Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Mutual Recognition Procedure

ILUVIEN® 190 micrograms Intravitreal Implant in Applicator

(Fluocinolone acetonide)

UK/H/3011/001/E01

UK licence no: PL 41472/0001

Alimera Sciences Limited

LAY SUMMARY

ILUVIEN® 190 micrograms intravitreal implant in applicator (fluocinolone acetonide)

This is a summary of the Public Assessment Report (PAR) for ILUVIEN® 190 micrograms intravitreal implant in applicator (PL 41472/0001; UK/H/3011/001/E01). It explains how ILUVIEN® 190 micrograms intravitreal implant in applicator was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use ILUVIEN® 190 micrograms intravitreal implant in applicator.

The product will be referred to as ILUVIEN throughout the remainder of this lay summary.

For practical information about using ILUVIEN, patients should read the package leaflet or contact their doctor or pharmacist.

What is ILUVIEN and what is it used for?

ILUVIEN is used to treat vision loss associated with diabetic macular oedema when other available treatments have failed to help. Diabetic macular oedema is a condition that affects some people with diabetes, and causes damage to the light-sensitive layer at the back of the eye responsible for central vision, the macula. The active ingredient, fluocinolone acetonide, helps to reduce the inflammation and the swelling that builds up in the macula in this condition. ILUVIEN can therefore help to improve the damaged vision or stop it from getting worse.

How is ILUVIEN used?

ILUVIEN is given as a single injection into the eye by a doctor. The patient's doctor must use antibiotic eye drops and wash the eye carefully before injecting this medicine to prevent infection. The doctor will also give the patient a local anaesthetic to prevent any pain that the injection might cause.

The patient may be advised to have another implant injected into the eye if the effect of the implant wears off.

ILUVIEN can only be obtained with a prescription.

For further information on how ILUVIEN is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

How does ILUVIEN work?

This medicinal product contains the active ingredient fluocinolone acetonide, which belongs to a group of medicines called corticosteroids. ILUVIEN is a tiny tube that is inserted into the eye and releases very small amounts of the active ingredient, fluocinolone acetonide, for up to 3 years.

What benefits of ILUVIEN have been shown in studies?

As well as an appropriate review of literature, the company provided its own data on pharmacokinetic, efficacy and safety studies. These studies have shown that ILUVIEN has a comparable degree of efficacy to other therapies at improving vision impairment in patients with diabetic macular oedema.

What are the possible side effects from ILUVIEN?
The very common side effects (which may affect more than 1 in 10 people) with ILUVIEN are increased eye pressure, clouding of the eye's natural lens (cataract) or eye surgery to correct the cataract.

Common side effects (which may affect between 1 and 10 out of 100 people) with ILUVIEN are bleeding in the white part of the eye or inside the eye, small particles or spots in vision (floaters), increased pressure in the eye which damages the optic nerve (glaucoma) may be more likely if the pressure inside the eye is higher than average before treatment, eye pain or irritation, reduced vision, or eye surgery or procedure to relieve increased eye pressure or to remove the gel material that fills the back of the eye.

For the full list of all side effects reported with ILUVIEN, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why is ILUVIEN approved?
The MHRA decided that the benefits of ILUVIEN are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of ILUVIEN?
A risk management plan has been developed to ensure that ILUVIEN is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for ILUVIEN, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about ILUVIEN
On 27th February 2012, Austria, France, Germany, Italy, Portugal, Spain and the UK agreed to grant a Marketing Authorisation for ILUVIEN 190 micrograms intravitreal implant in applicator via the Decentralised Procedure (UK/H/3011/001/DC; PL 27813/0001). A National Marketing Authorisation was granted to Campharm Limited, UK on 4th May 2012. Subsequent to a change of ownership procedure, ILUVIEN was granted to Alimera Sciences Limited (PL 41472/0001) on 26 September 2012.

A second-wave mutual recognition procedure (UK/H/3011/001/E01) involving the Concerned Member States (CMSs) Belgium, Czech Republic, Denmark, Finland, Luxembourg, Norway, Poland, Republic of Ireland, Sweden and The Netherlands was concluded on 26 June 2014.

The full PAR for ILUVIEN follows this summary. For more information about treatment with ILUVIEN, read the package leaflets or contact your doctor or pharmacist.

This summary was last updated in November 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Iluvien 190 micrograms intravitreal implant in applicator is approvable via the Mutual Recognition Procedure (UK/H/3011/001/E01). This product is a prescription only medicine (POM), indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies.

The application was made under Article 8.3 of Directive 2001/83/EC, as amended, for a known active substance, fluocinolone acetonide.

A licence was originally granted for ILUVIEN 190 micrograms intravitreal implant in applicator via the Decentralised Procedure (UK/H/3011/001/DC; PL 27813/0001), with the UK as the Reference Member State (RMS) and Austria, France, Germany, Italy, Portugal, Spain as Concerned Member States (CMSs). A National Marketing Authorisation was granted in the UK to Campharm Limited on 4th May 2012. This licence underwent a change of ownership procedure to the current Marketing Authorisation Holder, Alimera Sciences Limited (PL 41472/0001), on 26 September 2012.

A second-wave mutual recognition procedure (UK/H/3011/001/E01) involving the CMSs, Belgium, Czech Republic, Denmark, Finland, Luxembourg, Norway, Poland, Republic of Ireland, Sweden and The Netherlands was concluded on 26 June 2014.

Diabetic macular oedema is the result of retinal microvascular changes that occur in patients with diabetes. Thickening of the basement membrane and reduction in the number of pericytes is believed to lead to increased permeability and incompetence of retinal vasculature. This compromise of the blood-retinal barrier leads to the leakage of plasma constituents into the surrounding retina, resulting in macular thickening due to fluid accumulation, resulting in significant disturbances in visual acuity. Prolonged oedema can cause irreversible damage resulting in permanent visual loss.

Iluvien is a sustained-release intravitreal drug delivery system that releases submicrogram levels of fluocinolone acetonide, a glucocorticoid, in the vitreous humour for up to36 months. It is inserted into the eye via the pars plana through a 25-gauge needle attached to an inserter device. The drug product proposed for the market (0.25 µg/day initial release) consists of a drug core containing fluocinolone acetonide in a polyvinyl alcohol (PVA) matrix encased in a polyimide tube. One end of the tube is coated with PVA and the other end with silicone adhesive. The PVA end is permeable and controls the release of fluocinolone acetonide into the vitreous chamber.

Three non-clinical studies have been provided to support this application, one pharmacodynamics study (an in vitro glucocorticoid receptor binding assay), and two toxicity studies. Both of the toxicity studies performed with ILUVIEN were conducted in compliance with Good Laboratory Practice (GLP) for Non-clinical Laboratory Studies.

Three clinical studies have been provided to support this application. One phase 2b pharmacokinetic study and two phase 3 clinical efficacy studies. The studies were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

First Wave DCP: The Member States, Austria, France, Germany, Italy, Portugal, Spain and the UK agreed to grant a Marketing Authorisation for ILUVIEN 190 micrograms intravitreal implant in applicator via the Decentralised Procedure (UK/H/3011/001/DC) which concluded on 27th February 2012.

Second Wave MRP: The Member States considered that the application could be approved with the end of a second-wave mutual recognition procedure (UK/H/3011/001/E01) involving the Concerned Member States (CMSs) Belgium, Czech Republic, Denmark, Finland, Luxembourg, Norway, Poland, Republic of Ireland, Sweden and The Netherlands (Day 90 - 26th June 2014).

II QUALITY ASPECTS

II.1. INTRODUCTION

This product is presented in a pre-loaded applicator for intravitreal implantation. Each implant contains 190 micrograms of fluocinolone acetonide, as active ingredient. The excipients present are polyvinyl alcohol, polyimide tube and silicone adhesive. Appropriate justification for the inclusion of each excipient has been provided.

All excipients comply with their respective in-house specifications.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

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.

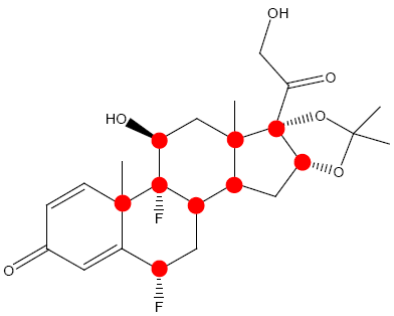
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

II.2 Drug Substance

INN: Fluocinolone acetonide

Chemical name(s): (6α,11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione
6α,9α-difluoro-16α-hydroxyprednisolone-16,17-acetonide
6α,9α-difluoro-11β,16α-17,21-tetrahydroxpregna-1,4-diene-3,20-dione
cyclic 16,17-acetal with acetone
6α,9α-difluoro-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20- dione

Structure:



Molecular formula: $C_{24}H_{30}F_2O_6$
Molecular weight: 452.5 g/mol
Appearance: White or almost white crystalline powder.
Solubility: Practically insoluble in water, soluble in methanol, ethanol, chloroform and in acetone, sparingly soluble in ether.

The source of fluocinolone acetonide used in the product complies with the European Pharmacopoeia monograph.

The manufacturer of the drug substance holds a valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificate of Suitability. The quality of the substance is suitably controlled in line with the current edition of the European Pharmacopoeia Monograph.

The manufacturing process, control of materials, control of critical steps, validation and process development for fluocinolone acetonide were assessed and approved by the EDQM in relation to the granting of the Certificate of Suitability and are therefore satisfactory.

Appropriate proof-of-structure data have been supplied for the active substance.

All potential known impurities have been identified and characterised.

An appropriate specification with suitable test methods and limits are provided for the drug substance. Non-pharmacopoeial analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. The methods of testing and limits for residual solvents are in compliance with current guidelines.

Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for all working standards.

The container closure system and re-test period for fluocinolone acetonide complies with the container closure system and re-test period specified on the Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development programme was to develop an intraocular delivery system which can provide release of the drug substance directly to the back of the eye over a period of months or years.

The applicant has provided a suitable product development section. Fluocinolone acetonide is known to exhibit polymorphism, with three polymorphs, Forms A, B & C identified in literature. Three batches of fluocinolone acetonide produced by the active substance manufacturer have been characterised and the results show that one batch comprise almost entirely of Form A while other batches comprise a mixture of polymorphs. Therefore, the synthetic process followed can be considered to lead to a mixture of polymorphs.

Comparison of drug release from drug product batches manufactured with fluocinolone acetonide batches of varying proportion of polymorph Form A show that drug release was unaffected. The applicant therefore concludes that the drug release rate is unaffected by polymorphic form. As drug release is not affected, determination of the solubility of the different polymorphic forms of fluocinolone acetonide is not required.

A control of polymorphism content is used to ensure a majority of Form A polymorph.

Valid justifications for the use and amounts of each excipient have been provided.

Profiles of *in vitro* release rates over time have been provided and are satisfactory. Comparative *in vitro* drug substance release rate profiles have been provided for the proposed product and the clinical batches.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on batches have been provided and are satisfactory.

Finished Product Specification
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the products
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years as packaged from the date of manufacture. The product should be stored below 30^{o}C, do not refrigerate or freeze. The sealed tray should not be opened until just before application. Once the lid has been opened, the product should be used immediately. This is satisfactory.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
This is an application for ILUVIEN, an intravitreal implant containing fluocinolone acetonide submitted under Article 8.3 (known active) of Directive 2001/83/EC, as amended.

As well as an appropriate review of literature, a total of 3 non-clinical studies have been provided to support this application. One pharmacodynamic study (an *in vitro* glucocorticoid receptor binding assay), and two toxicity studies:

• A 24-Month Toxicity Study of FA/Medidur™ Administered Via Intravitreal Injection to Pigmented Rabbits (Study JOK00002).

• A 9-Month Ocular Toxicity Study of Intravitreal Administered FA/Medidur™ to Pigmented Rabbits Following a Forced Degradation of the Test Article (Study JOK00001).

Brief summary
Fluocinolone acetonide (FA) (*6α,9-Difluoro-11β,16α,17,21-tetrahydroxypregna-1,4-diene- 3,20-dione cyclic 16,17-acetal with aceton*) is a medium potency synthetic fluorinated glucocorticoid that has been used as a dermal anti-inflammatory product for over thirty years. Although glucocorticoids are well known anti-inflammatory agents, they have also been shown to reduce the expression of vascular endothelial growth factor (VEGF).

Diabetic macular oedema is characterised by the development of intraretinal oedema, due to leakage from retinal vessels. VEGF is the primary mediator of the permeability changes and

angiogenesis-related progression of diabetic retinopathy (DR). Intraocular administration of a corticosteroid has shown to reduce intravitreal VEGF levels by turning off the gene for production of VEGF and causing regression of active neovascularization by direct inhibition of VEGF producing cells. Published data confirmed that FA inhibits expression of VEGF in ARPE- 10 cells. Intravitreal glucocorticoid administration (triamcinolone acetonide [Kenalog®]) has been shown to reduce intravitreal VEGF levels, decrease macular thickness, and increase visual acuity in man.

Additional pharmacological effects of glucocorticoids that contribute to efficacy in DR include inhibition of migration of many types of cells, including T-cells, that release heparin, growth factors, and other angiogenic substances, and secretion of proinflammatory cytokines which stimulate VEGF production.

Due to the longstanding clinical topical use of fluocinolone acetonide and the extensive information in the literature on the pharmacologic effects of glucocorticoids, the evaluation of the primary pharmacological effect was limited to several studies conducted with Retisert® and modified ILUVIEN implants in rabbit models of uveitis and proliferative vitreoretinopathy (PVR) and rat retinal neuroprotection assays. The results of these experiments are summarised below.

III.2 Pharmacology

Glucocorticoid receptor binding assay
Fluocinolone acetonide was evaluated in an in vitro glucocorticoid receptor binding assay (Study 06-2989) using triamcinolone acetonide as a reference compound. The reported IC50 for FA was 1.51 nM. The IC50 of triamcinolone acetonide was similar and that of dexamethasone was approximately an order of magnitude less potent in this assay.

VEGF expression in ARPE-19 cells Cultured human retinal pigment epithelial cells (ARPE-19 cells) were exposed to FA (0.0001–1 μM) to determine the effects on VEGF secretion, VEGF mRNA expression, using ELISA and RT-PCR, respectively. In addition, a glucocorticoid receptor antagonist (RU486) was utilized to determine if VEGF expression was dependent on glucocorticoid receptor activity. Finally, TNF-α–induced angiogenesis was studied using the chick chorioallantoic membrane (CAM) assay to determine the effects *in vivo*. At concentrations devoid of cytotoxicity, FA inhibited VEGF secretion as well as mRNA expression in ARPE-19 cells. RU486 (1 μM) prevented FA mediated – VEGF reductions in secretion and VEGF mRNA expression. Fluocinolone (50 ng/egg) inhibited angiogenesis induced by TNF-α. Serum stimulated ARPE-19 cell proliferation was inhibited by FA in a dose-dependent manner.

In conclusion FA inhibited VEGF expression in ARPE-19 cells via glucocorticoid receptor activity. In addition, FA inhibited proliferation of ARPE-19 cells and TNF-α–induced angiogenesis in chorioallantoic membranes.

Experimental proliferative vitreoretinopathy in rabbits
An efficacy study of a FA/Retisert-like system using a model of proliferative vitreoretinopathy (PVR) was conducted in rabbits. To induce PVR, lensectomy and vitrectomy were performed, and full thickness retinal breaks were created by endodiathermy in the right eye of 26 rabbits. In this model, PVR typically develops over an 8-12 week period. A 6 mg FA pellet was compressed, coated with PVA/silicone laminate, heat treated, then affixed to a PVA suture strut to create a sustained delivery system that releases FA at approximately 6 μg/day. The system was implanted in 13 eyes at the time PVR was first induced. In the remaining animals (control), only a PVA strut was inserted and secured. The severity of PVR in the two groups was graded by indirect ophthalmoscopy in a masked fashion by 2 observers at weekly intervals over 12 weeks. The

masked examinations indicated that the severity of PVR was significantly lower in the FA implant group compared to controls from weeks 8 through 12 ($p<0.05$). The number of eyes with moderate retinal detachments was also lower in the FA group.

FA/Retisert® in rabbit experimental uveitis
A study of intravitreal sustained release FA systems using the uveitis model in rabbits has been published which determined the safety and efficacy of FA.

A group of 46 rabbits were sensitized by subcutaneous injection of tuberculin antigen. Fourteen days later the rabbits were randomly assigned to receive intravitreal implants of either an empty system (placebo, N=14), a system releasing FA at 0.5 μg/day (N=16), or a system releasing FA at 0.1 μg/day (N=16). Uveitis was induced by intravitreal injection of tuberculin antigen.

