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A Sponsored Supplement From

the Ophthalmologist

A New Step Forward

Diabetic macular edema (DME) is one of the main causes of blindness globally. To address this challenge, we must have access to the best tools available – and match them to appropriate patients, explains Francesco Bandello. One such tool is ILUVIEN (fluocinolone acetonide intravitreal implant), indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies (i.e. DME that persists or recurs despite treatment). A recent conference in Rome (ILUVIEN Medical Expert User Group Meeting - an Alimera Sciences promotional meeting) on 17th Nov 2018 gathered international experts to discuss best practice and real-world experience with this sustained-release steroid implant.

Presenters:

Professor Francesco Bandello, Dept Ophthalmology, University Vita-Salute, Milan, Italy
Dr Clare Bailey, Consultant Ophthalmologist, Bristol Eye Hospital, UK
Professor Mario Stirpe, President GB Bietti Foundation for Study and Research in Ophthalmology, Rome, Italy
Professor Simona Frontoni, Dept. Systems Medicine, University Tor Vergata, Rome, Italy
Professor Manuel Falcao, University of Porto Hospital Sao Joao, Portugal.
Dr Javier Zarranz-Ventura, Institut Clinic d'Oftalmologia, Hospital Clinic, Barcelona, Spain
Dr Steve Morris, VP, Medical Director, Head of Medical Affairs, Alimera Sciences, UK
Professor Albert Augustin, Dept Ophthalmology, Karlsruhe, Germany
Dr Fahd Quhill, Consultant Ophhalmologist, Royal Hallamshire Hospital, Sheffield, UK
Antonio Cutino, VP Medical Communications, Alimera Sciences, USA

Note: Please find prescribing information on the last page of this supplement.

Introduction

Francesco Bandello

The ongoing and worsening epidemic of diabetes is accompanied by an increasing frequency of DME – and the consequences of untreated DME are tragic. But the growth in patient numbers doesn't tell the whole story; indeed, we have cause for optimism, as our intervention options are more numerous and effective than ever before. And this raises another problem: how do we choose from available treatments? Not all patients are the same; we must provide each with the therapy most appropriate to their circumstances. It is clear that ILUVIEN (fluocinolone acetonide intravitreal implant) has a key place in the management of DME – but what patients are best-suited for this product, and how should we employ it? Can we even be sure that results from ILUVIEN randomized clinical trials (RCTs) are relevant to real-world clinical situations? We all know of the difficulty in replicating anti-VEGF RCT results in actual clinical practice. In this supplement, we address these issues, and provide timely accounts of real-world, expert experience. Stepping forward with ILUVIEN is much easier when trailblazers show you the right path.

Part I – Context

Diabetic patients: prevalence and profile

Simona Frontoni

Diabetes is among the most devastating causes of morbidity and mortality (see Infographic) (1, 2). More worryingly, the positive correlation between diabetes frequency and income suggests that the issue will get worse as countries become wealthier and more westernized. However, the pattern is not uniform: Italy, for example, has a significantly higher prevalence of diabetic eye disease and proliferative diabetic retinopathy than many other European countries (Figure 1).

Furthermore, a significant proportion of patients are undiagnosed; indeed, their condition may remain unrecognized until ophthalmological examinations reveal recurrent or persistent retinal disease. The role of the ophthalmologist in diabetes management, however, goes beyond diagnostics – diabetes therapy and ocular outcomes are intimately connected. The standard approach to diabetes – reduction of blood glucose – ameliorates many chronic diabetes complications, such as nephropathy. By contrast, intensive glycaemia control does not always benefit diabetic retinopathy (DR), and may initially worsen the condition (3).

