ILUVIEN®

190 MICROGRAMS INTRAVITREAL IMPLANT IN APPLICATOR

M-01-12-001

AN OPEN LABEL, REGISTRY STUDY OF THE SAFETY OF ILUVIEN® 190 MICROGRAMS INTRAVITREAL IMPLANT IN APPLICATOR

Short Title:

IRISS (ILUVIEN Registry Safety Study)

Consolidated Protocol with Amendment No. 1 and 2

For the convenience of the Investigator and his/her Staff

Protocol Release Date: 15 February 2013

Revised Protocol,
including Amendment 1 24 November 2014
and Amendment 2 5 April 2017

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Phase IV Registry Study

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1. SYNOPSIS

Name of Sponsor/Company: Alimera Sciences Limited	
Name of Investigational Product: ILUVIEN® 190 micrograms intravitreal implant in applicator	
Name of Active Ingredient: Fluocinolone acetonide	
Title of Study: An open label, registry study of the safety of ILUVIEN® (fluocinolone acetonide 190 micrograms intravitreal implant in applicator)	
Study center(s): Approximately 45 clinical settings, hospitals or physicians' offices in European countries where marketing authorisation has been granted.	
Study period (years): Estimated date first patient enrolled: Third Quarter, 2013 Estimated date last patient completed: First Quarter, 2020	**Phase of development:** Phase 4 (Post-authorisation Registry Study)
Objectives: This study will assess the safety in patients treated with ILUVIEN. The specific objectives include the study of known safety risks of cataract formation or progression, increased intraocular pressure (both within 30 minutes post-treatment and long-term), changes in intraocular pressure and development of glaucoma, procedural complications such as endophthalmitis, retinal tears, retinal detachments, vitreous haemorrhage or vitreous detachments. Potential safety risks that have not been observed in clinical trials will also be monitored such as, retinitis secondary to reactivation of latent viral infections or other ophthalmic infections, potential systemic events associated with the use of corticosteroids or haemorrhagic events associated with the concurrent therapy with anticoagulant medications. Unknown safety risks will be captured as well. Information on significant retinal ischaemia, removal of the implant, long-term safety data, and repeat use will be evaluated. An evaluation of safety in patients who have received ILUVIEN in both eyes during the study will also be performed. Any use in paediatric patients, pregnant or lactating women and off-label use for other retinal oedema conditions will be reported. It should be understood that the sponsor does not advocate the use of ILUVIEN for any indication other than that which is specified on the Summary of Product Characteristics. However, it is also known that, in clinical practice with marketed products, off-label use is common. Therefore, the sponsor intends to collect safety data for any patient treated with ILUVIEN. Finally, the effect of ILUVIEN on visual acuity will be examined.	
Population: Patients who have been selected for treatment with ILUVIEN, including patients who were treated with ILUVIEN prior to enrolment into the study.	

Methodology: In this registry study, patients should be treated and monitored in accordance with the Summary of Product Characteristics. Baseline data will be collected prior to the first treatment and additional data will be collected approximately every 6 months for the duration of the study. **Study procedures:** Visual acuity, intraocular pressure, non-serious adverse event reports, serious adverse event reports, concomitant medications and ocular procedures.
Number of patients (planned): at least 550 patients.
Diagnosis and main criteria for inclusion: Patients who have been selected to receive treatment with ILUVIEN.
Investigational product, dosage and mode of administration: ILUVIEN 190 micrograms intravitreal implant in applicator with an initial release rate of 0.25µg/day. The implants are administered by injection through a 25 gauge needle into the inferior vitreous base.
Duration of treatment: Each implant releases fluocinolone acetonide for approximately 3 years. Retreatment is allowed any time after the Month 12 assessments have been completed, based on the physician's medical judgment and according to the recommendations in the Summary of Product Characteristics.
Reference therapy, dosage and mode of administration: No reference therapy will be administered.
Criteria for evaluation: **Safety:** Non-serious adverse events, serious adverse events and intraocular pressure. The change from baseline visual acuity will be evaluated. **Usage:** Descriptive statistics for demographic and baseline characteristics of patients by indication for which ILUVIEN was administered (Chronic diabetic macular oedema (DMO), Non-Chronic DMO, retinal vein occlusion, other indications).
Statistical methods: A sample size of 550 patients will provide approximately 80% probability of detecting one or more reports of any adverse event with a true underlying 5-year incidence of 0.3% assuming a 0.050 2-sided significance level. Data from all patients receiving an ILUVIEN implant will be included in the analyses of safety. Safety in specific subgroups, e.g., pregnant or lactating women and paediatric patients, will be evaluated. Formal study reports of analyses of study data will be performed at 3 years and at study completion. Analyses will also be conducted using preliminary data on an "as-needed" basis for marketing purposes and for Periodic Safety Update Reports. Safety analyses will be conducted to enumerate the number of patients with ocular and systemic adverse events, significant intraocular pressure related and cataract-related events, receiving retreatment, and undergoing implant explantation. Changes from baseline intraocular pressure and best corrected visual acuity will be summarized.