A masked observer graded corneal neovascularization, anterior chamber cell and flare, iris congestion and vitreous opacity on days 1-7, 9, 16 and 21 after uveitis induction. On days 6 and 9, the aqueous white blood cell count and protein measurement was conducted. Retinal function was evaluated by electroretinogram. Histologic sections of enucleated eyes were studied under light microscopy.

By clinical criteria, treated eyes were significantly less inflamed than untreated animals. Anterior chamber cell ($p=0.015$), flare ($p=0.008$) and vitreous opacity ($p=0.003$) were significantly reduced by AUC analysis between the three groups. Overall, inflammation (flare and vitreous opacity) was suppressed to a greater degree with the 0.5 μg/day dose than with the 0.1 μg/day dose. Aqueous white blood cell count, protein concentration and histopathologic examination paralleled this clinical assessment. Differences in the ERG b-wave amplitudes were not statistically significant.

FA Inserts (ASI-001) in rabbit experimental uveitis
A literature study investigated inserts of design similar to Iluvien delivering 0.6 (n=11) or 1.0 μg/day (n=9) in the rabbit uveitis model. Sustained-release FA inserts were placed into the vitreous of the right eyes of rabbits through a 25 gauge needle 7 days after a subcutaneous injection of tuberculin antigen. Control animals (N=9) received empty inserts. Uveitis was then induced with an intravitreal injection of tuberculin antigen. Masked observers graded anterior chamber flare, cell and vitreous opacity on days 1–7, 10, and 14 after uveitis induction. Enucleated eyes and recovered inserts were used to confirm drug release rates and vitreous drug concentrations. The test product was inserted into the vitreous cavity without complications. By clinical criteria, treated eyes were less inflamed than untreated eyes. Both dose levels significantly reduced vitreous opacity compared to controls ($p<0.04$). There was a significant reduction in anterior chamber flare ($p=0.03$) and vitreous opacity ($p<0.01$) among the 3 groups with more inflammation control at the higher dose level. The vitreous concentration of FA in enucleated eyes was comparable to that of eyes implanted with Retisert® (Driot et al 2004).

Secondary pharmacodynamics
Secondary pharmacodynamic studies from literature have been reported using a modified implant in rat models of retinal degeneration.

Intravitreal FA/Medidur™ (0.5 and 0.2 ug/day) was neuroprotective in the Royal College of Surgeons (RCS) rat model of retinal degeneration. The ERG-b wave amplitudes and outer nuclear layer cell counts were maintained following administration of test substance while in control animals these parameters were reduced at post natal weeks 2, 5 and 9. In addition, FA has profound effects on retinal microglia in this model. The numbers of microglia were reduced by 43% in

treated eyes by comparison to control eyes and the numbers of activated cells were further decreased. These findings are in keeping with previous observations since glucocorticoids have been used as neuroprotectants in spinal cord injury for at least 10 years and have been reported to have anti-apoptotic effects in retinal models of neurodegeneration.

Similar results were also observed in a second model of retinal degeneration, the S334-ter-4 rat model wherein photoreceptor degeneration occurs spontaneously at a slower rate than the RCS model, due to a mutant rhodopsin gene. The sustained delivery of FA to the retina was neuroprotective in that the outer nuclear layer morphology and the ERG a and b wave amplitudes were preserved.

Safety pharmacology
As the pharmacology of FA is well understood and the intraocular route of administration results in undetectable systemic exposure to FA following administration, no safety pharmacology studies have been conducted with the drug product and none are required.

Pharmacodynamic drug interactions
The pharmacological effect of FA will be restricted to the eye therefore no interactions systemically are anticipated. As there is clinical experience with intravitreal FA, no safety pharmacology studies and pharmacodynamic interaction studies with FA have been submitted and none are required.

Pharmacology Conclusion
The primary pharmacology data presented has been taken from the literature and mainly reports efficacy of FA in uveitis using FA intravitreal implants. The selection of the dose was based on clinical data and is therefore detailed in the clinical assessment. Although pharmacologic data in animals has not been provided due to the difficulties of long term animal models of diabetic macular oedema, FA is well established as a glucocorticoid and the clinical studies provide substantial evidence that the 0.2 μg/day dose provides the best balance of long-term efficacy and safety available with the current technology.

III.3 Pharmacokinetics

FA was approved as a topical dermal product approximately 35 years ago, so no systemic pharmacokinetic studies in animals or humans have been published in the last 25 years. In view of the finding that FA is not measurable in the plasma at any time following administration of either dose of FA inserts, no systemic pharmacokinetic studies were performed. In general, the systemic pharmacokinetics of FA are not well characterised, but this is not considered necessary given the long term usage of FA in humans and the absence of measurable FA in the systemic circulation following administration of FA inserts in rabbits and humans. The ocular pharmacokinetics in rabbits demonstrate sustained delivery of FA to the vitreous and retina which is supported by the demonstration of efficacy in phase III clinical studies.

An adequate summary of the available information on systemic pharmacokinetics of closely related glucocorticoids and a comparison of the published data for the ocular pharmacokinetics have been provided. Although systemic pharmacokinetic information is not available for fluocinolone acetonide, the general characteristics can be inferred by comparison to two close congeners of FA, triamcinolone acetonide and flunisolide.

The pharmacokinetics of the drug product were studied in a satellite arm of the 24-month repeat-dose toxicity study in rabbits and the toxicokinetic data is presented below (for further details see the repeat-dose toxicity section).

Methods of analysis
FA in rabbit ocular tissue and plasma was determined using a validated method. The limit of quantitation (LOQ) was defined to be 200 pg/mL. For each calibration standard, peak area for FA was determined.

Dexamethasone 21- Acetate was used as the external standard. A linear regression describing the calibration curve was then calculated using the reciprocal of the drug concentrations (1/x) as a weight. The assay is based on liquid-liquid extraction procedure using 100 µL of rabbit ocular tissues and rabbit ocular tissues homogenate. An appropriate method of analysis has been utilised.

Absorption
Iluvien 190 micrograms intravitreal implant in applicator inserts release very small amounts FA directly into the vitreous humor. In the 24-month repeat-dose toxicity study, absorption into the systemic circulation was not detectable (>200pg/ml) in rabbits following administration of low dose (0.2 µg/day), high dose (0.5 µg/day), or two high dose inserts during the peak release or at any other time during 24 months.

A discussion of the *in vivo* release rates from the 24-month repeat-dose toxicity study was provided. While the results do indicate a higher release rate *in vivo* than *in vitro*, this is based on limited data. In addressing the clinical relevance of this finding, the difference in the vitreous of young rabbits verses humans has been highlighted. Based on these limitations and the availability of both animal and PK data, it is considered that no further information is required.

Distribution
FA concentrations in aqueous humor were generally below the limit of quantitation (0.2 ng/mL) at the majority of time points. Vitreous humor, lens, choroid, pigmented epithelium and iris/ciliary body had measurable concentrations of FA at all time points. However, in the low dose (0.2 µg/day) group, FA levels fell below 0.2 ng/mL in the cornea and retina, typically after Day 89. At the 0.5 µg/day and 2 X 0.5 µg/day dose levels, FA concentrations in the cornea and retina generally reached below limit of quantitation (BLQ) on Day 271 after the first dose, increased again following the second dose (approximately Day 363) and then subsequently fell below the quantitation limit on Day 728 or Day 539 (retina at the mid dose).

Following a small initial peak release, near steady vitreous humor, lens, cornea, retina, choroids and pigmented epithelium and iris/ciliary body tissue concentrations of FA were maintained following intravitreal injection of ILUVIEN. The left and right eye mean tissue concentrations declined very gradually with elimination half-lives (T1/2) generally exceeding 2000 hours. In general, ocular tissue FA concentrations increased with the dose level and at the mid and high dose levels, concentrations were seen to increase following administration of the second dose at 12 months.

The terminal elimination phase could not be characterised (R2 (correlation coefficient) less than 0.8, or the extrapolation of the AUC to infinity more than 20% of the total area) at all dose levels for some ocular tissues.

The estimated T1/2 of FA in vitreous humor was 2670, 2772 or 3056 hours in males at 0.2, 0.5 and 1.0 μg/day, respectively, and 6138 and 1838 hours in females at 0.2 and 0.5 μg/day, respectively. Elimination of FA from the ocular tissues was very slow without apparent tissue or dose dependence, and was considered a reflection of the controlled (continued) release of FA from the FA/Medidur™ delivery system.

In general, the exposure of FA was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. The exposure of FA in aqueous humor was minimal at all dose levels. The local exposure of FA increased with the dose in both male and female rabbits; however, there was no clear evidence of dose proportionality in the ocular exposure of FA in the dose range of 0.2 to 1.0 μg/day. There were some differences in the C_{max} and $AUC_{(0\text{ -tlast})}$ of FA in the local ocular tissues between male and female rats, but there were no clear trends in gender differences at any dose level.

FA concentrations in the aqueous humour in rabbits were generally below the limit of quantification, however, in humans, FA was found in the aqueous humour in quantifiable amounts. While the level of FA in the aqueous humor of rabbits was below the limit of quantification, this may in part be due to the less sensitive method used in the rabbit study (LLOQ, 200 pg/mL for rabbit tissues; 100 pg/mL for human plasma and aqueous humor). In view of the strong demonstration of clinical efficacy through 3 years in the phase 3 clinical studies, further development of analytical methods is not required to support the non-clinical studies.

Metabolism
No drug metabolism/elimination studies have been provided and none are required. There is no available information on ocular metabolites from other published animal studies of FA.

There are also no reports of metabolite effects or systemic effects from FA or other corticosteroids administered intravitreally. The metabolism of corticosteroids is primarily by hepatic mechanisms. Ocular metabolism of FA released from the insert is not expected and is most likely that FA is eliminated by distribution into the systemic circulation, producing very low levels over a prolonged period of time.

The most active organ for metabolism of corticosteroids is the liver, and these low levels of FA are most likely metabolized by hepatic esterification. Because of the very limited systemic exposure expected from the FA insert, meaningful levels of FA metabolites or parent drug are not likely to occur. This is supported by the fact that plasma and urine levels of FA in rabbits were consistently below 200 pg/ml in the 24-month rabbit study despite exaggerated dosing. Furthermore, plasma levels of FA in patients treated with the drug product were below the limit of detection (<100 pg/mL) at all times for both doses of 0.2 and 0.5 μg/day (FAMOUS Study).

Excretion
No excretion studies have been provided and none are required. An appropriate risk assessment of the theoretical possibility of dose-dumping has been provided. Based on clinical pharmacokinetic data, it is unlikely that exposure to all the FA contained in the device would result systemic exposure and associated adverse events.

Pharmacokinetic drug interactions
No studies have been performed to investigate pharmacokinetic drug interactions and none are required, given that the systemic absorption of FA following intravitreal administration has been shown to be negligible and that clinical experience with intravitreal FA exists.

Pharmacokinetics Conclusion
A general discussion comprising a review of published data on the pharmacokinetics of FA has been provided. The only PK (TK) data available through use of the proposed product has been generated in the 24-month repeat-dose rabbit study. The distribution of FA following intravitreal administration of 0.2, 0.5 and 1.0 µg/day has been elucidated. Local exposure of FA increased with dose, but no clear evidence of dose proportionality was observed. It is noted that FA concentrations in the aqueous humour in rabbits were generally below the limit of quantification. No concerns relating to dose-dumping have been identified.

III.4 Toxicology

Intravitreal toxicity studies with the drug product were performed in rabbits to assess the local and systemic uptake and toxicity of FA. Genotoxicity studies of the FA component of the drug product were also conducted *in vitro* and *in vivo*.

Single dose toxicity
No single dose (acute) toxicity studies have been conducted with the drug product and none are required as a literature review is adequate.

In the literature, single subcutaneous doses of FA caused delayed mortality in adult mice and rats at dose levels of 12.5 and 3.12 mg/kg respectively. Decreases in thymus and spleen weights were also noted after administration of a single 4 mg/kg dose of FA to rats. The delayed mortality seen after administration of large acute doses of glucocorticoids has been ascribed to generalized infection resulting from immunosuppression (an expected pharmacologic effect). Delayed mortality and decreases in body weight gain were also reported in new born rats at dose levels of 0.02 to 0.05 mg FA/rat, consistent with the typical wasting syndrome observed after acute administration of glucocorticoids.

The effects reported in literature studies following administration of a single dose of FA are the result of exaggerated pharmacological action and are considered to be class-effects.

Repeat-dose toxicity
A 24-month ocular toxicity and pharmacokinetics study in rabbits and a 9-month ocular toxicity study in rabbits using test article that had undergone forced degradation were conducted with the drug product as described below. Continuous exposures of ocular tissues for the 9- and 24-month toxicity studies were achieved via one or two injections of the insert into the eye, followed by a sustained release of FA into the vitreous.

A 9-Month Ocular Toxicity Study of Intravitreal Administered FA/Medidur™ to Pigmented Rabbits Following a Forced Degradation of the Test Article (Study JOK00001)

The FA/Medidur™ (ASI-001A, Iluvien 0.5 µg/day dose) inserts evaluated in this study underwent forced degradation for 6 months at 40°C and 75% relative humidity before test article administration. At the completion of the 6-month storage under accelerated conditions, the FA/Medidur test articles met the specifications for assay, impurities, and release rate. The total impurity level was 3.91% (w/w %), while the highest single impurity, the known degradant product etianic acid, was 0.82% (w/w %).

The protocol experimental design included two control groups (one sham, one placebo insert) and one group treated with two 0.5 µg/day inserts (Table 1 below):

Table 1: Protocol experiment design for Study JOK00001.

Group Number	Number of Main Study Animals		Test Article	Number of Devices/Eye	Daily Dose of Fluocinolone Acetonide (FA) (µg/day/eye)[1]
	Males	Females			
1	4	4	Sham control	Sham control	0
2	4	4	Placebo	2 (Placebo)[2]	0
3	7	7	FA/Medidur[3]	2[4]	1.0

1 Based on the nominal release rate

2 Two inserts in the right eye

3 Forced degradation for 6 months at 40°C and 75% relative humidity prior to administration

4 Two inserts in the right eye

There were no findings that were definitively ascribed to administration of the FA/Medidur test article. Posterior lens opacity was observed on ophthalmic examination at 4-, 6- and 9-months in one rabbit in the sham control group and in two rabbits in the FA/Medidur group, and could have been the result of physical contact of the insert with the posterior lens capsule, rather than a direct result of the FA test article.

Histological findings that were present in the eyes of some animals administered FA/Medidur, but not in those receiving sham control or placebo, and that may have been related to the FA test article were observed. These observations were restricted to focal degenerative lesions affecting fibers in the posterior polar and posterior cortical regions of the lens. Other histological findings in the eyes such as focal scarring were seen in both the placebo and test groups and are likely to be caused by the dosing procedures, and were not considered test article-related.

Focal degenerative lesions which affected fibers in the posterior polar and posterior cortical regions of the lens were observed in 4/14 of the animals treated with Iluvien 1.0 µg/day FA. These findings are not surprising, as lens fiber degeneration/cataract development in the posterior subcapsular region of the lens has been reported following intravitreal dosing of corticosteroids, including FA (Retisert®). It should also be noted that cataract formation was seen clinically.

In conclusion, the test article FA/Medidur, after undergoing forced degradation, did not appear to induce ocular disease or systemic toxicity over a 9-month period after its placement in the vitreous of pigmented rabbits.

A 24-Month Toxicity Study of FA/Medidur™ Administered Via Intravitreal Injection to Pigmented Rabbits (Study JOK00002)

The objective of this study was to assess the potential local and systemic toxicity of the drug product when administered to rabbits via intravitreal injection on one or two occasions over a 24 month period. The experimental design included two control groups (one sham and one placebo insert) and three groups treated with active drug inserts (0.2, 0.5 or 1.0 µg/day) (table 2 below).

Table 2: Experiment design for Study JOK00002.

Group Number	Number of Main Study Animals		Number of Pharmacokinetic Animals		Test Article	Number of Devices	Daily Dose of Fluocinolone Acetonide (FA) (µg/day)[1]
	Males	Females	Males	Females			
1	4	4			Sham control	Sham control[2]	0
2	4	4			Placebo	1 (Placebo)[2]	0
3	4	4	10	10	FA/Medidur™	2	0.2
4	4	4	10	10	FA/Medidur™	2[3]	0.5
5	4	4	10	10	FA/Medidur™	4[4]	1.0

1 Based on the nominal release rate

2 Sham injections and placebo injections performed in the right and left eyes on Study Day 1

3 One device in the right and left eyes on Study Day 1, and another during Week 52

4 Two devices in the right and left eyes on Study Day 1, and two during Week 52

Observations consisted of the following: body weights, feed consumption, clinical pathology measurements, bioanalytical sample analysis, physical examinations, and ophthalmological evaluations (including electroretinography and tonometry). The main study animals were evaluated on Study Day 729, and the pharmacokinetic animals (1/sex/group on Study Days 2 and 8 and at Weeks 5, 8, 13, 26, 39, 52, 78, and 104). Evaluations included organ weights, gross examination, histopathology, and biodistribution sample collection. Toxicokinetic analyses were also performed.