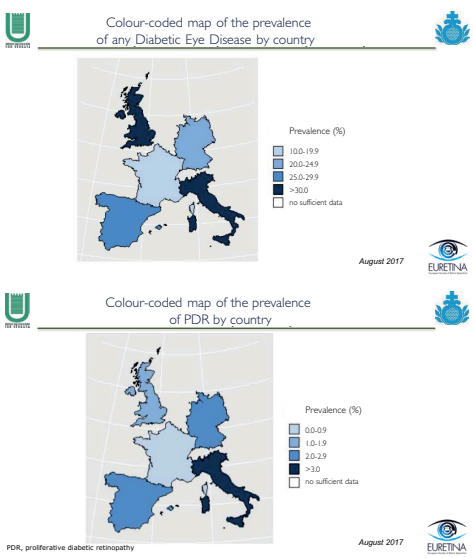


Figure 1. In Italy, the prevalence of diabetic eye disease is about double that of some other EU countries.

Potential explanations for this include drug side effects: although newer GLP-1R agonist drugs as a whole have no effect on DR, some older drugs – which remain broadly used – worsen DR (4, 5). The recently reported worsening in DR with semaglutide (6), however, is likely related to the rapid improvement in systemic glucose control, obtained with semaglutide.

Our own work indicates that glycaemic variability correlates with disease severity (7). This suggests transient hyperglycaemia may be more important than chronic hyperglycaemia in DR progression. Blood pressure is also important: intensive control of hypertension reduces microvascular events by 37 percent, and helps stabilize DR and preserve vision (8).

The multifactorial nature of DR suggests treatment should involve stringent control of the range of disease drivers. This ideal requires a holistic approach combining physicians and support networks – and requires the ophthalmologist to play an integral role. At present, only 8.6 percent of Italian diabetics are evaluated for DR (9) – to change that, diabetologists and ophthalmologists must work together!

Part II – The Current DME Treatment Paradigm

From clinical trials to clinical practice

Manuel Falcao

In the last ten years, DME management has evolved from laser treatments to anti-VEGF injections and steroid implants. For 99 percent of physicians, first-line therapy is intravitreal anti-VEGF (10), which is superior to the previous standard of care (macular laser treatment).

However, anti-VEGF drugs – despite a mean two-line VA improvement at one year (11) – are not perfect. The Protocol I study indicates that ~40 percent of patients are non-responders to ranibizumab: indeed, these can be detected – and outcomes predicted – after as few as three months of treatment (three injections) (Figure 2).

Furthermore, Protocol T indicates that between 30 and 66 percent of patients (Figure 3) require additional therapy after treatment of the eye with anti-VEGF (16). Even when patients receive a good number of injections and respond well, most (75 percent) continue to require close monitoring and treatment to maintain their visual acuity gains (15). In many practices, this is not always possible.

Furthermore, there is a discrepancy between anti-VEGF RCT results and real-world outcomes, which arises from the direct correlation between injections and visual acuity gain (12). There is an approximate 1:1 correspondence between injections received and letters gained in the first year of treatment – the more injections, the better the outcome. In RCTs, patients receive seven to twelve injections in year one, and the visual outcomes are correspondingly good. But in clinical practice, patients receive only about four injections – and about half receive less than three injections – in the first year (13). Consequently, real-world visual gains are lower than RCT outcomes: four letters rather than two lines (14). In brief, the real world does not reflect RCTs (Figure 4)!

