OPEN ACCESS

Safety and effectiveness of the fluocinolone acetonide intravitreal implant (ILUVIEN): 3-year results from the European IRISS registry study

Ramin Khoramnia ,[1] Tunde Peto ,[2] Frank Koch,[3] Simon R Taylor,[4] João Paulo Castro de Sousa,[5] Lauren Hill,[6] Clare Bailey,[7] Usha Chakravarthy ,[8] On behalf of the ILUVIEN Registry Safety Study (IRISS) Investigators Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjo-2022-321415).

[1]International Vision Correction Research Centre, Department of Ophthalmology, University Hospital Heidelberg, Heidelberg, Germany
[2]Centre for Public Health, Blackwell's Queen's University, Belfast, UK
[3]Department of Ophthalmology, Section of Vitreo-Retinal Surgery, Hospital of the Goethe University, Frankfurt am Main, Germany
[4]Department of Ophthalmology, University of Surrey, Guildford, UK
[5]Ophthalmology Department, Leiria Hospital Centre, Pousos, Portugal
[6]Consultant, Bozeman, Montana, USA
[7]Bristol Eye Hospital, Bristol, UK
[8]Queen's University Belfast, Belfast, UK

Correspondence to
Dr Usha Chakravarthy, Queen's University Belfast, Belfast BT7 1NN, UK;
u.chakravarthy@qub.ac.uk

Received 4 March 2022
Accepted 20 June 2022
Published Online First 15 July 2022

To cite: Khoramnia R, Peto T, Koch F, *et al*. *Br J Ophthalmol* 2023;**107**:1502–1508.

ABSTRACT

Background The ILUVIEN Registry Safety Study was a multicentre, open-label, non-randomised, observational, phase 4 study designed to assess the safety and effectiveness of the fluocinolone acetonide (FAc) implant in all indications in real-world practices in Europe.

Methods The study included data collected prospectively and retrospectively. Patients receiving FAc implants between 2013 and 2017 were included and monitored until the last patient reached ≥3 years of follow-up. Mean intraocular pressure (IOP) data over the course of the study, along with IOP events, use of IOP-lowering therapy, mean change in visual acuity (VA) and information on supplemental therapy use were analysed post-FAc implantation.

Results Six hundred and ninety-five eyes from 556 patients, with a mean±SD follow-up of 1150.5±357.36 days, were treated with a FAc implant. 96.7% of eyes had chronic diabetic macular oedema (cDMO). IOP lowering was achieved in 34.5% of eyes using topical agents and 4.3% by surgery. Seventy-three eyes (64.6% of 113 phakic) required cataract surgery during follow-up. Mean VA increased from a baseline of 52.2 letters to 57.1 letters at month 36, with improvement observed up to month 48. Supplementary therapies were given in 43.7% of eyes. When classified by length of cDMO less than or greater than the median duration those with a shorter history experienced greater VA gains than those with a longer history.

Conclusion This study confirms the favourable, long-term benefit-to-risk profile of the FAc implant in eyes with cDMO, with an additional benefit in patients when this therapy is administered earlier.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The safety and efficacy of the 190 µg fluocinolone acetonide (FAc) implant in diabetic macular oedema (DMO) has previously been established in the pivotal, phase 3 FAME studies. Real-world reports on the use of FAc are sparse and conducted in limited patient numbers.

WHAT THIS STUDY ADDS

⇒ This study adds real-world evidence in a large patient population from across Europe demonstrating the safety and effectiveness of the FAc implant in DMO, with evidence in support of earlier treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These data will assist in the identification of patients suitable for therapy with the FAc implant and deciding on the appropriate time to administer treatment.

INTRODUCTION

Diabetic macular oedema (DMO) is a major cause of vision loss among patients with diabetic retinopathy.[1 2] As the age of the wider population and life expectancy increases, the prevalence of diabetes and DMO is expected to rise.[2] Effective management of DMO is important as visual impairment has a significant impact on quality of life[3 4] and, without treatment, nearly half of those who develop DMO will lose two or more lines of visual acuity (VA) within 2 years.[5] Early diagnosis as well as early, effective therapy are therefore essential to avoid the detrimental effects of vision loss. The goal of therapy is to maintain or improve vision by reducing macular swelling.[6 7] Current treatment options include laser photocoagulation, anti-vascular endothelial growth factor (anti-VEGF) therapy and intravitreal corticosteroids; the latter two options are preferred for centre-involving DMO (where the fovea at the centre of the macula is affected).[8]

Inflammation plays an important role in the pathogenesis of DMO[9] and serves as an early contributor to vascular change and consequent oedema formation.[10] It is on this basis that intravitreal corticosteroids have gained a role as important therapies in reducing oedema, as they target several cytokines and chemokines involved in the pathophysiology of DMO.[11]

