

Intravitreal Fluocinolone Acetonide Implant (ILUVIEN[®]) for the Treatment of Retinal Conditions. A Review of Clinical Studies

Yusuf Mushtaq^{1,*}, Maryam M Mushtaq^{2,*}, Zisis Gatzoufas³, Matteo Ripa⁴, Lorenzo Motta⁵, Georgios D Panos¹

¹Department of Ophthalmology, Queen's Medical Centre, Nottingham University Hospitals NHS Trust & School of Medicine, University of Nottingham, Nottingham, UK; ²Department of Acute Medicine, Luton and Dunstable University Hospitals NHS Trust, Luton, UK; ³Department of Ophthalmology, Basel University Hospital & University of Basel School of Medicine, Basel, Switzerland; ⁴Ophthalmology Unit, "Fondazione Policlinico Universitario A. Gemelli IRCCS", Rome, Italy; ⁵Department of Ophthalmology, William Harvey Hospital, East Kent Hospitals University NHS Foundation Trust, Kent, UK

*These authors contributed equally to this work

Correspondence: Georgios D Panos, Department of Ophthalmology, Queen's Medical Centre, Derby Road, Lenton, Nottingham, NG7 2UH, UK, Tel +44 115 924 9924, Email gdpanos@gmail.com; Lorenzo Motta, Department of Ophthalmology, William Harvey Hospital, Kennington Road, Willesborough, Ashford, Kent, TN24 0LZ, UK, Tel +44 1233 633331, Email lorenzo.motta@nhs.net

Abstract: Fluocinolone acetonide (FAC) intravitreal implant (Iluvien[®]) is a corticosteroid implant indicated for the treatment of diabetic macular oedema (DMO) in patients who have previously received conventional treatment without good response, non-infectious posterior uveitis, and as an off-label treatment of the macular oedema secondary to retinal vein occlusion. FAC is a non-biodegradable 0.19 mg intravitreal implant which is designed to release FAC over 3 years at a rate of approximately 0.2 mcg per day. The aim of this review is to describe the special pharmacological properties of Iluvien and display the outcomes of the most important clinical trials and real-world studies regarding its efficacy and safety for the management of the above retinal disorders.

Keywords: Iluvien, steroid implant, diabetic macular oedema, intravitreal implant, posterior uveitis, retinal vein occlusion

Introduction

Intravitreal injection of pharmacological agents is a valuable tool to efficiently achieve therapeutic levels of medication directly in the vitreoretinal space and treat several retinal conditions.¹ This technique has been helpful when treating with corticosteroids, where high oral doses are often needed to achieve therapeutic levels in the eye and therefore increase the risk of adverse systemic side effects.²

With rare but serious complications associated with intravitreal injections, such as endophthalmitis, retinal detachment, and vitreous haemorrhage, sustained-release corticosteroid implants, have emerged to reduce the frequency of repeated intravitreal injections.² This ultimately reduces risk of complications and increases patient comfort through less frequent hospital visits. The 0.19-mg Fluocinolone acetate (FAC) implant (ILUVIEN[®]), is an intravitreal glucocorticoid implant that is designed to release fluocinolone acetate at a rate of 0.25µg per day and can have a therapeutic effect lasting 3 years.³ This review will explore the efficacy and safety of FAC in the treatment of retinal conditions, such as diabetic macular oedema (DMO), non-infectious posterior uveitis (NIPU) and retinal vein occlusion (RVO), highlighting important clinical trials and real-world studies.

Short Description of FAC

FAC is a non-erodible implant that is inserted via the pars plana through a 25-gauge injector system as an intravitreal injection. Each implant contains 0.19 mg of the synthetic corticosteroid, FAC, which is practically insoluble in water and

is slowly released into the vitreous cavity lasting up to 36 months. The FAMOUS study demonstrated this sustained release in the eye, assessing concentrations of FAc in aqueous humour, with levels of slightly more than 2 ng/mL for approximately the first 3 months followed by a maintained concentration of 0.5–1.0 ng/mL through a period of 36 months. It was also demonstrated that the drug was not detected in the systemic circulation, with FAc plasma concentrations always below the lower limit of quantification of the assay (100 pg/mL).⁴

FAc is indicated in Europe for the treatment of vision impairment associated with chronic DMO considered insufficiently responsive to available therapies and for prevention of relapse in recurrent NIPU. In 2014, the US Food and Drug Administration approved FAc for the treatment of DMO in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure (IOP).⁵

The 0.19mg FAc implant is contraindicated in the presence of pre-existing glaucoma with a cup-to-disc ratio of 0.8 and suspected or active ocular or periocular infections. Also, it is contraindicated in patients that have hypersensitivity to the active substance or any component of the product, such as silicone adhesive, polyvinyl alcohol and polyimide tube.⁶

Pharmacodynamics

FAc is a synthetic, medium-potency, fluorinated glucocorticoid receptor agonist with no mineralocorticoid activity.^{7,8} Corticosteroids primary method of action involves stimulating an increase in the synthesis of lipocortins, particularly phospholipase A2. This prevents the formation of prostaglandins and leukotrienes, which are potent inflammatory mediators, through inhibiting the release of their common precursor arachidonic acid from the phospholipid membrane.^{9,10} Along with their anti-inflammatory activity, glucocorticoids also reduce intravitreal levels of vascular endothelial growth factor (VEGF) through cell and gene inhibition, consequently causing regression of active neovascularisation.⁸ FAc has been shown to inhibit cell migration; the release of heparin, growth factors, and angiogenic factors; and the secretion of proinflammatory cytokines, which stimulate VEGF production.

In early studies of retinal degeneration in rat models, intravitreal FAc was shown to reduce the levels of neuroinflammation in both anterior and posterior chambers. There was also evidence seen of retinal electro-physiology and morphology preservation, inhibition of cell proliferation, and reduced angiogenesis.^{7,11,12} In a chick chorioallantoic membrane assay, it was also noted to inhibit tumour necrosis factor α -induced angiogenesis.¹³ Intravitreal FAc was shown to have positive effects in a human retinal pigment epithelial cell line (ARPE-19) by inhibiting VEGF secretion and mRNA expression. In Phase III trials, FAc at 0.2 mg/day improved best-corrected visual acuity (BCVA) and reduced foveal thickness in patients with DMO. As early as 3 weeks, there was an increase in BCVA of 15 letters ($p < 0.05$) compared with a placebo, which remained significant throughout the remainder of the trial (36 months).^{14,15} Reductions in foveal thickness were also sustained and rapid, with the central point thickness significantly lower ($p < 0.05$) in the treatment arm than in the placebo arm from as early as week 1. This difference remained notable at all measured points through the trial (24 months).^{14,15} An earlier Phase II study revealed that there was no statistically significant difference between patients receiving FAc at 0.2 versus 0.5 mg/day.^{7,16} Sustained-release FAc was also more effective in suppressing retinal microgliosis when compared with high-dose FAc.¹⁷

Pharmacokinetic Profile

A phase II study assessing the aqueous levels of FAc after administration of inserts/implants in patients with DMO revealed that the steroid is released into the aqueous humour in a sustained manner for a minimum of 36 months.⁴ This method of delivery of the 0.2mg/day FAc implant causes a steady-state concentration of 0.5 to 1.0 ng/mL to be reached by 6 to 9 months, with the average aqueous concentration reaching its maximum approximately 1 week after administration. The higher 0.5mg/day dose resulted in significantly higher aqueous levels for the first month, but no statistically significant difference in doses was noted after that time.¹⁸ For both lower (0.2mg/day) and higher-dose (0.5mg/day) implants, the plasma concentrations of FAc remained below the lower limit (100 pg/mL) from week 1 until completion of the trial at 36 months.⁸

Retinal Conditions and Their Management

The principal effects of corticosteroids are thought to be stabilisation of the blood-retinal barrier (BRB), reduction of exudation and downregulation of inflammatory stimuli.⁹ These properties make them an attractive therapeutic option for a variety of posterior segment diseases such as DMO, NIPU and RVO.