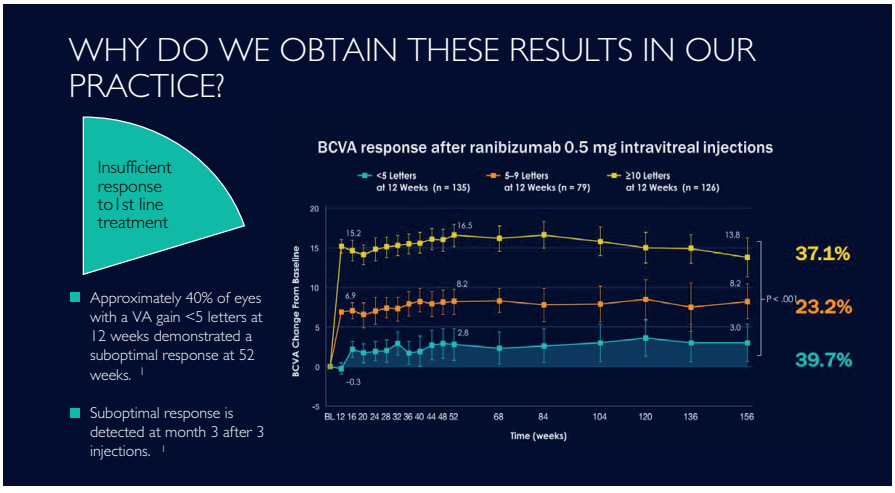


Figure 2. Non-responders are identifiable as early as three months from initiation of anti-VEGF therapy (17).

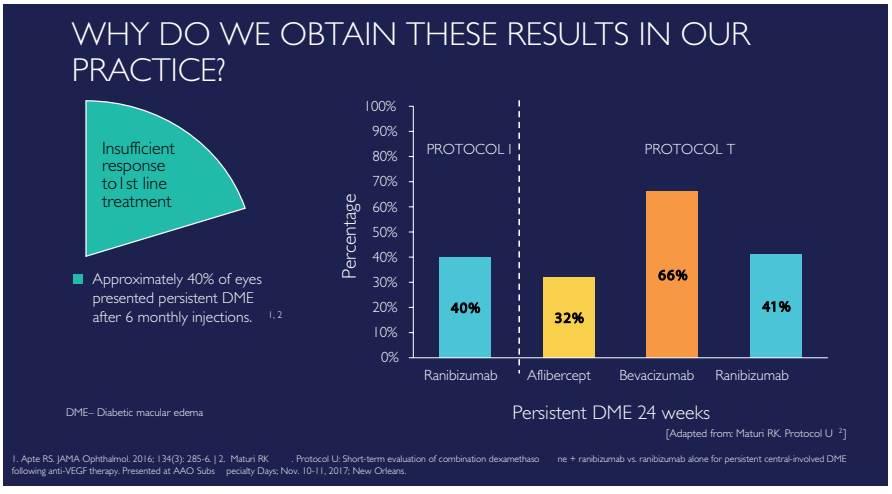


Figure 3. Suboptimal response after administration of various anti-VEGF products (16).

Why this discrepancy? One reason is related to an intensive injection regime of anti-VEGF treatments (repeated intravitreal injections) coupled with its short-term effect (one to two months). Put simply, the heavy treatment burden results in high levels of treatment non-adherence, and it is reported that patients' most desired improvement to the treatment regime is to have fewer injections and fewer appointments (18).

Another reason may be that RCT and real-world populations are different; for example, patients with significant hypertension, high HbA1C – both of which can affect long-term therapeutic responses – and very high or very low visual acuity are often excluded from RCTs. In the real world, we have to treat these people, too.

What should clinicians do when faced with a patient suboptimally responding to anti-VEGF? The first reaction is often to try a different anti-VEGF therapy – but all current anti-VEGF therapies have the similar administration regimes, and therefore the same adherence issues. More seriously, persisting with anti-VEGF does not account for the underlying evolution of DME from a VEGF-driven condition to an inflammation-

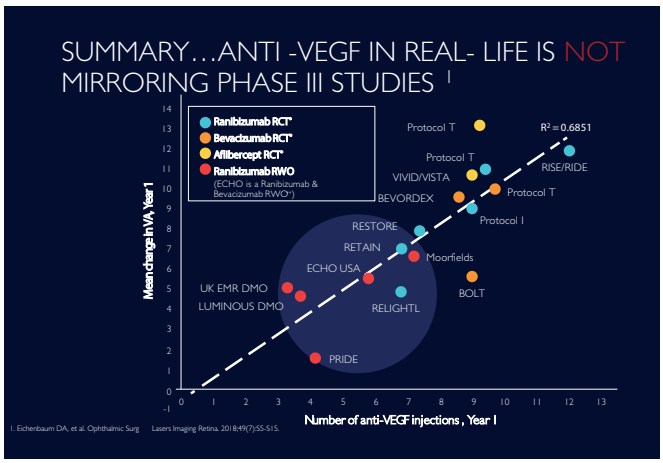


Figure 4. Visual outcomes correlate with number of anti-VEGF injections, and fewer injections are received by real-world patients than by RCT patients (12).