The ILUVIEN 190 µg implant (Alimera Sciences, Hampshire, UK) was designed as a non-bioerodible implant that can release a sustained, low daily dose (0.2 µg per day) of fluocinolone acetonide (FAc) over a 3-year period.[12] Its indications in Europe include both DMO and non-infectious uveitis. In DMO, it is indicated for the treatment of vision impairment associated with chronic DMO (cDMO) that is considered insufficiently responsive to available therapies, that is, DMO that has persisted or recurred despite treatment.[13] In uveitis,

it is indicated for the prevention of relapse of recurrent non-infectious uveitis affecting the posterior segment of the eye.[14–16]

The safety and efficacy of the FAc implants were first established in the pivotal, phase 3 FAME studies in which they were shown to improve best-corrected VA (BCVA) when compared with sham treatment. In these studies, two important adverse events were identified, namely raised intraocular pressure (IOP) and the development of cataract.[17] These findings are supported by multiple subsequent real-world studies; however, to date, these studies have comprised relatively small patient populations, retrospectively studied over limited follow-up periods.[18 19]

The ILUVIEN Registry Safety Study (IRISS; NCT01998412) post-approval study was designed as part of a European regulatory requirement following the licensing of the FAc implant in Europe. Its aim was to address these limitations by providing high-quality data regarding real-world outcomes from the use of the FAc implant. The study included any patient treated with the FAc implant in countries where a marketing authorisation had been granted such that broader safety and usage information could be obtained in a real-world setting. The study was also designed to examine the effect of the FAc implant on visual acuity.

An interim report from IRISS was published in 2018, after a mean follow-up of 1.2 years.[13] The study has now completed; here, we describe the safety outcomes and VA changes in 556 patients (695 eyes) studied for up to 5.5 years and enrolled from 31 sites in the UK, 11 in Germany and 5 in Portugal. Our findings should help in identifying suitable patients for this therapy and deciding on the appropriate time to administer.

MATERIALS AND METHODS

Patient population

Patients were included if they had been treated with the 0.2 μg/day slow-release FAc implant (ILUVIEN 190 µg) for any clinical indication, including the licensed indication Fof cDMO. Data were collected from patient records from each participating site, and ethics committee approval was obtained in all countries prior to study inception. Real-world safety and tolerability data—including incidence and management of IOP rise, and the change in VA—and functional outcomes were acquired from patients receiving the 0.2 µg/day FAc implant.

Study design

IRISS (NCT01998412) is a European, multicentre, open-label, observational registry study of patients treated with the FAc implant for any reason. Data were collected prospectively when patients were enrolled at the time of FAc implantation. Subsequently following an amendment to the protocol clinical sites were permitted to retrospectively enrol participants who fulfilled the following requirements: (1) treatment with ILUVIEN no more than 36 months prior to their first study visit; (2) met the data requirements as specified in the protocol, that is, baseline data collected within 7 days prior to treatment with ILUVIEN and additional data subsequently collected approximately every 6 months thereafter until enrolment into the study and (3) follow-up for at least 1 year prior to the planned end of the study. Patients who were unable to understand and sign the informed consent form were excluded from the study.

IRISS was a post-regulatory approval study designed as part of the regulatory requirement within European countries where the FAc implant is currently marketed.

The observational phase had a planned duration of follow-up of 5 years and the sample size was calculated (n=550) to give an 80% probability of detecting events with a true 5-year incidence of 0.3%.

The study involved 31 sites in the UK, 11 in Germany and 5 in Portugal and ran from January 2014 to January 2020 when the last patient reached 3 years of follow-up. The first enrolled patient was screened on 27 July 2013 and treated on 13 August 2013. The last patient treated with FAc implant was screened and treated on 20 January 2017 and completed the study on 9 January 2020.

For the overall study population, 562 patients were enrolled; 556 of these received ILUVIEN (N=695 eyes) and had a follow-up visit. Maximum follow-up was 1978 days (65.03 months). The data extract for this final analysis was performed on 28 April 2020.

Safety outcome measures

The key safety outcome was treatment-induced raised IOP. Specific parameters included: change in IOP over time; cumulative incidence of raised IOP events; an increase in IOP of ≥10 mm Hg; IOP >30 mm Hg at any point; percentage of patients receiving IOP-lowering medication; IOP-lowering surgery and time to first IOP-lowering medication or to first IOP-lowering surgery (Kaplan-Meier estimation).

Other safety outcomes included: cataract-related events in eyes that were phakic at baseline; diagnosis of cataract; occurrence of cataract extraction surgery and time to cataract extraction surgery.

VA outcomes

The key efficacy outcome was VA and assessments were performed using standard ETDRS charts or the investigator's standard procedure. In the study protocol, patients were to be tested with their own (if any) habitual spectacle correction and repeated at every visit. Specific measures of VA included: changes in VA over time; absolute VA ≥6/12 Snellen fraction over time; percentage of eyes with stable vision or improvement (defined as any gain, or any loss ≤4 letters from baseline[7]; and the percentage of eyes achieving ≥15 letter changes in VA from baseline.

For eyes with DMO (N=672) and a DMO duration (N=641; not all eyes with DMO had a duration available (N=31)), the median duration of cDMO in the eligible cohort was calculated as 3.6 years. Participants with a DMO duration ≤3.6 years were classified as 'short-term cDMO' (N=319), while a duration >3.6 years (N=322) was classed as 'long-term cDMO.'