Diabetic Macular Oedema (DMO)

DMO is the most common form of sight-threatening retinopathy in people, with more than 20 million cases worldwide.¹⁹ Approximately 14% to 25% of patients diagnosed with diabetes appear to develop DMO within 10 years of presentation.²⁰ Disruption of the BRB due to an inflammatory cascade of events, involving chronic hyperglycaemia, oxidative stress and upregulation of anti-VEGF, results in the accumulation of fluid in the extravascular space. Corticosteroid intravitreal injections have been proven to inhibit the inflammatory cascade and can effectively treat this macular oedema.²¹ However, some patients can develop chronic DMO, with oedema persisting despite treatment. This is problematic as repeated injections (anti-VEGF or steroid) or macular laser sessions are required to attempt to stabilise visual acuity with a suboptimal response. The long-acting therapeutic effect of FAc aims to provide a solution to these challenging cases and has obtained approval for use in Europe and the USA following recent clinical trials and studies. The FAME clinical trial, which compared a total of 768 patients given varied strength doses of the FAc implant to 185 patients receiving a sham injection, demonstrated a mean improvement in BCVA and foveal thickness (FT) at 24 months' post administration.¹⁵ The mean improvement in BCVA letter score was 4.4 and 5.4 in the low- and high-dose groups, respectively, compared with 1.7 in the sham group ($P = 0.02$ and $P = 0.016$). This has also been highlighted in the ICE-UK study, which analysed 233 eyes treated with the FAc implant. In the 12 months prior to the implant, the visual acuity (VA) of these patients declined. However, in the 12 months' post implant, there was improvement of VA from a median of 0.66 LogMAR units or 52.0 ETDRS letters to 0.60 (0.38–0.90) LogMAR units or 55.0 letters ($p < 0.001$).²² Similar results were reported by El-Ghrably et al with a mean increase of 5.1 letters in BCVA at month 12.²³

A reduction in retinal thickness following FAc implants is acknowledged in many literatures and was noticed as early as 7 days after implantation and maintained for up to 3 years after the injection, with an average 20% to 30% reduction in macular oedema.^{24–26} A case report by Bertelmann et al showed how bilateral FAc implants in a phakic patient with a 20-year history of refractory DMO (left eye at baseline, right eye at month 6), resulted in a decrease in central retinal thickness (CRT) in the left eye from 642 to 372 μ m at month 13 and from 473 to 334 μ m in the right eye at month 6.²⁷ Elaraoud et al investigated earlier outcomes in 22 eyes across three different UK sites, which demonstrated a mean reduction in CRT of 148.9 μ m at 3 months and a mean visual gain of 6.4L.²⁸ In patients with bilateral implants and DMO, later data at 6 and 23 months established a sustained CRT reduction at months 6 and 12.^{29,30} Massin et al conducted a prospective Phase IV study in France, whereby participants were divided into two groups: chronic DMO insufficiently responsive to laser (group 1) with or without anti-VEGF (group 2), and given the FAc implant. A decrease in CRT was seen as early as week 1, with a mean reduction of 239 and 147 μ m at month 1 for groups 1 and 2, respectively.³¹ This effect was seen to be maintained at every 3-monthly interval, up to 12 months where a 299 μ m (group 1) and 251 μ m (group 2) reduction was established.

Greater oedema ($>400\ \mu$ m) is linked to a higher implant efficacy, with a thickness reduction of up to 50% in 21% of treated eyes.³² In a certain study, the results were noticeably better, with a decrease from 960 to 246 μ m in just 3 months.²⁸ There is substantial debate regarding the relationship between reduced macular thickness and increased visual acuity; in some studies, visual improvement was less significant than structural improvement. This is probably because of other factors that affect vision in diabetic patients besides macular thickness, like ischaemia, DMO duration, or structural retinal damage.^{31–33}

A recent real-world study from East London reported worse VA and CRT results, compared to the other published studies, in a predominantly BAME (black, Asian and minority ethnic) population.³³ Interestingly, in comparison to white subjects, BAME patients were found to respond less favourably in terms of VA gains, CRT improvement, and the need for additional treatment.

Although FAc has been found to be efficient in improving patient vision for up to 3 years in real-world studies, ophthalmic practitioners should remember that typically more than one injection or supplementary treatment with anti-VEGF or steroid injections is needed. The second FAc injection is typically given at 12 months.²⁴ In the FAME studies, approximately two-third of patients needed additional treatment.¹⁴ In the MEDISOFT study 44% of patients required additional therapy within a 2-year follow-up period and more specifically 6.4% received additional macular laser, 1.2% received bevacizumab, 13.6% received aflibercept, 17.7% received ranibizumab, 2.3% received intravitreal dexamethasone and the same percentage received intravitreal triamcinolone, while 0.53% received another FAc implant.²⁵ According to published studies, the proportion of patients requiring supplementary treatment range from 44% to 83%.^{14,24,25,33,34}

A summary of the studies on Iluvien in the treatment of DMO is depicted in Table 1. Important side-effects that have been associated with Iluvien usage are also included.

Non-Infectious Posterior Uveitis (NIPU)

There are several treatment options available to improve visual outcomes for those with posterior uveitis, including systemic corticosteroids and immunomodulatory therapy (IMT).³⁵ However, corticosteroids are associated with many side effects and direct intravitreal therapy offers promise to provide therapeutic levels directly to the eye while avoiding systemic complications. Until recently, there have been no intravitreal treatments offering sustained therapeutic effect for more than 6 months.³⁶

Bodaghi et al stresses the importance of avoiding cumulative damage in uveitis by preventing recurrent episodes of inflammation.³⁷ It has been hypothesised that the total insult to a uveitic eye from repeated inflammatory attacks may be greater than the sum of the individual insults and the consequences can be irreversible.¹⁸ FAc can provide sustained long-term treatment directly to the eye and reduce the cycle of treat, recur and treat.³⁷

Recent studies have shown that FAc is effective in treating NIPU. Jaffe et al performed a randomised controlled trial in 11 eyes with a history of recurrent noninfectious intermediate uveitis, posterior, or panuveitis.³⁸ Participants were randomized to receive either a low- or a high-dose FAc. Eyes were observed on day 0 (day the implant was injected) and then at regular intervals through 2 years. The average number of inflammation recurrences in the 12 months before implantation was 1.54 episodes per eye. During the follow-up period, none of the study eyes experienced a recurrence. None of these eyes also required a dose of posterior sub-tenon triamcinolone acetate (PSTA) injection, which was given an average of 1.5 times preceding implantation in 5 of the 11 eyes.

Pavesio and Heinz also carried out a prospective, randomised, double-masked, multicentre comparison of FAc and control-treated (sham injection plus standard of care) participants.³⁹ Eligible subjects had over a one-year recurrent NIPU history and either at least two separate recurrences requiring treatment or corticosteroid therapy (systemic or ocular) in the 12 months preceding study entry. Bilateral disease was present and analysed in 59/87 FAc-treated participants. In these patients, the more severely affected eye was treated with the FAc implant. Over 36 months, more FAc treated than fellow eyes remained recurrence-free (28.8% vs 5.1%, $P=0.001$; mean 1.9 vs 4.7 recurrences, respectively, $P<0.0001$). Topical corticosteroid use was also lower in FAc-treated than fellow eyes (27.1% vs 52.5%, $P=0.0041$). However, cataract surgery occurred in 72.0% of FAc-treated and 37.0% of fellow eyes. Although it appears to be relatively common for phakic eyes treated with FAc needing to undergo cataract surgery at some point in the follow-up, Weber et al demonstrated in 11 eyes with non-infectious uveitic macular oedema, treated with FAc implant, that intraocular pressure increases did not require additional treatment and no major ophthalmic complications occurred.⁴⁰

Jaffe and Pavesio on behalf of the Study Investigators conducted a Phase 3, prospective, double-masked, multicenter study on 129 participants ($n=87$ FAc-treated; $n=42$ sham-treated) over 36 months.⁴¹ In comparison to sham-treated eyes, FAc-treated eyes had significantly lower rates of uveitis recurrence over the course of the study (65.5% vs 97.6%; $P<0.001$), significantly longer periods without recurrence (median 657.0 vs 70.5 days; $P<0.001$), fewer recurrence episodes among those who had recurrences (mean 1.7 vs 5.3; $P<0.001$), less adjunctive therapy (57.5% vs 97.6%), and an acceptable side-effect profile.