Figure 5. VA and central retinal thickness improve after ILUVIEN implantation (20).

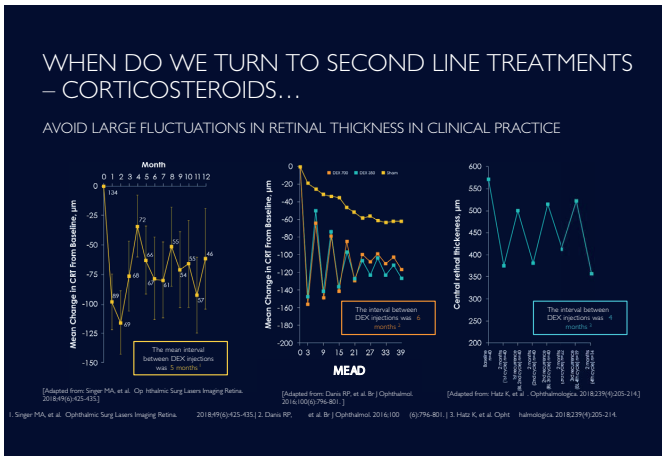


Figure 6. Dexamethasone implants have a short-term effect, resulting in a see-saw pattern of intermittent improvement and regression (21, 22, 23).

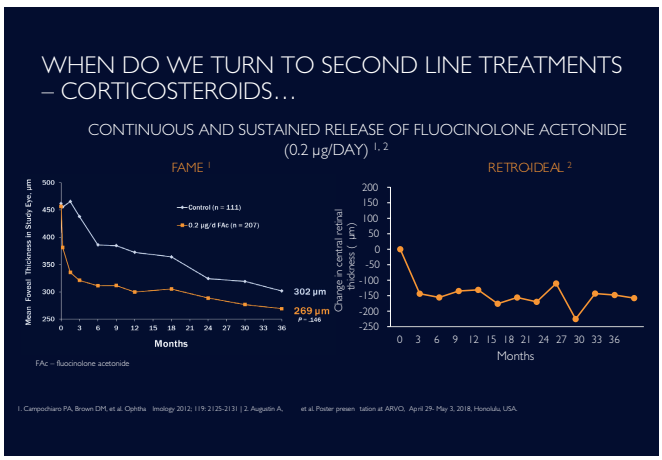


Figure 7. ILUVIEN implantation provides stable and predictable macular thickness outcomes for up to 3 years post-implantation (24).

driven condition. There are alternatives to anti-VEGF therapies available for these kinds of patients – in particular, steroid implants. Overall, patients who suboptimally respond to prior therapies, and who switch to steroid implants, exhibit improved visual acuity (VA) and reduced macular thickness. This holds for both dexamethasone (19) and ILUVIEN implants (Figure 5).

In practice, the relatively short duration of the dexamethasone implant tends to result in intermittent improvement, such that the edema returns before an additional implantation is performed – hence the characteristic see-saw pattern of macular swelling over time, with the corresponding potential risk of additional retinal damage due to recurrence of edema. (Figure 6 (21, 22, 23)).

By contrast, the three-year drug release capability of ILUVIEN maintains macular thickness at around 300 microns throughout this period (Figure 7). This is attributed to the implant design (see "ILUVIEN: The Backstory," below), which permits continuous microdosing of active ingredient, in the vicinity of the target tissue, for up to 3 years.