1.1. Table of Contents

1.2. List of Tables

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1.4. List of Abbreviations and Definitions of Terms

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation	Term
AE	Adverse Event
CRF	Case Report Form
DMO	Diabetic Macular Oedema
EC	Ethics Committee
E-ETDRS	Electronic-ETDRS
ETDRS	Early Treatment Diabetic Retinopathy Study
FAc	Fluocinolone Acetonide
FAME	Fluocinolone Acetonide in Diabetic Macular Edema
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IOP	Intraocular pressure
MHRA	Medicines and Healthcare products Regulatory Agency

PVA	Polyvinyl alcohol
SAFE	Safety data set
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
VA	Visual acuity

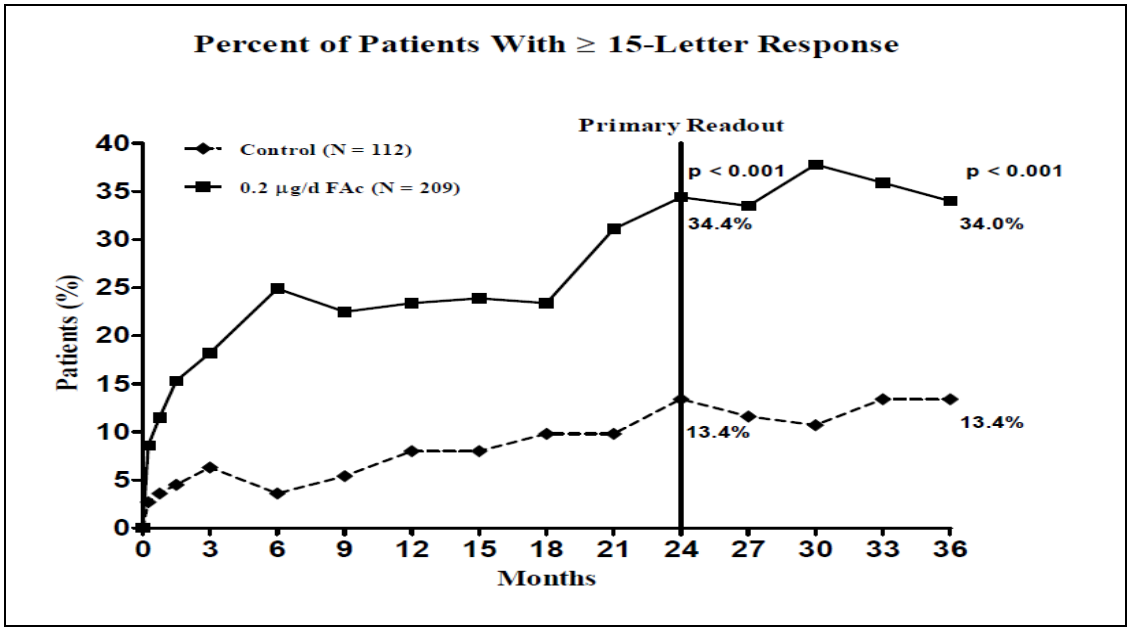
2. INTRODUCTION

ILUVIEN 190 micrograms intravitreal implant in applicator is a sustained-release intravitreal drug delivery system that releases submicrogram levels of the corticosteroid, fluocinolone acetonide (FAc), in the vitreous humor for approximately 36 months. The product was first approved in selected countries in the European Union in the second quarter of 2012. The approved indication is:

"**ILUVIEN is indicated for treatment of vision impairment associated with chronic diabetic macular oedema considered insufficiently responsive to available therapies."**

The efficacy of ILUVIEN was assessed in two randomized, multicenter, double-masked, parallel studies enrolling subjects with diabetic macular oedema who had previously been treated with laser photocoagulation at least once, each involving three years of follow-up (the FAME studies). The primary efficacy endpoint, the proportion of subjects whose vision improved by 15 ETDRS letters or greater at Month 24 was statistically significantly greater in subjects treated with ILUVIEN than the sham control group. (Campochiaro *et al* 2012) When efficacy was assessed as a function of duration of disease, those subjects with duration of diabetic macular oedema (DMO) greater than the median (≥3 years) had a significant beneficial response to ILUVIEN, whilst those with shorter duration DMO did not show an additional benefit over sham control treatment with regard to visual improvement (Figure 1).