Supplementary treatments given after FAc implantation were also analysed.

Data analyses

The above measures (eg, IOP) and outcomes (VA) were analysed at 12, 24, 36 and 48 months post-FAc implantation. Data are presented as descriptive statistics with values being reported as mean±SD, median or as a percentage of eyes or patients, unless otherwise stated.

Kaplan-Meier curves were used to assess the mean time (in months) to the second FAc implant, first IOP-lowering medication, first IOP-lowering procedure and to cataract extraction post-treatment with the FAc implant.

In the full group and subgroup analyses, changes in VA were compared with baseline. Changes in VA over time by median duration of cDMO (ie, short-term vs long-term cDMO) were also analysed.

Table 1 Baseline characteristics and indications for use

Characteristics	Patients (N=556)
Male, % (n)	55.8 (310)
Mean age, years±SD	67.4±10.8
Prospective/retrospective data collection, % (n)	51.6/48.4 (287/269)
Lens status, % (n) Pseudophakic Phakic Aphakic Missing	82.3 (572) 16.3 (113) 0.7 (5) 0.7 (5)
Mean duration of follow-up, days±SD (range)	1150.5±357.4 (21–1978)
Mean visual acuity (letters) (SD)	52.2±19.1
Mean IOP (mm Hg)* (SD)	15.4±3.1
Indications	Study eye (N=695), % (n)
Any disease/condition indicated for treatment†	100.0 (695)
Chronic diabetic macular oedema	96.7 (672)
Cystoid macular oedema	5.3 (37)
Macular oedema secondary to neovascular age-related macular degeneration	0.1 (1)
Macular oedema secondary to retinal vein occlusion	1.0 (7)
Posterior uveitis	0.6 (4)
Other	1.9 (13)
No disease/condition indicated	0.7 (5)

Eyes presented as a percentage of the total study eyes and not the sum of all eyes.
*4.2% of eyes had IOP >21 mm Hg at baseline.
†An eye could have multiple disease history terms so these numbers will sum to more than 695.
IOP, intraocular pressure.

Table 2 IOP-related events for all, DMO and non-DMO eyes over the full duration of the study

IOP-related event	All eyes, % (n) (N=695)	DMO eyes, % (n) (N=672)	Non-DMO eyes, % (n) (N=23)
Treatment-emergent IOP-lowering medication	34.5 (240)	35.1 (236)	17.4 (4)
IOP increase of ≥10 mm Hg	15.0 (104)	15.3 (103)	4.3 (1)
IOP increase to >30 mm Hg	14.4 (100)	14.7 (99)	4.3 (1)
IOP-lowering procedures*	5.5 (38)	5.5 (37)	4.3 (1)
► Trabeculoplasty†	1.2 (8)	1.2 (8)	0.0 (0)
► Trabeculectomy‡	1.9 (13)	1.9 (13)	0.0 (0)
► Other procedure‡	2.4 (17)	2.4 (16)	4.3 (1)

*IOP-lowering procedures (non-penetrating and penetrating) included: Ahmed valve, Baerveldt tube, cyclophotocoagulation, canaloplasty, cyclodiode laser, Express Implant, Glaukos iStent, Xen implant, laser trabeculoplasty, trabeculectomy, surgical iridectomy, Molteno implant and viscocanalostomy.
†Non-surgical/penetrating procedures.
‡Surgical procedures.
DMO, diabetic macular oedema; IOP, intraocular pressure; N, total number; n, subgroup number.

For all comparisons, a statistically significant difference was taken as a $p<0.05$. Tests were performed using SAS V.9.4.

RESULTS

Full population

Baseline characteristics

The baseline characteristics of the registry population are presented in table 1. Data are presented from 556 patients (695 eyes) with a mean follow-up period of 1150 days (range, 21–1978 days) or 37.8 months (range, 0.7–65.0 months). Around one half of the data was solely from the prospectively observed group of participants. Six hundred and seventy-two (96.7%) eyes had an indication for DMO.

Prior to implant administration, the population history included records of ocular hypertension (n=27, 3.88%), trabeculoplasty (n=3, 0.43%) and trabeculectomy (n=3, 0.43%). None of the eyes had had an IOP >30 mm Hg at baseline.

Indications for treatment

The main indication for treatment in 96.7% of the cohort was DMO. A small number of eyes had more than one diagnosis. Indications are presented in table 1.

Number of FAc implants

A mean of 1.07 FAc implants per eye were administered over the duration of the study (online supplemental table S2). Most eyes (N=648; 93.2%) received only one implant during the study. A small number of eyes (N=46; 6.6%) received two implants and a single patient (N=1; 0.1%) received three implants. In those that received a second implant, this occurred after 986.1±318.0 days (range 224–1742). The mean follow-up time for the 47 eyes with ≥2 implants was 1387±219.3 days and the mean follow-up time for the 648 eyes with 1 implant was 1142±357.8 days.