In conclusion, anti-VEGF RCT results are difficult to replicate in real-world situations. Some patients respond suboptimally to anti-VEGF; switching to steroids at the first sign of anti-VEGF non-response – visible after as little as three months. Sustained-release steroid implants offer low-burden administration regimes and continuous microdosing, resulting in non-fluctuating normalization of macular thickness; this avoids the sawtooth pattern of macular thickness over time seen with shorter-duration therapies (Figure 6). Furthermore, ILUVIEN is used in clinical practice just as in RCTs – as a single administration that has been designed to deliver a daily low dose of fluocinolone acetonide for up to three years. Thus, ILUVIEN outcomes are not dependent on numbers of injections – only injection is required per three-year period – and we should therefore expect ILUVIEN real-world outcomes to closely reflect RCT outcomes, in contrast to the situation with anti-VEGF.

Part III – DME: Multifactorial Pathogenesis and Treatment Options

Javier Zarranz-Ventura

DME pathogenesis is not a steady-state phenomenon; it evolves as the disease progresses over time. In particular, although VEGF levels remain constant (i.e., their relative importance decreases over time: Figure 8), the inflammatory component of DME becomes increasingly important.

Inflammation in DME involves a multiplicity of processes including: breakdown of the blood-retina barrier; microvascular activation; and Muller cell dysfunction. These are driven by many inflammatory factors. The relative contribution of these factors changes over time, and varies with DME heterogeneity (different cytokines may drive focal DME and diffused DME, respectively (28). Also, OCT-measured macular volume in DME correlates with cytokine levels (29).

Today, we have two steroid implant options: 0.7 mg dexamethasone and ILUVIEN. One key difference between the two is the continuous microdosing – with zero-order kinetics over a three-year period – provided by a single ILUVIEN administration (Figure 9).

Unfortunately, these products have not been tested in head-to-head studies. However, we have investigated their comparative efficacy using an indirect method (32). Briefly, we applied an area-under-the-curve (AUC) analysis to the MEAD and FAME clinical trial data (Sidebar). This approach, based on VA measurements over a three-year period (see Figure 10), revealed significant AUC differences that favored ILUVIEN.

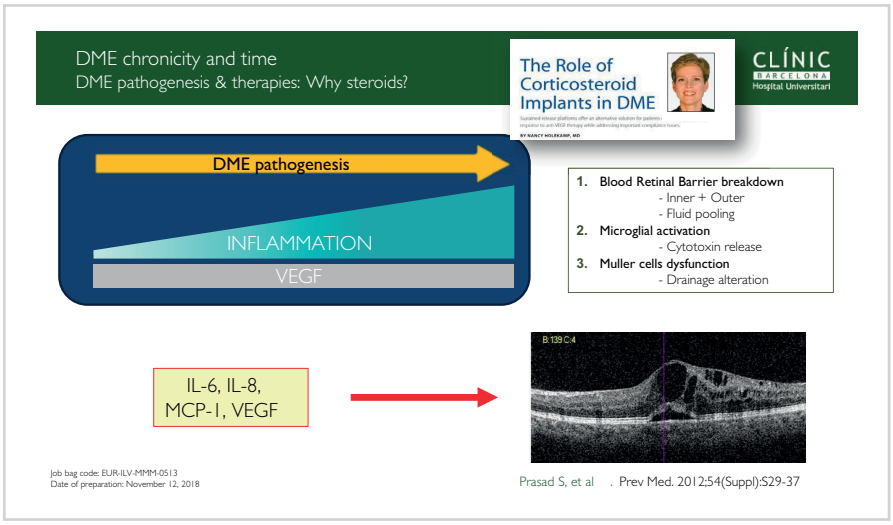


Figure 8. The relative contribution of inflammation to DME pathogenesis increases over time (27).