Figure 1: Comparison of Percent of Subjects with ≥15 letter Improvement from Baseline Best Corrected Visual Acuity in Subjects with Chronic DMO



The main safety findings from the FAME studies were that essentially all phakic subjects treated with ILUVIEN experienced development of, or progression of, cataract and required cataract surgery. The proportion of ILUVIEN-treated subjects requiring treatment with intraocular pressure lowering medication was 38% compared to 14% in the sham-treated group. This proportion increased to 47% in those subjects with greater than average IOP at baseline (>15

mmHg). Surgical interventions for the treatment of ocular hypertension were required in 4.8% of subjects treated with ILUVIEN compared to 0.5% of subjects treated with sham control. Therefore, ILUVIEN should be used with caution in patients with high baseline IOP, and IOP must be monitored closely.

ILUVIEN is contraindicated in the presence of pre-existing glaucoma, or active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. ILUVIEN is also contraindicated in patients with a known hypersensitivity to any components of this product.

3. RATIONALE

This study is being performed at the request of the Reference Member State, the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA), as a Specific Obligation and recommended condition for marketing authorisation application for ILUVIEN. The study may include any patient treated with ILUVIEN at designated sites in European countries where marketing authorisation has been granted in order to obtain broader safety and usage information. Safety data for at least 550 patients treated with ILUVIEN will be collected for five years from the date of enrolment of the first prospectively enrolled patient.

4. STUDY OBJECTIVES AND PURPOSE

The study will assess the safety and usage in patients treated with ILUVIEN.

The specific objectives include the study of known safety risks of cataract formation or progression, increased intraocular pressure (both within 30 minutes post-treatment and long-term), changes in intraocular pressure and development of glaucoma, procedural complications such as endophthalmitis, retinal tears, retinal detachments, vitreous haemorrhage or vitreous detachments. Potential safety risks that have not been observed in clinical trials will also be monitored such as, retinitis secondary to reactivation of latent viral infections or other ophthalmic infections, potential systemic events associated with the use of corticosteroids or haemorrhagic events associated with the concurrent therapy with anticoagulant medications. Unknown safety risks will be captured as well. Information on significant retinal ischaemia, removal of the implant, long-term safety data, and repeat use will be evaluated. An evaluation of safety in patients who have received ILUVIEN in both eyes during the study will also be performed. The change from baseline visual acuity (VA) will be evaluated.

Any use in paediatric patients, pregnant or lactating women and off-label use for other retinal oedema conditions will be reported. It should be understood that the sponsor does not advocate the use of ILUVIEN for any indication other than that which is specified on the Summary of Product Characteristics (SPC). However, it is also known that, in clinical practice with marketed products, off-label use is common. Therefore, the sponsor intends to collect safety data of any patient treated with ILUVIEN.

This study will collect data for 6.5 years from the date of enrolment of the first prospectively enrolled patient. As a result, patients will have varying numbers of study visits.

Amendment 1 to this protocol allows for the retrospective enrollment of patients treated with ILUVIEN prior to enrolment into the study provided that they satisfy the same entry criteria as applied to patients enrolled prospectively.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This study is a non-randomized, open label, uncontrolled, multi-centre, study in which safety data on at least 550 patients who are treated with ILUVIEN for any reason will be collected over a 5 year period from the date of enrolment of the first prospectively enrolled patient. Patients should be treated and monitored in accordance with the Summary of Product Characteristics; however, any patient who is treated with ILUVIEN can be enrolled in the study.

5.2. Number of Patients

At least 550 patients will be enrolled in the study including those selected prospectively, as well as, those enrolled retrospectively.

5.3. Treatment Assignment

All patients will receive ILUVIEN.

5.4. Dose Adjustment Criteria

The dose cannot be adjusted; however, the implant can be removed by vitrectomy, if necessary.

5.5. Criteria for Study Termination

The study will only be terminated prior to completion in the event that the product is removed from the market in the participating countries.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Number of Patients

At least 550 patients will be enrolled in the study.

6.2. Patient Inclusion Criteria

Any patient treated with ILUVIEN may be included in the study.

6.3. Patient Exclusion Criteria

Patients/Guardians who are unable to understand and sign the Informed Consent Form will be excluded from the study.

6.4. Retrospective Enrolment Criteria

Patients treated with ILUVIEN prior to study initiation may be included provided they satisfy the inclusion and exclusion criteria, where applicable, as well as, the following requirements:

1. The site is allowed to enrol a patient who was treated with ILUVIEN no more than 36 months prior to bringing the patient in for their first study visit.
2. The eligible patient must meet the data requirements as specified in the protocol, i.e., baseline data collected within 7 days prior to treatment with ILUVIEN and additional data subsequently collected approximately every 6 months thereafter until enrolment into the study.
3. The eligible patient must be enrolled at least one year prior to the planned end of the study.