A number of real-world studies demonstrated favourable functional and anatomical outcomes of FAc in patients with NIPU. More specifically, two retrospective studies showed a mean CRT reduction of approximately 150 μ m with a complete resolution of the macular oedema in about 70% of the cases over 12 months.^{42,43} Battista et al found that

Table 1 Summary of Most Important Studies of ILUVIEN and DMO

Study	Design	Number of Subjects	Number of Eyes	Follow Up	Key Results
Diabetic macular oedema					
ICE UK Study ²²	A retrospective, observational cohort study involving 13 ophthalmology centers.	208	233: 207 pseudophakic and 26 phakic	12 months	1. Median (interquartile range, IQR) VA was 0.66 (0.48–1.00) LogMAR units (equivalent to 52.0 ETDRS letters) at implant, improving to 0.60 (0.38–0.90) LogMAR units (55.0 letters) at 12 months post-implant ($p < 0.001$). 2. In total, 44%, 30%, and 18% of people achieved an improvement in ETDRS score of ≥ 5, ≥ 10, and ≥ 15 letters, respectively, over the same period. Adverse effects: 1. A small but significant ($p < .001$) increase in median IOP was observed (median = 15.0, IQR = 13.0–18.0 mmHg at implant to 18.0, 15.0–21.0 mmHg at 12 months). 2. In the 12 months following implant, additional IOP-lowering therapy was prescribed in 15% of subjects previously not requiring such therapy.
El-Ghrably et al ²³	Prospective, observational, multicentre study.	57	57: 44 pseudophakic and 13 phakic. (Phakic eyes received the FAc implant following phacoemulsification).	12 months	1. Mean change from baseline CMT (452 μm) was $-102 \mu\text{m}$ at month 3, $-117 \mu\text{m}$ at month 6, and $-126 \mu\text{m}$ at month 12. 2. The mean increase in BCVA from baseline (52.7 ETDRS letters) was 5.8 letters after 3 months, 6.7 letters at month 6, and 5.1 letters at month 12 Adverse effects: 1. 7/22 eyes lost VA, 3 lost ≥ 10 EDTRS letters and 2 lost ≥ 15 letters. Reasons for loss of VA were not provided but could have included lack of response to therapy, progression of disease state, or poor diabetic control. 2. 6 patients were on IOP-lowering medications from month 3 onwards, but none required glaucoma surgery.
FAME Studies ^{14,15}	Two parallel, prospective, randomised, sham injection-controlled, double-masked, multicentre clinical trials.	Sham, n = 185 0.2 $\mu\text{g/day}$, n = 375 0.5 $\mu\text{g/day}$, n = 393	Sham, n = 185 0.2 $\mu\text{g/day}$, n = 375 0.5 $\mu\text{g/day}$, n = 393	36 months	1. Visual gain of >15 ETDRS letters by 24 months in 0.5ug group. 2. BCVA letter score gain at 24 months: Sham: 1.7; 0.2 μg: 4.4; 0.5 μg: 5.43. Adverse effects: 1. Glaucoma surgery required: Sham: 0.5%; 0.2 μg: 3.7%; 0.5 μg: 7.6%.

(Continued)

Table I (Continued).

Study	Design	Number of Subjects	Number of Eyes	Follow Up	Key Results
IRISS ⁶⁰	Prospective, observational, multicentre study.	563	593	36 months	1. 76.7% of patients did not require IOP-lowering therapy following treatment with the FAc implant. 2. 69% of eyes did not require additional DMO treatments. 3. Mean VA in the overall population increased from 51.9 letters at baseline to 55.6 letters at month 12, with a significant increase of 2.9 letters at last observation.
Medisoft Audit Group ²⁵	Retrospective review of 14 clinical centres in the UK using electronic pseudo-anonymised medical record system.	305 patients	345	24 months	1. At 24 months, mean best-recorded visual acuity increased from 51.9 to 57.2 letters and 20.8% achieved ≥ 15 -letter improvement. 2. Mean CSFT reduced from 451.2 to 355.5 μm . Adverse effects: 1. Overall, 13.9% of patients required IOP-lowering drops (included initiation, addition and switching of current drops), 7.2% had IOP elevation >30 mm Hg and 0.3% required glaucoma surgery.
Panos et al ³³	Single-centre retrospective analysis.	24 (Approx 75% of patients were black or South Asian ethnicity).	24	36 months	1. Improvement in mean best corrected visual acuity was seen at year 1 and year 3 improving from 0.62 LogMAR at baseline to 0.55 LogMAR at year 1 and 0.47 LogMAR at year 3 (all $p > 0.05$). 2. Mean central retinal thickness also showed a progressive reduction from 471 μm at baseline to 397 μm at year 1 and 339 μm at year 3 (all $p < 0.05$). Adverse effects: 1. Four eyes required intraocular pressure-lowering drops post-implant. 2. Supplementary treatment for persistent or recurrent diabetic macular oedema was necessary in 13 eyes over the total study period of 3 years. 3. Blacks, Asians and minority ethnic patients had a worse response compared with white patients.
Paladin Study ³⁴	Phase 4, nonrandomised, open-label observational, prospective study.	159	202	36months	1. mean central subfield thickness change of -60.69 μm ($P < 0.0001$) 2. mean BCVA change of $+3.61$ letters ($P < 0.0222$) 3. treatment burden reduction of 70.5% 4. 25.53% of eyes remained rescue free Adverse effects: 1. IOP > 30 mmHg occurred in 10.89% of eyes. 2. surgical rate of 1.49% attributable to steroid use

the area under the curve (AUC) of BCVA after FAc correlates with the BCVA at the time of injection but not with macular thickness, whereas the AUC of central macular thickness (CMT) correlates with baseline CMT and may be negatively associated with uveitis duration.⁴⁴

A recent large retrospective study on 57 patients with NIPU treated with FAc 0.19mg from a tertiary referral centre in Germany specialising in uveitis reported a significant CRT reduction of approximately 54µm over 12 months and a reduction in intraocular inflammation over the first 9 months of the follow-up without significant adverse events.⁴⁵

More real-world studies with patients of different racial and ethnic backgrounds are expected with great interest.

A summary of the studies on Iluvien in the treatment of NIPU is depicted in [Table 2](#).

Retinal Vein Occlusion (RVO) and Irvine – Gass Syndrome

RVO is one of the main causes of sudden, painless vision loss in adults older than 50 years old. It is the occurrence of macular oedema in RVO that most frequently leads to visual loss.⁴⁶ Thrombosis within a retinal vein can lead to partial obstruction of blood flow from the eye. Sufficiently high increased intraluminal pressure can cause transudation of blood products into the retina resulting in increased interstitial fluid and protein. This can increase interstitial oncotic pressure, worsening tissue oedema and vascular perfusion, ultimately leading to ischaemia. Several chemical factors are involved in this inflammatory process, with Yoshimura et al finding significantly elevated vitreous levels of the soluble cytokines interleukin (IL) 6 and 8, monocyte chemoattractant protein-1, and VEGF in RVO, and especially in central RVO (CRVO).⁴⁷ This makes corticosteroids a useful class for their treatment.