IOP-related events

Mean IOP increased slightly during the first 12 months, but then declined to near baseline levels by month 48 (online supplemental figure 1). This was reflected in the absolute IOP changes. Throughout the 48-month period, mean IOP remained within normal limits (<21 mm Hg).

Cumulative IOP-related events for all (N=695), DMO (N=672) and non-DMO (N=23) eyes over the entire follow-up are presented in table 2. Outcomes were similar when comparing all eyes with DMO eyes.

In patients with DMO, 35.1% of eyes (n=236) required IOP-lowering medication (table 2); the mean time to first IOP-lowering medication was 13.3±11.6 months (median, 10.2 months). A rise in pressure of ≥10 mm Hg was observed in 15.3% of eyes (n=103) and a reading of >30 mm Hg recorded in 14.7% of eyes (n=99). A small proportion (4.3% of eyes (n=29)) required surgery to lower IOP (table 2); the mean time to the first procedure (surgery or non-penetrating) was 25.9±10.6 months (median, 23.7 months).

While the safety profiles were similar, the IOP-related adverse events were generally less common in non-DMO eyes compared with DMO eyes (table 2).

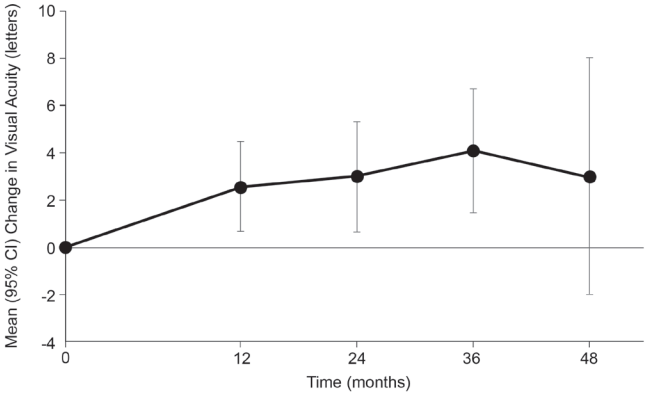
Cataract-related events

From the total population, 113 eyes (16.3% of eyes) were phakic at baseline (table 1). Thirty-three (29.2% of phakic eyes) underwent cataract extraction when the FAc implant was administered. Following therapy with the implant, 73 of the phakic eyes (64.6%) underwent cataract extraction at a mean of 13.6±7.6 months.

VA changes

Following FAc implantation, improved relative to baseline (52.2±19.1 letters) at all timepoints through to month 48 (figure 1). When looking at years 1–4, the highest mean value was recorded at month 36 (57.1±18.9 letters) and statistically significant increases were seen at the 12-month, 24-month and 36-month timepoints (p=0.0022, 0.0040 and 0.0010, respectively).

For other VA outcomes (figure 1), there was improvement in the number of eyes having ≥6/12 VA with the largest change seen at Month 36 (34.8% vs 22.8% at baseline). VA

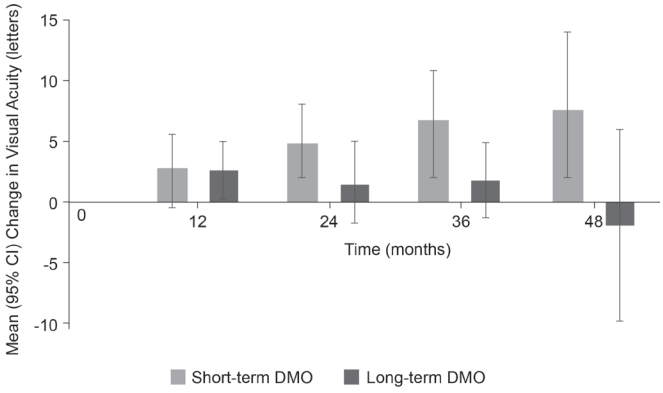


Changes in mean VA from baseline were statistically significant at Month 12 (P=0.0022), Month 24 (P=0.0040): and Month 36 (P=0.0010); not statistically significant at Month 48 (P=0.2248).

VA outcomes	Baseline	Month 12	Month 24	Month 36	Month 48
Observed eyes (N=695), N	443	446	371	306	106
Mean (±SD) VA, letters	52.2±19.1	55.6±17.9	56.6±17.9	57.1±18.9	54.8±18.2
Median VA, letters	55.0	58.5	60.0	60.0	55.0
≥6/12 VA, % (n)	22.8 (101)	29.0 (128)	33.3 (123)	34.8 (106)	27.4 (29)
Stable or improved*, % (n)	N/A	75.1 (220)	73.9 (190)	71.8 (148)	71.0 (49)
≥15 letters gained, % (n)	N/A	17.7 (52)	21.8 (56)	22.3 (46)	18.8 (13)

*Loss of 4 letters to gain in letters
CI, Confidence Interval; FAc, fluocinolone acetonide; SD, standard deviation; VA, visual acuity.

Figure 1 VA changes following treatment with the FAc implant in all eyes. N/A, not available.