One Group 5 animal (4 inserts, 1.0 µg/day) died on Study Day 239. No test article-related effects were detected, and the cause of death remains undetermined. One animal in Group 2, three animals in Group 3, and one animal in Group 5 were found dead on Study Day 1. These deaths were considered likely a consequence of complications related to the administration of anesthesia, and the animals were replaced on study.

There were no test article-related changes in clinical observations, body weights, feed consumption, physical examinations, clinical pathology parameters, or organ weights. Test article-related ophthalmologic findings were observed in Group 4 (2 devices, 0.5 µg/day) and Group 5 (4 devices, 1.0 µg/day). Posterior cortical/capsular cataract was the predominant lesion observed, and the frequency of cataract formation increased with increasing test article dosage and duration of exposure.

There were no test article-related gross findings with the possible exception of one animal each in Groups 4 and 5; these animals had a finding of lens deformity (rough surface area). There were no apparent abnormal test article-related changes to the morphology of the eye. Histopathologic examination revealed focal retinal scarring, which was seen more frequently in the area of the injection site in the eyes of the rabbits treated with inserts than in rabbits subjected only to the sham injection. This effect was more apparent in the rabbits from the groups which received multiple inserts, and is probably related to the injection procedure. No changes were detected in the lenses to indicate any cataractogenic activity, and there was no apparent retinal or optic nerve damage suggestive of glaucoma. Cataracts were observed in Groups 4 and 5 on ophthalmologic examination, but similar findings were not noted upon histological examination. A plausible explanation for the discrepancy between the evaluations may be secondary effects of tissue fixation, resulting in the masking of cataract detection using hematoxylin and eosin staining.

Quantifiable FA concentrations were not observed at any dose level in the plasma of rabbits administered FA/Medidur (quantitation limit of 200 pg/mL); therefore, systemic pharmacokinetics of FA could not be assessed. In general, FA exposure was generally highest in the choroid and pigmented epithelium, followed by the lens or retina, the iris/ciliary body, the vitreous humor or cornea. With the exception of one eye of one animal (at 0.2 μg/day), FA was undetectable in aqueous humor up to 0.5 μg/day, and the exposure of FA in aqueous humor was minimal at 1.0 μg/day. The local exposure of FA generally increased with the dose in both male and female rabbits; however, there was no clear evidence of dose proportionality in the ocular exposure of FA in the dose range of 0.2 to 1.0 μg/day.

Overall, elimination of FA from the ocular tissues was very slow without apparent tissue or dose dependence, and was considered a reflection of the controlled (continuous) release of FA from the FA/Medidur delivery system. Near-steady vitreous humor, lens, cornea, retina, choroid and pigmented epithelium, and iris/ciliary body tissue concentrations of FA were maintained following intravitreal administration of FA/Medidur. The left and right eye mean tissue concentrations declined very gradually with elimination half-lives (t1/2) generally exceeding 2000 hours. The pharmacokinetic data do not demonstrate a notable difference in the T1/2 of males and females.

Conclusion of Studies
In conclusion, from the studies, there appeared to be no toxicity associated with Iluvien 0.2 μg/day. The FA appeared to induce posterior cortical/capsular cataracts in pigmented rabbits at 0.5 and 1.0 μg/day, as indicated by the increased incidence of cataracts at these concentrations. The development of these cataracts may be associated with the extended t1/2 of FA in the lens. Lens deformity upon gross examination was recorded only in one animal each out of 8 animals receiving 0.5 or 1.0 μg/day. Reports of focal retinal scarring in the 9-and 24-month toxicity studies was observed at the anterior edge of the rabbit retina. The reports of focal scarring in rabbits are due to the insertion procedure and, because of the relative difference in the size of the lens versus the globe in a rabbit versus a human, are not considered relevant to the procedure in humans. The risk of the rare possibility of damage to the globe due to entrapment of the insert in the sclera is considered inconsequential compared to the benefit of improved vision in subjects who are considered unresponsive to standard of care.

Product Device
A discussion of the device part of the product and long-term safety implications of retreatment has been provided. The materials used in the composition of the Iluven insert are commonly used in other medicinal or device products including those intended for ocular use. No observations from the non-clinical or clinical long-term studies have identified concerns relating to a compromise in the device integrity.

Genotoxicity

Table 3: Overview of genotoxicity studies

Type of test/Study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria Study no. 961864	*Salmonella typhimurium* (TA1535, TA1537, TA98, TA100)	0, 1.58, 5.0, 15.8, 50.0, 158.0, 500.0, 1581.0, 5000.0 μg/plate	Negative

GLP	*Escherichia Coli* (WP2 *uvrA*)	+/- S9	
Gene mutations in mammalian cells Study no. 962441 GLP	Mouse lymphoma L5178Y TK	Preliminary Assay: 0.379, 0.675, 1.20, 2.13, 3.79, 6.75, 12.0, 21.3, 37.9, 67.5, 120, 213, 379, 675, 1200 µg/mL Main Test: 4.69, 9.38, 18.8, 37.5, 75.0, 86.5, 100, 115, 150, 300, 600, 1200µg/mL +/- S9	Negative
Chromosomal aberrations in vivo Study no. 961866 GLP	Mouse, micronuclei in bone marrow	0, 50, 100 and 200 mg/kg (FA); 6 mg/kg (Mitomycin C) +/- S9	Negative

FA was not found to be genotoxic in a standard battery of genotoxicity tests conducted in accordance with relevant guidelines.

Carcinogenicity

No carcinogenicity studies were conducted and none are required because of the very low systemic exposure of FA (below the limit of quantification, <200 pg/mL in rabbit plasma) after administration of the drug product. This is satisfactory, as FA was not genotoxic in the standard battery of tests and no signs of neoplastic lesions were detected in the 24-month toxicity study.

Reproductive and Developmental Toxicity

No reproductive and developmental toxicity studies were conducted and none were required because of the very low systemic exposure of FA (below the limit of quantification, <200pg/mL in rabbit plasma) after administration of the drug product.

Phototoxicity
No phototoxicity studies have been submitted and none are required. Available information indicates that solid FA is not significantly degraded by visible light. FA is released daily in the vitreous where the light levels are relatively low. Due to the limited exposure of solubilized FA in the vitreous to ultraviolet light, phototoxicity is not considered likely.

Local Tolerance
See the repeat-dose toxicity section.

Studies on Impurities
See the study, 9-Month Ocular Toxicity Study of Intravitreal Administered FA/Medidur™ to Pigmented Rabbits Following a Forced Degradation of the Test Article (Study JOK00001).

No local toxicity attributed to the impurities was seen following use of the degraded test substance in the 9-month study. Furthermore, no additional toxicity can be attributed to the presence of impurities at the stated level on comparison of the results from the 9-month and 24-month studies. As such, the impurities are considered to be toxicologically qualified up the levels present in this degraded product (total impurity level of 3.91% (w/w %), highest single impurity, etianic acid, was 0.82% (w/w %)). The impurity limits in the final specification are higher than those present in the material used in the 9-month toxicity study on a per insert basis; however, in this study each animal received 2 inserts in one eye on Day 1. This resulted in twice the level of impurities and the levels tested provide support and justification for the specification for impurities. Therefore, no further toxicological qualification of impurities is required.

Toxicology Conclusion
No new single-dose, carcinogenicity and reproductive and developmental toxicity studies have been provided and none are required, given the lack of systemic exposure following intravitreal administration and clinical experience with FA intraocularly. Discussion of the device part of the product has been provided and the lack of phototoxicity studies adequately justified.

The reports of focal scarring in rabbits due to the insertion procedure, was found to not be relevant to the product use in humans, because of the relative difference in the size of the lens versus the globe in a rabbit versus a human. The risk of the rare possibility of damage to the globe due to entrapment of the insert in the sclera is outweighed by the benefit of improved vision in subjects who are considered unresponsive to standard of care.

III.5 Ecotoxicity/environmental risk assessment (ERA)
An environmental risk assessment for FA has been submitted in line with relevant guidance.

Table 4: Summary of main study results for the environmental risk assessment

Substance (INN/Invented Name): Fluocinolone acetonide			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Predicted log K_{ow} Experimentally-based K_{ow}	2.47 2.48	Potential PBT (N)
PBT-statement **:**	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC surface water , default or refined (e.g. prevalence, literature)	0.000000049	µg/L	> 0.01 threshold (N)

As the $PEC_{surfacewater}$ value and log Kow value for fluocinolone acetonide are below the threshold, fluocinolone acetonide is not classifiable as a Persistent, Bioaccumulative and Toxic (PBT) substance. No phase II investigation is required.

Toxicology Conclusion
No new single-dose, carcinogenicity and reproductive and developmental toxicity studies have been provided and none are required, given the lack of systemic exposure following intravitreal administration and clinical experience with FA intraocularly. Discussion of the device part of the product has been provided and the lack of phototoxicity studies adequately justified.

The reports of focal scarring in rabbits due to the insertion procedure, was found to not be relevant to the product use in humans, because of the relative difference in the size of the lens versus the globe in a rabbit versus a human. The risk of the rare possibility of damage to the globe due to entrapment of the insert in the sclera is outweighed by the benefit of improved vision in subjects who are considered unresponsive to standard of care.

Non-Clinical Overview
The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS

IV.1 Introduction
A total of 3 clinical studies have been provided to support this application. One phase 2b pharmacokinetic study and two phase 3 clinical efficacy studies:

• The FAMOUS Study:
A randomised, open label, multicentre pharmacokinetic and efficacy Phase 2b study of 0.5 µg/day and 0.2 µg/day FA intravitreal inserts in subjects with diabetic macular oedema (with centre point retinal thickness ≥250 microns and visual acuity ≥19 ETDRS letters. (An *in vitro-in vivo* correlation study also included).

• FAME A & FAME B
Randomised, double-masked, sham injection-controlled, parallel-group multi-centre studies to assess the safety and efficacy of 0.2 and 0.5 µg/day FA intravitreal inserts in subjects with diabetic macular oedema who had undergone previous laser therapy.

IV.2 Pharmacokinetics and IV.3 Pharmacodynamics
Study C-01-06-002 (the FAMOUS study)
A randomised, open label, multicentre pharmacokinetic and efficacy Phase 2b study of 0.5 µg/day and 0.2 µg/day FA intravitreal inserts in subjects with diabetic macular oedema (with centre point retinal thickness ≥250 microns and visual acuity ≥19 ETDRS letters.

Objectives
The primary objective of this trial was to characterise the systemic and intraocular levels of FA. In addition, the effect of FA on change from baseline in central retinal thickness was to be assessed.

An attempt to correlate the aqueous humour concentration of FA with pharmacodynamic (PD) effect was to be undertaken.

Methods
An interim report including data for subjects through Month 36 has been provided. The treatment was administered to only one eye, referred to as the "study" eye. The other eye, referred to as the "non-study" eye, received any ocular treatment other than systemic treatments for diabetic macular oedema or DR. All study data, were collected for both eyes with the exception of ultrasounds and aqueous humour samples. At Visit 1 (Day 0, screening/baseline), subjects were evaluated for eligibility, and 1 eligible eye per qualifying subject received either the 0.2 μg/day or 0.5 μg/day FA intravitreal insert. The remaining visits were scheduled at Day 1, Week 1, Month 1, Month 3, and every 3 months after the Month 3 visit through Month 24, and every 6 months thereafter through Month 36 (Visit 14). If progression of oedema occurred, the subject could have received retreatment after 12 months. After retreatment, there were 2 post-treatment visits at 1 day and 1 week.

Study Participants
Although 30 adult subjects were planned, to ensure sufficient data 37 subjects were enrolled since 3 subjects died of non-study-related causes during the enrolment period. Of the 37 subjects randomised into the study (20 subjects in the 0.2 μg/day group and 17 subjects in the 0.5 μg/day group), all were included in the Intent-to-Treat and Safety populations.

All subjects had a clinical diagnosis of diabetic macular oedema, a diagnosis of diabetes mellitus (type 1 or type 2), and had undergone at least one macular laser treatment more than 12 weeks prior to screening. The diagnosis of diabetic macular oedema was based on investigator's clinical evaluation and demonstrated on fundus photographs, fluorescein angiograms, and optical coherence tomography (OCT).

Treatments
The FA intravitreal inserts were inserted through the pars plana into the vitreous using a modified 25 gauge needle. For subjects with unilateral diabetic macular oedema, the "study eye" was the affected eye; for subjects with bilateral diabetic macular oedema, the "study eye" was the more severely affected eye fitting the inclusion/exclusion criteria. If both eyes were equally affected and eligible, the "study eye" was determined by the subject number (even, right eye and odd, left eye). Subjects were eligible for retreatment any time after the Month 12 assessments, but no later than the Month 30 assessments, if they experienced vision loss (documented reduction of ≥5 letters in Early Treatment Diabtic Retinopathy Study (ETDRS) visual acuity (VA) or retinal thickening per OCT (minimum increase of 50 microns at the centre of the fovea) as compared to the subject's best status during the previous 12 months. If the subjects were retreated, they received the same treatment they received on Day 0 (ie, their randomised treatment).

Outcomes/endpoints
PK and PD Measurements
• Plasma and aqueous humour samples were obtained throughout the study and evaluated for FA levels using a validated liquid chromatography-tandem mass spectrometry method (LC/MS-MS) method.

• For PK/PD correlation analyses, parameters such as centre point retinal thickness and visual acuity were used as measures of anatomical and functional changes resulting from resolution of oedema. Efficacy measurements were OCT and ETDRS Visual acuity. Safety measurements were

also taken. The mean change from baseline in central foveal thickness measured by OCT was considered the primary efficacy variable.

Statistical methods
On Study Day 0 (Visit 1), eligible subjects were randomised in a 1:1 ratio to one of two treatment groups and received either a 0.2 or a 0.5 μg/day FA intravitreal insert in the study eye. The randomisation schedule was stratified by centre and was computer-generated.

The Intent-to-Treat (ITT) population was created from all randomised subjects who had at least 1 post-baseline efficacy assessment. All efficacy variables were analysed using this dataset. The ITT population was the primary population for the analysis of efficacy. The safety population included all randomised subjects who received any study drug and for whom at least one safety assessment was obtained.

PK/PD variable and analyses
• PK parameters including area under the curve (AUC), T_{max} and C_{max} were calculated
• PK/PD comparisons were performed, including change from baseline in average foveal thickness, best corrected visual acuity (BCVA), and Intraocular Pressure (IOP) vs. aqueous humour levels of FA.

Efficacy measurements were by OCT, BCVA letter score, ETDRS chart, The International Clinical Diabetic Retinopathy Disease Severity Scale (0 to 4 scale).

Subgroup analyses were performed on the ITT data set, including the following variables: age, race, gender, study centre, iris colour, location of insert, lens status, BCVA.

Results
Participant flow
The analysis provided by the applicant is based on data for all subjects to Month 36. One subject in the 0.2 μg/day group was discontinued due to withdrawal of consent at Month 15.

Most of the subjects had type 2 diabetes (89%), and the median time since diagnosis of diabetes was 16 years (range 1 to 44 years). Subjects were being treated with oral therapy alone (32%), insulin alone (38%), or a combination of the two (27%).

One subject received a prohibited therapy (vitrectomy) in the study eye which had potential confounding effects on their diabetic macular oedema. As a result, subsequent data for this subject was excluded from the ITT analysis. One subject did not fulfil the diagnosis of diabetes mellitus as defined in the protocol.

Pharmacokinetic data analysis
All FA plasma concentrations were below the lower limit of quantitation of the assay (100 pg/mL); therefore, no PK analyses were performed on plasma samples. Drug concentrations of FA in aqueous humour generally followed a consistent pattern for both doses over time (Figure 1).

The maximal aqueous humour FA concentrations were observed on Day 7 for most of the subjects in the 0.2 μg/day dose group and at either Day 7 or Month 1 for subjects in the 0.5 μg/day dose group. In both treatment groups, aqueous humour FA concentrations decreased over the first 3−6 months and then stabilised to approximately the same concentration between Months 6 and 18.

Based on Month 18 data, the duration of drug release was at least 18 months. Dose proportionality was not demonstrated because the 2 doses performed similarly after the first 3 months.