With macular oedema persisting for a long time post CRVO, the prolonged therapeutic effect of FAc could be helpful and reduce the burden of multiple intravitreal injections.⁴⁸ Coelho et al reported a case of non-ischaemic CRVO that was successfully treated with a single intravitreal FAc implant.⁴⁹ Initially, repeated injections of shorter-acting dexamethasone were given, but resulted in fluctuations of vision between 20/32 and 20/200, based on the presence of macular oedema. This constant fluctuation on visual acuity was very uncomfortable for the patient being a frequent complaint. The FAc implant was successful in providing sustained improvement in visual acuity from 20/200 to 20/25.

The FAc implant has been demonstrated by Ribeiro et al to be effective in a case of ischaemic CRVO and BRVO. The patient with the ischaemic CRVO presented a baseline BCVA of 29 letters and a CRT of 664 µm.⁵⁰ In the absence of response to anti-VEGF (bevacizumab and aflibercept) and triamcinolone intravitreal injections, she was proposed to a dexamethasone implant (OZURDEX). She showed an anatomical improvement (CRT of 364 µm), although not sustained, despite a total of 5 implants. After the FAc implant was administered, a significant and sustained functional (BCVA of 38 letters) and anatomical (CRT of 271 µm) improvement was noted. This was similarly proven in the patient with BRVO, with sustained resolution of macular oedema at 12 months following the FAc implant.

Despite these clinical case studies, the volume of data regarding the use of FAc for RVO remains limited, and therefore its use is “off-label.” Further studies with longer follow-ups and sample sizes are needed to improve the confidence in the efficacy and safety of the FAc implant in these patients.

The post-operative macular oedema or Irvine – Gass syndrome is a common complication following intraocular surgery and can potentially lead to reduced visual acuity. The pathogenesis of this condition is related to postoperative inflammation and inflammatory mediator release and, therefore, steroids play an important role in the treatment and prevention.⁵¹ Miguel-Escuder et al presented four clinical cases of vitrectomised eyes with post-operative CMO irresponsive to conventional treatment including dexamethasone implant (Ozurdex).⁵² After treatment with Iluvien, macular oedema resolved in three cases, while one patient required additional treatment with Ozurdex. A recent study from Germany showed favourable outcomes in terms of visual and anatomical improvement in patients with refractory post-op CMO treated with a single Iluvien implant.⁵³

The volume of published data regarding the use of FAc for post-operative CMO remains limited and therefore its use is “off-label.” Further larger studies are needed to reliably assess the efficacy and safety of the FAc implant in these cases.

A summary of the reports on Iluvien in the treatment of RVO and Irvine – Gass syndrome is depicted in [Table 3](#).

Table 2 Summary of Most Important Studies of ILUVIEN and NIPU

Study	Design	Number of Patients	Number of Eyes	Follow Up	Key Results
Non-infectious uveitis					
Jaffe and Pavesio on behalf of the Study Investigators ⁴¹	Phase 3, prospective, double-masked, multicenter study. 33 clinical centres.	129	129	36 months	1. Recurrence rate 65.5% Fac vs 97.6% Sham 2. Median period (days) without recurrence 657.0 Fac vs 70.5 Sham. 3. Mean recurrence episodes 1.7 Fac vs 5.3 Sham 4. Adjunctive therapy 57.5% Fac vs 97.6% Sham Adverse effects: 1. IOP (mmHg) mean $\pm$ standard deviation 14.5 $\pm$ 5.1 Fac vs 14.8 $\pm$ 5.3 Sham. 2. IOP-lowering surgery 5.7% Fac vs 11.9% Sham 3. Cataract surgery 73.8% Fac vs 23.8% Sham
Jaffe et al ³⁸	Randomised controlled trial	11	11	24 months	1) Mean study eye visual acuity improved from +0.56 to +0.25 and +0.17 logMAR at 12 and 24 months after implantation, respectively (P = 0.041 and P = 0.016). 2) The average number of inflammation recurrences in the 12 months before implantation was 1.54 episodes per eye. None of the study eyes experienced a recurrence during the follow-up period. 3) Five of 11 eyes received an average of 1.6 posterior sub-Tenon triamcinolone acetonide (PSTA) injections in the 12 months preceding implantation. None required a PSTA injection after FAc implantation.
Weber et al ⁴⁰	Retrospective observational clinical study	8	11	42 months	1. The mean maximum decrease of central retinal thickness throughout the follow-up period was 168 $\pm$ 202 μm ($\pm$ standard deviation). 2. Nine out of 11 eyes showed an improvement in corrected distance visual acuity (between +1 and +8 lines). 3. Intraocular pressure increases did not require additional treatment and no major ophthalmic complications occurred. Adverse effects: 1. Both phakic eyes required cataract surgery.

Parvesio and Heinz, ³⁹	Prospective, randomised, double-masked, multicentre comparison.	87	87	36 months	1. Over 36 months, more FAc treated than fellow eyes remained recurrence-free (28.8% vs 5.1%, $P = 0.001$; mean 1.9 vs 4.7 recurrences, respectively, $P < 0.0001$). 2. FAc-treated eyes gained +9.6 letters BCVA, versus a loss of -4.4 in fellow eyes ($P < 0.0001$). 3. Intra/periocular adjunctive injections were lower in FAc-treated than fellow eyes (20.3% vs 66.1%, $P < 0.0001$). 4. Topical corticosteroid use was also lower in FAc-treated than fellow eyes (27.1% vs 52.5%, $P = 0.0041$). Adverse effects: 1. Cataract surgery occurred in 72.0% of FAi-treated and 37.0% of fellow eyes.
Pockar et al ⁴³	A retrospective observational clinical study.	-	11	12 months	1. Mean central retinal thickness (CRT) at baseline was $435 \mu\text{m} \pm 176$, improving to $296 \mu\text{m} \pm 67$ at 12 months. 2. The mean best corrected visual acuity (BCVA) was stable at 12 months. 3. There were no observed recurrences of uveitis. Adverse effects: 1. Two eyes received adjunctive treatment for worsening CRT.
Battista et al ⁴⁴	Retrospective observational study	7	10	12 months	1. The area under the curve for BCVA significantly improved from month 6 ($p = 0.03$). 2. The CMT improved from month 1 and was persistently lower than baseline until month 12 ($p < 0.001$). 3. No adverse events were recorded over 1 year.
Hikal et al ⁴²	Retrospective chart review.	26	34 (30 pseudophakic and 4 phakic)	18 months	1. Macular oedema was completely resolved in 24 (70.6%) cases treated with FAc. 2. In 20 eyes (58.5%), visual acuity (VA) improved (from +1 to +5 lines) and remained stable in 9 eyes (26.5%). Adverse effects: 1. Five of the treated eyes had a relapse after 23.2 ± 14 months. Three FAc reinjections were performed and a drying of the macula was observed. 2. Three of these eyes had a cataract prior to therapy and the other developed a cataract 2.5 years after the FAc implant was administered
Buhl et al ⁴⁵	Retrospective cohort study	57	76	12 months	1. BCVA remained stable 2. CRT reduction (362.7 vs $309.1 \mu\text{m}$; $p = 0.04$) 3. Reduced intraocular inflammation (0.82 vs 0.3; $p = 0.007$) Adverse effects: 1. IOP increase (13.68 vs 15.6; $p = 0.0507$) 2. cataract development (20% of phakic eyes)

Table 3 Summary of Most Important Studies of ILUVIEN and RVO & Irvine – Gass Syndrome

