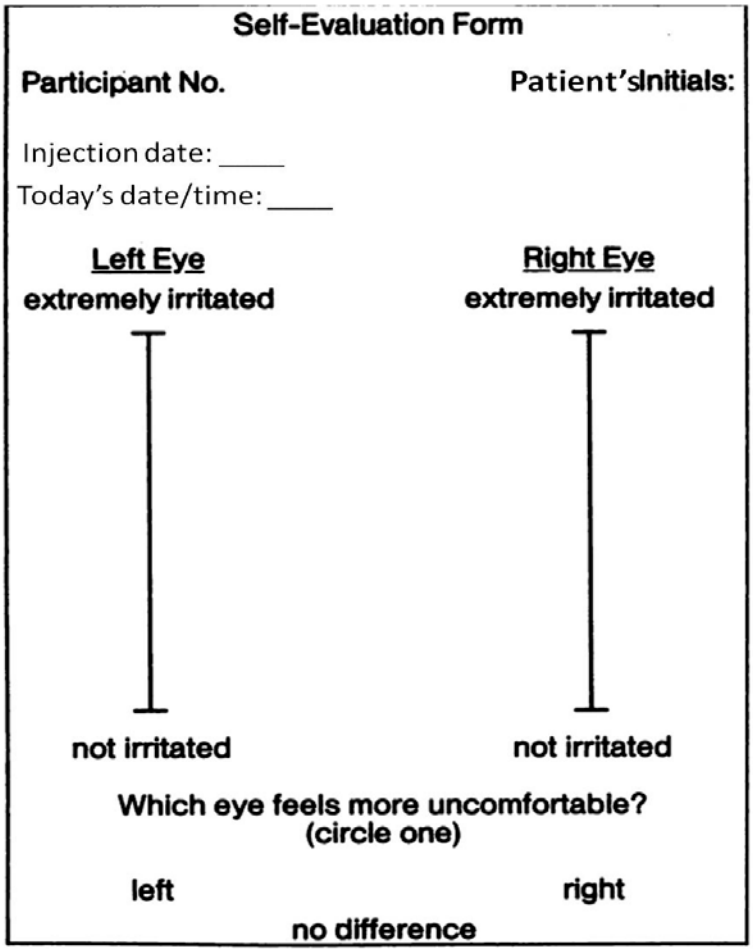
Grade 2: Moderate

Grade 3: Severe

Grade 4: Intolerable

Subjective tolerability using visual analog scale for pain

Subjects will assess tolerability using the following 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 pain. A mark of '0' represents no sensation while '100' indicates the worst imaginable pain. The location of the mark on the line then is measured with a mm ruler to provide a numeric score.


Self-Evaluation Form
Participant No.
Patient's Initials:
Injection date: ____
Today's date/time: ____
Left Eye
extremely irritated
not irritated
Right Eye
extremely irritated
not irritated
Which eye feels more uncomfortable?
(circle one)
left
right
no difference