6.5. Patient Withdrawal

Investigators may withdraw a patient from the study if it is in the patient's best interest according to the investigator's clinical judgment. Every effort should be made to retain the patient in the study.

If a patient is prematurely withdrawn from the study, the reason(s) for withdrawal must be recorded on the relevant page of the patient's case report form (CRF).

Patients can voluntarily withdraw from the study at any time during the study. If a patient refuses to undergo the study follow-up procedures, the reason for refusal should be fully documented. Patients who refuse to continue in the study should undergo all end-of-study assessments.

Patients who withdraw from the study will not be replaced; however, patients who have withdrawn from the study may resume data collection during the five year study.

It is important to obtain follow-up information on any patient withdrawn prematurely from study treatment. Every effort must be made to undertake protocol specified follow-up procedures.

Refer to Section 10 for details on study procedures. Refer to Section 11 for details on follow-up for adverse events (AEs).

For patients willing to continue study follow-up procedures, the investigator should review the follow-up procedures with the patient, including the number of visits, the specific procedures to be done, and the total length of the follow-up period. The investigator must also ensure the patient understands that all medical records will continue to be available for the entire study period as described in the approved informed consent form.

7. RANDOMIZATION AND MASKING

This is a non-randomized, open label study. All patients enrolled in the study will receive ILUVIEN.

As an open label registry study, commercially available ILUVIEN will be utilized.

8. STUDY TREATMENTS

Initially, one eye of each patient will be treated with ILUVIEN at the discretion of the investigator. Study data will only be collected for the eyes which are treated with ILUVIEN. If a patient's fellow eye is to be treated during the study, baseline assessments will be performed prior to treatment.

The study treatment will be the commercially available ILUVIEN 190 micrograms intravitreal implant in applicator. ILUVIEN is an intraocular sustained-release delivery system for FAc preloaded into an applicator device. Each implant contains 190 µg of FAc the active ingredient within a cylindrical polyimide tube 3.5 mm long with an external diameter of 0.37 mm. Inactive ingredients are polyimide, polyvinyl alcohol (PVA) and silicone adhesive. The polyimide tubes and silicone adhesive are impermeable to FAc, while the cured PVA coated end of the tube acts as a diffusion port allowing the drug to be released. ILUVIEN is to be inserted through the pars plana into the vitreous by sliding the button of the injection device forward (complete instructions for injection are outlined in section 8.1).

The investigator will be responsible for obtaining ILUVIEN through commercial distribution channels. The lot number and expiry date for the dose administered will be recorded in the case report form for each patient.

8.1. Study Drug Administration

Patients should be treated and monitored in accordance with the Summary of Product Characteristics.

8.2. Other Investigational Product Considerations

Decisions regarding implant removal are according to the medical judgment of the investigator. Consideration will be given to the patient's wishes, general physical condition, ongoing adverse reactions and other factors that impact the decision to remove the implant. No modification of drug dose is possible other than surgical removal of the implant.

8.3. Concomitant Medications

The patient can receive concomitant medications as needed throughout the study according to the medical judgment of the investigator.

9. RISKS/PRECAUTIONS

Patients should be treated and monitored in accordance with the Summary of Product Characteristics.

10. STUDY PROCEDURES

Table 2 provides the schedule of visits and assessments for this five-year study. Study follow-up visits will be scheduled according to the standard practice of the site and to the physician's best judgment and clinical data, including adverse events, will be collected. At a minimum, follow-up visits will occur every 6 months until the study ends. As a result, patients will have varying numbers of visits.

In an attempt to optimize consistency of adverse event reporting, the patient should be asked a standard question to elicit any adverse events. At each clinic or telephone evaluation of the patient, study personnel will ask the following question: "Have you had any problems since your last visit or telephone call?"

All visits should be scheduled as closely as possible to the defined visit date. For the purposes of this study one month is defined as 30 days.

Table 2: Schedule of Assessments

	Day 0	Day 2 to 7	Every 6 Months Through End Of Study	Study Termination
Medical/Ophthalmic history	X			
Visual Acuity	X		X	X
IOP[1]	X	X	X	X
Ophthalmic Examination	X	X	X	X
ILUVIEN Administration	X			
Adverse Events	X	X	X	X
Concomitant Treatments/Medications	X	X	X	X
Study Completion Form				X

[1] IOP should be assessed prior to and up to 30 minutes post administration of ILUVIEN.

10.1. Screening and Baseline Procedures

The investigator will explain the study purpose, procedures, and patient responsibilities to a potential study participant. The patient's willingness and ability to meet the protocol requirements will be determined.