Study	Design	Number of Subjects	Number of Eyes	Follow Up	Key Results
Retinal vein occlusion					
Coelho et al ⁴⁹	Case report	1	2 (1 was treated with FAc and 1 was used as a control)	12 months	1. BCVA improved from 20/100 to 20/25. 2. Central foveal thickness decreased from 578 μm to 393 μm . 3. IOP maintained normal, controlled by medication.
Ribeiro et al ⁵⁰	Prospective international review	2 (1 patient had branch retinal vein occlusion and 1 patient had ischaemic central retinal vein occlusion).	2	12 months	1. The patient with BRVO improved BCVA from counting fingers to 38 letters and central retinal thickness also improved from 616 μm to 198 μm . 2. The patient with the ischemic CRVO had BCVA improve from 29 to 38 letters. She also had a CRT improve from 664 μm to 271 μm .
Miguel-Escuder et al ⁵²	Case series	4	4	Variable	1. Complete resolution of the CMO (related to Irvine – Gass syndrome) in 3 of the 4 cases 2. One case required an additional Ozurdex implant 3. Two cases developed ocular hypertension and required drops.
Chronopoulos et al ⁵³	Retrospective study	16	16	24 months	1. At month 12, BCVA improved in 11 eyes, stabilised in 4 eyes, and decreased in 1 eye. 2. At month 24, BCVA remained improved in 5 eyes, remained stable in 5 eyes, and decreased in 1 eye 3. At 12 months, CRT improved in 13 eyes and remained unchanged in 2 eyes 4. At 24 months, CRT improved further in 8 eyes, and remained stable in 3 eyes Adverse events 1. IOP > 21mmHg in only 4 eyes, all treated successfully with drops.

Safety

The most significant concerns surrounding intravitreal injection of steroids revealed by the FAME trials, were the development of visually significant cataract and ocular hypertension, or glaucoma. During the trials, four cases of endophthalmitis occurred, in which half of these were considered secondary to FAc injection (days 13 and 16 post-injection).²⁵ Surprisingly, there have only been a few reported cases of endophthalmitis that have been published in real-world studies to date, despite steroid injections known to be immunosuppressive in already compromised patients, such as those with diabetes.⁵⁴ This also highlights the need for increased caution with steroid use in patients with a history of herpetic or viral eye disease, as these injections may lead to a higher recurrence rate.

Ocular hypertension is one of the most common adverse events associated with the use of intraocular steroids; with up to 13% of patients potentially developing an IOP of >30 mmHg³⁶ (range of occurrence, 7–50%).^{24,55,56} Comparisons with the untreated eye show no ocular hypertension present when specifically assessed.⁵⁷ This is echoed in the FAME study, where IOP was raised in 37.1% of patients who received the 0.2-mg/day FAc implant ($n = 375$), compared to 11.9% of those who received a placebo ($n = 185$). This pattern remained true with both the overall population, and in those without prior ocular corticosteroid exposure; with a >30 -mmHg rise in IOP more frequently seen in patients who received the 0.2-mg/day FAc implant ($p < 0.001$) than in those who received placebo.^{14,15}

A retrospective study of 26 vitrectomised eyes (with a mean follow-up of 255 days) was performed by Meireles et al, where a mean IOP increase of 1.4 mmHg was found between baseline and the last visit (range, 9.0 to ≥ 8.0 mmHg); with eight eyes (30.7%) initiating or continuing anti-glaucoma drops.⁵⁸ Pessoa et al also performed a retrospective study with 43 eyes (24 vitrectomised and 19 non-vitrectomised), and a mean follow-up of 8.5 months.⁵⁹ There was no difference in the IOP changes between the two groups; however, vitrectomised eyes demonstrated a higher mean IOP elevation (1.6 vs 0.8 mmHg). The conclusions of the FAME study were supported in a multicentre study from three European countries (United Kingdom, Germany, and Portugal), published by the IRISS group. They found that roughly 23% of patients required IOP-lowering medication, but with no associated clinically significant changes in their cup-to-disc ratio (CDR).⁶⁰ The percentage of administered glaucoma drops varied from 0% to 15%, with some larger series having an even higher rate.^{22,25,55,60} These larger percentages are more in accordance with the FAME study, in which 26% of patients required glaucoma drops. However, 5.2% of patients in IRISS had a baseline IOP of >21 mmHg, which was an exclusion criterion in the FAME trials. Despite appropriate topical treatment, glaucoma surgery was deemed necessary in up to 14.3% of cases.⁵⁵

From these studies we can conclude that careful patient selection is of high importance in avoiding complications related to ocular hypertension. Currently, the FAc implant is contraindicated in patients with pre-existing glaucoma, and it is not approved for use in steroid responders in the United States.⁶¹ An idea to improve safety in administration would be through introducing a steroid provocation test to patients. Such a test could highlight individuals who may require surgical intervention and prevent them from FAc treatment; however, it could not definitely predict the absence of ocular hypertension.⁶² The PALADIN study showed that 96.92% of eyes with a previous IOP response of <25 mmHg after the steroid challenge, would have a similar outcome to FAc implant.³⁴ In the FAME study, 6.1% of steroid-naïve patients needed IOP-lowering surgery ($n = 18$), stressing the importance of identifying the individuals who have a strong IOP response to corticosteroid therapy.⁶² Dosing also needs to be highlighted, with no measured increase found in the CDR with a 0.2-mg/day dose after 36 months, compared to an increase of 0.1 in the 0.5-mg/day group.⁶² Subsequently, a 0.2-mg/day dose is the implant globally used; however, careful long-term follow-up focusing on IOP is still required.

Besides ocular hypertension, cataract formation is another important issue to tackle when it comes to the use of intraocular corticosteroids. It was discovered that cataracts usually develop within the first year of treatment and in almost all patients receiving implants after 3 years of follow-up.⁶³ The percentages of cataract surgery were 46% and 55% in patients with and without chronic macular oedema, respectively; which correlates to the 21% and 11% in the matched placebo group.⁶⁴ At the 36-month follow-up in the FAME study, cataracts developed in 81.7% of baseline phakic patients who received the 0.2-mg/day implant ($n = 14235$), as opposed to the 50.4% of those who received a placebo ($n = 121$).^{14,15} The visual outcome, however, following extraction, was measurable, if not better, than that in

patients with pseudophakia at baseline.^{14,15,63} These results demonstrate that patients with chronic DMO are more likely to gain a 15-letter improvement than those without DMO following cataract extraction.^{14,15}

As is the case with all intravitreal injections, adverse events may occur which are not currently reported in the literature. Such events include vitreous haemorrhage, transient ocular hypertension, and retinal tears or detachment.⁵⁴ Inside the eye, the presence of the steroid implant can also lead to problems in patients who undergo vitreo-retinal surgery, as it can become dislodged into the infusion cannula and cause globe pressurisation difficulties during surgery. These implants also run the risk of alternatively migrating to the anterior chamber.⁶⁵ The benefit–risk ratio of FAc use should therefore be acknowledged with each patient before use, as there are associated significant risks of adverse events, despite some studies supporting safe bilateral use.^{29,30,66}

Cost-Effectiveness

Retinal conditions, including DMO, can lead to blindness with significant financial impact; the annual cost of blindness for UK patients is more than GBP 5 billion.⁶⁷ Numerous analyses suggest that the FAc implant is a cost-effective treatment for both phakic and pseudophakic patients with insufficiently responsive DMO.^{55,68} A recent systematic literature review conducted in Germany over 3 years used a short-term cost–cost model to compare choosing an FA implant as a treatment for insufficiently anti-VEGF responding foveas in patients with DMO over other treatments, including ranibizumab, aflibercept, and a dexamethasone implant (Ozurdex).⁶⁹ The review concluded that a single FA implant was the most cost-effective (in-label) therapeutic option, with total costs of EUR 10,826, compared to EUR 17,542, EUR 15,896 and EUR 12,365, for ranibizumab, aflibercept, and the dexamethasone implant, respectively. The model determined drug costs as the predominant cost component, followed by the expenses of injections and optical coherence tomography.