Figure 1. Mean PK Profiles of FA in Aqueous Humour (all subjects, n = 37)

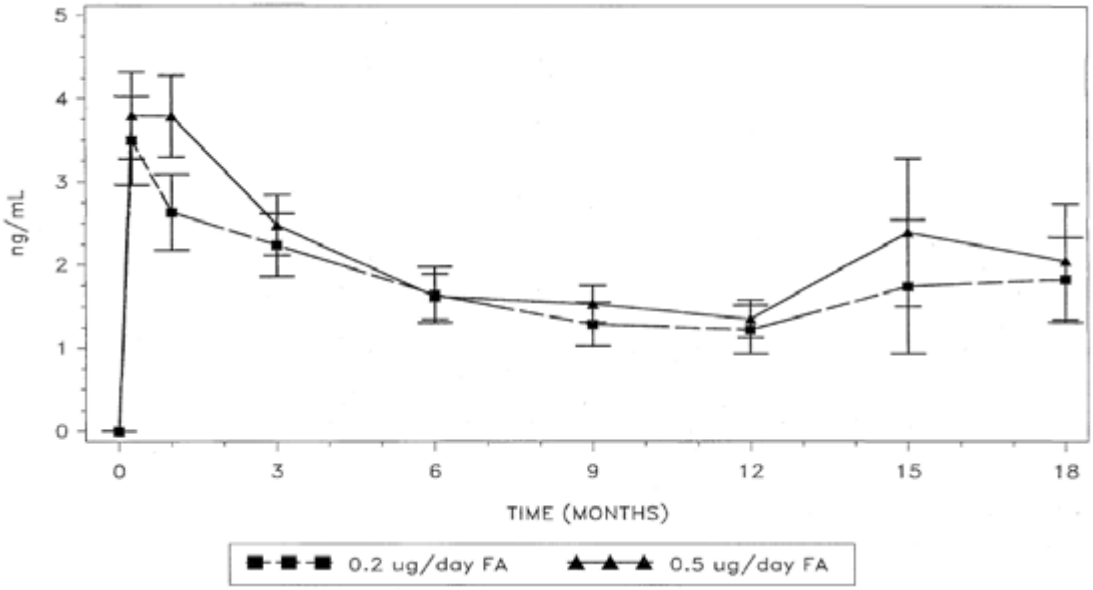


Figure 2. Mean PK Profiles of FA in Aqueous Humour (all subjects not re-treated; n = 24)

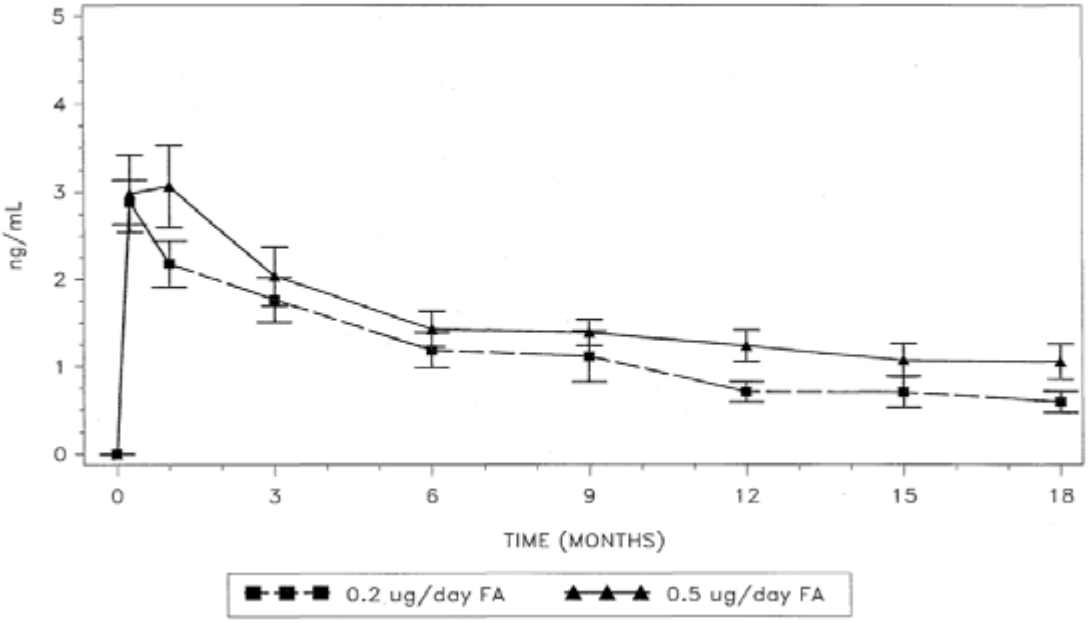
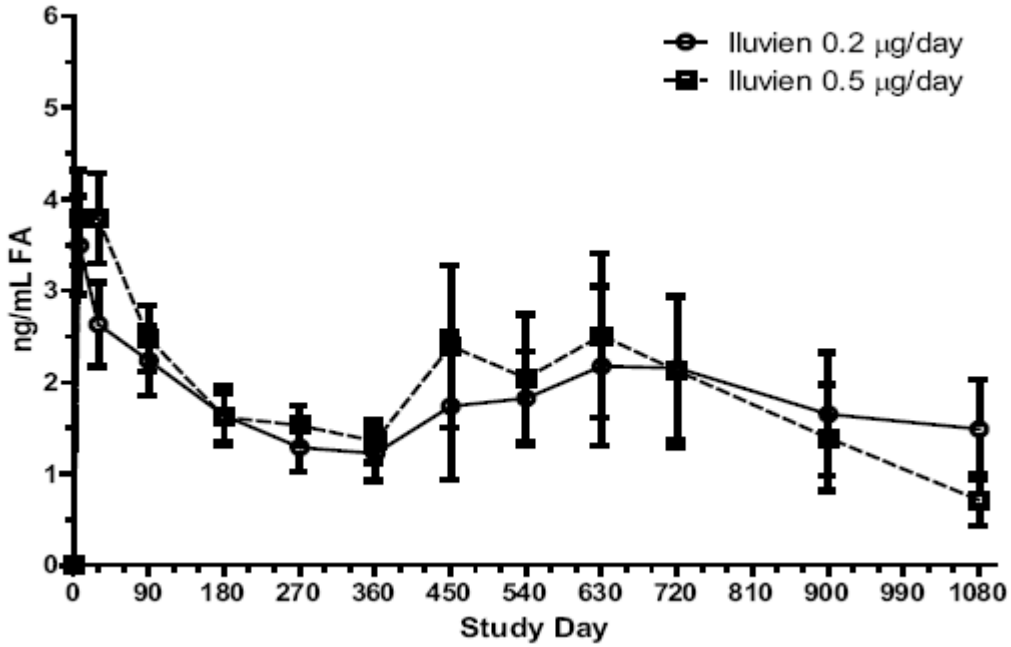


Table 5. PK parameters for FA in Aqueous Humour (all subjects)

	Mean Aqueous PK parameters (range)				
Group (Dose)	C_{max} (ng/mL)	$AUC_{(0-90)}$ (day*ng/mL)	$AUC_{(0-180)}$ (day*ng/mL)	$AUC_{(0-270)}$ (day*ng/mL)	$AUC_{(0-360)}$ (day*ng/mL)
1 (0.2 µg/day)	3.55 (0.506 – 11.3)	233 (41.1 – 776)	408 (75.6 – 1388)	545 (98.0 – 1842)	662 (120 – 2216)
2 (0.5 µg/day)	4.11 (1.65 – 9.03)	280 (90.6 – 626)	464 (162 - 1092)	603 (220 – 1470)	726 (267 – 1808)

Figure 3 provides the aqueous levels of FA over time for both doses through Month 36 for those who received more than one insert and 2 shows levels for subjects after only a single implant.

Figure 3 Mean (SEM) Fluocinolone Acetonide Levels in the Aqueous Humour in Subjects Who Received Retreatment



FA aqueous humour concentrations were above the lower limit of quantification (LLOQ) of the assay (0.2 ng/mL) in predose samples from three subjects in the 0.2 µg/day dose group. These concentrations were at least one order of magnitude lower than those observed on the following sampling occasion (Day 7). Because the "predose" sample was in fact collected at approximately the same time as the insert was implanted, these predose concentrations most probably result from early release of FA from the insert. No FA was quantifiable prior to treatment in samples from the 0.5 µg/day dose group.

The majority of subjects received 1 intravitreal insert (24 subjects, 65%); the remaining subjects received 2 intravitreal inserts (13 subjects, 35%). 40% of subjects in the low-dose group were retreated versus 29% of subjects in the high-dose group. However, more subjects (4/17) had discontinued from the study in the high dose group by Month 12 than in the low dose group (1/20). As a result the proportion of number of subjects who were available for retreatment (which could

occur anytime after the Month 12 evaluations) was actually similar (high dose, 38% [5/13]; low dose, 42% [8/19]).

Subjects who were retreated experienced a second FA peak concentration similar to that following the initial dose. After retreatment, aqueous humour concentrations of FA returned to levels approximately similar to those observed at the time of first treatment. Subjects could be retreated any time after the Month 12 assessments if visual acuity had decreased or retinal thickness had increased. The number of subjects who were retreated in the FAMOUS study was small, so limited conclusions can be drawn about reasons for their retreatment. Of the 8 subjects retreated in the 0.2 µg/day group the mean last fluocinolone concentration in the aqueous humour prior to retreatment was 1.58 ng/mL (median 0.93, range 0.26-4.31). These figures do not appear to be particularly low, and suggest that more complex factors may be involved in the requirement for retreatment than levels of intraocular fluocinolone alone. Furthermore no specific baseline factors have been identified that can predict need for retreatment from the FAMOUS and FAME studies.

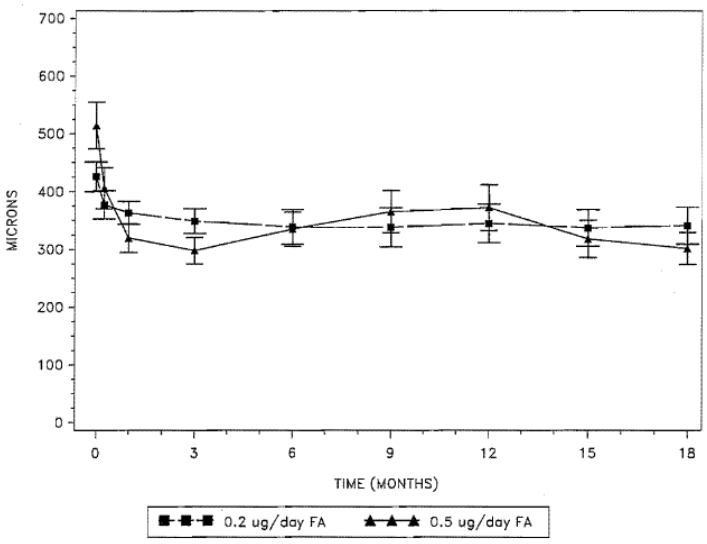
Overall, PK analysis demonstrates that there is no apparent systemic exposure of FA following intraocular administration of either high or low dose FA inserts. Measurable levels of FA in the aqueous humour have been shown for up to 36 months after a single treatment. The FAMOUS Study demonstrated that measurable levels of FA are found in human aqueous humor through Month 36 following treatment with the Iluvien.

Efficacy data analysis

- Primary efficacy variable: change from baseline in centre point thickness

Mean decreases from baseline in centre point thickness were observed in each treatment group throughout the study. These changes from baseline achieved statistical significance at all time-points up to Month 18 in both treatment groups. Statistically significant differences were observed between treatment groups (in favour of 0.5 µg/day FA) at Month 1 (mean difference of 132.2 microns [95% CI: 28.07, 236.35]; p=0.014), Month 3 (mean difference of 139.7 microns [95% CI: 33.54, 245.80]; p=0.011), and Month 18 (mean difference of 128.2 microns [95% CI: 2.93, 253.51]; p=0.045).

Figure 4. Mean (SEM) centre point macular thickness



Secondary efficacy variables

• Change from baseline in BCVA letter score

Mean increases from baseline in BCVA letter scores were consistently observed through Month 12 in the 0.2 µg/day FA group and through Month 18 in the 0.5 µg/day FA group. These changes from baseline only achieved statistical significance at 2 time-points in the 0.2 µg/day FA group (Months 1 and 3). No statistically significant differences were observed between treatment groups at any time point.

In the 0.2 µg/day FA group 3 subjects (15%) had a ≥15 letter increase from baseline at Month 12, and none at Month 18. In the 0.5 µg/day FA group 4 subjects (23.5%) had a ≥15 letter increase from baseline at Months 12 and 18. No statistically significant differences were observed between treatment groups at any time point.

• Change from baseline in macular volume

Mean decreases from baseline in retinal volume were consistently observed in each treatment group through Month 18. The degree of reduction in retinal volume was not statistically different between the two treatment groups.

• Change from baseline in level of diabetic retinopathy

The majority of subjects in each treatment group did not exhibit any shift from baseline in the level of DR at Months 6, 12, or 18.

• Treatment for diabetic macular oedema with laser therapy

Ten (27%) subjects, 6 (30%) in the 0.2 µg/day FA group and 4 (24%) in 0.5 µg/day FA group, received a total of 14 laser treatments for diabetic macular oedema.

For both anatomic and functional changes, it should be noted that the subjects in the high dose group had a consistently worse baseline status, making the two groups very nonhomogeneous for purposes of comparing outcomes with respect to these two parameters.

• Analysis of PK/PD correlation

The PK/PD relationships of the concentration of FA in the aqueous humour and changes from baseline in selected efficacy (centre point thickness and BCVA) and safety (IOP) parameters did not reveal any clinically relevant correlations.

• Examination of subgroups

No clear trends were observed to indicate that changes from baseline in centre point thickness and BVCA are appreciably affected by age, race, gender, study centre, iris colour, location of insert, or lens status.

Conclusion

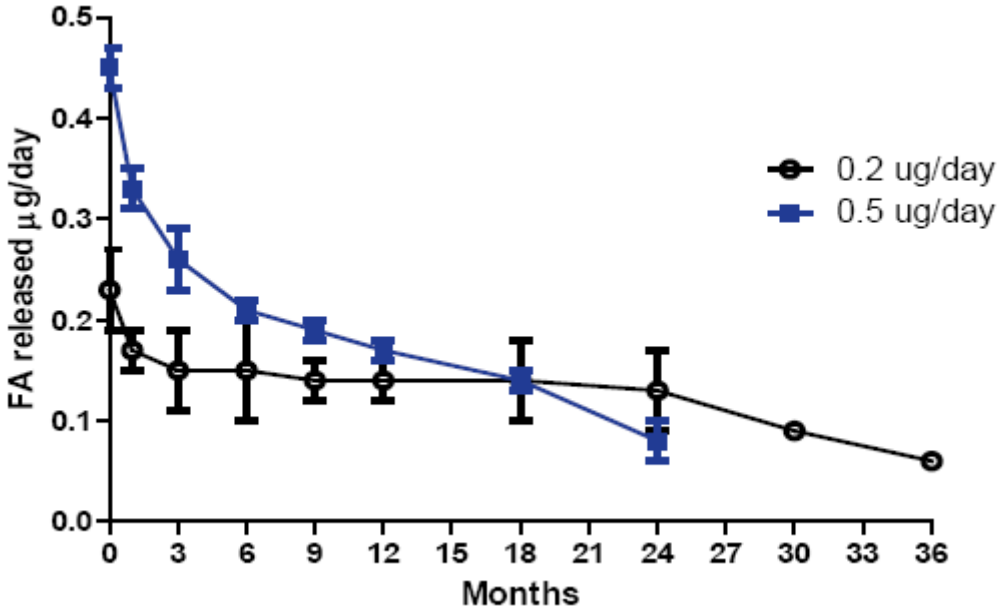
The primary objective of this trial was to characterise the systemic and intraocular levels of FA. This study shows that the low dose formulation has preferable release rate characteristics, with a sustained release close to the predicted level through 36 months.

***In vitro - in vivo* correlation study (Report 480271)**

The objective of this analysis was to perform an *in vitro*/*in vivo* correlation of FA released from Iluvien intravitreal inserts, to describe the relationship between *in vitro* dissolution data and the corresponding *in vivo* response.

In vitro dissolution data from Iluvien was generated for targeted release rates of 0.2 and 0.5 µg/day in phosphate buffer. Samples were collected for high-performance liquid chromatography (HPLC) determination of FA concentrations at Day 1, Months 1, 3, 6, 9, 12, 18, 24 and 36. The daily amount of FA released was measured for either 8 or 4 days. The 0.2 µg/day inserts had an initial average release rate of 0.23 µg FA/day, but decreased to approximately 0.13 µg FA/day at 24 months. The *in vitro* study of the implant shows that the low dose formulation has preferable release rate characteristics, with a sustained release close to the predicted level through 36 months.