When it has been established that the patient may be eligible, prior to any study-specific procedure, written informed consent will be obtained. The patient or guardian will sign and date one copy of the consent form in the presence of the investigator or his designee. The original copy will be retained with the patient records and a copy will be given to the patient.

Prospective Patients

After signing the informed consent form and before treatment administration, the Day 0 procedures and tests outlined in the Schedule of Events will be performed. All ophthalmic assessments will be performed on both eyes. Screening procedures consist of:

- Medical history and ophthalmic history, concomitant medications

- Ophthalmic examination consisting of VA, IOP, slit lamp examination, and dilated ophthalmoscopy

If for any reason ILUVIEN is not administered on the day the baseline assessments are performed, the patient may be treated within 7 days. If the time between baseline assessments and the date of drug administration is greater than 7 days, the baseline assessments should be repeated.

Retrospective Patients

After signing the informed consent form historical data relating to the dosing of ILUVIEN and follow up visits may be collected including:

- Medical history and ophthalmic history (prior to ILUVIEN implantation), concomitant medications
- Ophthalmic examination consisting of VA, IOP, slit lamp examination, and dilated ophthalmoscopy

Once enrolled, follow up visits at 6 month intervals, at a minimum, should be maintained until the end of the study.

10.2. Procedures

10.2.1. Enrolment into the Study

Each site should invite all eligible patients to participate in the study who present during the enrolment period until at least 550 patients have been enrolled. Potential patients will be approached by a member of the staff and will be asked to review a copy of the consent form. The investigator and/or staff will review the consent form with potential patients and address any questions or concerns prior to obtaining written informed consent for participation.

The enrolment and retention rates will be monitored by the sponsor on a monthly basis. A newsletter will be sent to all of the sites once per month during the enrolment period and every other month once enrolment is complete. If enrolment and retention rates are not as expected at a site, a teleconference will be scheduled with the investigator to discuss.

Information pertaining to procedures is provided in the following subsections.

10.2.2. Slit Lamp Examination

Slit lamp examination should be performed at every office visit in the study using the investigator's standard procedure. This procedure should be the same for all patients examined at the site and use the same equipment. Significant clinical abnormalities which develop during the study should be recorded as an adverse event. All findings are to be documented in the source documentation and the appropriate CRF.

10.2.3. Ophthalmoscopy

Dilated ophthalmoscopy should be performed as part of each ophthalmic examination at every office visit. This procedure should be the same for all patients examined at the site and use the same equipment. Significant clinical abnormalities which develop during the study should be

recorded as an adverse event. All findings are to be documented in the source documentation and the appropriate CRF.

10.2.4. Visual Acuity

Visual acuity assessment should be performed using standard ETDRS charts or the investigator's standard procedure. Patients should be tested with their own (if any) habitual spectacle correction. The same procedure should be performed at every office visit. (All visual acuity assessments will be converted to ETDRS letter scores for data analysis.)

10.2.5. Intraocular Pressure

IOP measurements will be recorded using the investigator's standard procedure at every office visit. The same procedure should be performed at every office visit.

10.3. Unscheduled Visits

In the event that the patient's vision deteriorates between scheduled study visits, the patient should have an unscheduled visit. In addition to the assessments necessary to evaluate the cause of the vision loss, information on AEs, concomitant medications and any treatment required, should be obtained. An unscheduled visit evaluation form should be completed.

11. EVALUATION, RECORDING AND REPORTING OF ADVERSE EVENTS

All adverse events either observed by the investigator or site staff, or reported by the patient spontaneously, or in response to the direct question below, will be noted in the adverse events section of the patient's CRF and/or in the source document. Only treatment-emergent adverse events (those occurring during or after the start of ILUVIEN treatment) should be recorded as adverse events. Events reported before the initial ILUVIEN treatment should be recorded as medical history. For serious adverse events (SAEs) however, any SAE occurring after the patient has been consented will be recorded and reported as an SAE to Alimera within 24 hours.

In an attempt to optimize consistency of adverse event reporting, the patient should be asked a standard question to elicit any adverse events. At each clinic or telephone evaluation of the patient, study personnel will ask the following question: "Have you had any problems since your last visit or telephone call?"

If any adverse event is reported, the date of onset, intensity, action taken, relationship to study medication or treatment, date of resolution (or the fact that it is still continuing or has become chronic) and whether the adverse event is serious or not will be recorded (see Section 11.3.1).

To prevent duplicate reporting, please report AEs or SAEs to the registry study in lieu of report to a health authority. The sponsor has the responsibility to report relevant events to the appropriate health authority.