In a recent NHS study, Quhill and Beiderbeck analysed the overall cost of treatment over 3 years with a single FAc implant, compared to using an average of 14 ranibizumab as needed.⁶⁸ The study took into account the expenses of the drugs and administration; along with the costs involved in monitoring patients, any additional interventions needed and management of adverse events. These authors calculated that by using the FAc implant over ranibizumab, and taking into account the added cost of cataract surgery, savings of roughly £6068 in pseudophakic eyes and £5341 in phakic eyes could occur. Therefore, within 3 years following the FAc implant, the need for adjunctive treatment was found to be lower than that needed with average anti-VEGF treatment regimens.^{24,25}

These studies demonstrate that the long-acting efficacy, safety profile and tolerability of the FAc implant allows it to be a considerable cost-saving option when compared to other treatments. Additionally, minimising the number and need for treatments is important for both patients and health-care staff, as department workloads are reduced and treatment time can be made available to other patients who need it. An increase in the frequency of injections has also been shown to decrease patients' quality of life, causing an increase in work leave and anxiety.⁷⁰

Conclusion

Overall, most clinical studies discussed have shown that FAc can be useful in the treatment of several retinal diseases. The common thing between DMO, NIPU and RVO is the inflammatory component associated with them and this makes corticosteroids a good therapeutic option. However, one of the biggest challenges faced is the chronicity of these diseases. FAc provides an option for long-term, stabilization of retinal conditions through constant, slow release of therapeutic substance directly to the vitreous cavity of the eye. Other intravitreal therapies, such as anti-VEGF and triamcinolone acetate (TA), have provided good therapeutic outcomes for patients with the mentioned retinal conditions, however the need for multiple injections is inconvenient for patients with an increase in associated risks.⁷¹ FAc offers a plausible alternative for patients with persistent or recurrent symptoms despite multiple anti-VEGF injections.¹⁵

The most frequently occurring adverse events related to FAc use are cataracts requiring surgery and an increase in IOP. Often, phakic eyes developed cataracts requiring surgery; however, the visual outcomes post-cataract surgery were similar to the outcomes from the already pseudophakic patients used at baseline.¹⁵ IOP measurements were also included in most studies and when ocular hypertension occurred, it was often well controlled by topical therapy.

Therefore, there is growing evidence for the use of FAc in many retinal conditions that are not completely responsive to current, short-term therapies, as it offers several advantages over other, and because it is a slow-release implant, patients require fewer injections or appointments with their ophthalmologist, which can reduce the burden of treatment. Additionally, FAc has been shown to be effective in maintaining visual acuity over the long term, making it a valuable option for patients with chronic DMO, recurrent NIPU, and eventually other retinal conditions.

Disclosure

Yusuf Mushtaq and Maryam M Mushtaq are co-first authors for this study. Lorenzo Motta and Georgios D Panos are co-correspondence authors for this study. The authors report no conflicts of interest in this work.

References

1. Peyman GA, Lad EM, Moshfeghi DM. Intravitreal injection of therapeutic agents. *Retina*. 2009;29(7):875–912. doi:10.1097/IAE.0b013e3181a94f01
2. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye*. 2013;27(7):787–794. doi:10.1038/eye.2013.107
3. Massa H, Nagar AM, Vergados A, Dadoukis P, Patra S, Panos GD. Intravitreal fluocinolone acetonide implant (ILUVIEN(R)) for diabetic macular oedema: a literature review. *J Int Med Res*. 2019;47(1):31–43. doi:10.1177/0300060518816884
4. Campochiaro PA, Nguyen QD, Hafiz G, et al. Aqueous levels of fluocinolone acetonide after administration of fluocinolone acetonide inserts or fluocinolone acetonide implants. *Ophthalmology*. 2013;120(3):583–587. doi:10.1016/j.ophtha.2012.09.014
5. Drugs.com. FDA approves iluvien; 2014. Available from: <https://www.drugs.com/newdrugs/fda-approves-iluvien-diabetic-macular-edema-4092.html>. Accessed March 23, 2023.
6. Cadth.ca. Clinical review report: fluocinolone acetonide intravitreal implant (Iluvien): (Knight Therapeutics Inc.): indication: for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. Ottawa (ON); 2019. Available from: <https://www.cadth.ca/sites/default/files/cdr/relatedinfo/sr0608-illuvien-clinical-review-report.pdf>. Accessed March 28, 2023.
7. Medicine and Healthcare products Regulatory Agency. Iluvien 190 micrograms intravitreal implant in applicator (fluocinolone acetonide): public assessment report; 2016.
8. Alimera Sciences Inc. Iluvien (fluocinolone acetonide intravitreal implant) 0.19 mg for intravitreal injection: US prescribing information; 2014. Available from: <http://www.fda.gov>. Accessed March 23, 2023.
9. Sarao V, Veritti D, Boscia F, Lanzetta P. Intravitreal steroids for the treatment of retinal diseases. *ScientificWorldJournal*. 2014;2014:989501. doi:10.1155/2014/989501
10. Kang BS, Chung EY, Yun YP, et al. Inhibitory effects of anti-inflammatory drugs on interleukin-6 bioactivity. *Biol Pharm Bull*. 2001;24(6):701–703. doi:10.1248/bpb.24.701
11. Holmquist F, Lundin S, Larsson B, Hedlund H, Andersson KE. Studies on binding sites, contents, and effects of AVP in isolated bladder and urethra from rabbits and humans. *Am J Physiol*. 1991;261(4 Pt 2):R865–874. doi:10.1152/ajpregu.1991.261.4.R865
12. Glybina IV, Kennedy A, Ashton P, Abrams GW, Iezzi R. Photoreceptor neuroprotection in RCS rats via low-dose intravitreal sustained-delivery of fluocinolone acetonide. *Invest Ophthalmol Vis Sci*. 2009;50(10):4847–4857. doi:10.1167/iovs.08-2831
13. Ayalamayajula SP, Ashton P, Kompella UB. Fluocinolone inhibits VEGF expression via glucocorticoid receptor in human retinal pigment epithelial (ARPE-19) cells and TNF-alpha-induced angiogenesis in chick chorioallantoic membrane (CAM). *J Ocul Pharmacol Ther*. 2009;25(2):97–103. doi:10.1089/jop.2008.0090
14. Campochiaro PA, Brown DM, Pearson A, et al. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. *Ophthalmology*. 2012;119(10):2125–2132. doi:10.1016/j.ophtha.2012.04.030
15. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology*. 2011;118(4):626–635 e622. doi:10.1016/j.ophtha.2010.12.028
16. Syed YY. Fluocinolone acetonide intravitreal implant 0.19 mg (ILUVIEN(R)): a review in diabetic macular edema. *Drugs*. 2017;77(5):575–583. doi:10.1007/s40265-017-0722-4
17. Glybina IV, Kennedy A, Ashton P, Abrams GW, Iezzi R. Intravitreal delivery of the corticosteroid fluocinolone acetonide attenuates retinal degeneration in S334ter-4 rats. *Invest Ophthalmol Vis Sci*. 2010;51(8):4243–4252. doi:10.1167/iovs.09-4492
18. Campochiaro PA. Pharmacokinetics of sustained-delivery fluocinolone acetonide for DMO. *Retina Today*. 2009;2009:55–56.
19. Tan GS, Cheung N, Simo R, Cheung GC, Wong TY. Diabetic macular oedema. *Lancet Diabetes Endocrinol*. 2017;5(2):143–155. doi:10.1016/S2213-8587(16)30052-3
20. Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin epidemiologic study of diabetic retinopathy. XV. The long-term incidence of macular edema. *Ophthalmology*. 1995;102(1):7–16. doi:10.1016/S0161-6420(95)31052-4
21. Pacella F, Ferraresi AF, Turchetti P, et al. Intravitreal Injection of Ozurdex(R) implant in patients with persistent diabetic macular edema, with six-month follow-up. *Ophthalmol Eye Dis*. 2016;8:11–16. doi:10.4137/OED.S38028
22. Holden SE, Currie CJ, Owens DR. Evaluation of the clinical effectiveness in routine practice of fluocinolone acetonide 190 microg intravitreal implant in people with diabetic macular edema. *Curr Med Res Opin*. 2017;33(sup2):5–17. doi:10.1080/03007995.2017.1366645
23. El-Ghrably I, Steel DHW, Habib M, Vaideanu-Collins D, Manvikar S, Hillier RJ. Diabetic macular edema outcomes in eyes treated with fluocinolone acetonide 0.2 microg/d intravitreal implant: real-world UK experience. *Eur J Ophthalmol*. 2017;27(3):357–362. doi:10.5301/ejo.5000929
24. Fusi-Rubiano W, Mukherjee C, Lane M, et al. Treating Diabetic Macular Oedema (DMO): real world UK clinical outcomes for the 0.19mg Fluocinolone Acetonide intravitreal implant (Iluvien) at 2 years. *BMC Ophthalmol*. 2018;18(1):62. doi:10.1186/s12886-018-0726-1