Figure 5. *In vitro* release rates of Iluvien



In vivo exposure data from Iluvien generated from the human PK study detailed above was compared to the toxicity study of Iluvien at targeted FA dose levels of 0.2 µg/day, 0.5 µg/day, and 1.0 µg/day in eyes of male and female rabbits (Study No. JOK00002). There was no quantifiable systemic exposure of FA at any dose level. The exposure of FA was generally highest in the choroid and pigmented epithelium followed by the lens or retina, the iris/ciliary body, the vitreous humour or cornea. The ocular exposure of FA in the aqueous humour in rabbits was minimal at all dose levels. This comparison suggested that the concentrations observed in the human aqueous humour are probably substantial under estimations of the concentrations in the retina at the same time points.

Pharmacokinetic and Pharmacodynamic Conclusion

The phase 2b PK study (FAMOUS) adequately demonstrates that that intravitreal insertion of Iluvien implants does not result in a measurable systemic exposure to the active substance, and that following a single implantation there is a sustained release of FA within the eye (measurable in the aqueous humour) for 36 months. However, pharmacodynamic data showed no dose proportionality was found between the two dose levels and a dose-response relationship was not observed for the measured efficacy parameters. This initially raised a concern regarding the dose levels selected for the pivotal Phase 3 studies, but the benefit-risk balance of the low dose implant was considered on its own merits.

IV.4 Clinical efficacy

Two phase 3 pivotal studies (FAME A and FAME B) were conducted to determine efficacy.

Please note that although the higher dose of 0.5 μg/day was also used in the studies, only the 0.2 μg/day dose was chosen for the licence application, and therefore only this dose should be considered.

FAME A & FAME B Studies

Both studies were randomised, double-masked, sham injection-controlled, parallel-group multi-centre studies to assess the safety and efficacy of 0.2 and 0.5 μg/day FA intravitreal inserts in subjects with diabetic macular oedema who had undergone previous laser therapy. The 2 trials (FAME A and FAME B) were identical in design and conduct.

The applicant has presented data up to Month 36 for all subjects.

Objectives

This study was designed to assess the safety and efficacy of FA intravitreal inserts (0.2 μg/day and 0.5 μg/day) in subjects with diabetic macular oedema in comparison to a sham-injection control.

The primary objective was to determine if either dose level of FA intravitreal insert is superior to the control group with respect to the proportion of subjects with a ≥15-letter increase in BCVA at Month 24 compared to baseline.

Secondary study objectives were to 1) choose the optimum dose level of intravitreal FA, 2) compare the 2 dose levels versus the control group at other time points, and 3) evaluate the efficacy of 0.2 μg/day and 0.5 μg/day FA intravitreal inserts in diabetic macular oedema and DR using other relevant measures.

Secondary efficacy variables included mean change from baseline in BCVA and in the excess average foveal thickness, proportion of subjects with ≥3-step worsening in the study eye compared to baseline in the ETDRS Multi-Step Eye Scale of DR.

There were numerous exploratory variables related to BCVA; ETDRS multi-step eye scale of DR, OCT, colour fundus photographs, fluorescein angiography, contrast sensitivity, use of laser therapy and disallowed treatments, retreatment, Health-Related Quality of Life (HRQOL) (questionnaire based).

Pharmacodynamic analyses were performed and safety was also assessed. The objectives of the study are appropriate. The primary efficacy variable of gain of at least 3 lines on the ETDRS chart is considered to be a clinically relevant outcome.

Methods

Study Participants

Male and female diabetics (type 1 or type 2) >18 years of age with diabetic macular oedema (based on clinical evaluation). Participants had to have had at least 1 macular laser treatment >12 weeks before the screening visit. Also a mean foveal thickness of at least 250 μm by OCT in the study eye. BCVA of ≥19 and ≤68 letters (20/50 or worse but at least 20/400) in the study eye. BCVA of the non-study eye ≥20/400.

Treatments
The selection of dose levels was based on the *in vitro* and *in vivo* release data. The data shows that the 0.2 µg/day insert produces less of an initial 'burst' release of fluocinolone than the 0.5 µg/day insert, and that release is sustained until 36 months.

On Study Day 0, eligible subjects received a single 0.2 µg/day FA intravitreal insert, 0.5 µg/day FA intravitreal insert, or sham injection in the study eye. The FA intravitreal inserts were inserted through the pars plana into the vitreous using a modified 25 gauge needle. The sham injection consisted of pressing the hub against the sclera of the eye with approximately the same pressure as for an injection of an insert.

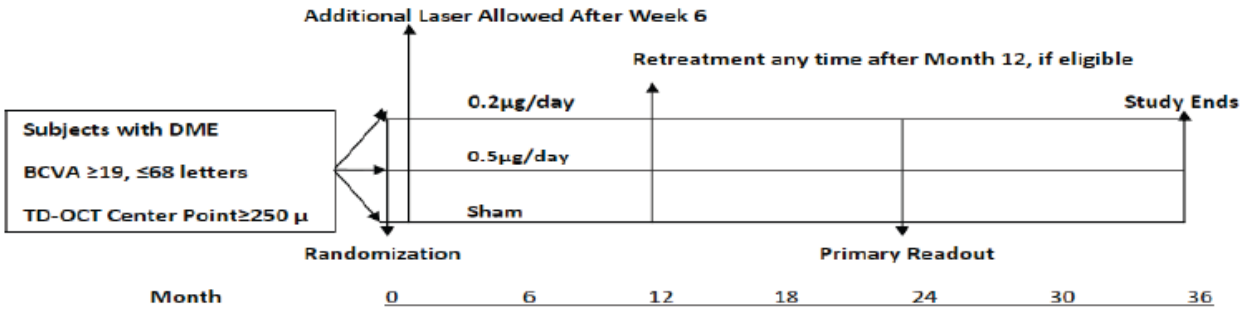
Topical antibiotics were administered prior to the injection for all subjects and for 3-5 days following the treatment day.

For subjects with unilateral diabetic macular oedema, the "study eye" was the affected eye; for subjects with bilateral diabetic macular oedema, the "study eye" was the more severely affected eye fitting the criteria. If both eyes were equally affected and eligible, then the 'study eye' was determined by the subject number (even, right eye and odd, left eye).

Subjects were eligible for retreatment any time after the Month 12 assessments if they experienced vision loss (documented reduction of ≥5 letters in ETDRS VA) or retinal thickening per OCT (minimum increase of 50 microns at the centre of the fovea) as compared to the subject's best status during the previous 12 months. Retreatments were not allowed after the Month 33 visit. In the event of retreatment, subjects were to receive the same treatment they received on Day 0 (ie, their randomised treatment).

Additional laser treatment for macular oedema was permitted in the study eye at the 6 week visit if the eye showed no improvement in oedema compared to baseline. At later study visits, additional laser treatment was permitted on the judgment of the investigator provided the patient had not received retreatment with study drug within the previous 6 weeks. Additionally, laser treatments should not have been performed less than 6 weeks from a visit where OCT was to be performed

Figure 6. FAME A & B study design



An adequate sample size for this study was determined based on the primary efficacy endpoint.

Randomisation
Subjects were randomly assigned in a ratio of 2:2:1 to 0.2 µg/day insert, 0.5 µg/day insert, or sham injection control group, respectively. The randomisation schedule was stratified by centre and baseline BCVA (≤49, >49 letters) and was computer-generated.

Blinding (masking)
To eliminate bias, two investigators were used at each study site. One investigator was the treating investigator and the other was an assessing investigator. The subjects, assessing investigator, VA examiner, reading centre and sponsor personnel involved in the monitoring or conduct of the study were masked to the study medication identity, except in the case of an emergency. Any event of unmasking would be recorded. Any unmasked subject was to remain in the study. Treatment codes were unmasked for data analysis after all data were collected, the database was finalised, and determination of protocol violations and appropriateness of the data was made.

Statistical methods
The populations used in the analysis of data are as follows in Table 6.

Table 6. Description of analysis populations.

Population Name	Subjects Included	Data Excluded	Data Imputation
All Randomized	All randomized and treated	None	LOCF for all missing data
Intent to Treat	All randomized and treated	Data after disallowed therapies for DME set to missing.	LOCF for all missing data
Per Protocol	All randomized and treated	Data after disallowed therapies for DME and significant protocol violations set to missing.	None
Full Analysis	All Randomized	None	LOCF for missing data
Safety	All Randomized and treated	None	None

- Primary efficacy variable
• The primary efficacy variable was the proportion of subjects with a gain of ≥15 letters from baseline in BCVA at Month 24. Pair-wise comparisons between treatment groups were also made by the baseline VA score in the study eye (≤49, >49 letters).

- Secondary efficacy variables
• Mean change from baseline in VA letter score as measured by the ETDRS chart.
• Mean change from baseline in the excess centre point thickness as assessed by OCT.
• Proportion of subjects with ≥3-step worsening in the study eye compared to baseline in the ETDRS Multi-Step Eye Scale of Diabetic Retinopathy.

These variables provided supportive evidence to the primary efficacy analysis at Month 24 and testing of each was done in a hierarchical manner to control the overall type I error rate.

Exploratory subgroup analyses were performed on the primary and secondary efficacy variables to determine if the effect of treatment is consistent between the 2 baseline VA strata. Additional exploratory subgroup analyses were performed on the primary efficacy variable to determine the treatment effect within specific subgroups. The methods chosen to analyse the data are acceptable.

Results

Participant flow

In FAME A, one subject in the 0.5 µg/day FA group withdrew from the study before the investigator was able to perform the insertion procedure. Therefore, this subject was randomised but not treated. In FAME B one subject in each of the 0.2 and 0.5 µg/day FA groups withdrew from the study before the insertion procedure. One of these subjects was withdrawn due to a protocol violation and the other was lost to follow-up. Therefore, these subjects were randomised but not treated.

Demographics

In the full analysis population the mean age was 63 years in FAME A and 62 years in FAME B. The majority of subjects in both studies were Caucasian. Lens status was phakic for 64% in FAME A and 63% in FAME B. In FAME A 91% of subjects had type 2 diabetes with a mean duration of 17 years. In FAME B 94% of subjects had type 2 diabetes with a mean duration of 16 years. The proportion of subjects taking oral diabetes medicines versus insulin were similar in both studies, with just under half on oral therapy alone. Mean baseline HbA1c values were also similar in both studies, at around 8%.

The demographic characteristics are balanced between the groups and across the studies. The vast majority of subjects had type 2 diabetes, which has been adequately reflected in the SmPC.

In FAME A 74 % of subjects had at least one protocol deviation. In FAME B 84% of subjects had at least one protocol deviation.

The majority relate to administrative issues (ie, missing visit). The most common protocol violation was the use of prohibited medication/therapy in the study eye that had potentially confounding effects on diabetic macular oedema (FAME A 20%; FAME B 12%). In FAME A, the percentage of subjects with this type of protocol violation was higher in the sham group (31%) compared with the 0.2 µg/day FA (17%) and 0.5 µg/day FA (19%) groups.

Numbers analysed

The full analysis set was used to analyse the primary and secondary efficacy variables; including all randomised subjects. The method of last observation carried forward (LOCF) was used to input values for all missing data. This dataset was used, on the basis that this population most closely follows the intention-to-treat principle as defined in ICH E9. This analysis includes data for 3 subjects who were randomised and not treated (1 subject in FAME A, and 2 subjects in FAME B).

Data for all subjects was included in the Per Protocol Analysis unless one or more of the reasons for exclusion were met. The most common reason for exclusion from the per protocol set was use of prohibited treatments for diabetic macular oedema (DME), which was more prevalent in FAME A, and much more prevalent in the sham arm of both studies (34.7%, FAME A; 31.1%, FAME B).

Primary and Secondary Outcomes

- Primary efficacy variable: 15-letter improvement in visual acuity at Month 24

• FAME A

The table below summarises outcome data for subjects in the full analysis, ITT, and per protocol populations at Months 18 and 24.

Table 7. Number (%) of subjects with ≥15-letter gain in BCVA in study eye for FAME A

	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
Visit	**N**	**n (%)**	**N**	**n (%)**	**N**	**n (%)**
Full Analysis Population						
Month 18	95	14 (14.7)	190	36 (18.9)	196	44 (22.4)
Difference (95% CI)[1]			−4.2 (−13.3, 4.8)		−7.7 (−16.9, 1.5)	
P-value[2]			0.466		0.135	
Month 24	95	14 (14.7)	190	51 (26.8)	196	51 (26.0)
Difference (95% CI)[1]			−12.1 (−21.6, −2.6)		−11.3 (−20.7, −1.9)	
P-value[2]			0.029		0.034	
Intent to Treat Population						
Month 18	95	13 (13.7)	190	32 (16.8)	195	41 (21.0)
Difference (95% CI)[1]			−3.2 (−11.9, 5.6)		−7.3 (−16.3, 1.6)	
P-value[2]			0.586		0.146	
Month 24	95	12 (12.6)	190	43 (22.6)	195	47 (24.1)
Difference (95% CI)[1]			−10.0 (−18.9, −1.1)		−11.5 (−20.5, −2.5)	
P-value[2]			0.057		0.026	
Per Protocol Population						
Month 18	51	9 (17.6)	126	25 (19.8)	126	31 (24.6)
Difference (95% CI)[1]			−2.2 (−14.8, 10.4)		−7.0 (−19.8, 5.9)	
P-value[2]			0.941		0.346	
Month 24	46	7 (15.2)	112	33 (29.5)	115	35 (30.4)
Difference (95% CI)[1]			−14.2 (−27.6, −0.9)		−15.2 (−28.6, −1.9)	
P-value[2]			0.112		0.048	

Statistical significance was only demonstrated for the two doses in the full analysis population at Month 24. Neither dose was significantly different from sham at Month 18.

• **FAME B**

The table below summarises outcome data for subjects in the full analysis, ITT, and per protocol populations at Months 18 and 24.

Table 8. Number (%) of subjects with ≥15-letter gain in BCVA in study eye for FAME B

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
Full Analysis Population						
Month 18	90	10 (11.1)	186	44 (23.7)	199	47 (23.6)
Difference (95% CI)[1]			−12.5 (−21.5, −3.6)		−12.5 (−21.3, −3.7)	
P-value[2]			0.018		0.020	
Month 24	90	16 (17.8)	186	57 (30.6)	199	62 (31.2)
Difference (95% CI)[1]			−12.9 (−23.2, −2.6)		−13.4 (−23.6, −3.2)	
P-value[2]			0.030		0.027	
Intent to Treat Population						
Month 18	90	10 (11.1)	185	44 (23.8)	198	45 (22.7)
Difference (95% CI)[1]			−12.7 (−21.6, −3.7)		−11.6 (−20.3, −2.9)	
P-value[2]			0.017		0.030	
Month 24	90	12 (13.3)	185	55 (29.7)	198	58 (29.3)
Difference (95% CI)[1]			−16.4 (−26.0, −6.8)		−16.0 (−25.4, −6.5)	
P-value[2]			0.004		0.005	
Per Protocol Population						
Month 18	51	6 (11.8)	131	36 (27.5)	140	35 (25.0)
Difference (95% CI)[1]			−15.7 (−27.4, −4.0)		−13.2 (−24.6, −1.8)	
P-value[2]			0.045		0.096	
Month 24	40	6 (15.0)	125	45 (36.0)	140	48 (34.3)
Difference (95% CI)[1]			−21.0 (−34.9, −7.1)		−19.3 (−32.9, −5.7)	
P-value[2]			0.023		0.050	

Statistical significance was demonstrated for the two doses in both the full analysis and ITT populations at both Month 18 and 24. In the PP population statistical significance was only demonstrated for the 0.2 µg/day dose at Month 24. However, the analysis presented does not include controlling for centre, a variable that was used in the stratification of the randomisation. The most appropriate analysis is one that adjusts for both baseline visual acuity, and centre. This has been provided as a sensitivity analysis. The results are given for the Full Analysis Set below:

Table 9: Full Analysis Set for the FAME studies

	Sham (N=95)			0.2 ug/day (N=190)			0.5 ug/day (N=196)		
Visit	N	n	%	N	n	%	N	n	%
FAMEA									
Month 24	95	14	14.7	190	51	26.8	196	51	26.0
Difference						-12.1			-11.3
95% CI						(-21.6, -2.6)			(-20.7, -1.9)
P-value						0.093			0.033
FAME B									
Month 24	90	16	17.8	186	57	30.6	199	62	31.2
Difference						-12.9			-13.4
95% CI						(-23.2, -2.6)			(-23.6, -3.2)
P-value						0.023			0.007

The analysis that correctly includes the centre effect shows that FAME A has a p-value of 0.093, although curiously the point estimate has not changed, and the upper limit of the confidence interval is identical to that presented for the analysis not including centre. To clarify this, an analysis was provided. The analysis shows that adjusting for centre does not alter the interpretation of the results.