If a patient is enrolled retrospectively, then the investigator should add into the CRF all adverse events noted in the source documents which occurred after treatment with ILUVIEN and prior to the patient providing informed consent for this study.

11.1. Definitions

11.1.1. Adverse Event

An AE is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the administration of a medicinal product, whether or not considered related to the investigational product.

Medical conditions or diseases present before a patient starts study treatment are only considered AEs if they worsen after the patient starts study treatment.

An example of a non-serious adverse event would be conjunctival hemorrhage following administration of ILUVIEN.

11.1.2. Serious Adverse Events

Serious Adverse Event is defined as any AE that:

- Results in death
- Is life-threatening (The term “life-threatening” refers to an event in which the patient 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 inpatient hospitalization or prolongs existing hospitalization

- Results in persistent or significant disability / incapacity
- Is a congenital anomaly / birth defect
- May jeopardize the patient 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.

A patient admitted to a hospital as a result of an AE, even if released on the same day, would qualify for inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for inpatient hospitalization. However, emergency room visits that do not result in admission to the hospital would not qualify for inpatient hospitalization and, instead, should be evaluated for one of the other criteria for SAEs (e.g., life-threatening AE or medically significant event).

Surgery or hospitalization should always be reported as an outcome of an AE. Disability/ incapacity refers to a substantial disruption of a patient's ability to carry out normal life functions.

11.2. Adverse Event Descriptions

11.2.1. Intensity

The intensity of AEs will be characterized as mild, moderate, or severe, as follows:

Mild	Usually transient, requiring no special treatment, and does not interfere with the patient's daily activities
Moderate	Introduces a low level of inconvenience or concern to the patient and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures
Severe	Significantly interferes with a patient's usual daily activities and requires systemic drug therapy or other treatment, if available

11.2.2. Relationship to Study Treatment

The causal relationship to study drug or treatment will be determined by the investigator according to best medical judgment, as follows:

Suspected	There is a reasonable possibility that the AE is associated with use of the study treatment, such as a temporal relationship of the event to study treatment administration, or when other drugs, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
Not suspected	A relationship between the AE and the study treatment can reasonably be ruled out based on lack of any temporal relationship of the event to study treatment administration, or when the patient's underlying condition, medical history, or other therapy provide sufficient explanation for the observed event.

11.3. Reporting and Evaluation of Serious Adverse Events and Other Clinically Significant Adverse Events

11.3.1. Serious Adverse Events

Any SAE occurring in this study must be reported immediately (within 24 hours) to the sponsor safety contact using the SAE Form provided by the sponsor.

Patients enrolled retrospectively may have experienced an SAE after ILUVIEN administration but prior to providing informed consent for the study. These "retrospective" SAEs should be reported to the sponsor, via the SAE form, as soon as possible after the patient has provided informed consent for the study.

The investigator or sponsor, if appropriate, must also submit documentation of the following to the Ethics Committee (EC):

Center-specific SAEs and follow-up to these SAEs: The type of SAE that must be submitted (e.g., all SAEs or only suspected SAEs), as well as the required timing of submission (e.g., within 15 days of occurrence), is defined by the EC or regulatory authorities.

All reportable SAEs from the study: The sponsor will provide the investigator with documentation of reportable SAEs, from all study centers, during the conduct of the study.

The investigator should ensure that the patient receives appropriate medical treatment and that the patient is followed up until the SAE resolves or becomes chronic, as defined in Section 11.5.

11.3.2. Other Clinically Significant Adverse Events

Serious ocular adverse events include the following:

- Any ocular surgical intervention (e.g., cataract surgery, glaucoma surgery).

11.4. Events Due to Disease Progression

Events that are judged to be definitely due to disease progression should be recorded in the source documents, but not reported as AEs.

However, events that meet the criteria for SAEs (as defined in Section 11.1.2) even though they are judged definitely due to disease progression should be reported as SAEs (as described in Section 11.3.1).

The unequivocal nature of the disease progression must be indicated in the source documents.

11.5. Follow-up for Adverse Events

Throughout the study to the final study visit, all AEs will be followed until they resolve or become chronic (as judged by the investigator).

At the final study visit, new AEs, as well as follow-up information for continuing AEs, will be recorded in the CRF and source document. Beyond the final study visit, AEs will be followed only until 30 days after the final study treatment.

If a serious AE (defined in Section 11.3) is unresolved within 30 days after the final study visit, it will be followed by the investigator until it resolves or becomes chronic (as judged by the investigator). Follow-up data for such SAEs will be recorded on the CRF and source documents and reported to the safety contacts until the event resolves or becomes chronic (as judged by the investigator) or until 30 days after the final study visit, whichever comes first.