25. Bailey C, Chakravarthy U, Lotery A, Menon G, Talks J, Medisoft Audit G. Real-world experience with 0.2 mug/day fluocinolone acetonide intravitreal implant (ILUVIEN) in the United Kingdom. *Eye*. 2017;31(12):1707–1715. doi:10.1038/eye.2017.125
26. Figueira J, Henriques J, Amaro M, Rosas V, Alves D, Cunha-Vaz J. A nonrandomized, open-label, multicenter, phase 4 pilot study on the effect and safety of ILUVIEN(R) in chronic diabetic macular edema patients considered insufficiently responsive to available therapies (RESPOND). *Ophthalmic Res*. 2017;57(3):166–172. doi:10.1159/000455235
27. Bertelmann T, Schulze S. Long-term follow-up of patient with diabetic macular edema receiving fluocinolone acetonide intravitreal implant. *Ophthalmol Ther*. 2015;4(1):51–58. doi:10.1007/s40123-015-0028-0
28. Elaraoud I, Andreatta W, Kidess A, et al. Use of fluocinolone acetonide for patients with diabetic macular oedema: patient selection criteria and early outcomes in real world setting. *BMC Ophthalmol*. 2016;16:3. doi:10.1186/s12886-015-0178-9
29. Elaraoud I, Attawan A, Quhill F. Case series investigating the efficacy and safety of bilateral fluocinolone acetonide (ILUVIEN((R))) in patients with diabetic macular edema. *Ophthalmol Ther*. 2016;5(1):95–104. doi:10.1007/s40123-016-0045-7
30. Elaraoud I, Quhill H, Quhill F. Case series investigating the efficacy and safety of bilateral fluocinolone acetonide (ILUVIEN((R))) in patients with diabetic macular edema: 10 eyes with 12 months follow-up. *Ophthalmol Ther*. 2016;5(1):105–109. doi:10.1007/s40123-016-0049-3
31. Massin P, Erginay A, Dupas B, Couturier A, Tadayoni R. Efficacy and safety of sustained-delivery fluocinolone acetonide intravitreal implant in patients with chronic diabetic macular edema insufficiently responsive to available therapies: a real-life study. *Clin Ophthalmol*. 2016;10:1257–1264. doi:10.2147/OPHTH.S105385
32. Currie CJ, Holden SE, Owens DR. Patterns of retinal thickness prior to and following treatment with fluocinolone acetonide 190 microg intravitreal implant for diabetic macular edema. *Curr Med Res Opin*. 2017;33(sup2):33–43. doi:10.1080/03007995.2017.1366662
33. Panos GD, Arruti N, Patra S. The long-term efficacy and safety of fluocinolone acetonide intravitreal implant 190 mug (ILUVIEN((R))) in diabetic macular oedema in a multi-ethnic inner-city population. *Eur J Ophthalmol*. 2021;31(2):620–629. doi:10.1177/1120672119898414
34. Singer MA, Sheth V, Mansour SE, Coughlin B, Gonzalez VH. Three-year safety and efficacy of the 0.19-mg fluocinolone acetonide intravitreal implant for diabetic macular edema: the PALADIN study. *Ophthalmology*. 2022;129(6):605–613. doi:10.1016/j.ophtha.2022.01.015
35. Uy HS, Yu-Keh E, Chan PS. Posterior Uveitis. *Dev Ophthalmol*. 2016;55:163–166.
36. Massa H, Georgoudis P, Panos GD. Dexamethasone intravitreal implant (OZURDEX((R))) for macular edema secondary to noninfectious uveitis: a review of the literature. *Ther Deliv*. 2019;10(6):343–351. doi:10.4155/tde-2019-0024
37. Bodaghi B, Nguyen QD, Jaffe G, Khoramnia R, Pavesio C. Preventing relapse in non-infectious uveitis affecting the posterior segment of the eye - evaluating the 0.2 mug/day fluocinolone acetonide intravitreal implant (ILUVIEN((R))). *J Ophthalmic Inflamm Infect*. 2020;10(1):32. doi:10.1186/s12348-020-00225-z
38. Jaffe GJ, Lin P, Keenan RT, Ashton P, Skalak C, Stinnett SS. Injectable fluocinolone acetonide long-acting implant for noninfectious intermediate uveitis, posterior uveitis, and panuveitis: two-year results. *Ophthalmology*. 2016;123(9):1940–1948. doi:10.1016/j.ophtha.2016.05.025
39. Pavesio C, Heinz C. Non-infectious uveitis affecting the posterior segment treated with fluocinolone acetonide intravitreal implant: 3-year fellow eye analysis. *Eye*. 2022;36(6):1231–1237. doi:10.1038/s41433-021-01608-9
40. Weber LF, Marx S, Auffarth GU, et al. Injectable 0.19-mg fluocinolone acetonide intravitreal implant for the treatment of non-infectious uveitic macular edema. *J Ophthalmic Inflamm Infect*. 2019;9(1):3. doi:10.1186/s12348-019-0168-9
41. Jaffe GJ, Pavesio CE, Study I. Effect of a fluocinolone acetonide insert on recurrence rates in noninfectious intermediate, posterior, or panuveitis: three-year results. *Ophthalmology*. 2020;127(10):1395–1404. doi:10.1016/j.ophtha.2020.04.001
42. Hikal M, Celik N, Auffarth GU, Kessler LJ, Mayer CS, Khoramnia R. Intravitreal 0.19 mg fluocinolone acetonide implant in non-infectious uveitis. *J Clin Med*. 2021;10(17):3966. doi:10.3390/jcm10173966
43. Pockar S, Leal I, Chhabra R, Jones NP, Steeples LR. Intravitreal fluocinolone 0.19mg implant in the management of chronic non-infectious uveitis: 12-month outcomes from a single tertiary centre. *Ocul Immunol Inflamm*. 2021;1–7:54.
44. Battista M, Starace V, Cicinelli MV, et al. Efficacy of 0.19 mg fluocinolone acetonide implant in non-infectious posterior uveitis evaluated as area under the curve. *Ophthalmol Ther*. 2022;11(1):215–224. doi:10.1007/s40123-021-00426-2
45. Buhl L, Thureau S, Kern C. Fluocinolone acetonide 0.19-mg implant for the treatment of noninfectious uveitis with involvement of the posterior segment: a real-world study. *Graefes Arch Clin Exp Ophthalmol*. 2022. doi:10.1007/s00417-022-05893-2
46. Orskov M, Vorum H, Bjerregaard Larsen T, et al. A review of risk factors for retinal vein occlusions. *Expert Rev Cardiovasc Ther*. 2022;20(9):761–772. doi:10.1080/14779072.2022.2112667
47. Yoshimura T, Sonoda KH, Sugahara M, et al. Comprehensive analysis of inflammatory immune mediators in vitreoretinal diseases. *PLoS One*. 2009;4(12):e8158. doi:10.1371/journal.pone.0008158
48. Ford JA, Clar C, Lois N, et al. Treatments for macular oedema following central retinal vein occlusion: systematic review. *BMJ Open*. 2014;4(2):e004120. doi:10.1136/bmjopen-2013-004120
49. Coelho J, Pessoa B, Meireles A. Long-term management of non-ischemic central retinal vein occlusion with fluocinolone acetonide intravitreal implant 190 mug (ILUVIEN(R)). *Ther Adv Ophthalmol*. 2019;11:2515841418820755. doi:10.1177/2515841418820755
50. Ribeiro M, Pereira AF, Penas S, Falcão-Reis F, Beato JN. 12-Month Effectiveness of the Fluocinolone Acetonide Implant (ILUVIEN®) in Retinal Vein Occlusions – Two Clinical Cases. *EURETINA*; 2021.
51. Kessel L, Tendal B, Jorgensen KJ, et al. Post-cataract prevention of inflammation and macular edema by steroid and nonsteroidal anti-inflammatory eye drops: a systematic review. *Ophthalmology*. 2014;121(10):1915–1924. doi:10.1016/j.ophtha.2014.04.035
52. Miguel-Escuder L, Olate-Perez A, Sala-Puigdoners A, et al. Intravitreal fluocinolone acetonide implant for the treatment of persistent post-surgical cystoid macular edema in vitrectomized eyes. *Eur J Ophthalmol*. 2021;2021:11206721211046718.
53. Chronopoulos A, Chronopoulos P, Hattenbach LO, et al. Intravitreal fluocinolone acetonide implant for chronic postoperative cystoid macular edema - two years results. *Eur J Ophthalmol*;2022;11206721221124688. doi:10.1177/11206721221124688
54. Alfaqawi F, Lip PL, Elsherbiny S, Chavan R, Mitra A, Mushtaq B. Report of 12-months efficacy and safety of intravitreal fluocinolone acetonide implant for the treatment of chronic diabetic macular oedema: a real-world result in the United Kingdom. *Eye*. 2017;31(4):650–656. doi:10.1038/eye.2016.301
55. Ch'ng SW, Brent AJ, Empeslidis T, Konidaris V, Banerjee S. Real-world cost savings demonstrated by switching patients with refractory diabetic macular edema to intravitreal fluocinolone acetonide (Iluvien): a retrospective cost analysis study. *Ophthalmol Ther*. 2018;7(1):75–82. doi:10.1007/s40123-017-0114-6