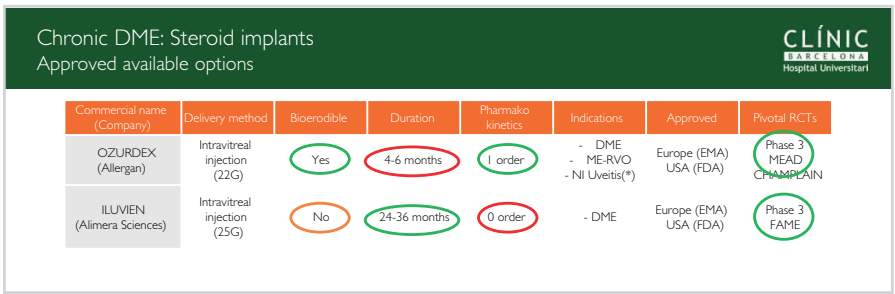


Figure 9. Dexamethasone implant versus ILUVIEN.

In conclusion, we should remember that persistent or recurrent DME is common after anti-VEGF therapy – the incidence is reported to be as much as 40 percent in Protocol I over a 3 year period. In particular, inflammatory drivers start to dominate mechanisms of DME progression, suggesting that patients who respond suboptimally to anti-VEGF should be y switched to steroid if they are to achieve effective edema control and hence optimal VA outcomes. Sustained control of cytokine levels over periods of years seems likely to require an implant which releases drug at effective levels over an equivalent period; indeed, our indirect comparison of FAME and MEAD, using the AUC methodology, indicates that FAME (ILUVIEN) is associated with significantly better VA gains than MEAD (dexamethasone) over a three year period (32).

"In real life conditions, we cannot sustain monthly treatment schedules in the current and worsening diabetes epidemic – we need longer-lasting drugs." – Javier Zarranz-Ventura

Part IV: Times have changed, patients have changed

Steve Morris

The FAME studies took place in 2005-2009; today's patients are different. In particular, they tend to be older, to have had longer duration of DME, and – prior to the approval of steroids for DME – they will have had several prior intravitreal therapies (mainly anti-VEGF) over a highly variable period. FAME patients, however, would have received only macular laser treatments, not anti-VEGF (which only became available from 2012 in Europe).

Real-world data has provided us with a better and broader appreciation of the role of inflammation in DME pathogenesis: the disease is not driven by VEGF alone, and should not always be treated with anti-VEGF alone. ILUVIEN was approved for use in Europe in 2012; since FAME, over 18,000 patients have received the implant to date. Three-year data from real-world practices are now available – so what have we learnt about ILUVIEN's performance in today's patients?

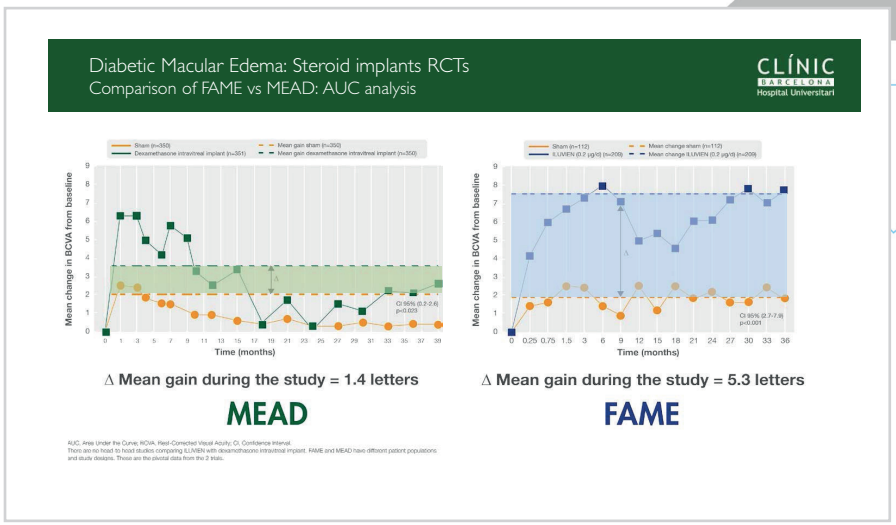


Figure 10. Comparison of FAME and MEAD by AUC analysis. The ILUVIEN visual gains (blue: FAME study) are significantly greater than the Dexamethasone visual gains (green: MEAD study), indicating the benefit of microdosing over a three-year period.