For short-term DMO: Mean change in VA from baseline was statistically significant at Month 24 (P=0.0071), Month 36 (P=0.0019) and Month 48 (P=0.0228), and reached near significance at Month 12 (P=0.0879). For long-term DMO: Mean change in VA from baseline was statistically significant at Month 12 (P=0.0288).

VA outcomes	Baseline	Month 12	Month 24	Month 36	Month 48
Observed eyes with short-term DMO (N=319), n	210	211	168	136	47
Mean (±SD) VA, letters	52.9±19.3	56.8±17.3	59.6±16.5	59.8±18.6	57.9±16.5
Observed eyes with long-term DMO (N=322), n	206	204	175	151	49
Mean (±SD) VA, letters	51.6±18.8	54.6±18.6	54.0±18.6	55.5±17.9	50.9±19.9

CI, confidence interval; DMO, diabetic macular oedema; FAc, fluocinolone acetonide; SD, standard deviation; VA, visual acuity.

Figure 2 Mean change in VA following treatment with the FAc implant in eyes with short-term and long-term chronic DMO.

was stabilised (any gain, or any loss ≤4 letters from baseline) or improved in ≥71% of eyes over 48 months. The proportion of eyes achieving a change in VA of ≥15 letters from baseline ranged from 18% to 22% between months 12 and 48.

Prior and supplementary treatments

Most patients had received laser and/or intravitreal treatments prior to FAc implant injection. Intravitreal anti-VEGF was the most common therapy administered (n=548; 78.8% of eyes) (online supplemental table S3); 56.3% of eyes did not receive supplemental therapy following implant injection. The mean times to administration of additional treatments (eg, laser, corticosteroid or anti-VEGF) are shown in online supplemental table S4. When limited to the 36-month period, the largest proportion of additional therapies were given in year 2 (44.1%), followed by year 1 (35.6%) and year 3 (20.3%).

Duration of cDMO

IOP-related events

Over 36 months, eyes with short-term cDMO (participants with a median DMO duration ≤3.6 years) had a marginally lower frequency of IOP-related events compared with eyes with long-term cDMO (median DMO duration >3.6 years; online supplemental table S5).

VA changes by cDMO subgroups

On analysing the change in mean VA by duration of cDMO, eyes in the short-term group experienced statistically significant improvements at all timepoints from month 24 onwards ($p<0.05$; figure 2). In the long-term cDMO group, there is an initial statistically significant rise in mean VA by Month 12, but this gain is subsequently lost through to month 48.

Analyses of proportions of eyes that (1) achieved ≥6/12 vision; (2) experienced maintained or improved VA compared with baseline and (3) achieved an increase in VA of ≥15 letters from baseline showed that all three favourable outcomes occurred in higher proportions in short-term cDMO than in long-term cDMO (table 3).

DISCUSSION

The present analysis from the IRISS is the longest and largest real-world study to date on the outcomes of FAc implantation in European clinical practice. In this cohort of 556 patients deemed as suboptimal responders to previous therapies (most had cDMO), treatment with the FAc implant identified no new or unexpected safety signals, and was associated with clinically meaningfully improvements in VA. These effectiveness benefits were largely achieved with a single implant (93.2% of patients, online supplemental table S2). Visual benefits were particularly evident in eyes with a shorter duration of cDMO prior to treatment, thereby positively tilting the benefit–risk profile when patients are treated earlier with the FAc implant. An observation that is in accord with other real-world findings where the implant is used earlier in the treatment pathway to manage inflammation.[20]

Increased IOP and the development of cataract remain the primary safety signals in patients receiving an intravitreal corticosteroid. These risks are well-documented following therapy with all corticosteroids, including the FAc implant, and routine risk-minimisation activities are mostly sufficient to manage

Table 3 Other visual acuity outcomes following treatment with the FAc implant in with short- and long-term chronic DMO

Observed eyes with short-term DMO, (N=319)	Baseline	Month 12	Month 24	Month 36	Month 48
≥6/12 VA, % (n)	23.8 (50)	30.0 (63)	39.2 (65)	40.4 (55)	34.0 (16)
Stable or improved, % (n)	N/A	69.9 (95)	78.1 (89)	79.3 (73)	82.4 (28)
≥15 letters gained, % (n)	N/A	20.6 (28)	25.4 (29)	28.3 (26)	26.5 (9)
Observed eyes with long-term DMO, (N=322)	**Baseline**	**Month 12**	**Month 24**	**Month 36**	**Month 48**
≥6/12 VA, % (n)	21.4 (44)	29.2 (59)	28.6 (50)	30.5 (46)	22.4 (11)
Stable or improved, % (n)	N/A	78.0 (110)	67.7 (86)	63.5 (66)	58.1 (18)
≥15 letters gained, % (n)	N/A	15.6 (22)	18.1 (23)	17.3 (18)	12.9 (4)

DMO, diabetic macular oedema; FAc, fluocinolone acetonide; N/A, not applicable (cannot be assessed); VA, visual acuity.

