SYNOPSIS FOR M-01-12-001 6 YEARS

Name of Sponsor/Company: **Alimera Sciences Inc.**		*(For National Authority Use Only)*
Name of Finished 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® 190 Micrograms Intravitreal Implant in Applicator		
Investigators and study center(s): **S**ubjects were enrolled across 47 sites in the United Kingdom (31 sites), Germany (11 sites), and Portugal (5 sites). Investigators were listed in the Final Clinical Study Report (Refer to Module 5.3.5.1, Study M-01-12-001-6Y, Appendix 16.1.4).		
Publications (reference): none		
Study period: 6 years Date first subject enrolled: 23 January 2014 Date last subject completed: 09 January 2020		**Phase of development:** 4
Objectives: The study was being conducted at the request of the Reference Member State, the United Kingdom Medicines and Healthcare products Regulatory Agency, as a Specific Obligation and recommended condition for marketing authorisation application for ILUVIEN. The study objectives include the evaluation of known safety risks of ILUVIEN, including cataract formation or progression, increased intraocular pressure (IOP) (both within 30 minutes post-treatment and long-term), changes in IOP and development of glaucoma, and procedural complications such as endophthalmitis, retinal tears, retinal detachments, vitreous haemorrhage and vitreous detachments. Potential safety risks that have not been observed in clinical trials will be monitored, such as retinitis secondary to reactivation of latent viral infections, other ophthalmic infections, and 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. Information on significant retinal ischaemia, removal of the implant, long-term safety data, and repeat use is being evaluated. An evaluation of safety in subjects who received ILUVIEN in both eyes during the study will be performed. Any use in paediatric subjects, pregnant or lactating women and off-label use for other retinal oedema conditions will be reported. Lastly, the effect of ILUVIEN on visual acuity is being examined.		

Methodology: This study is a non-randomised, open label, uncontrolled, multi-centre study in which safety data on at least 550 subjects who are treated with ILUVIEN for any reason will be collected over a 6.5-year period from the date of enrolment of the first prospectively enrolled subject. Subjects should be treated and monitored in accordance with the Summary of Product Characteristics (SmPC); however, any subject who is treated with ILUVIEN can be enrolled in the study.

All subjects will receive ILUVIEN. The dose cannot be adjusted; however, the implant can be removed by vitrectomy, if necessary. The study will only be terminated prior to completion in the event that the product is removed from the market in the participating countries.

Study follow-up visits are being scheduled according to the standard practice of the site and to the physician's best judgment. Clinical data, including adverse events (AEs), are being collected. At a minimum, follow-up visits will occur every 6 months until the study ends. As a result, subjects will have varying numbers of visits.

In an attempt to optimise consistency of AE reporting, the subject should be asked a standard question to elicit any AEs. At each clinic or telephone evaluation of the subject, 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, 1 month is defined as 30 days.

Number of subjects (planned and analyzed): At least 550 subjects were planned to be enrolled in the study including those selected prospectively, as well as those enrolled retrospectively. In total, 562 subjected were enrolled, and 559 subjects received Iluvien. Of the 562 subjects enrolled in the study, 556 were treated with ILUVIEN and had at least 1 post-baseline follow-up visit, these subjects (N=556, 695 treated eyes) comprised the Safety Population.

Diagnosis and main criteria for inclusion: The study includes any subject treated with ILUVIEN at designated sites in European countries where marketing authorisation has been granted. Subjects should be treated and monitored in accordance with the SmPC for ILUVIEN, however, any patient who is treated with ILUVIEN can be enrolled in the study. Subjects/guardians who are unable to understand and sign the informed consent form are excluded from the study.

Test product, dose and mode of administration, batch number: Subjects received at least 1 dose of commercially-available ILUVIEN 190 micrograms intravitreal implant in applicator under the care of his/her physician.

Duration of treatment: 36 months.

Reference therapy, dose, and mode of administration, batch number: none

Criteria for evaluation:

Efficacy: not applicable.

Safety: The safety assessment was based on medical/ophthalmic history, concomitant medications and treatments, AE monitoring (including deaths and other serious AEs [SAEs]), and comprehensive ophthalmic evaluation, including IOP, slit lamp examination, dilated ophthalmoscopy, and visual acuity.

Statistical methods: Continuous variables (including changes from baseline) were summarised over time using descriptive statistics; categorical variables were described using counts and percentages. AE summaries were presented separately for ocular AEs that occurred in eyes treated with ILUVIEN; all other AEs (i.e., systemic AEs and ocular AEs that occurred in an eye not treated with ILUVIEN) were added together and summarised. Treatment-emergent AEs (TEAEs) are AEs that occurred on or after the administration of ILUVIEN or pre- existing events which worsened after administration. Subgroup analyses were conducted on TEAEs, deaths, serious TEAEs, and TEAEs leading to study discontinuation, changes from baseline in IOP and IOP-related events, and visual acuity. The subgroup categories consisted of age, gender, geographic location, enrollment status, diagnosis, number of implants, phakic status, and prior treatment/therapy.

SUMMARY OF STUDY RESULTS

EXPOSURE: The total number of patients enrolled and treated with ILUVIEN was 556 patients, with 417 patients receiving unilateral and 139 patients receiving bilateral ILUVIEN (695 eyes). The study duration was about 6 years from the date of enrolment of the first prospectively enrolled patient.

INDICATION TREATED: Of the 695 eyes, 672 (96.7%) were diagnosed with DMO. Due to the small number of eyes with a non-DMO diagnosis, outcomes from this subgroup were therefore not separately analysed. However, when comparing outcomes for all eyes and DMO eyes, there are expected to be no significant differences for the non-DMO eyes. The breakdown of the non-DMO diagnoses is located in the Final Clinical Study Report (Refer to Module 5.3.5.1, Study M-01-12-001-6Y, Table 6).

SAFETY RESULTS: In this study, 209 patients (30.1%) experienced IOP elevation that was considered an adverse event, and 240 patients (34.5%) required IOP lowering medications. Thirty-eight (5.5%) patients required IOP-lowering procedures (including laser based procedures). These rates are similar to or lower than those reported in registration trials and included in the SmPC (37%, 38%, and 5.6% respectively). In addition, subgroup analyses did not indicate that any particular group is at higher risk of increased IOP. While it remains a safety concern, IOP elevation is well documented in ILUVIEN prescribing information, and it appears that routine risk-minimisation activities are adequate for mitigating and managing this identified risk.

Amongst the 113 phakic patients at baseline, there were 32 (28.3%) new cataract diagnoses during this study, with 73 (64.6%) requiring cataract removal surgery. Cataract is a known adverse drug reaction during treatment with ILUVIEN and is described in the SmPC with a frequency of "very common" (≥ 1/10). The rate of development of cataract and surgical resections of cataracts in this population (28.3% and 64.6) were lower than those reported in the registration trials and included in the SmPC (82% and 80%).

There have been 2 cases (0.3%) of serious treatment-emergent endophthalmitis in this study. Both events were severe and suspected by the investigator to be treatment related. Endophthalmitis is a risk of all intravitreal procedures. There was one case of treatment-emergent vitreous detachment and no events of retinal tears. Of other ocular adverse events of interest, 20 (2.9%) patients developed vitreous haemorrhage and only 1 patient (0.1%) experience an adverse event of retinal detachment. Retinal detachment and vitreous haemorrhage are known adverse drug reactions during treatment with ILUVIEN and are described in the SmPC.

CONCLUSION: Overall, this long-term safety registry of patients receiving ILUVIEN did not show any additional safety risks to those identified in previous trials and included in the SmPC. Increased IOP and development of cataract remain the primary safety concerns in patients receiving ILUVIEN. However, both are well documented in ILUVIEN prescribing information, and it appears that routine risk-minimisation activities are adequate for mitigating and managing these identified risks.

Analysis of visual acuity data showed that ILUVIEN treatment consistently provided clinical benefits to patients as evidenced by improvement in ETDRS visual acuity scores. Therefore, this study confirms previous findings of a favourable benefit-risk profile of ILUVIEN. The sponsor concludes that, Study M-01012-001 has fulfilled the agency's requests for further information to obtain broader safety and usage information.

Date of the report: 15 December 2020