56. Schmit-Eilenberger VK. A novel intravitreal fluocinolone acetonide implant (Iluvien(R)) in the treatment of patients with chronic diabetic macular edema that is insufficiently responsive to other medical treatment options: a case series. *Clin Ophthalmol*. 2015;9:801–811. doi:10.2147/OPTH.S79785
57. Currie CJ, Holden SE, Berni E, Owens DR. Evaluation of the clinical effectiveness of fluocinolone acetonide 190 microg intravitreal implant in diabetic macular edema: a comparison between study and fellow eyes. *Curr Med Res Opin*. 2017;33(sup2):19–31. doi:10.1080/03007995.2017.1366659
58. Meireles A, Goldsmith C, El-Ghrably I, et al. Efficacy of 0.2 mug/day fluocinolone acetonide implant (ILUVIEN) in eyes with diabetic macular edema and prior vitrectomy. *Eye*. 2017;31(5):684–690. doi:10.1038/eye.2016.303
59. Pessoa B, Coelho J, Correia N, Ferreira N, Beirao M, Meireles A. Fluocinolone acetonide intravitreal implant 190 mug (ILUVIEN(R)) in vitrectomized versus nonvitrectomized eyes for the treatment of chronic diabetic macular edema. *Ophthalmic Res*. 2018;59(2):68–75. doi:10.1159/000484091
60. Chakravarthy U, Taylor SR, Koch FHJ, Castro de Sousa JP, Bailey C. Changes in intraocular pressure after intravitreal fluocinolone acetonide (ILUVIEN): real-world experience in three European countries. *Br J Ophthalmol*. 2019;103(8):1072–1077. doi:10.1136/bjophthalmol-2018-312284
61. ILUVIEN. Summary of product characteristics. Available from: <https://www.medicines.org.uk/emc/medicine/27636>. Accessed March 23, 2023.
62. Parrish RK, Campochiaro PA, Pearson PA, Green K, Traverso CE. Characterization of intraocular pressure increases and management strategies following treatment with fluocinolone acetonide intravitreal implants in the FAME trials. *Ophthalmic Surg Lasers Imaging Retina*. 2016;47(5):426–435. doi:10.3928/23258160-20160419-05
63. Yang Y, Bailey C, Holz FG, et al. Long-term outcomes of phakic patients with diabetic macular oedema treated with intravitreal fluocinolone acetonide (FAc) implants. *Eye*. 2015;29(9):1173–1180. doi:10.1038/eye.2015.98
64. Cunha-Vaz J, Ashton P, Iezzi R, et al. Sustained delivery fluocinolone acetonide vitreous implants: long-term benefit in patients with chronic diabetic macular edema. *Ophthalmology*. 2014;121(10):1892–1903. doi:10.1016/j.ophtha.2014.04.019
65. Andreatta W, Elaraoud I, Mitra A. Dislodgement of fluocinolone acetonide intravitreal implant into the infusion cannula during vitrectomy for retinal detachment. *Retin Cases Brief Rep*. 2020;14(3):215–217. doi:10.1097/ICB.0000000000000678
66. de Oliveira Dias JR, Nunes RP, Goldhardt R. New drugs and new posterior delivery methods in CME. *Curr Ophthalmol Rep*. 2017;5(2):160–168. doi:10.1007/s40135-017-0134-3
67. Royal National Institute of Blind People (UK). Sight loss UK 2013. The latest evidence (2013); 2013. Available from: www.rnib.org.uk/sites/default/files/sight_loss_UK_2013.pdf. Accessed March 23, 2023.
68. Quhill F, Beiderbeck A. Cost advantage of fluocinolone acetonide implant (ILUVIEN) versus ranibizumab in the treatment of chronic diabetic macular oedema. *Glob Reg Health Technol Assess*. 2017;3(2):25.
69. Neubauer AS, Haritoglou C, Ulbig MW. Kostenvergleich zugelassener intravitrealer Therapien bei nicht ausreichend auf primäre Therapie ansprechendem diabetischem Makulaödem mit fovealer Beteiligung in Deutschland [Cost comparison of licensed intravitreal therapies for insufficiently anti-VEGF responding fovea involving diabetic macular edema in Germany]. *Klin Monbl Augenheilkd*. 2019;236(2):180–191. German. doi:10.1055/s-0043-125076
70. Sivaprasad S, Oyetunde S. Impact of injection therapy on retinal patients with diabetic macular edema or retinal vein occlusion. *Clin Ophthalmol*. 2016;10:939–946. doi:10.2147/OPTH.S100168
71. Sampat KM, Garg SJ. Complications of intravitreal injections. *Curr Opin Ophthalmol*. 2010;21(3):178–183. doi:10.1097/ICU.0b013e328338679a

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>