11.6. Reporting of Product Complaints

Product 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 (failure of the applicator to deliver the implant, etc.), or defect of the product (dispensing characteristics, labeling, packaging, etc.).

Any product complaint should be reported by email to the sponsor's Quality Assurance Department (alimeraquality@alimerasciences.com) or fax (+1 678 990 5743) within 24 hours.

Patients enrolled retrospectively may have experienced a product complaint after ILUVIEN administration. These "retrospective" product complaints should be reported to the sponsor as soon as possible after the patient has provided informed consent for the study.

The preferred method is via email. The complaint report should include the following information:

- ILUVIEN Lot Number
- ILUVIEN Expiration Date
- Investigator name, study center name, and contact number (phone, email address)
- Date the complaint occurred
- Brief description of the complaint

- Patient 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 11.1).

If the complaint falls under these two categories (1) bent/damaged needle and/or (2) difficulty in actuating the applicator button to insert the drug implant, the sponsor's Quality Assurance Department will issue an identification sequence to be used prior to sending the ILUVIEN applicator in its original container (tray and carton) which initiated the complaint to:

Quality Department
AndersonBrecon (UK) Limited
Wye Valley Business Park
Hay-on-Wye, Hereford HR3 SPG
United Kingdom

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

12. STATISTICS

12.1. Sample Size

The sample size for this registry study was determined in conjunction with the United Kingdom MHRA during the marketing authorisation application review. A sample size of 550 patients will provide approximately 80% probability of detecting one or more reports of any adverse event with a true underlying 5-year incidence of 0.3% assuming a 0.050 2-sided significance level.

12.2. Data Sets to be Analyzed

The safety data set will include data from all patients who receive an ILUVIEN treatment, and for whom at least one post-baseline safety follow-up is obtained. All patient data will be used; no data will be excluded because of protocol violations.

12.3. Schedule of Analyses

The total study duration will consist of 6.5 years from the date of enrolment of the first prospectively enrolled patient. Formal study reports summarizing the study data will be prepared after Year 3 of the trial and after the study has completed. Analyses will also be conducted on an "as-needed" basis for marketing purposes and for Periodic Safety Update Reports.

12.4. Analysis of Demographic and Baseline Data

The demographic and baseline characteristics will be summarized for the Safety data set. These data will be presented in tabular summaries to describe the patients enrolled into the study. Continuous variables will be summarized by mean, standard error, standard deviation, median, minimum, and maximum; and by counts and percentages for categorical variables.

12.5. Safety Variables

Safety analyses will be performed on all patients who receive ILUVIEN. Ocular safety will be assessed by evaluating ocular adverse events, retreatments with ILUVIEN, visual acuity, intraocular pressure, and concomitant ocular medications and therapies. If a patient receives bilateral ILUVIEN, then each eye will be summarized.

Systemic safety will be assessed by evaluating non-ocular adverse events, and concomitant non-ocular medications and therapies.

Adverse events will be summarized by presenting the number and percentage of patients having at least one occurrence of any adverse event during the study, having at least one occurrence of an adverse event within each system organ class, and having at least one occurrence of each individual adverse event. Each reported adverse event will be coded to a corresponding preferred term from the MedDRA coding dictionary.

For continuous safety variables, e.g., visual acuity, intraocular pressure, the observed and change from baseline values will be summarized descriptively (n, mean, standard error, standard deviation, median, minimum, maximum and frequency distribution) at each visit.

Specific adverse events of interest will be tabulated: IOP-related and cataract-related events, procedural complications such as endophthalmitis, retinal tears, retinal detachments, vitreous

haemorrhage or vitreous detachments. Potential safety risks that have not been observed in clinical trials will also be monitored such as, retinitis secondary to reactivation of latent viral infections or other ophthalmic infections, potential systemic events associated with the use of corticosteroids or haemorrhagic events associated with the concurrent therapy with anticoagulant medications. Information on retinal ischaemia, removal of the implant, and long-term safety data will be evaluated.

An evaluation of safety in patients who have received ILUVIEN in both eyes during the study will also be performed.

Summaries for specific subgroups of patients will be performed on all safety data. Analyses will be performed to determine the effect of treatment within specific subgroups of interest. Subgroups to be considered include:

- Patients diagnosed with diabetic macular oedema for 3 or more years
- Patients diagnosed with diabetic macular oedema for less than 3 years
- Patients not diagnosed with diabetic macular oedema
- Patients receiving a single ILUVIEN during the study
- Patients receiving more than a single ILUVIEN in the same eye during the study
- Patients receiving ILUVIEN bilaterally at any time during the study
- Patients who are pseudophakic at baseline in the eye receiving ILUVIEN
- Patients who are phakic at baseline in the eye receiving ILUVIEN
- Women who are pregnant at enrolment or who become pregnant during the course of the study
- Women who are lactating at enrolment or who begin lactating during the course of the study
- Paediatric patients, defined as patients less than 18 years of age on the day of ILUVIEN treatment

If there are a sufficient number of patients enrolled with diagnoses other than diabetic macular oedema, e.g., retinal venous occlusion, uveitis, separate summaries will be prepared for each diagnosis.