them. Furthermore, despite inclusion of patients who would not have fulfilled the eligibility criteria for the FAME pivotal studies (eg, patients with ocular hypertension, an IOP >21 mm Hg, or using IOP-lowering eye-drops[12]), the frequency of safety signals observed in routine clinical care remain consistent with these studies[17] and with those of recent real-world experience.[13 20 21]

Indeed, the IOP-related events observed in this study are consistent with the results of the phase 3 Fluocinolone Acetonide for Diabetic Macular Edema (FAME) studies, in which 38.4% of patients treated with the FAc implant needed IOP-lowering medication and 4.8% required IOP-lowering surgeries.[17] This is consistent with the findings for other intravitreal corticosteroids, including dexamethasone[22] and triamcinolone acetonide (used off-label),[23] supporting the understanding that this is a class effect of intravitreal corticosteroids.

Overall, these findings are encouraging. IOP has been a concern with intravitreal corticosteroids, but the low average increase in IOP seen over the follow-up period, and the manageable numbers of patients requiring IOP-lowering drops, suggest that even in this real-world population, whose characteristics are broader than those included in the pivotal trials, the need for IOP-lowering drops and surgery to manage IOP-lowering is not substantially increased. Because mean IOP remained <21 mm Hg for the entire duration of the study, and few required invasive surgery, our data show that IOP rise can be effectively managed with topical agents. However, quarterly IOP checks and close monitoring (as shown by the time to first IOP-lowering medication after 1 year, and the mean time to IOP-lowering surgery at the end of year 2) are necessary to detect treatment-emergent adverse ocular events and to avoid related complications.[24]

Cataract development, and need for cataract surgery, were the most common treatment-related adverse events in the FAME studies, and have been documented in real-world findings.[13 21 25] The proportion of phakic patients who needed cataract extraction after FAc implantation was lower in the current study than in the FAME studies, which, along with many other study parameters, highlights some significant differences between patients treated in real-world practice versus those in a controlled clinical trial setting. One explanation for this is the high proportion of pseudophakes enrolled into IRISS. Most patients in IRISS were from sites in the UK where use of the FAc implant is restricted to pseudophakic patients as this is a requirement based on the commissioning guidance from the National Institute for Health and Care Excellence (NICE).[26] Furthermore, one report suggests that FAc implantation carried out before cataract surgery, leading to continuous low-dose corticosteroid exposure, may protect from inflammation in the period directly after cataract surgery (although, in the UK, NICE guidelines do not cover this use).[27]

While the key objective was to demonstrate safety, a further important objective was to examine whether early treatment had any additional benefit. Subgroup analysis showed that eyes with a shorter duration of cDMO experienced improvements in mean VA that were statistically significant, as well as clinically relevant (roughly ≥5 letters over an extended time period, figure 2). Further visual benefits were observed in the short-term cDMO group, as they tended to have a higher proportion of eyes gaining ≥15 letters from baseline, attaining driving vision and achieving stable or improved VA. We observed that IOP-related lowering procedures were needed less frequently in eyes with short-term cDMO compared with those with long-term cDMO (2.5% vs 6.2%, respectively; online supplemental table S5), but as this was not a prespecified objective we did not test for significance. Overall, we contend that there is an improved benefit-to-risk profile of treating patients with DMO earlier before chronicity leads to tissue damage and permanent vision loss.

The achievement of UK driving-level vision (≥6/12 Snellen fraction; around 70 EDTRS letters) is an important measure of vision improvement. In IRISS, the percentage of eyes having driving vision increased from just over one-fifth at baseline to over one-third in the 3 years following FAc implantation (figure 1), with most of this improvement occurring in the first year. In the pivotal FAME studies, a comparable proportion of patient eyes achieved a similar outcome. This outcome is likely to have a significant impact on the quality of life of these patients, as at least this level of vision is needed for reading and driving,[4] particularly if the contralateral eye is impaired (ie, worse than a Snellen fraction of 6/12). It is worth noting that, over the follow-up period, 56.3% of eyes required no additional treatments (online supplemental table S4), thus reducing the burden of repeated treatments observed prior to therapy with the FAc implant. Our study provides preliminary evidence that the FAc implant may confer visual benefit in patients without DMO, although numbers of patients treated for indications other than DMO were small.

The key strengths of this study are its pre-specified objectives, the large sample size with extended duration of monitoring without loss to follow-up, the inclusion of participants representing the profile encountered in routine clinical care, and the careful documentation of baseline characteristics and reasons for FAc implant use. In addition, duration of DMO was captured in over 90% of those enrolled.

As with all data collected during routine clinical care, this study has limitations,[13] including the absence of BCVA measurement and a control arm. No imaging data were collected in IRISS, which would provide information on structural changes following treatment with FAc implant in this real-world cohort with cDMO. Lastly, analyses were performed for adverse

events and VA changes that were stratified for patients enrolled prospectively and retrospectively. Over the duration of the study, adverse events and VA outcomes were similar between patients when evaluated by enrolment status.

The IRISS clinical repository represents one of the largest and longest studies to have assessed the safety of the FAc implant in European real-world practice. The study has demonstrated the long-term safety and effectiveness of the FAc implant in patients predominantly treated for cDMO. For both IOP and VA outcomes, this study demonstrates a favourable long-term benefit-to-risk profile when patients with cDMO are treated earlier with the FAc implant.

Collaborators ILUVIEN Registry Safety Study (IRISS) Investigators Group: Robin Hamilton, Usha Chakravarthy, Guzaliya Safiullina, Geeta Menon, Ramesh Sivaraj, Haralabos Eleftheriadis, Simon Taylor, Saad Younis, Konstantinos Balaskas, Vasant Raman, Fahd Quhill, Bushra Mushtaq, Nicholas Glover, Ben Burton, David Steel, Salim Natha, Somnath Banerjee, Deepthi Seneviratne, Nishal Patel, Spyridon Mourtzoukos, Riaz Asaria, Ajay Bhatnagar, Rehna Khan, Ahmed Kamal, Clare Bailey, Louise Downey, Anil Kumar, Gonçalo Almeida, Patrick Richardson, Hadi Zambarakji, Colin Jones, Katrin Lorenz, Karl U. Bartz-Schmidt, Frank Holz, Lars Wagenfeld, Peter Wiedemann, Rainer Guthoff, Manfred Tetz, Gerd U. Auffarth, Christian Ksinsik, Frank Koch, Helmut Sachs, Dirk Sandner, Berthold Seitz, João Figueira, Ângela Carneiro, José Henriques, Rufino Silva, Miguel Amaro, Angelina Meireles, João Paulo Castro Sousa, António Rodrigues, Rui Carvalho.

Contributors All authors made substantial contributions to conception, design, analysis and interpretation of data and contributed to writing the article and approved the current version. The principal investigator (UC) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This was a company-sponsored study funded by Alimera Sciences. Medical writing assistance was provided by Prescript Communications Ltd., Letchworth, England, UK and funded by Alimera Sciences.

Competing interests RK - Reports grants from Chengdu Kanghong; grants, personal fees, and non-financial support from Alimera, Bayer, Novartis and Roche, personal fees and non-financial support from Allergan outside the submitted work. TP—speaker honoraria and advisory board member from Alimera Sciences, Allergan, Bayer, Novartis, Boehringer-Ingelheim and Roche. FK—reports a commercial relationship with Alimera Sciences. SRT—reports financial relationships with GlaxoSmithKline and Novartis, and speaker honoraria, advisory boards and travel grants from Alimera Sciences, Allergan, Bayer, GlaxoSmithKline, Novartis and Santen. JPCdS—reports financial support from Alcon, Alimera Sciences and Novartis. LH—statistical consultant to Genentech, Recens Medical, Polyphotonix, and Alimera Sciences. CB—advisory board member for Alimera Sciences, Bayer Novartis, Roche, Janssen, Boehringer-Ingelheim. UC—a speaker and advisory board member for Alimera Sciences, an advisory board member for Allergan, Bayer, Novartis and Roche, and has received grants from Bayer, Novartis and Roche.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by UK Health and Social Care Research Ethics Committee 2 (14/NI/0002). Portugal Comissão de Ética para a Saúde da AIBILI (N/A), Comissões de Ética para a Saúde Instituto de Retina de Lisboa (N/A), Comissão de Ética para a Investigação Clínica (2014-EO-03), Comissões de Ética para a Saúde Hospital Vila Franca de Xira (N/A), Comissões de Ética para a Saúde Centro Hospitalar do Porto (2015.130 (117-DEFI/107-CES)), Comissões de Ética para a Saúde Centro Hospitalar de Leiria (N/A), Comissões de Ética para a Saúde Centro Hospitalar de Setúbal (0015/2016F), Comissões de Ética para a Saúde Centro Hospitalar de Lisboa Ocidental, Entidades Públicas Empresarial (N/A), Comissão de Ética da Unidade de Saúde Local Matosinhos (36/CE/JAS). Germany Ethikkommission Landesärztekammer Rheinland-Pfalz (837.501.13 (9186-F)), Ethikkommission Universitäts Klinikum Tubingen (088/2014BO2), Ethikkommission Rheinische Friedrich-Wilhelms-Universität (044/14), Ethikkommission der Ärztekammer Hamburg (N/A), Ethik kommission Universität Leipzig (N/A), Ethikkommission Universität Dusseldorf (4585), Ethikkommission der Ärztekammer Berlin (N/A), Ethikkommission Heidelberg (S-058/2014). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data are available on request from Alimera Sciences who are the sponsors of the study

ORCID iDs
Ramin Khoramnia http://orcid.org/0000-0002-6237-7773
Tunde Peto http://orcid.org/0000-0001-6265-0381
Usha Chakravarthy http://orcid.org/0000-0002-2606-3734

REFERENCES

1 Browning DJ, Stewart MW, Lee C. Diabetic macular edema: evidence-based management. *Indian J Ophthalmol* 2018;66:1736–50.
2 Lee R, Wong TY, Sabanayagam C. Epidemiology of diabetic retinopathy, diabetic macular edema and related vision loss. *Eye Vis* 2015;2:17.
3 Gonder JR, Walker VM, Barbeau M, *et al*. Costs and quality of life in diabetic macular edema: Canadian burden of diabetic macular edema observational study (C-REALITY). *J Ophthalmol* 2014;2014:1–9.
4 Singer MA, Wykoff CC, Grewal DS. Effects of long-term DME control with 0.2 µg/day fluocinolone acetonide implant on quality of life: an exploratory analysis from the fame trial. *Ophthalmic Surg Lasers Imaging Retina* 2020;51:658–67.
5 Ferris FL, Patz A. Macular edema. A complication of diabetic retinopathy. *Surv Ophthalmol* 1984;28:452–61.
6 Estebainha R, Goldhardt R, Falcão M. A new approach for diabetic macular edema treatment: review of clinical practice results with 0.19 Mg fluocinolone acetonide intravitreal implant including vitrectomized eyes. *Curr Ophthalmol Rep* 2020;8:1–10.
7 Bailey C, Chakravarthy U, Lotery A, *et al*. Extended real-world experience with the ILUVIEN® (fluocinolone acetonide) implant in the United Kingdom: 3-year results from the Medisoft® audit study. *Eye* 2022;36:1012–8.
8 Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, *et al*. Guidelines for the management of diabetic macular edema by the European society of retina specialists (EURETINA). *Ophthalmologica* 2017;237:185–222.
9 Udaondo P, Hervas-Ontiveros A, Rosemblatt A, *et al*. Impact of different clinical baseline characteristics on intravitreal dexamethasone implant Ozurdex® outcomes. *Clin Ophthalmol15* 2021;15:4153–62.
10 Rübsam A, Parikh S, Fort P. Role of inflammation in diabetic retinopathy. *Int J Mol Sci* 2018;19:942.
11 Sohn HJ, Han DH, Kim IT, *et al*. Changes in aqueous concentrations of various cytokines after intravitreal triamcinolone versus bevacizumab for diabetic macular edema. *Am J Ophthalmol* 2011;152:686–94.
12 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;120:583–7.
13 Chakravarthy U, Taylor SR, Koch FHJ, *et al*. Changes in intraocular pressure after intravitreal fluocinolone acetonide (ILUVIEN): real-world experience in three European countries. *Br J Ophthalmol* 2019;103:1072–7.
14 Hikal M, Celik N, Auffarth GU, *et al*. Intravitreal 0.19 Mg fluocinolone acetonide implant in non-infectious uveitis. *J Clin Med* 2021;10. doi:10.3390/jcm10173966. [Epub ahead of print: 01 09 2021].
15 Bodaghi B, Nguyen QD, Jaffe G, *et al*. Preventing relapse in non-infectious uveitis affecting the posterior segment of the eye – evaluating the 0.2 µg/day fluocinolone acetonide intravitreal implant (ILUVIEN®). *J Ophthalmic Inflamm Infect* 2020;10.
16 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.
17 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;119:2125–32.
18 Fallico M, Maugeri A, Lotery A, *et al*. Fluocinolone acetonide vitreous insert for chronic diabetic macular oedema: a systematic review with meta-analysis of real-world experience. *Sci Rep* 2021;11:4800.
19 Kodjikian L, Baillif S, Creuzot-Garcher C, *et al*. Real-world efficacy and safety of fluocinolone acetonide implant for diabetic macular edema: a systematic review. *Pharmaceutics* 2021;13:72
20 Singer MA, Sheth V, Mansour SE, *et al*. Three-year safety and efficacy of the 0.19-mg fluocinolone acetonide intravitreal implant for diabetic macular edema: the paladin study. *Ophthalmology* 2022;129:605–13.

21 Augustin AJ, Bopp S, Fechner M, *et al*. Three-year results from the Retro-IDEAL study: real-world data from diabetic macular edema (DME) patients treated with ILUVIEN ® (0.19 mg fluocinolone acetonide implant). *Eur J Ophthalmol* 2020;30:382–91.
22 Boyer DS, Yoon YH, Belfort R, *et al*. Three-year, randomized, sham-controlled trial of dexamethasone intravitreal implant in patients with diabetic macular edema. *Ophthalmology* 2014;121:1904–14.
23 Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology* 2008;115:1447–59.
24 Goñi FJ, Stalmans I, Denis P, *et al*. Elevated intraocular pressure after intravitreal steroid injection in diabetic macular edema: monitoring and management. *Ophthalmol Ther* 2016;5:47–61.
25 Carneiro A, Meireles A, Castro Sousa JP, Sousa C, *et al*. Clinical impact of the 0.2 µg/day fluocinolone acetonide intravitreal implant: outcomes from the ILUVIEN ® clinical evidence study in Portugal. *Ther Adv Ophthalmol* 2020;12:251584142091776.
26 NICE, Technology appraisal guidance [TA301]. Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy, (2013). Available: https://www.nice.org.uk/guidance/ta301 [Accessed *27* Nov 2013].
27 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;29:1173–80.