The applicant has also presented the results for the sensitivity analyses using worst case imputation, missing as failure and average observed case imputation (not shown). All of these yielded results that were statistically significant with point estimate slightly larger than those presented here. This provides reassurance the results are robust to the method used to handle the missing data, and the method pre-specified was in fact suitably conservative.

Broad consistency across the analysis populations has been demonstrated. The results of FAME A are clearly less impressive than those of FAME B. Given the overall impressive results of FAME B, this can be concluded from a statistical perspective that efficacy has been demonstrated.

Integrated analysis for FAME A and FAME B

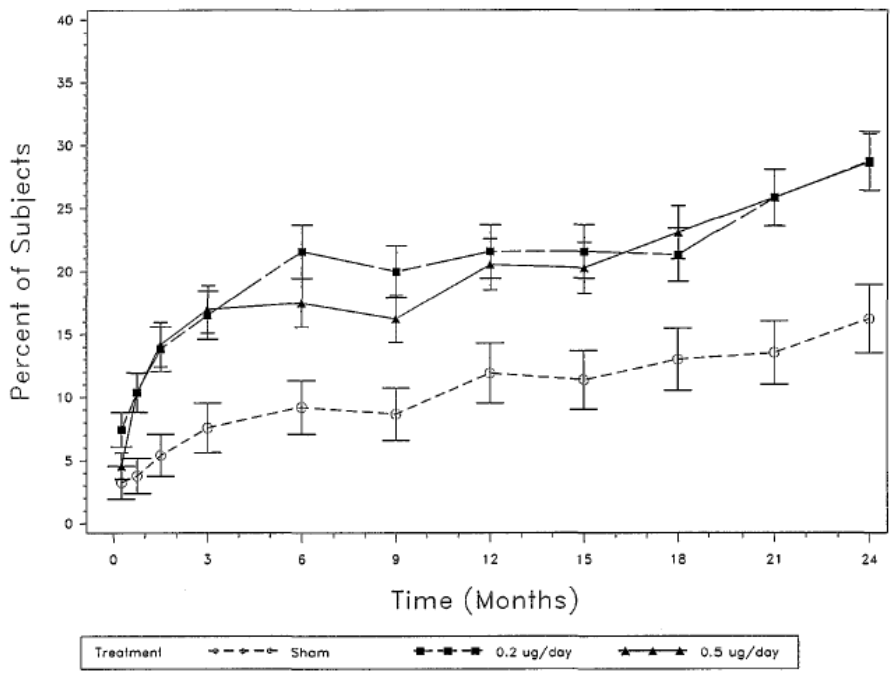
The table below summarises integrated outcome data for the full analysis, ITT, and per protocol populations for subjects in both studies at Months 18 and 24.

Table 10. Number (%) of subjects with ≥15-letter gain in BCVA in study eye for the integrated FAME studies

Visit	Treatment Group					
	Sham		0.2 µg/day FA		0.5 µg/day FA	
	N	n (%)	N	n (%)	N	n (%)
Full Analysis Population (LOCF)						
Month 18	185	24 (13.0)	376	80 (21.3)	395	91 (23.0)
Difference (95% CI)[1]			–8.3 (–14.7, –1.9)		–10.1 (–16.4, –3.7)	
P-value[2]			0.027		0.007	
Month 24	185	30 (16.2)	376	108 (28.7)	395	113 (28.6)
Difference (95% CI)[1]			–12.5 (–19.5, –5.5)		–12.4 (–19.3, –5.5)	
P-value[2]			0.002		0.002	
PP Population						
Month 18	102	15 (14.7)	257	61 (23.7)	266	66 (24.8)
Difference (95% CI)[1]			–9.0 (–17.6, –0.4)		–10.1 (–18.7, –1.5)	
P-value[2]			0.128		0.067	
Month 24	86	13 (15.1)	237	78 (32.9)	255	83 (32.5)
Difference (95% CI)[1]			–17.8 (–27.4, –8.1)		–17.4 (–26.9, –7.9)	
P-value[2]			0.005		0.005	

Data for the proportion of subjects achieving a ≥15-letter gain throughout the study is summarised in the figure below.

Figure 7. Subjects with ≥15-letter gain in integrated FAME studies (full analysis population)



At Month 24 (the primary endpoint of the studies) approximately 29% of patients treated with Iluvien (low dose) had gained ≥15 letters, compared with 16% of sham-treated subjects. This represents a 13% difference between active treatment and control. The result is statistically significant, as are the individual results of FAME A and B. Maximal efficacy is seen at Month 30, with 38% of treated-subjects gaining ≥15 letters (16% difference vs. control), though a slight decrease in efficacy is seen at Month 36 to 34% (10% difference vs. control), possibly because the majority of implants were reaching the end of their predicted 3-year lifespan, and subjects were not to be retreated within the last 3 months of the study. The outcome is better in patients with poorer baseline vision in both FAME studies, though the results were not statistically significant (the studies were not powered for this).

It was found that the per protocol population failed to show a significant difference from sham for the 0.2 μg/day dose of FA in FAME A (p=0.112), and the difference was only just significant in FAME B (p=0.023) after accounting for the multiplicity correction. In the integrated analysis of both studies, however, the difference was highly significant in this population (p=0.005). The reason for the failure of the PP population to show statistical significance for the primary endpoint in FAME A may be that there was a higher use of disallowed medications in FAME A compared to FAME B. A high drop out was maybe due to the trial design where patients would not be able to use alternative treatments. This rationale and design is acceptable, as the data suggest that the reason for the failure in the PP population is due to the smaller sample size, rather than an inherently smaller treatment effect.

In the FAME Study protocol, the ITT population was actually a *modified* ITT population which included data for all subjects who were randomized and treated; however, data collected after disallowed therapies for diabetic macular oedema was set to missing. All missing data was imputed using the LOCF method. The results of the modified ITT analysis, as proposed in the study protocol were provided. The results demonstrated that efficacy is maintained through the end of the study in both FAME A and FAME B.

The biggest gain in vision for subjects treated in the FAME studies appears to come from patients with DME duration of ≥3 years. In both FAME A and B statistically significant differences were seen between the low-dose and sham treatment groups at Months 24, 30, and 36. In this subgroup, at the end of the study 32% of subjects in FAME A and 36% of subjects in FAME B had gained ≥15 letters of vision, compared to around 13% of control patients. This subgroup analysis also reveals that subjects with more recently diagnosed DME (<3 years duration) do not demonstrate additional benefits from treatment with Iluvien over standard of care. The demographics and baseline characteristics of these two subgroups are similar, other than certain notable differences. At baseline, subjects with shorter duration of DME were both more likely to be phakic, and to have a smaller area of cystoid macular changes. Although there were more phakic subjects in the subgroup with duration of DME <3 years, this does not account for the reduced visual response of the subgroup because the confounding effect of cataract on vision was resolved by the third year of the study (the majority of subjects with significant cataract had been operated on by Month 24).

• **Other subgroups**

The applicant has presented further data for several subgroups. Outcomes for the primary efficacy variable when taking into account baseline visual acuity were summarised. The results for the primary endpoint in subjects with baseline visual acuity ≤49 letters were not statistically significant. Subjects with poorer baseline visual acuity had more disallowed treatments during the course of the study than those with better vision. Likewise a higher proportion of subjects in the

sham arm received laser or disallowed therapies than those in the active treatment arms. Therefore the response rate for sham-treated subjects was higher than expected.

In terms of other baseline disease characteristics, in the active treatment groups, the proportion of subjects with a ≥15-letter increase from baseline in BCVA at Month 24 in the study eye was greater, relative to sham, in subjects with a longer duration of diabetic macular oedema, in subjects with definite cystoid oedema at baseline, and in subjects with a greater centre point macular thickness at baseline.

In terms of lens status at baseline, the treatment effect tended to be greater, relative to sham, in subjects in the pseudophakic subgroup vs. the phakic subgroup. It is noted that visual outcome is potentially confounded by the development and removal of cataracts during the study in phakic subjects.

Demographic characteristics had little effect on response to treatment with intravitreal FA inserts. In the active treatment groups, the proportion of subjects with a ≥15-letter increase from baseline in BCVA at Month 24 in the study eye tended to be greater in younger subjects.

In general, younger subjects, and pseudophakes had a better outcome at Year 2 and 3.

- **Secondary efficacy variables**

• **Change From Baseline In BCVA Letter Score**

In FAME A there was a mean increase in BCVA from baseline at Month 24 of 3.2, 3.7, and 4.0 letters in the sham, 0.2 μg/day FA, and 0.5 μg/day FA groups respectively. The changes in the active treatment groups were not statistically significantly different to sham.

In FAME B there was no mean change in BCVA from baseline at Month 24 in the sham group, whilst in the active treatment groups there was an increase of 5.1 and 6.7 letters in the 0.2 μg/day FA and 0.5 μg/day FA groups respectively. These changes in the active treatment groups were statistically significantly different to sham.

In the integrated analysis of FAME A & B there was a mean increase in BCVA from baseline at Month 24 of 1.7, 4.4, and 5.4 letters in the sham, 0.2 μg/day FA, and 0.5 μg/day FA groups respectively. These changes in the active treatment groups were statistically significantly different to sham. Analyses of the results in the per protocol populations did not show any significant differences to sham treatment.

However, in the subgroup of patients with duration of DME ≥3 years, the results for this secondary endpoint are more convincing. In both studies, from Month 24 onwards the mean change in vision was over 5 letters. The difference from the control group results was impressive in FAME B, reaching 8.5 letters at Month 30. This is a clinically relevant result and is consistent with those seen for the primary analysis variable.

• **Change From Baseline In Excess Centre Point Macular Thickness**

In FAME A there was a mean decrease in excess centre point macular thickness from baseline at Month 24 of 86.4, 155.3, and 154.9 microns in the sham, 0.2 and 0.5 μg/day FA groups respectively. The changes in the active treatment groups were both statistically significantly different to sham.

In FAME B there was a mean decrease in excess centre point macular thickness from baseline at Month 24 of 115.0, 156.9, and 177.4 microns in the sham, 0.2 and 0.5 μg/day FA groups respectively. The changes in the active treatment groups were statistically significantly different to sham only for the higher dose group.

In the integrated analysis of FAME A & B there was a mean decrease in excess centre point macular thickness from baseline at Month 24 of 100.5, 156.1, and 166.2 microns in the sham, 0.2 and 0.5 μg/day FA groups respectively. The changes in the active treatment groups were both statistically significantly different to sham.

Analyses of the results in the per protocol populations show similar findings, and a subgroup analysis on baseline vision in the integrated full analysis population did not reveal any relevant differences between groups.

When analysed together the FAME studies show a mean reduction in the thickness of the oedematous retina of 156 microns in the 0.2 μg/day group. For the anatomic secondary endpoint of change from baseline in excess centre point thickness, the results show that treatment with Iluvien reduces retinal thickness in a sustained fashion over the course of the studies. The difference from the reduction seen in the control groups is not marked in the latter stages of the study, and contrary to the findings for the visual function endpoints, the results of FAME A were more impressive than those of FAME B.

• 3-Step worsening in ETDRS multi-step eye scale of diabetic retinopathy
Few subjects (12) had a worsening of at least 3 steps in the ETDRS multi-step eye scale of DR in the study eye during either study. The proportions between the treatment groups were similar. Therefore the trials have shown no effect of the FA implant on prevention of progression of DR.

- Exploratory Efficacy Analyses
The results of the exploratory analyses are generally supportive of the efficacy of the active treatment. In particular subjects who were treated with steroid implants had improved anatomical outcomes (on OCT, fluorescein angiogram and photographic analysis) and were less likely to require supplemental treatment with focal laser, VEGF-inhibitors, steroids, etc.

• Effect of cataract on BCVA
The development of cataracts and their removal clearly had an influence on BCVA during the study. The majority of cataracts were reported between Months 6 and 18 in the active treatment groups. This time-frame coincided with a plateau in the proportion of subjects with a ≥15-letter increase from baseline in BCVA between Months 6 and 18 and an increased proportion of active-treated subjects who had a ≥15-letter decrease from baseline in BCVA. Likewise, in phakic subjects, mean decreases from baseline in BCVA letter scores were observed in each active treatment group starting at Month 9, whereas mean scores remained relatively unchanged in the sham group. The majority of cataract operations occurred after Month 12. In phakic subjects who became pseudophakic, improvement in mean BCVA letter scores was observed in active-treated subjects starting at Month 18. Likewise, the proportion of active-treated subjects who experienced a ≥15-letter decrease from baseline in BCVA began to fall by Month 18.

• Optical coherence tomography outcomes
In the integrated analysis of the FAME studies statistically significant decreases in macular volume were detected at Month 24 in each active treatment group as compared to sham treatment. At

Month 24, a difference of 0.67 mm3 (95% CI: 0.26 mm3, 1.08 mm3; p=0.001) was observed between the 0.2 µg/day FA group and the sham group.

• Colour fundus photography outcomes
The probability of achieving complete resolution of macular oedema at Month 24 was lowest in the sham group and highest in the 0.5 µg /day FA group. A treatment effect and dose response (with a higher probability in the 0.5 µg/day FA group vs. the 0.2 µg/day FA group) was observed at Month 6 through Month 24.

• Fluorescein angiography outcomes
In the integrated analysis of the FAME studies statistically significant decreases in mean total area of fluorescein leakage (total disc areas) were detected at Month 24 as compared to sham treatment. The difference in mean change in total area of fluorescein leakage (disc areas) between the 0.2 µg/day FA and sham groups was 1.42 (95% CI: 0.61, 2.23; p=0.001), and the difference between the 0.5 µg/day FA and sham groups was 1.93 (95% CI: 1.12, 2.73; p<0.001). A similar trend was observed when total area of cystoid change was measured on fluorescein angiography.

• Patients with Vitrectomy and Intra-ocular Pressure
Although prior vitrectomy was an exclusion criterion, in the FAME studies, 71 subjects experienced a vitrectomy during the study. The outcome in these patients is likely to be affected by numerous confounding variables, such as post-vitrectomy cataract and underlying severity of diabetic eye disease. In addition the number of patients is small, and the variability of the results precludes firm conclusions of comparable efficacy. There is insufficient evidence to conclusively confirm whether the life of the insert is affected by vitrectomy from the data presented by the applicant, and this is reflected in the SmPC.

Data presented on the subgroups of patients with greater or less than median baseline IOP show a significant correlation between the risk of IOP-related adverse events (and requirement for IOP-lowering treatment) and baseline IOP. A small number of subjects recruited to the studies had pre-existing ocular hypertension and were taking IOP-lowering medication. As expected, greater increases in IOP were noted in these patients than in other subjects. However, significant improvements in anatomical and functional endpoints were seen in these patients. In conclusion, it is apparent that the magnitude of increase in IOP is proportional to IOP at baseline and therefore a warning has been included in the SmPC.

• Efficacy in Type I diabetes Vs Type II diabetes
Consonant with the prevalence of patients with Type 1 and Type 2 diabetes in the general population, the majority of subjects in the FAME studies had Type 2 diabetes. There is no evidence that the pathogenesis of diabetic macular oedema differs by type of diabetes and no evidence that diabetic macular oedema in patients with Type 1 diabetes responds differently. Although the number of subjects with Type 1 diabetes in the FAME studies is small (sham, 7%; 0.2 µg/day 8%; 0.5 µg/day, 5%), the data from the FAME studies indicate that these subjects respond very well to Iluvien. The percent of the subgroup of subjects with type 1 diabetes with ≥15 letter improvement at Month 24 was clinically and statistically different from the sham group (sham, 0%; 0.2 µg/day, 41.4%, p=0.022; 0.5 µg/day, 38.1%, p=0.026). The mean change from baseline BCVA was consistently greater for Type 1 diabetic subjects than for Type 2 diabetic subjects throughout the study. Although only approximately 7% of subjects in the FAME studies had Type 1 diabetes, the visual function and anatomical changes indicate that type 1 diabetic subjects respond well to Iluvien. The superiority of Iluvien over sham treatment was statistically superior in subjects with type 1 diabetes. This shows that there is no loss of efficacy in Type 1 diabetics.

• Use of laser therapy and disallowed treatments
Additional laser treatment for macular oedema was permitted in the study eye at the investigator's discretion, starting at the 6-week visit, if the eye showed no improvement. At later study visits, additional laser treatment was permitted provided the subject had not received retreatment with study drug within the last 6 weeks. Additionally, laser treatments were not to be performed less than 6 weeks from a visit where OCT was performed. Subjects were not to receive any non-approved treatments (eg, VEGF inhibitors) in the study eye for diabetic macular oedema or any systemic treatments for diabetic macular oedema.