13. ESTIMATED DURATION OF THE STUDY

The expected study duration is 6.5 years from the date of the first prospectively enrolled patient. The study is expected to start in the third quarter of 2013 and to end in the first quarter of 2020.

14. STUDY ETHICAL CONSIDERATIONS

14.1. Ethical Considerations of the Study

This study will be conducted according to ethical standards, based on standard operating procedures of the Sponsor or designee, and taking into account national ethics guidelines as required by regulation and law, and as appropriate to a registry study. The following guidance has been consulted in preparing the study's protocol and procedures:

- World Medical Association (WMA), Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Patients, Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and last revised in Seoul in October 2008 by the WMA General Assembly.

14.2. Informed Consent

It is expected that standard consent for treatment will be obtained by the site in the normal course of clinical practice. The informed consent forms for data collection used for the study must comply with the Declaration of Helsinki, and must have been approved by the sponsor (prior to review by the EC). Any subsequent changes required by the EC must also be approved by the sponsor. An investigator/designee must explain the medical aspects of the study, including the nature of the study and the treatment, orally and in writing, in such a manner that the patient is aware of potential benefits and risks. Other elements of the informed consent process may be delegated by the investigator/designee. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Documentation of the discussion and the date of informed consent must be recorded in the source documentation. Patients must give informed consent for data collection in writing.

The informed consent process must be conducted, and the form must be signed, before the patient undergoes any study specific procedures determined by the protocol.

14.3. Ethics Committee

The protocol, protocol amendments (as specified by the EC), and the informed consent form for the proposed study, along with any other documents required by the center's EC must be submitted by the investigator to the center's duly constituted EC for review and approval. The investigator must also ensure that the EC reviews the progress of the study on a regular basis and, if necessary, renews its approval of the study on an annual basis. A copy of each EC approval letter must be forwarded to the sponsor before the study is implemented. Documentation of subsequent reviews of the study must also be forwarded to the sponsor.

15. ADMINISTRATIVE PROCEDURES

15.1. Investigator's Responsibilities

15.1.1. Reporting and Recording of Study Data

Data will be captured and compiled using procedures developed by the sponsor or their representatives. All requested study data must be recorded clearly on the CRF and other study forms as required.

The protocol, informed consent form, protocol amendments, safety information, and other required documents must be submitted to the EC in a timely manner as per the EC's requirements, as described in Section 11.3 (for safety information) and Section 14.3 (for other documents).

15.1.2. Study Drugs

The investigator is responsible for acquiring commercially available ILUVIEN.

15.1.3. Records Retention

The investigator must ensure that clinical study records are retained according to national regulations, as documented in the clinical trial agreement entered into with the sponsor in connection with this study.

The sponsor will maintain correspondence with the investigator after study close to ensure that study documentation is retained for the appropriate amount of time. Patient files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice. The investigator must inform the sponsor immediately if any documents are to be destroyed, to be transferred to a different facility, or to be transferred to a different owner.

16. POLICY FOR PUBLICATION AND PRESENTATION OF DATA

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

17. LIST OF REFERENCES

Campochiaro PA, Brown DM, Pearson A, Chen S, Boyer D, Ruiz-Moreno J, Garretson B, Gupta A, Hariprasad, S, Bailey C, Reichel E, Soubrane G, Kapik B, Billman K, Kane FE, Green K and the FAME Study Group, 2012. Sustained Delivery Fluocinolone Acetonide Vitreous Inserts Provide Benefit for at Least 3 Years in Patients with Diabetic Macular Edema. *Ophthalmology*, 119 (10): 2125-2132.

18. APPENDICES

18.1. Appendix 1 – Investigator Approval

SIGNATURE PAGE

Protocol Number: M-01-12-001

Title of Protocol: An Open Label, Registry Study of the Safety of ILUVIEN® (Fluocinolone Acetonide 190 Micrograms Intravitreal Implant in Applicator)

I confirm that I have read and understood the protocol for this clinical study. I will conduct the study in all respects in accordance with the study protocol, the ethical principles of the Declaration of Helsinki, with GCP and applicable regulatory requirements.

_____	_____	_____
Type/Print Investigator Name	Signature	Date

Site name and address:

Phone Number: