

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ILUVIEN 190 micrograms intravitreal implant in applicator

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each implant contains 190 micrograms of fluocinolone acetonide.

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Intravitreal implant in applicator.

Light brown coloured cylinder, approximately 3.5mm x 0.37mm in size.

Implant applicator with 25 gauge needle.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ILUVIEN is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, (DMO) considered insufficiently responsive to available therapies (see Section 5.1).

ILUVIEN is indicated for prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye (see Section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is one ILUVIEN implant in the affected eye. Administration in both eyes concurrently is not recommended (see Section 4.4).

Each ILUVIEN implant releases fluocinolone acetonide for up to 36 months.

Diabetic Macular Oedema

An additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema (see Section 5.1).

Retreatments should not be administered unless the potential benefits outweigh the risks.

Only patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema should be treated with ILUVIEN.

Non-Infectious Uveitis affecting the Posterior Segment

There are no data available to support the retreatment of patients with an additional implant when used for the prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye.

Paediatric population

There is no relevant use of intravitreally administered fluocinolone acetonide in the paediatric population in diabetic macular oedema (DMO).

The safety and efficacy in uveitis in the paediatric population has not been established.

Special populations

No dosage adjustments are necessary in elderly patients, or those with renal or hepatic impairment.

Method of administration

FOR INTRAVITREAL USE ONLY.

Treatment with ILUVIEN is for intravitreal use only and should be administered by an ophthalmologist experienced in intravitreal injections. The intravitreal injection procedure should be carried out under controlled aseptic conditions, which include use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anaesthesia and a broad-spectrum microbicide should be given prior to the injection.

The injection procedure for ILUVIEN is as follows:

1. Preoperative antibiotic drops may be administered at the discretion of the treating ophthalmologist.
2. Just prior to injection, administer topical anaesthesia over the injection site (inferotemporal quadrant recommended) as one drop followed by either a cotton-tipped applicator soaked in anaesthetic or as subconjunctival administration of adequate anaesthesia.
3. Administer 2-3 drops of adequate topical antiseptic into the lower fornix. The lids may be scrubbed with cotton-tipped applicators soaked with an adequate topical antiseptic. Place a sterile lid speculum. Have the subject look up and apply a cotton-tipped applicator soaked with an adequate antiseptic to the injection site. Allow 30-60 seconds for the topical antiseptic to dry prior to injection of ILUVIEN.
4. The exterior of the tray should **not** be considered sterile. An assistant (non-sterile) should remove the tray from the carton and examine the tray and lid for damage. If damaged, do not use unit. If acceptable, the assistant should peel the lid from the tray **without touching the interior surface**.
5. Visually check through the viewing window of the preloaded applicator to ensure that there is a drug implant inside.
6. Remove the applicator from the tray with sterile gloved hands **touching only the sterile surface and applicator**. The protective cap on the needle should not be removed until ILUVIEN is ready to be injected. Prior to injection, the applicator tip must be kept above the horizontal plane to ensure that the implant is properly positioned within the applicator.
7. To reduce the amount of air administered with the implant, the administration procedure requires two steps. Before injecting the needle in the eye, push the button down and slide it to the first stop (at the curved black marks alongside the button track). At the first stop, release the button and it will move to the UP position. If the button does not rise to the UP position, do not proceed with this unit.
8. Optimal placement of the implant is inferior to the optic disc and posterior to the equator of the eye. Measure 4 millimeters inferotemporal from the limbus with the aid of calipers.
9. Carefully remove the protective cap from the needle and inspect the tip to ensure it is not bent.
10. Gently displace the conjunctiva so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Care should be taken to avoid contact between the needle and the lid margin or lashes. Inject the needle in the eye. To release the implant, while the button is in the UP position, advance the button by sliding it forward to the end of the button track and remove the needle. Note: Ensure that the button reaches the end of the track before removing the needle.
11. Remove the lid speculum and perform indirect ophthalmoscopy to verify placement of the implant, adequate central retinal artery perfusion and absence of any other complications. Scleral depression may enhance visualisation of the implant. Examination should include a check for perfusion of the optic nerve head immediately after the injection. Immediate intraocular pressure (IOP) measurement may be performed at the discretion of the ophthalmologist.

Following the procedure, patients should be monitored for potential complications such as endophthalmitis, increased intraocular pressure, retinal detachments, and vitreous haemorrhages or detachments and ocular hypotony (observed up to 8 days post treatment). Biomicroscopy with tonometry should be performed between two and seven days after the implant injection.

Thereafter it is recommended that patients are monitored at least quarterly for potential complications, due to the extended duration of release of fluocinolone acetonide, of approximately 36 months (see Section 4.4).

4.3 Contraindications

An intravitreal implant with 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 contraindicated in patients with:

- hypersensitivity to the active substance or to any of the excipients listed in Section 6.1.
- infectious uveitis.

4.4 Special warnings and precautions for use

Intravitreal injections have been associated with endophthalmitis, increase or decrease in intraocular pressure, retinal detachment and vitreous haemorrhage or detachment. Patients should be instructed to report without delay any symptoms suggestive of endophthalmitis. Patient monitoring within two to eight days following the injection may permit early identification and treatment of ocular infection, decrease or increase in intraocular pressure or other complication. It is recommended that intra-ocular pressure be monitored at least quarterly thereafter.

Use of intravitreal corticosteroids may cause cataracts, increased intraocular pressure, glaucoma and may increase the risk of secondary infections.

The safety and efficacy of ILUVIEN administered to both eyes concurrently have not been studied. It is recommended that an implant is not administered to both eyes at the same visit. Concurrent treatment of both eyes is not recommended until the patient's systemic and ocular response to the first implant is known (see Section 4.2).

Phase 3 Diabetic Macular Oedema (FAME) Studies

80% of phakic subjects treated with fluocinolone acetonide underwent cataract surgery (See Section 4.8). Phakic patients should be closely monitored for signs of cataract after treatment.

38% of patients treated with fluocinolone acetonide required treatment with IOP-lowering medication (see Section 4.8). Fluocinolone acetonide should be used with caution in patients with high baseline IOP, and IOP must be monitored closely. In the event of IOP increases that do not respond to IOP-lowering medications or IOP-lowering procedures, the ILUVIEN implant can be removed by vitrectomy.

There were 24% of subjects in the sham treated group who were treated at any time with either anti-coagulant or anti-platelet medications as compared to 27% in the ILUVIEN treated subjects. Subjects treated with ILUVIEN concomitantly or within 30 days of cessation of treatment with anti-coagulant or anti-platelet medications experienced a slightly higher incidence of conjunctival haemorrhage versus the sham treated subjects (0.5% sham and 2.7% ILUVIEN treated). The only other event reported at a higher incidence rate in the ILUVIEN treated subjects was eye operation complication (0% sham and 0.3% ILUVIEN treated).

There is limited experience of the effect of fluocinolone acetonide in eyes following vitrectomy. It is likely that drug clearance would be accelerated after vitrectomy, though steady state concentrations are not expected to be affected. This may shorten the duration of action of the implant.

Phase 3 Uveitis Studies

In the uveitis studies, patients treated with fluocinolone acetonide intravitreal implant underwent cataract surgery. Phakic patients should be closely monitored for signs of cataract after treatment.

Additionally, some patients developed elevated intraocular pressure requiring treatment with IOP lowering medication.

Patients in studies treated with fluocinolone acetonide developed hypotony, which started within days of treatment, with many on Day 1 and mostly resolving within 1 week of onset. Patient monitoring of increased or decreased IOP immediately after and within two to eight days following the injections is recommended.

In the treatment of patients with uveitis, it is very important to exclude possible infective causes of uveitis prior to commencing therapy with ILUVIEN

There is a potential for implants to migrate into the anterior chamber, especially in patients with an absent posterior lens capsule, or posterior capsule defect or tear, following intraocular surgeries. If untreated, implant migration may lead to corneal oedema and in severe cases could lead to corneal injury requiring a corneal transplant. Patients presenting with visual disturbance complaints should be evaluated to allow for early diagnosis and management of implant migration.

4.5 Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of intravitreally administered fluocinolone acetonide in pregnant women. Animal studies are insufficient with respect to the reproductive toxicity of intravitreally administered fluocinolone acetonide (See Section 5.3). Although fluocinolone acetonide is undetectable in the systemic circulation after local, intraocular treatment, fluocinolone is nonetheless a potent corticosteroid and even very low levels of systemic exposure may present some risk to the developing foetus. As a precautionary measure it is preferable to avoid the use of ILUVIEN during pregnancy.

Breast-feeding

Systemically administered fluocinolone acetonide is excreted in breast milk. Although the systemic exposure of the breast-feeding woman to intravitreally administered fluocinolone acetonide is expected to be very low, a decision must be made whether to discontinue breast-feeding or to abstain from ILUVIEN therapy, taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data available. However, effects on either male or female fertility are unlikely since the systemic exposure to fluocinolone acetonide following intravitreal administration is very low.

4.7 Effects on ability to drive and use machines

ILUVIEN has minor influence on the ability to drive and use machines. Patients may experience temporarily reduced vision after administration of ILUVIEN and should refrain from driving or using machines until this has resolved.

4.8 Undesirable effects

Summary of the safety profile

Diabetic Macular Oedema

Intravitreally administered fluocinolone acetonide was evaluated in 768 subjects (375 in the 0.2 µg/day/ILUVIEN group; 393 in the 0.5 µg/day group) with diabetic macular oedema across the FAME clinical trials. The most frequently reported adverse drug reactions included cataract operation, cataract and increased intraocular pressure.

In the Phase 3 studies, 38.4% of subjects treated with ILUVIEN required IOP-lowering medication and 4.8% required IOP-lowering surgeries. The use of IOP-lowering medication was similar in subjects who received two or more treatments with ILUVIEN.

Two cases of endophthalmitis were reported in subjects treated with ILUVIEN during the Phase 3 studies. This represents an incidence rate of 0.2% (2 cases divided by 1,022 injections). While the majority of subjects in the FAME clinical trials received only one implant (see Section 5.1), the long-term safety implications of retention of the non-bioerodable implant inside the eye are not known. In the FAME clinical trials, 3-year data show that events such as cataract, increased intraocular pressure and floaters occurred only slightly more frequently in subjects receiving 2 or more implants. This is considered a function of the increased exposure to the drug rather than an effect of the implant itself. In non-clinical studies, there were no indications of an increase in safety issues other than lens changes in the rabbit eyes with 2-4 implants over 24 months. The implant is made of polyimide and is essentially similar to an intraocular lens haptic; it is therefore expected to remain inert inside the eye.

Non-Infectious Uveitis affecting the Posterior Segment

The safety profile for the non-infectious uveitis affecting the posterior segment of the eye is based on two 36 month -pivotal uveitis studies (PSV-FAI-001 and PSV-FAI-005). Data are available currently for 36 months for PSV-FAI-001 and 12 months for PSV-FAI-005. The most frequently reported adverse drug reactions included increased intraocular pressure, cataract and conjunctival haemorrhage. The less frequently reported but more serious adverse reactions were optic disc haemorrhage and retinal detachment

Tabulated list of adverse events

The following undesirable effects were assessed to be treatment-related from the Phase III clinical trials (DMO and uveitis) and spontaneous reporting and are classified according to the following convention: very common (≥ 1/10); common

($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); and very rare ($\leq 1/10,000$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations	<i>Uncommon:</i> endophthalmitis
Nervous system disorders	<i>Uncommon:</i> headache
Eye disorders	<i>Very Common:</i> cataract ¹ , increased intraocular pressure ² <i>Common:</i> glaucoma ³ , retinal detachment, optic disc haemorrhage*, vitreous haemorrhage, reduced visual acuity, visual field defect*, macula fibrosis*, conjunctival haemorrhage ⁴ blurred vision ⁵ , hypotony of eye ⁶ , vitreous floaters ⁷ , anterior chamber cells*, vitreous opacities*, foreign body sensation in eyes*, dry eye*, photopsia*, eye pain ⁸ . <i>Uncommon:</i> retinal vascular occlusion ⁹ , optic nerve disorder, maculopathy, optic atrophy, conjunctival ulcer, iris neovascularisation, retinal exudates, vitreous degeneration, vitreous detachment, choroidal detachment*, corneal erosion*, corneal deposits, posterior capsule opacification, iris adhesions, blepharospasm*, eye oedema ¹⁰ , ocular hyperaemia, sclera thinning, eye discharge, eye pruritus
Injury, poisoning and procedural complications	<i>Uncommon:</i> extrusion of implant, implant in line of sight, procedural complication, procedural pain
Surgical and medical procedures	<i>Very Common:</i> cataract operation <i>Common:</i> trabeculectomy, glaucoma surgery, vitrectomy, trabeculoplasty <i>Uncommon:</i> removal of extruded implant from sclera
General disorders and administration site conditions	<i>Uncommon:</i> Device dislocation(implant migration), which may lead to corneal oedema

* Observed only in patients with Uveitis

¹ Includes MedDRA terms for cataract (NOS), cataract subcapsular, cataract cortical, cataract nuclear and cataract diabetic.

² Includes MedDRA terms for intraocular pressure increased and ocular hypertension.

³ Includes MedDRA terms for glaucoma, open angle glaucoma, borderline glaucoma, optic nerve cupping and optic nerve cup/disc ratio increased.

⁴ Includes MedDRA terms for conjunctival haemorrhage, conjunctival hyperaemia

⁵ Includes MedDRA terms for vision blurred and visual impairment.

⁶ Includes MedDRA terms for intraocular pressure decreased

⁷ Includes MedDRA terms for myodesopsia

⁸ Includes MedDRA terms for eye pain, eye irritation and ocular discomfort.

⁹ Includes MedDRA terms for retinal vein occlusion, retinal artery occlusion and retinal vascular occlusion

¹⁰ Includes MedDRA terms for eye oedema, conjunctival oedema, corneal oedema

Description of selected adverse reactions

The long-term use of corticosteroids may cause cataracts and increased intraocular pressure. The frequencies stated below reflect the findings in all patients in the FAME studies. The observed frequencies in patients with chronic DMO were not significantly different to those in the overall population.

Diabetic Macular Oedema Phase 3 Studies

The incidence of cataract in phakic subjects was approximately 82% in ILUVIEN treated subjects and 50% in sham treated subjects in the Phase 3 clinical trials. 80% of phakic subjects treated with ILUVIEN required cataract surgery by Year 3 compared to 27% of the sham treated subjects, with most subjects requiring surgery by 21 months. Posterior subcapsular cataract is the most common type of corticosteroid -related cataract. Surgery for this type of cataract is more difficult and may be associated with greater risk of surgical complications.

In the DMO studies subjects with a baseline IOP of > 21 mm Hg were excluded. The incidence of increased intraocular pressure was 37%, and 38% of subjects required IOP-lowering medication, with half of these requiring at least two medications to control the IOP. The use of IOP-lowering medication was similar in subjects who received retreatment with an additional implant during the study. Additionally, 5.6% (21/375) of subjects who received an implant required a surgical or laser procedure to control the IOP (trabeculoplasty 5 (1.3%), trabeculectomy 10 (2.7%), endocycloablation 2 (0.5%), and other surgical procedures 6 (1.6%).

In the subset of subjects with greater than median IOP at baseline (≥ 15 mmHg), 47% required IOP-lowering medication and the proportion of surgical or laser procedures increased to 7.1%. In this subset, there were 5 (2.2%) subjects treated with trabeculoplasty, 7 (3.1%) with trabeculectomy, 2 (0.9%) with endocycloablation and 4 (1.8%) with other glaucoma surgical procedures.

Uveitis Phase 3 Studies

Table 1: IOP, Cataract and Hypotony Adverse Events in the Intent To Treat (ITT) Population: PSV-FAI-001 and PSV-FAI-005

ITT Population				
	PSV-FAI-001 (36 months)		PSV-FAI-005 (12 months)	
	FAI Insert	Sham Injection	FAI Insert	Sham Injection
Number of subjects randomised	87	42	101	52
Duration of exposure (days) mean (SD)	1055 (139.47)	1029 (191.09)	354 (37.56)	354 (37.56)
IOP lowering medications n(%)	37 (42.5)	14 (33.3)	51 (50.5)	27 (51.9)
IOP > 25 mmHg, n(%)	21 (24.1)	10 (23.8)	22 (21.8)	2 (3.8)
IOP > 30 mmHg, n(%)	14 (16.1)	5 (11.9)	15 (14.9)	1 (1.9)
IOP lowering surgery, n(%)	5 (5.7)	5 (11.9)	1 (1.0)	0
IOP AE, n(%)	28 (32.2)	13 (31.0)	30 (29.7)	1 (1.9)
Cataract surgery, n (%) based on Phakic patients)	31 (73.8)	5 (23.8)	11 (18)	4 (11.4)
Cataract AE, n(%)	37 (42.5)	10 (23.8)	29 (47.5)	11 (31.4)
Hypotony, n(%)	9 (10.3)	5 (11.9)	13 (12.9)	0 (0.0)

There were no cases of endophthalmitis in the fluocinolone acetonide group in the Phase 3 uveitis studies.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

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4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIINFLAMMATORY AGENTS, corticosteroids, plain

ATC code: S01BA15

Corticosteroids inhibit the inflammatory response to a variety of inciting agents. They inhibit the oedema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

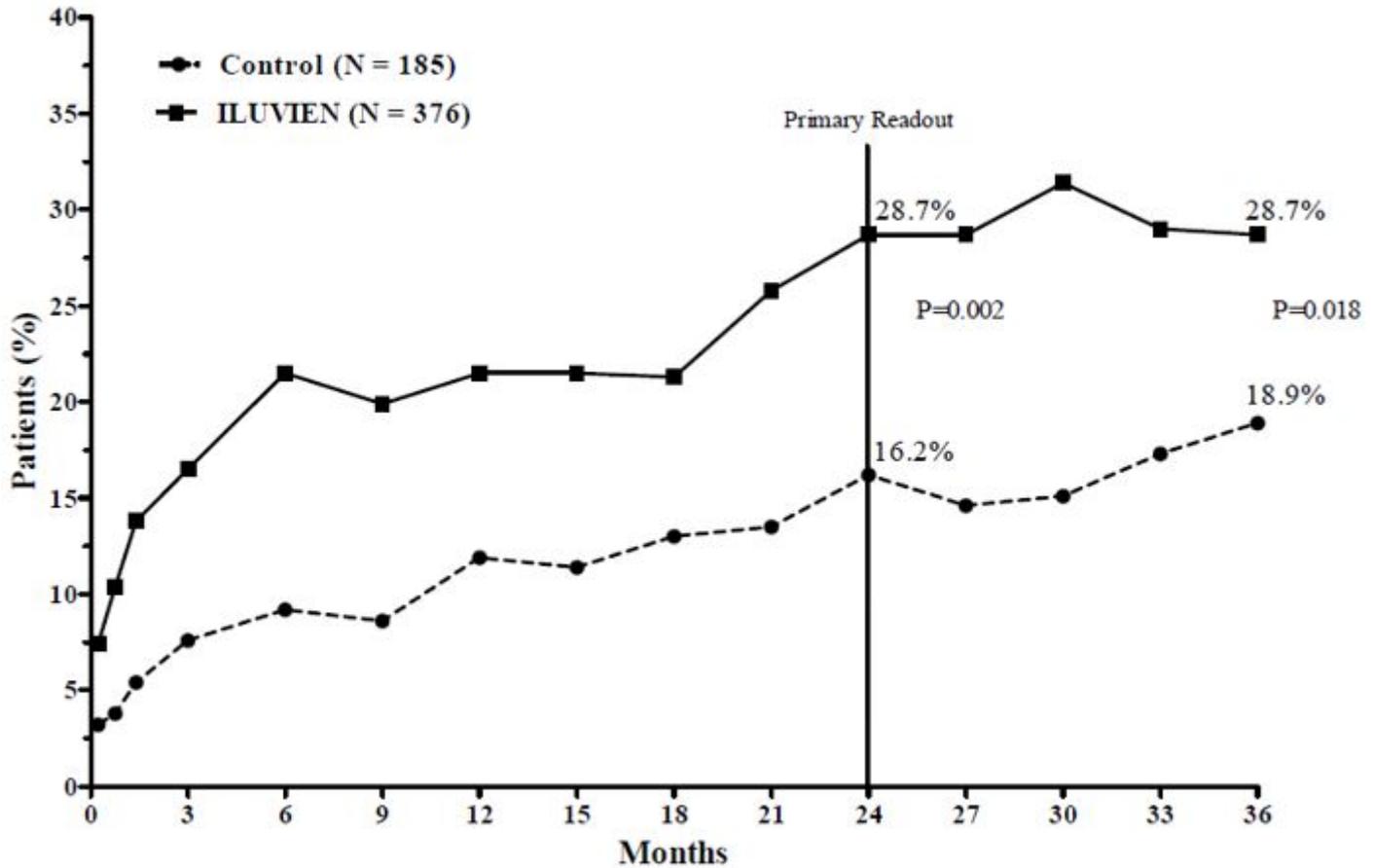
Corticosteroids are thought to act by the induction of phospholipase A inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of the common precursor arachidonic acid. Arachidonic acid is released from membrane

phospholipids by phospholipase A₂. Corticosteroids have also been shown to reduce levels of vascular endothelial growth factor, a protein which increases vascular permeability and causes oedema.

Diabetic Macular Oedema

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. There were 74.4% of subjects treated with 1 implant, 21.6% with 2 implants, 3.5% with 3 implants and 0.5% with 4 implants and 0% > 4 implants). The primary efficacy endpoint in both trials was the proportion of subjects whose vision improved by 15 letters or greater after 24 months. In each of these trials, the primary endpoint was met for ILUVIEN (see Figure 1 for the integrated results of the primary efficacy endpoint).

Figure 1: Percentage of Subjects with ≥ 15 Letter Improvement Over Baseline, Integrated FAME Studies



When efficacy was assessed as a function of duration of disease, those subjects with a duration of 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 control treatment with regard to visual improvement (Figures 2 and 3). These subgroup data support the indication in Section 4.1, of use in patients with chronic DMO (ie, duration of at least 3 years).

Figure 2: Comparison of Percent of Subjects with ≥15 letter Improvement from Baseline BCVA and Mean Change from Baseline Excess Center Point Thickness by Duration of DMO Subgroup ≥ 3 years.

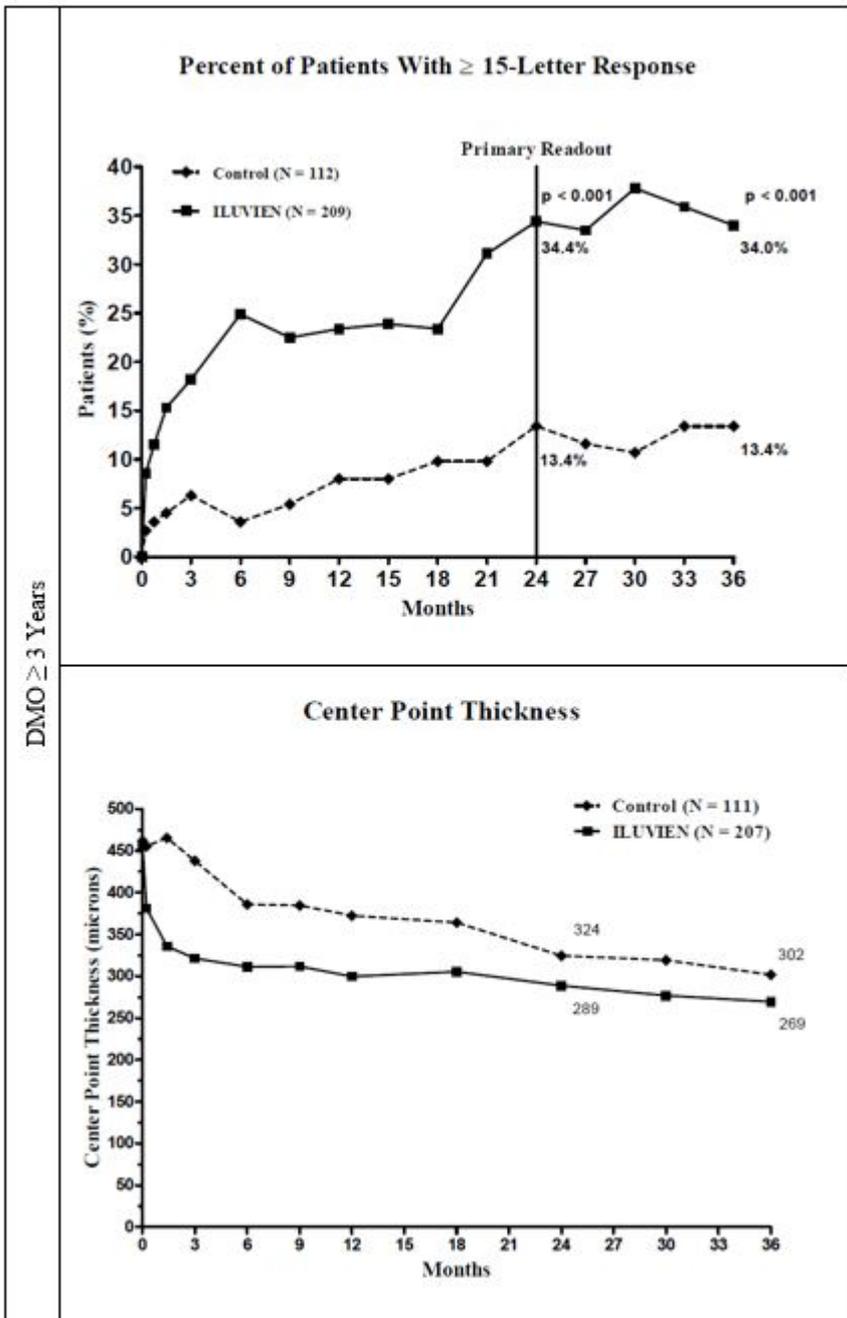
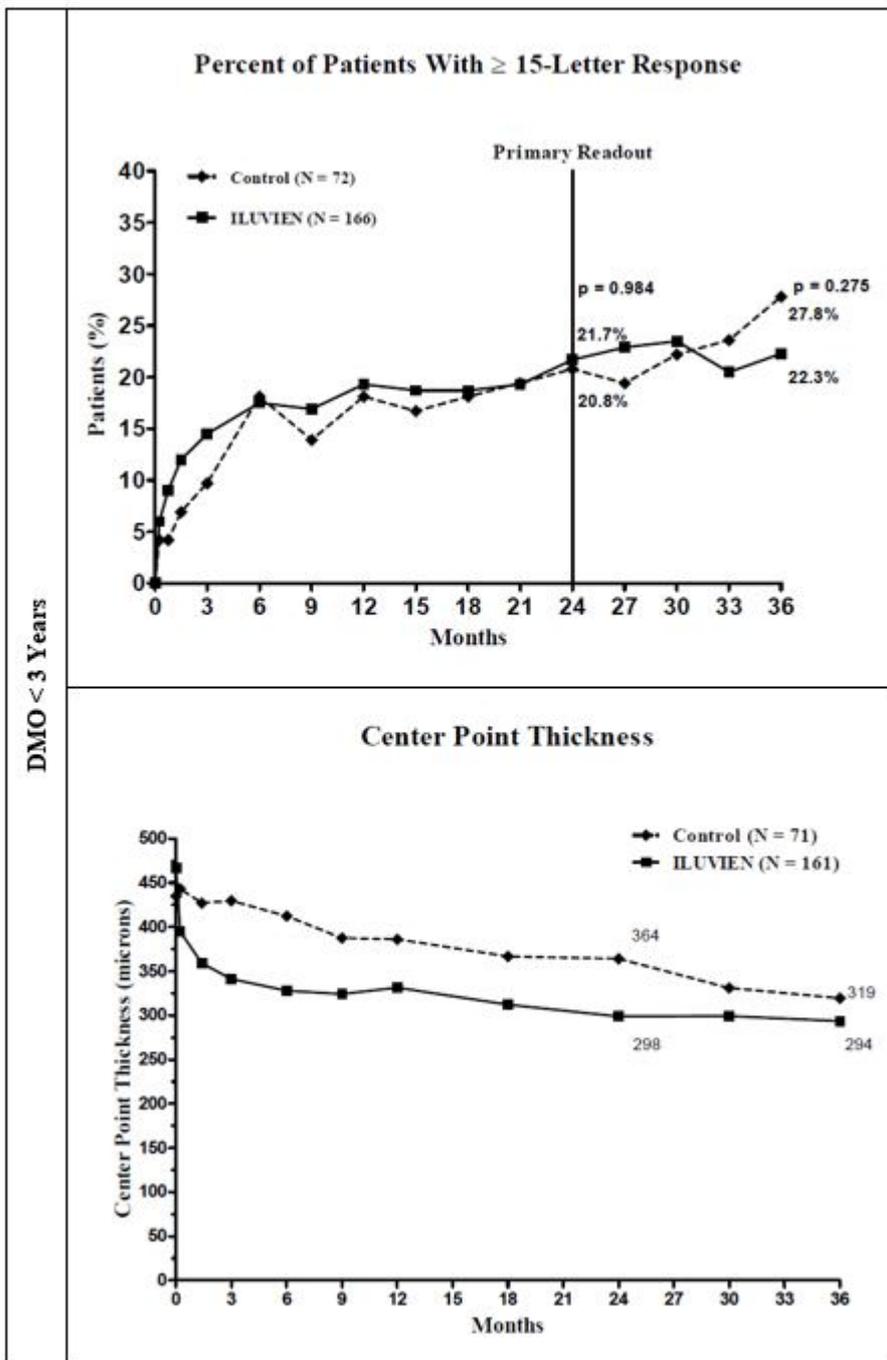


Figure 3: Comparison of Mean Change from Baseline Excess Center Point Thickness and Percent of Subjects with ≥15 letter Improvement from Baseline BCVA by Duration of DMO Subgroup < 3 years



A 6 year Post Approval Safety Registry Study (M-01-12-001), the IRISSstudy comprising of data from 556 patients (695 eyes), was completed and did not show any additional safety risks to those identified in the FAME studies.

Non-Infectious Uveitis-Posterior Segment

The ILUVIEN development programme for non-infectious uveitis affecting the posterior segment of the eye consists of two phase 3 studies to assess the safety and efficacy of 0.2 µg/day fluocinolone acetonide compared to sham injection over a 36-month period. Both studies are prospective, randomised, double-masked, sham-injection controlled, multicentre studies, of 282 patients in total who received either a single treatment with fluocinolone acetonide (188 subjects) or sham injection (94 subjects). The eligibility criteria were designed to enrol subjects with recurrent and persistent disease. At baseline, the ocular characteristics of patients enrolled in the studies are included in Table 2.

Table 2: Baseline Ocular Characteristics for the Study Eye (Intent To Treat (ITT) Population): PSV-FAI-001 and PSV-FAI-005

ITT Population	PSV-FAI-001		PSV-FAI-005	
	FAI insert (N=87)	Sham (N=42)	FAI insert (N=101)	Sham (N=52)
BCVA letters, Mean (SD)	66.9(15.49)	64.9(15.53)	66.4(15.85)	63.6(16.82)
Vitreous Haze severity 0/0.5+	48(55.2)	21(50.0)	37(36.6)	14(27.0)

1/2+	39(44.8)	21(50.0)	64(63.3)	38(73.1)
3/4+	0	0	0	0
Anterior Chamber Cells 0/0.5+	77(88.5)	33(78.6)	93(92.0)	49(94.3)
1/2+	10(11.5)	9(21.4)	8(7.9)	3(5.8)
3/4+	0	0	0	0
Intraocular Pressure (IOP) Mean (SD)	13.9(3.12)	13.6(3.15)	13.3(3.07)	13.1(2.60)
Severity of macular odema (μm) CST <300	37(42.5)	14(33.3)	70(69.3)	36(69.2)
CST \geq 300	48(55.2)	27(64.3)	30(29.7)	14(26.9)

BCVA = best corrected visual acuity; CST = central subfield thickness; SD=standard deviation

Data are No. (%) except where specified.

The primary efficacy endpoint was based on the proportion of subjects with an absence of recurrence of uveitis between randomization and month 6, where recurrence was defined as:

- ≥ 2 step increase in number of cells per high powered field compared with baseline or any visit time point prior to month 6; or
- an increase in vitreous haze of ≥ 2 steps compared to baseline or any visit time point prior to month 6; or
- a loss of best-corrected visual acuity of ≥ 15 letters compared to baseline at any visit time point prior to month 6.

Any criterion used to define recurrence was required to be attributable only to non-infectious uveitis. A subject who had not previously experienced a recurrence as defined in (a), (b), (c), and took a systemic corticosteroid or immunosuppressant, or an intra/peri-ocular or topical corticosteroid in the study eye at any time during the study prior to Month 6 was considered as having a recurrence. Recurrence could be treated using standard of care according to protocol defined criteria.

In each phase 3 clinical trial, the primary endpoint was met. See Tables 3 and 4 for the results of the primary efficacy endpoint comparing the proportion of recurrence of uveitis in the study eye versus the sham control. See figure 4 for a comparison of the time to recurrence of uveitis in these treatment groups.

Table 3: Proportion of Subjects with Recurrence of Uveitis in the Study Eye within 6 Months (ITT Population): PSV-FAI-001 and PSV-FAI-005

ITT Population				
	PSV-FAI-001		PSV-FAI-005	
	FAI Insert (N=87)	Sham Injection (N=42)	FAI Insert (N=101)	Sham Injection (N=52)
Recurrence w/in 6 months, n (%)	24(27.6)	38(90.5)	26 (25.7%)	31 (59.6%)
No recurrence w/in 6 months, n (%)	63(72.4)	4(9.5)	75(74.3%)	21(40.4%)
Difference from sham ¹				
Odds ratio	24.94		4.26	
95% CI	8.04, 77.39		2.09, 8.67	
P value	<0.001		<0.001	
Difference from sham ²				
Percent difference	62.9%		33.9%	
95% CI	(50.0%, 75.8%)		(18.0%, 49.7%)	
P value	<0.001		<0.001	

¹ The odds ratio and 95% confidence interval are based on Mantel-Haenszel. The p-value is from a continuity-adjusted chi-square test comparing between treatment groups the number of subjects with and without recurrence of uveitis at 6 months.

² P-value is from a Cochran-Mantel-Haenszel chi-square test for general association comparing between treatment groups the number of subjects with and without recurrence of uveitis at 6 months.

Table 4: Proportion of Subjects with Recurrence of Uveitis in the Study Eye within 6 Months (ITT Population): Pooled Uveitis Studies

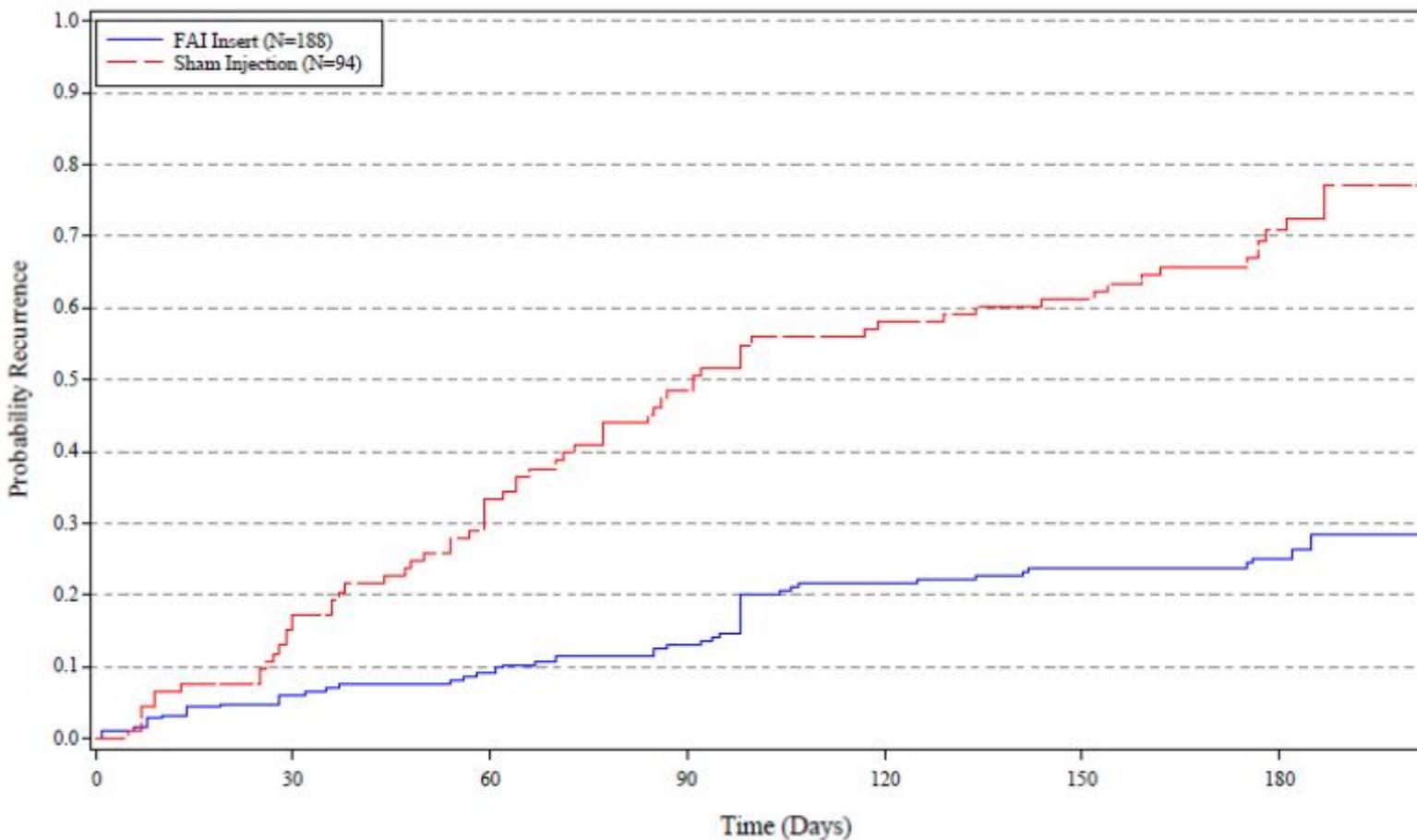
ITT Population

	FAI Insert (N=188)	Sham Injection (N=94)
Recurrence w/in 6 months, n (%)	50 (26.6)	69 (73.4)
No recurrence w/in 6 months, n (%)	138 (73.4)	25 (26.6)
Difference from sham ¹		
Odds ratio	7.62	
95% CI	(4.35, 13.34)	
P value	<0.001	
Difference from sham ²		
Percent difference	46.8%	
95% CI	(35.9%, 57.8%)	
P value	<0.001	

¹ The odds ratio and 95% confidence interval are based on Mantel-Haenszel. The p-value is from a continuity-adjusted chi-square test comparing between treatment groups the number of subjects with and without recurrence of uveitis at 6 months.

² P-value is from a Cochran-Mantel-Haenszel chi-square test for general association comparing between treatment groups the number of subjects with and without recurrence of uveitis at 6 months.

Figure 4: Kaplan-Meier Plot of Time to First Recurrences of Uveitis in the Study Eye within 6 Months (ITT Population): Pooled Uveitis Studies



The p-value ($p < 0.001$) comparing the two distributions of time-to-recurrence of uveitis are based on a log-rank test.

In the ITT population, the recurrence of uveitis in the study eye reported at 6 months was notably ($p < 0.001$) lower in the ILUVIEN group (37.9%) compared with the sham injection group (73.4%); the odds ratio for the difference from sham injection was 7.62 (95% CI: 4.35, 13.34).

Persistence of efficacy was demonstrated using the 36-month results of the phase 3 study initiated first (PSV-FAI-001) (see table for PSV-FAI-001 results of the primary efficacy endpoint comparing the proportion of recurrence of uveitis in the study eye versus the sham control and figure for a comparison of the time to recurrence of uveitis in these treatment groups).

Table 5: Proportion of Subjects with Recurrence of Uveitis in the Study Eye within 36 Months (ITT Population)

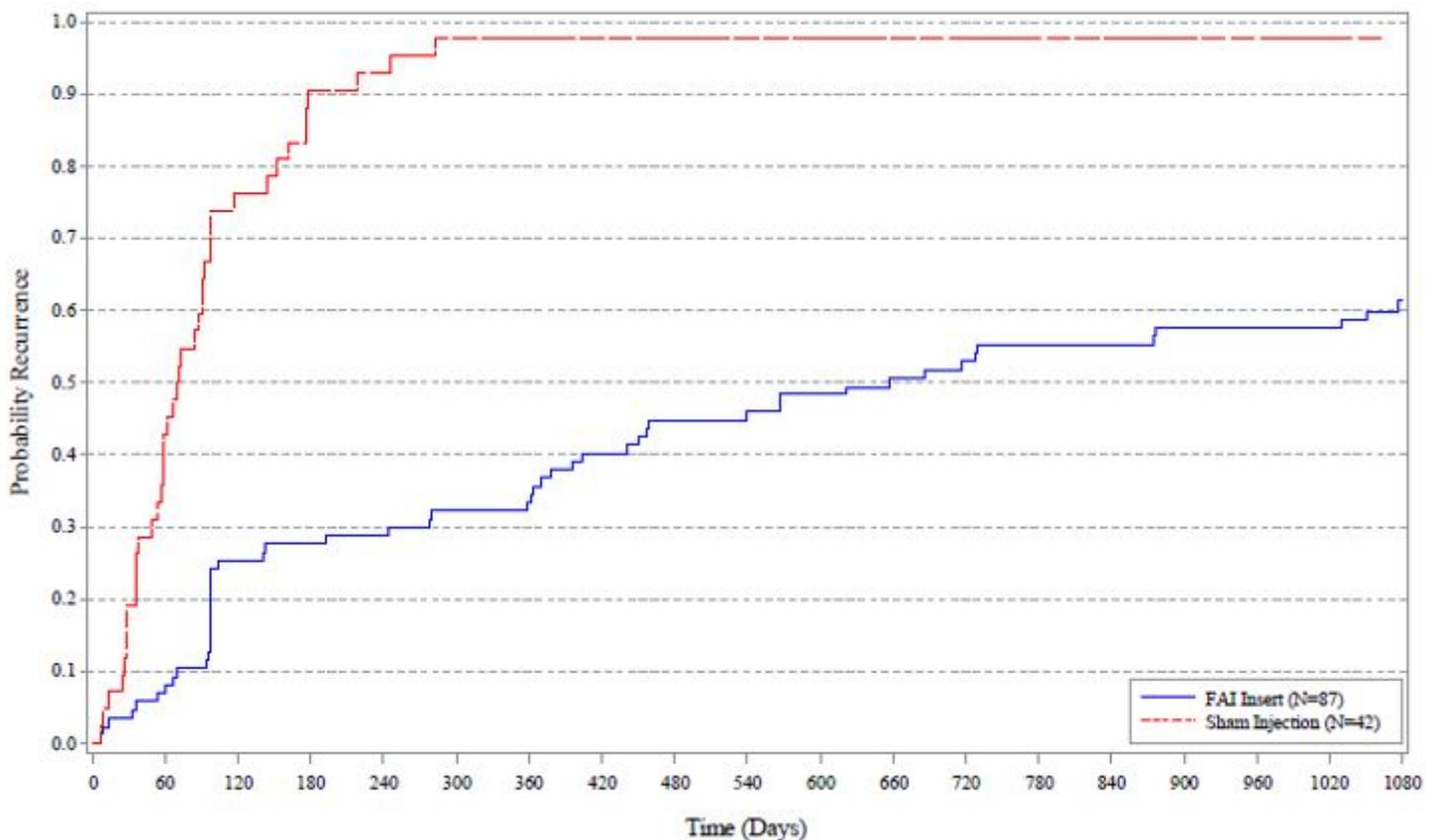
PSV-FAI-001

ITT Population		
	FAI Insert (N=87)	Sham Injection (N=42)
Recurrence w/in 36 months, n (%)	57(65.5%)	41(97.6%)
No recurrence w/in 36 months, n (%)	30(34.5%)	1(2.4%)
Difference from sham ¹		
Odds ratio	21.58	
95% CI	(2.83, 164.70)	
P value	<0.001	
Difference from sham ²		
Percent difference	32.1%	
95% CI	(21.1%, 43.1%)	
P value	<0.001	

¹ The odds ratio and 95% confidence interval are based on Mantel-Haenszel. The p-value is from a continuity-adjusted chi-square test comparing between treatment groups the number of subjects with and without recurrence of uveitis at 36 months.

² P-value is from a Cochran-Mantel-Haenszel chi-square test for general association comparing between treatment groups the number of subjects with and without recurrence of uveitis at 36 months.

Figure 5: Kaplan-Meier Plot of Time to First Recurrences of Uveitis in the Study Eye within 36 Months (ITT Population): PSV-FAI-001



In the ITT population, the recurrence of uveitis in the study eye within 36 months was significantly lower ($p < 0.001$) in the ILUVIEN group compared with the sham injection group.

Table 6: Number of Recurrence of Uveitis in the Study Eye within 6 Months (ITT Population): PSV-FAI-001 and PSV-FAI-005

ITT Population				
	PSV-FAI-001		PSV-FAI-005	
	FAI Insert (N=87)	Sham Injection (N=42)	FAI Insert (N=101)	Sham Injection (N=52)

Total number of recurrences	36	70	59	53
Number of patients with at least one recurrence	24	38	26	31
Number of recurrences per patient				
N	87	42	101	52
Mean (SD)	0.4 (0.76)	1.7 (1.07)	0.6 (1.34)	1.0 (1.21)
Median	0.0	1.0	0.0	1.0
Minimum, maximum	(0, 3)	(0, 5)	(0, 9)	(0, 6)
0	63 (72.4%)	4 (9.5%)	75 (74.3%)	21 (40.4%)
1	14 (16.1%)	18 (42.9%)	12 (11.9 %)	18 (34.6%)
2	8 (9.2%)	10 (23.8%)	4 (4.0 %)	8 (15.4%)
3	2 (2.3%)	9 (21.4%)	7 (6.9%)	3 (5.8 %)
4	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.9%)
5	0 (0.0%)	1 (2.4%)	1 (1.0%)	0 (0.0%)
>5	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (1.9%)
Difference from sham ¹				
Estimate	-1.3		-0.4	
95% CI	(-1.62, -0.88)		(-0.87, 0.00)	
P value	<0.001		0.051	

¹ P-value is from a one-sample analysis of variance with treatment group as the fixed effect comparing the mean number of recurrences of uveitis within 36 months.

Table 7: Number of Recurrence of Uveitis in the Study Eye within 36 Months (ITT Population): PSV-FAI-001

ITT Population		
	FAI Insert (N=87)	Sham Injection (N=42)
Total number of recurrences	149	223
Number of patients with at least one recurrence	57	41
Number of recurrences per patient		
N	87	42
Mean (SD)	1.7 (2.42)	5.3 (3.84)
Median	1.0	5.0
Minimum, maximum	(0, 15)	(0, 15)
0	30 (34.5%)	1(2.4%)
1	29 (33.3%)	5 (11.9%)
2	7 (8.0%)	7 (16.7%)
3	8 (9.2%)	4 (9.5%)
4	4 (4.6%)	3 (7.1%)
5	2 (2.3%)	5 (11.9%)
>5	7 (8.0%)	17 (40.5%)
Difference from sham ¹		
Estimate	-3.6	
95% CI	(-4.89, -2.30)	
P value	<0.001	

¹ P-value is from a one-sample analysis of variance with treatment group as the fixed effect comparing the mean number of recurrences of uveitis within 36 months.

Patients treated with ILUVIEN experienced significantly fewer recurrences within 36 months than those treated with sham (1.7 recurrences vs. 5.3 recurrences, respectively, $p < 0.001$).

Table 8: Number of Adjunctive Therapies for Uveitis in the Study Eye within 6 Months (ITT Population): PSV-FAI-001 and PSV-FAI-005

ITT Population				
	PSV-FAI-001		PSV-FAI-005	
	FAI Insert (N=87)	Sham Injection (N=42)	FAI Insert (N=101)	Sham Injection (N=52)
Systemic Steroid or Immunosuppressant				

Total number of recurrences	21	24	25	14
Number of subjects with at least one recurrence	13 (14.9%)	16 (38.1%)	14 (13.9%)	11 (21.2%)
Difference from sham ¹				
Percent difference	23.2%		7.3%	
95% CI	(6.7%, 39.6%)		(-5.7%, 20.3%)	
P value	0.003		0.249	
Intra/periocular steroid				
Total number of recurrences	5	35	2	19
Number of subjects with at least one recurrence	5(5.7%)	24(57.1%)	2(2%)	19(36.5%)
Difference from sham ¹				
Percent difference	51.4%		34.6%	
95% CI	(35.7%, 67.1%)		(21.2%, 47.9%)	
P value	<0.001		<0.001	
Topical steroid				
Total number of recurrences	17	22	11	17
Number of subjects with at least one recurrence	15(17.2%)	18(42.9%)	10 (9.9%)	12(23.1%)
Difference from sham ¹				
Percent difference	25.6%		13.2%	
95% CI	(8.7%, 42.6%)		(0.3%, 26.0%)	
P value	0.002		0.028	

¹ P-value is from a Cochran-Mantel-Haenszel chi-square test for general association comparing between treatment groups, the number of subjects with and without use of adjunctive therapy.

Table 9: Number of Adjunctive Therapies for Uveitis in the Study Eye within 36 Months (ITT Population): PSV-FAI-001

ITT Population		
	FAI Insert (N=87)	Sham Injection (N=42)
Systemic Steroid or Immunosuppressant		
Total number of recurrences	61	45
Number of subjects with at least one recurrence	30 (34.5%)	21 (50.0%)
Difference from sham ¹		
Percent difference	15.5%	
95% CI	(-2.6%, 33.6%)	
P value	0.092	
Intra/periocular steroid		
Total number of recurrences	23	99
Number of subjects with at least one recurrence	17 (19.5%)	29 (69.0%)
Difference from sham ¹		
Percent difference	49.5%	
95% CI	(33.2%, 65.8%)	
P value	<0.001	
Topical steroid		
Total number of recurrences	40	47
Number of subjects with at least one recurrence	24 (27.6%)	24 (57.1%)
Difference from sham ¹		
Percent difference	29.6%	
95% CI	(11.9%, 47.2%)	
P value	0.001	

¹ P-value is from a Cochran-Mantel-Haenszel chi-square test for general association comparing between treatment groups, the number of subjects with and without use of adjunctive therapy.

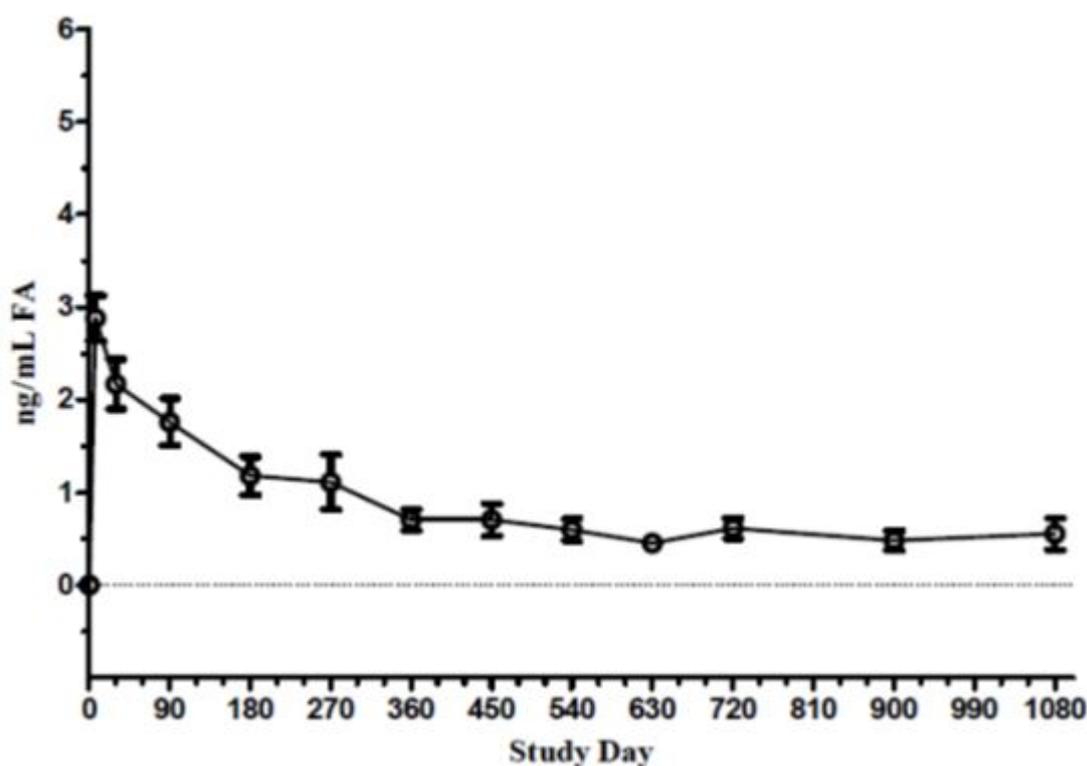
Significantly fewer patients treated with ILUVIEN versus sham required adjunctive intra/peri-ocular steroids (19.5% vs 69.0% respectively, $p < 0.001$) or topical steroids (27.6% vs 57.1% respectively, $p = 0.001$). Fewer patients required adjunctive systemic steroid or immunosuppressive therapy (34.5% vs 50.0% respectively, $p = 0.092$).

The European Medicines Agency has waived the obligation to submit results of studies with intravitreally administered fluocinolone acetonide in all subsets of the paediatric population for the treatment of diabetic macular oedema. See Section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

In a human pharmacokinetic study (C-01-06-002, the FAMOUS Study) fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all time points from Day 1 through Month 36. The maximal aqueous humor fluocinolone acetonide concentrations were observed on Day 7 for most of the subjects. Aqueous humor fluocinolone acetonide concentrations decreased over the first 3–6 months and remained essentially the same through Month 36 for subjects who were not retreated. Subjects who were retreated experienced a second fluocinolone acetonide peak concentration similar to that following the initial dose. After retreatment, aqueous humor concentrations of fluocinolone acetonide returned to levels approximately similar to those observed at the time of first treatment.

Figure 4: FA Levels in Human Aqueous Humor in Subjects Receiving 1 ILUVIEN Implant (FAMOUS Study)



5.3 Preclinical safety data

Fluocinolone acetonide has been shown to be teratogenic in mice and rabbits following systemic administration. No mutagenicity, carcinogenicity or developmental toxicity data are available for intravitreally administered fluocinolone acetonide. However, intravitreally administered fluocinolone acetonide was not detectable systemically and thus no systemic effects are anticipated.

Local effects (focal degenerative lesions affecting fibers in the posterior polar and posterior cortical regions of the lens) were observed in rabbits at doses of intravitreal fluocinolone acetonide in excess of the clinically used dose. Local effects (focal retinal scarring) were also seen in rabbits treated with both placebo and fluocinolone acetonide containing device. This scarring was not seen clinically in humans and is postulated to be due to anatomical differences between the rabbit and human eye.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyvinyl alcohol
Polyimide tube
Silicone adhesive

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
After first opening the lid, use immediately.

6.4 Special precautions for storage

Store below 30°C. Do not refrigerate or freeze.
Do not open the sealed tray until just before application.

6.5 Nature and contents of container

The implant is supplied in a single use applicator with a 25 gauge needle. Each sterile applicator contains a light brown 3.5 mm long cylindrical implant. The applicator is packaged in a plastic tray sealed with a lid.

6.6 Special precautions for disposal and other handling

Dispose of the applicator safely in a biohazard sharps container.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA22620/001/001

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10 DATE OF REVISION OF THE TEXT

September 2021