In the integrated analysis of the FAME studies 49% of subjects in the sham group received at least one focal laser treatment for diabetic macular oedema, compared with 31% subjects in the 0.2 μg/day FA group and 29% in the 0.5 μg/day FA group. A similar trend was observed for proportions of subjects receiving scatter laser therapy for proliferative DR (23% in sham group, 10% in 0.2 μg/day FA group, and 11% in 0.5 μg/day FA group).

The results for disallowed treatments are similar, with 29% of subjects in the sham group receiving treatment as compared with 13% and 14% in the 0.2 and 0.5 μg/day FA groups.

Efficacy of the low dose insert appears improved in the subgroup of patients who did not receive any laser during the study, particularly in those subjects with a duration of DME ≥3 years. This provides reassurance that the efficacy seen during the study was not due to concomitant laser therapy. As mentioned by the applicant, this finding is reflected in results from the secondary endpoints of mean change in BCVA from baseline, and mean change in excess centre point thickness.

• Health-related quality of life
At the time of enrolment, the study eye was the better eye for 23% of all FAME study subjects. Thus the HRQOL would be dependent on the non-study eye in the majority of subjects. Treatment with FA had no effect on HRQOL. This lack of effect may be due to the fact that subjects only received treatment in 1 eye during the 2 FAME studies and results are typically dependent on the better eye.

• Retreatments
Subjects were eligible for retreatment with study drug any time after the Month 12 assessments if they experienced vision loss (documented reduction of ≥5 letters in ETDRS VA) or retinal thickening per OCT (minimum increase of 50 microns at the centre of the fovea).

In the integrated analysis of the FAME studies the percentage of subjects who received at least 1 retreatment of study drug during the study was 24%, 23%, and 25% in the sham, 0.2 and 0.5 μg/day FA groups, respectively. Of subjects who did require retreatment, in the 0.2 μg/day FA group 6% were retreated by 12 months, 49% by 18 months, and 89% by 24 months.

Of subjects who had received only a single treatment, 34% in the low dose group had a positive result with regard to the primary outcome (compared with 19% in the sham group, p=0.014). Mean change from baseline in BCVA was not significantly different to sham (6.8 letters in low dose group compared to 3.8 letters in sham group, p=0.138). The mean change from baseline in excess centre point thickness was also not significantly different to the sham group (-183 microns in low dose treatment group vs. -151 microns in sham group, p=0.429). Further, when response rates for subjects who received only a single treatment and no disallowed therapies is examined (a per

protocol population) there was only a 13% increase in response for the primary endpoint over sham, and this result was not statistically significant. The mean change in baseline vision was also barely different to the sham group (7.7 letter gain in 0.2 µg/day FA group vs. 6.5 letter gain in sham group).

Only a small number of phakic subjects in the FAME studies were retreated on the basis of decrease in BCVA alone, and there is no indication that retreatment of subjects meeting only the BCVA criterion had a significant impact on the efficacy outcomes of the FAME study.

Comparative data for the primary and secondary outcomes (at Month 24, with confidence intervals and p values) for those subjects who had 2, 3 or more treatments in the pivotal studies have been provided. It is accepted that the comparison of efficacy in subjects receiving a single and more than 1 treatment during the study is confounded, since subjects receiving retreatment were by nature more likely to have less responsive disease. However, the same reasoning can be applied to the subjects in the sham arm, and the decrease in the proportion of sham-treated subjects gaining ≥15 letters at Months 24 and 36 for subjects treated with a single versus multiple treatments is of a lower magnitude than in the 0.2 µg/day group. A recommendation regarding cessation of retreatment in subjects who fail to respond has been included in the SmPC.

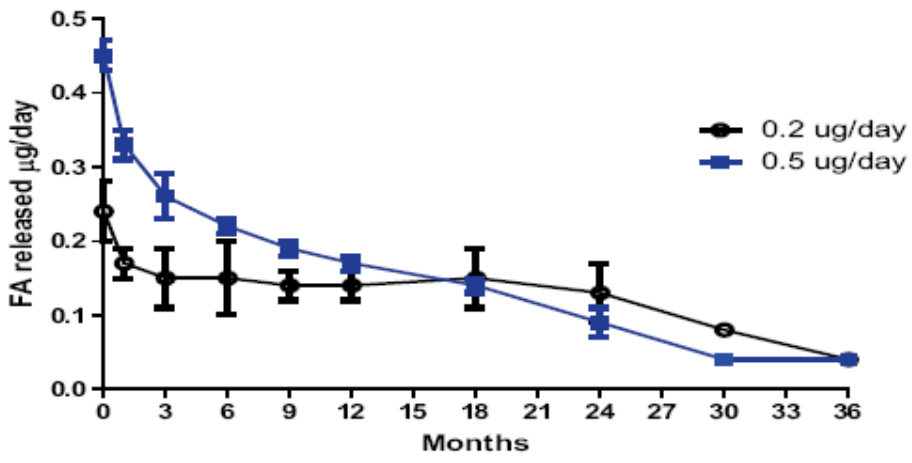
The efficacy of a single implant

In the FAME studies, no retreatments were allowed during the first 12 months. After this point, retreatments were allowed if the subject experienced a loss of vision of ≥5 letters or an increase in central retinal thickness of ≥50 microns *as compared to the subject's best status in the previous 12 months*. This design was chosen because the precise duration of an efficacious FA level was not known and was expected to vary with the clearance of FA from the vitreous. Thus, the purpose of the retreatment was not to address treatment failures, but to permit sustained therapy based on individual response. This approach is commonly used for treatment of retinal diseases because intravitreal injections are only performed when necessary due to the risks of the injection.

Based on the final data for the FAME studies, efficacy is seen in subjects who received only a single implant. In the FAME studies, the majority of subjects received only one treatment prior to Month 36 (sham, 71%; 0.2 µg/day, 74%; 0.5µg/day, 71%).

Figure 8 shows the duration of a single FA insert.

Figure 8 Average *In Vitro* Release Rates over Time of the Low Dose and High Dose ILUVIEN



With regard to the *in vivo* study the duration of release can be demonstrated for the subjects who received only a single insert. As of Month 36, the levels of FA in the aqueous humor of the low dose and the high dose were measurable in the aqueous humor (0.45 ng/mL and 0.30 ng/mL, respectively). These data confirm that the low dose insert consistently maintains the same level of FA in the aqueous from Month 12 through at least Month 36.

As designed, the high dose FA insert (0.5 μg/day) has greater initial release but contains the same total amount of FA (190 μg). As a result, the duration of the 0.5 μg/day insert is expected to be shorter than that of the 0.2 μg/day insert. The low dose was expected to release for up to 3 years.

Consistent with the *in vitro* and human PK data, the duration of efficacy of a single insert has been demonstrated in the FAME studies. The subgroup analysis of the subjects receiving a single dose of either dose of FA insert in the integrated FAME studies demonstrates the efficacy of a single insert through 36 months for the majority of subjects. The low dose group receiving a single insert was also statistically greater than sham (which included laser and disallowed therapies) at Month 30. In the subjects with duration of diabetic macular oedema ≥3 years who received only 1 insert, clinically and statistically significant improvements in vision were demonstrated throughout the third year of the study even in subjects who received no other treatments.

Outcome data for the subgroup of subjects with diabetic macular oedema ≥3 years and only a single implant are adequate. The difference in the proportion of subjects achieving ≥15 letters between the 0.2 μg/day and sham arms rises to 28.1% ($p<0.001$) in this subgroup. In those subjects with diabetic macular oedema <3 years a higher proportion of subjects in the sham arm achieved ≥15 letters at Year 3 than in the 0.2 μg/day arm.

In conclusion, Year 3 data show that a single implant can produce valuable improvements in vision in nearly 37% of patients. The result is statistically significantly different from sham treatment, in subjects with a duration of DME ≥3 years, of whom 42% gained at least 3 lines of vision by Year 3. However, in subjects with more recent (<3 years duration) DME, a single implant is not effective and is hence reflected in the indication in the SmPC.

Potential for bias

It is possible that the masked assessing investigator could have been unblinded due to visualisation of an implant during dilated funduscopy, and the degree of any potential selection bias is unknown (though it is likely to be small since retreatment criteria were predefined). The retreatment rates were similar across all groups; a slightly lower proportion of subjects in the 0.2 μg/day FA arm required retreatment than those in the sham arm (26% vs. 29%), and the time to retreatment was also slightly longer for active treated subjects (844 days vs. 815 days).

The applicant has provided a detailed explanation for subjects retreated without meeting the retreatment criteria. This explanation is acceptable, and does not highlight any obvious biases that would influence the analysis of the results of the studies.

The potential for significant bias from unblinding of assessors or unauthorised retreatments affecting the results of the studies is low.

Assessor's overall conclusions on clinical efficacy

The FAME studies provide a comparison of Iluvien against the current standard of care i.e. laser photocoagulation with or without adjunctive use of steroids and/or anti-VEGF therapy.

None of these treatment modalities had formal regulatory approval for the indication at the time the study was conducted. In line with current practice, the standard of care was administered to subjects on an "as required" basis. The data from the FAME studies give a clear indication of where Iluvien fits in the total management of DME: following first line of treatment with laser therapy, if the response is inadequate to available therapies, ILUVIEN is appropriate. If the clinical picture indicates it, additional laser or intravitreal anti-VEGF products may be used. The applicant has presented an explanation for the chosen comparator (ie, sham implantation ± laser or alternative (disallowed) therapies as required). This is acceptable, since at the time of the study design there were no approved treatments for DME. It is also considered that this is reflected in the amended indication (ie, that the product be used in those subjects considered insufficiently responsive to available therapy). The indication is also supported by the subgroup analysis which demonstrated that subjects with longer duration DME respond significantly better than subjects with duration of DME <3 years.

Regarding dose selection, FA was measurable in human aqueous through month 36 in the FAMOUS Study and FA release was measurable *in vitro* for all lots of 0.2 μg/day FA inserts through Month 24. At Months 30 and 36, FA was measurable in some but not all lots. Further, Iluvien (0.2 μg/day FA) demonstrated a statistically significant, clinically relevant therapeutic effect through Month 33 in the overall population of the FAME studies. Statistically significant improvements in visual function and retinal thickness were also observed through Month 36 in the subset of subjects receiving only 1 insert with duration of diabetic macular oedema ≥3 years (the optimal target population). In view of the results of the FAME studies, the dose intended for marketing is the 0.2 μg/day FA dose. The results from both the phase II study measuring FA levels in the anterior chamber of humans, and the efficacy results, especially in the subpopulation of diabetic macular oedema subjects with duration of disease of ≥3 years, clearly support duration of effect for 3 years for the 0.2 ug/day FA dose.

Regarding the results of the FAME studies, a difference for the primary endpoint of 13% over placebo is not of certain clinical relevance. However, the control group is not a true placebo comparison, since around a third received a disallowed treatment for DME (eg, steroid or VEGF inhibitor) and over a half received macular laser. With this in mind, the 13% increase in the proportion gaining ≥15 letters at Year 2 looks more impressive, though still needs to be balanced against the risks. The difference to control group increases for the subgroup of patients with poorer baseline vision (18% at Year 3 in FAME A, 22% at Year 3 in FAME B). Since subjects in the studies were not treatment-naïve and were to have received macular laser prior to enrolment, this subgroup of patients with poor baseline vision is reflected in the amended indication (ie, considered insufficiently responsive to available therapy). The subgroup of patients with chronic DME (≥3 years duration) displayed the best outcome: nearly 35% of subjects gained ≥15 letters (21% more than control group), and the mean increase in vision was 6 letters at Year 2 and 7.6 letters at Year 3. These are clinically relevant improvements in visual function, and demonstrate a meaningful benefit over sham treatment (standard of care). Furthermore, three-quarters of patients in the low-dose arm only required a single treatment during the three year study period, demonstrating the long-term efficacy of a single implant.

Overall, the results of the FAME studies demonstrate a comparable degree of efficacy for Iluvien to other therapies for DME. In the DRCR Network study the primary outcome was measured at 1 year. Ranibizumab plus prompt or deferred laser was compared to sham plus prompt laser. Ranibizumab produced a mean improvement in vision of around 9 letters (a difference of 6 from sham), and around 30% of patients gained ≥15 letters of vision (a difference of 15% from sham). In the RESTORE study ranibizumab alone or with laser was compared against laser alone, with a

primary endpoint again at 1 year. The mean improvement in vision was 6 letters for ranibizumab (a difference of 5 from laser), and around 22% of patients gained ≥15 letters of vision (a difference of 14% from laser).

IV.5 Clinical safety

Introduction

The safety review of Iluvien has been prepared from data collected from the open-label, phase 2b pharmacokinetic study (the FAMOUS study) and the two phase 3, pivotal studies (FAME A and FAME B) through Month 36.

The FAMOUS Study

A total of 37 subjects were randomised into the FAMOUS study. The most common treatment-emergent adverse events (TEAEs) were cataract, conjunctival haemorrhage, myodesopsia (perception of vitreous floaters), cataract operation, and increased intraocular pressure.

Four deaths were reported and were due to events systemic in nature and unrelated to study drug.

The FAME Studies

A total of 956 subjects were randomised into the 2 FAME studies. Of these, 3 subjects withdrew from the study before the investigator was able to place the insert into the subject's eye. Therefore, these subjects were randomised but not treated. These subjects are not included in the Safety Population.

Safety was assessed by adverse event (AE) reporting, HbA1c, vital signs, intraocular pressure (IOP) increases and cataract formation, loss of VA, lens opacity measurements, dilated ophthalmoscopy, slit-lamp examination, and specular microscopy.

Patient exposure

The time on study did not reveal any disproportionate dropout rate between the groups. Overall, median time on study was 734 days.

A total of 37 subjects were randomised into the FAMOUS study; 20 subjects received 0.2 µg/day FA and 17 received 0.5 µg/day FA. The majority of subjects in the FAMOUS study (65%) received 1 intravitreal insert during the first 18 months. Median time on study was less in the FAMOUS study (533 days) than in the integrated FAME studies because enrolment for the FAMOUS study began later than the FAME studies.

Of the 990 subjects treated in the three clinical studies 395 were exposed to at least one implant at the strength intended for marketing. The remainder were either treated with sham, or exposed to a higher dose implant.

Adverse events

Almost all subjects had at least 1 TEAE during the FAME studies. The majority of subjects had at least 1 drug-related TEAE. The overall incidence of drug-related TEAEs in the study eye was lower in the sham group compared with the 0.2 µg/day FA and 0.5 µg/day FA groups.

- **Cataract**

The commonest ocular AEs which occurred were those related to cataract. Of the phakic subjects (ie, those with a natural, crystalline lens at the start of the study) who received the dose intended for

marketing, 80% had developed cataract within 2 years, and 94% of these underwent cataract surgery. This is approximately twice as high as the incidence of cataract in the sham group or in the non-study eye of those in the active treatment groups. A dose response relationship was observed between the high and low strength implants, and between those receiving single and multiple implants. However it is encouraging that the visual outcome was good in those subjects who did require cataract extraction, perhaps due in part to the anti-inflammatory effect of the corticosteroid. To put this in context, 71% of the phakic subjects in the low dose group entered the study with some degree of cataract, which is not surprising since diabetes is a risk factor for cataract. Therefore phakic subjects who receive an implant are very likely to experience worsening of their cataract, and to require surgical treatment.

Although subjects treated with FA were at a much higher risk of developing cataract and requiring surgery there is some evidence that actively treated subjects had a better response to cataract surgery with regard to visual acuity than controls. This may be because diabetics undergoing cataract surgery are at risk of developing macular oedema, and are often treated with peri-operative topical steroids.

In relation to the number of cataract operations performed, the number of surgical complications reported is low. However, the reporting rate for such complications is unknown, and may be low. Rates of posterior capsule opacification and corneal oedema are in fact low when considered in relation to the number of procedures performed in each arm, rather than the total number of patients in each arm. However posterior subcapsular cataracts are more likely in subjects treated with Iluvien, and are known to present technical difficulties during surgery. This has been mentioned in the SmPC.

• **Intraocular pressure**

In the study eye, elevated intraocular pressure was reported as a TEAE in fewer subjects in the sham group compared with the active treatment groups (37%). Similar figures were observed for subjects with an increase in IOP of at least 12 mmHg from baseline, and for subjects with an increase in IOP to over 25 mmHg at any time. There is little difference in these outcomes when the number of treatments received is considered as a variable.

In the low dose group the greatest mean increase was between 2.5 and 3 mmHg, occurring from Month 3 onwards. Increases in IOP decrease gradually from Month 12 onwards, presumably due to treatment.

The rate of IOP ‘elevation considered an adverse event’ (including adverse event reports of ocular hypertension and IOP increased) rose from 33.3% at Year 2 to 37.1% at Year 3 in the low dose group. The proportion of subjects requiring pressure-relieving medication or a surgical procedure also rose proportionately.

No significant findings were detected with regard to optic nerve head pallor, optic disc haemorrhage or disc notching.

Whilst it is clear that the risk of a subject requiring some degree of pressure-relieving intervention are high, the IOP does appear controllable with the mean IOP of all subjects treated with the low dose implant being around 2 mmHg above baseline at Year 3. Furthermore, the rates of complications of increased IOP appear low.

The potential for transient increases in IOP (ie, within 1 hour) was assessed only by visualisation of the central retinal artery after the procedure. IOP was not measured until day 7. The risk of a transient increase in IOP is apparently small, since the injection volume is less than 1 µl, as opposed to volumes of 50 µl which are administered with VEGF inhibitors and which are known to be associated with a small risk of transient increased IOP.

• **Endophthalmitis**
Five cases of endophthalmitis (including one of fungal eye infection) were reported during the studies. One occurred in the non-study eye, and the other 4 in the study eye of subjects treated with low dose implants, though only two of these appear drug-related.

• **Myodesopsia**
Myodesopsia, the perception of vitreous floaters, is common with aging and in subjects who have had an intraocular procedure. It is also possible that the patient could see the intravitreal insert, if it floated into the line of vision. Myodesopsia was reported as a TEAE. There was only a very slight increase in the proportion of AEs of myodesopsia in those treated with 2 or more inserts as opposed to a single insert.

• **Systemic adverse events**
Common (≥5%) systemic adverse events are anaemia, congestive cardiac failure, constipation, nausea and vomiting, nasopharyngitis, pneumonia, sinusitis, hypercholestraemia, headache, renal failure and hypertension. Three adverse events occurred with at least twice the incidence in an active treatment group as compare with the sham group. It is proposed that the increased incidence of anaemia in the active treatment groups may be indirectly caused by use of a carbonic anhydrase inhibitor (as treatment for raised intra-ocular pressure, a more common finding in the active treatment groups). Carbonic anhydrase inhibitors are known to exacerbate renal dysfunction which may have compromised erythropoietin production. A post-hoc analysis categorising subjects for anaemia and use of a carbonic anhydrase inhibitor reveals a statistically convincing relationship. With regard to constipation and pneumonia, no mechanistic explanation has been provided.

• **Safety of Multiple Inserts in Rabbits and Humans**
No specific concerns arise from the results of the non-clinical study in rabbits involving multiple administrations of Iluvien. Focal retinal scarring was observed, but this was likely to be caused by the injection procedure. This does not represent a significant clinical concern in humans, mainly due to the peripheral site of injection at the pars plana. Posterior cortical/capsular cataract was observed with a high frequency in the rabbit study. In the clinical studies the risk of subcapsular (presumably posterior subcapsular) cataract increased, from 5% to 10.5%, in subjects who had at least one retreatment. It is likely that this figure represents an underestimation of the total number of posterior subcapsular cataracts, since a significant proportion are likely to have been reported under the general heading of ‘cataract’. The high frequency of such cataracts is likely to be due to higher local concentrations of fluocinolone at the posterior pole of the lens near to the implant, which may well be exaggerated in rabbit eyes, being far smaller in relation to the size of the insert. Such cataracts can be technically difficult to remove, and are associated with a high degree of complications, such a capsular rupture. This risk has been reflected in the SmPC.

Serious adverse events (SAE) and deaths
The majority of subjects experienced at least 1 SAE.

The most common systemic SAEs were congestive cardiac failure and myocardial infarction. The most common ocular SAE was cataract operation, followed by vitrectomy, vitreous haemorrhage, trabeculectomy, increased intraocular pressure, and glaucoma or open-angle glaucoma.

A small number of deaths were reported during the FAME studies. The overall incidence of deaths was comparable among treatment groups. In each case, cause of death was systemic in nature. The most common events resulting in death were myocardial infarction, cardiac arrest, and renal failure. None of the deaths in any study were considered related to the study drug.

Laboratory findings
The only laboratory test performed was HbA1c. Mean HbA1c values were comparable among treatment groups at baseline. Mean changes from baseline in HbA1c values were small and comparable among treatment groups.

Mean systolic and diastolic blood pressure values were comparable among treatment groups at baseline. Mean changes from baseline in blood pressure were small and comparable among treatment groups.

Safety in special populations
Analysis by gender, race, and iris colour failed to show substantial differences between subject groups.

The risk of IOP-increase or cataract does not appear to be significantly greater in any particular age subgroup. Younger subjects were more likely to undergo pressure-reducing surgery, but as mentioned by the applicant, such surgery is more common in younger patients in order to minimise the long term effects of chronically raised IOP.

Safety for use in pregnancy and lactation has not been established. This has been addressed in the SmPC.

Safety related to drug-drug interactions and other interactions
Use of intravitreal, sub-Tenon's, or peri-ocular steroids prior to the study had no notable effect on the percentage of subjects with IOP-related TEAEs during the study. Prior exposure to intraocular steroids was associated with a slightly increased incidence of cataract operation.

Due to the small number of subjects who concomitantly received anti-VEGF therapy (11- 22 subjects per treatment group), no definitive conclusions can be drawn regarding possible drug-drug interaction with this class of drugs; however, there is no indication of an interaction between anti VEGF therapy and the use of FA inserts.

Potential drug-drug interactions involving concomitant use of IOP-lowering medications were also examined. A comparison was made between common TEAEs reported while subjects received ocular hypotensive treatments and those that did not occur while subjects were on such medications. The most common type of IOP-lowering drugs used included beta-blockers, prostaglandins, and alpha agonists. There was no indication of an interaction between IOP-lowering medications and the use of FA inserts. Due to the low systemic exposure, systemic drug interactions are not expected.

Discontinuation due to AEs
A number of subjects discontinued the study due to a TEAE, however most events leading to discontinuation were systemic in nature. Some subjects discontinued the study due to at least 1 ocular TEAE in the study eye, and 1 subject discontinued due to an ocular event in the non-study eye.

Assessor's overall conclusions on clinical safety
A dose response relationship was observed between the high and low strength implants, and between those receiving single and multiple implants. However the visual outcome was good in those subjects who did require cataract extraction, perhaps due in part to the anti-inflammatory effect of the corticosteroid.

Of the phakic subjects in the low dose group, 71% entered the study with some degree of cataract (based on the reading centre assessment), which is not surprising since diabetes is a risk factor for cataract. Therefore, phakic subjects who receive an implant are very likely to experience worsening of their cataract, and to require surgical treatment.

A number of subjects in the low-dose treatment group had an adverse event of raised intraocular pressure, and required treatment with medication. At least half of these subjects required treatment with more than one IOP-lowering medication, and a few in this group required a laser or surgical procedure for raised intraocular pressure. At Month 36 small increases from baseline in intraocular pressure were seen in the low dose group which reflects effective treatment. Significant anatomical signs of development of glaucoma were not detected in the studies.

The general risks in the new target population (those with chronic DME insufficiently responsive to available therapy) were no higher than in the general population.

In summary, the potential risks associated with Iluvien appear generally manageable. Diabetic patients develop cataract earlier than non-diabetics, and therefore Iluvien can be seen to accelerate this inevitable, but treatable, complication. Furthermore, the increase in IOP is manageable in most patients with medication (though more than one medication is often required), with only a small proportion requiring an invasive intervention.

IV.6 The Pharmacovigilance System and Risk Management Plan

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory Risk Management Plan (RMP) has been provided. Please see the table below for the RMP summary:

Safety concern	**Proposed Pharmacovigilance (PV) Activities (routine and additional)**	**Proposed Risk Minimisation Activities (routine and additional)**
Important Identified Risks		
Increased intraocular	Routine pharmacovigilance	Product Information: See Section 4.2, 4.3, 4.4 and 4.8

pressure / development of glaucoma	5 year post authorisation registry study	of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Formation or progression of cataract	Routine pharmacovigilance 5 year post authorisation registry study	See warnings in Section 4.4 and 4.8 of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Endophthalmitis	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2, 4.3 and 4.4 of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Retinal complications	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2 and 4.4 of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Vitreous complications	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2 and 4.4 of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Haemorrhagic events occurring with the concurrent use of anti-coagulant and anti-platelet agents	Routine pharmacovigilance 5 year post authorisation registry study	See Section 4.4 of the SmPC and Section 2 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Important Potential Risks		
Systemic corticosteroid effects	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2, 4.4 and 4.6 of the SmPC and Section 2 of the PIL

Procedural complications	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2, 4.3 and 4.4 of the SmPC and Sections 2 and 4 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Retinitis secondary to reactivation of latent viral or other ophthalmic infections	Routine pharmacovigilance 5 year post authorisation registry study	See Section 4.3 of the SmPC
Important Missing Information		
Use in paediatric population	Routine pharmacovigilance	See Section 4.2 of the SmPC and Section 2 of the PIL
Use in pregnant women	Routine pharmacovigilance	See Section 4.6 of the SmPC and Section 2 of the PIL
Use in lactating women	Routine pharmacovigilance	See Section 4.6 of the SmPC and Section 2 of the PIL
Long-term safety data	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2 and 4.8 of the SmPC
Repeat use	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.2 and 4.8 of the SmPC and Section 3 of the PIL Physician training DVD/printed guide for administration of implant and details of important adverse events
Implant removal	Routine pharmacovigilance 5 year post authorisation registry study	See Section 4.4 of the SmPC Physician training DVD/printed guide for administration of implant and details of important adverse events
Off-label use	Routine pharmacovigilance 5 year post authorisation registry study	See Sections 4.1 and 4.4 of the SmPC and Section 1 of the PIL
Significant retinal ischaemia	Routine pharmacovigilance	See Section 4.2 of the SmPC

IV.7 Discussion on the clinical aspects

The grant of a Marketing Authorisation is recommended.

V User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the package information leaflet (PIL) was English.

The results show that the package leaflet meets the criteria for readability as set out in the *guideline on the readability of the label and package leaflet of medicinal products for human use.*

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Iluvien 190 micrograms intravitreal implant in applicator are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

The primary pharmacology data presented in the non-clinical dossier is taken from the literature and mainly reports efficacy of FA in uveitis using intravitreal implants. As there is clinical experience with intravitreal FA, the lack of safety pharmacology studies and pharmacodynamics interaction studies with FA is acceptable.

The only PK (TK) data available through use of the proposed product has been generated in the 24-month repeat-dose rabbit study. The distribution of FA has been elucidated. Local exposure of FA increased with dose, but no clear evidence of dose proportionality was observed. FA concentrations in the aqueous humour in rabbits were generally below the limit of quantification.

The lack of single-dose, carcinogenicity and reproductive and developmental toxicity studies with the proposed product is acceptable, given the lack of systemic exposure following intravitreal administration and clinical experience with FA intra-occularly.

Toxicity studies over 9- and 24-months in rabbits revealed cataract formation and Focal degenerative lesions which affected fibers in the posterior polar and posterior cortical regions of the lens. These findings are not surprising, as lens fiber degeneration/cataract development in the posterior subcapsular region of the lens has been reported following intravitreal dosing of corticosteroids. Focal retinal scarring was also found, this was mainly due to the insertion procedure and due to the differences between the rabbit and human eye, and this was considered not clinically relevant to humans.

Appropriate discussion of the device part of the product has been provided. Discussion of the device part of the product has been provided and the lack of phototoxicity studies adequately justified.

An appropriate environmental risk assessment has been submitted in line with relevant guidance.

EFFICACY/SAFETY

The pharmacokinetic information provided by the applicant is adequate. An *in vitro* study of the implant shows that the low dose formulation has preferable release rate characteristics, with a sustained release close to the predicted level through 36 months. In addition a Phase 2b pharmacokinetic study has been conducted in humans. This demonstrates that intravitreal insertion of Iluvien implants does not result in a measurable systemic exposure to the active substance, and that following a single implantation there is a sustained release of FA within the eye (measurable in the aqueous humour) for 36 months.

The results of the FAME studies demonstrate a comparable degree of efficacy for Iluvien to other therapies for DME. The response rates for the control groups in the FAME studies was higher than expected, but these subjects received laser and other disallowed therapies. Even despite this, treatment with Iluvien has been shown to produce meaningful and persistent improvements in vision over three years.

The general risks in the new target population were no higher than in the general population and the potential risks associated with Iluvien appear generally manageable. Diabetic patients develop cataract earlier than non-diabetics, and therefore Iluvien can be seen to accelerate this inevitable, but treatable, complication. Furthermore, the increase in IOP is manageable in most patients with medication (though more than one medication is often required), with only a small proportion requiring an invasive intervention.

The SmPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable. An adequate review of published non-clinical data has been provided. Extensive clinical experience with fluocinolone acetonide is considered to have demonstrated the therapeutic value of the compound and clinical studies have demonstrated the efficacy and safety of the product.

In the wider population of all patients with DME the potential benefits of Iluvien over the control group are not sufficient to outweigh the risks, particularly when considering that those patients with more recent onset DME (<3 years) gained no additional benefit over sham. However, in the subgroup of patients with chronic DME (≥3 years duration) who have not responded sufficiently to available therapies, significant benefits have been demonstrated which are sufficient to outweigh the potential risks.

Therefore, the benefit-risk profile of Iluvien in '*the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies' is considered positive.*

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels

The Summaries of Product Characteristics and Patient Information Leaflets (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Labelling

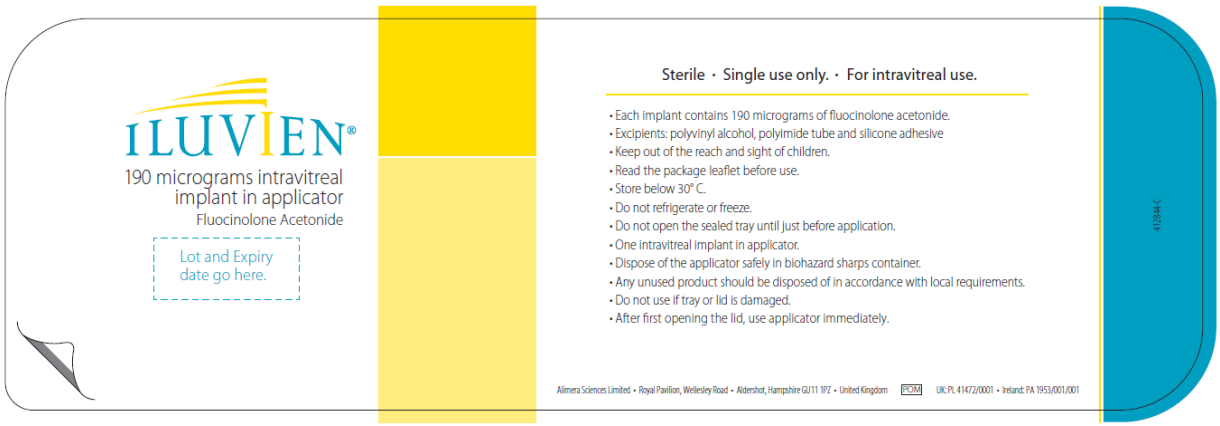


Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
To update sections 4.2, 4.4, 4.6, 4.8, 5.2 and 5.3 of the SmPC following a Repeat Use Mutual Recognition Procedure (RU-MRP) to implement Day 50 comments from the CMSs, Denmark, Sweden, The Netherlands and Belgium. Additionally, to update sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.2 in line with the Quality Review Document (QRD) template and to add administrative corrections. As a consequence, the Patient Information Leaflet (PIL) has been updated.	UK/H/3011/ 001/II/013/G	SmPC and PIL	03/03/2015	13/10/2015	Approved	Yes

Annex 1

Our Reference: PL 41472/0001 - 0028
Product: ILUVIEN 190 micrograms Intravitreal implant applicator
Marketing Authorisation Holder: Alimera Sciences Limited
Active Ingredient(s): Fluocinolone acetonide

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number: UK/H/3011/001/II/013/G

Reason:
To update sections 4.2, 4.4, 4.6, 4.8, 5.2 and 5.3 of the SmPC following a Repeat Use Mutual Recognition Procedure (RU-MRP) to implement Day 50 comments from the CMSs, Denmark, Sweden, The Netherlands and Belgium. Additionally, to update sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.2 in line with the Quality Review Document (QRD) template and to add administrative corrections. As a consequence, the Patient Information Leaflet (PIL) has been updated.

Supporting Evidence
The applicant has submitted updated sections of the SmPC and the leaflet.

Evaluation
The amended sections of the SmPC and the leaflet are satisfactory.

Conclusion
The variation was approved on 13th October 2015 and the updated SmPC fragments and the PIL have been incorporated into this Marketing Authorisation. The proposed changes are acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) – Update

Following approval of the variation on 13th October 2015 the SmPC was updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) - Update

Following approval of the variation on 13th October 2015 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.