Regarding safety, the post-authorization safety study, IRISS, is assessing five-year ILUVIEN safety outcomes in centers throughout Europe. This is complemented by our clinical audits of patient electronic medical records, and by the periodic safety update reports (PSUR) submitted to the EMA as part of Alimera Sciences pharmacovigilance process and intended to monitor the risk-benefit balance of medicinal products. Regarding effectiveness, there are a number of studies that provide critical insights. These include the IRISS study (563 patients, 593 eyes), the UK-specific data from the UK Medisoft audit (85 patients, 93 eyes), the ICE-UK study (208 eyes) and the German Retro-IDEAL study (76 patients, 94 eyes: the largest post-FAME ILUVIEN patient cohort yet). There are also US data from the USER (130 patients, 160 eyes) and PALADIN (153 patients, 201 eyes) studies. The picture of ILUVIEN's real-world, post-FAME safety and effectiveness is now becoming clearer, and will be clearer still as additional patients complete the three-year post-ILUVIEN follow-up.

ILUVIEN: the Backstory

- **1980s** – Steroids known to be effective in treatment of inflammatory conditions
- **1980s/1990**s – Academia works on sustained-release steroid formulations (33, 34).
- Clear objectives behind ILUVIEN concept:
  - Sustained release, near zero-order kinetics: extend DME treatment intervals, minimize treatment burden for both ophthalmologists and patients
  - Lipophilic chemistry and localized administration route: minimize drug use and systemic exposure (decrease side-effects)
- **1990s** – Patent filed (see Figures 11 and 12 for key features)
- **Mid-1990s** – US patent rights licensed to pSivida Inc. (now EyePoint Inc.); non-US patent rights licensed to Alimera Sciences
- **2005-2009** – key clinical trials (FAME studies) examined drug levels up to 36 months after implantation (35).
- **2012:** EU approval
- **2013:** EU market launch
- **2014:** US market approval
- **2017:** First 36-month post-market data
- **2018:** >18,000 patients treated with ILUVIEN

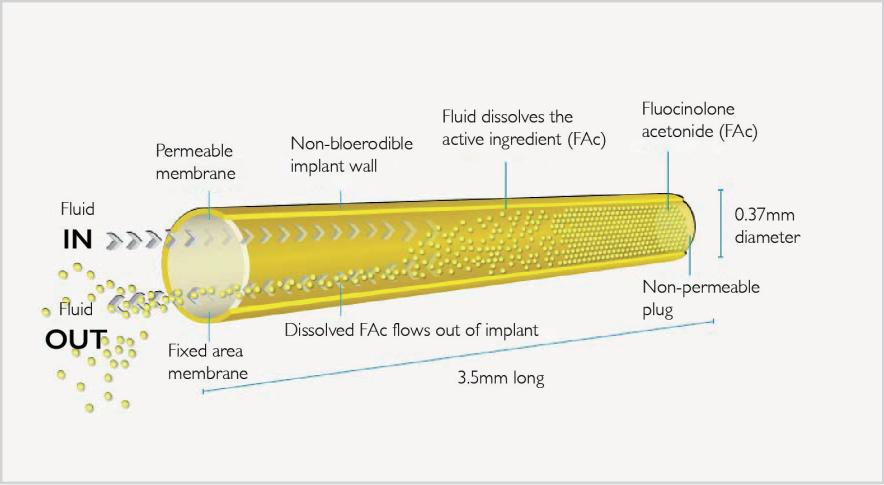


Figure 11. ILUVIEN device architecture. The fixed-lumen tube capped at one end permits zero-order drug release such that low, localized drug levels are continually maintained.

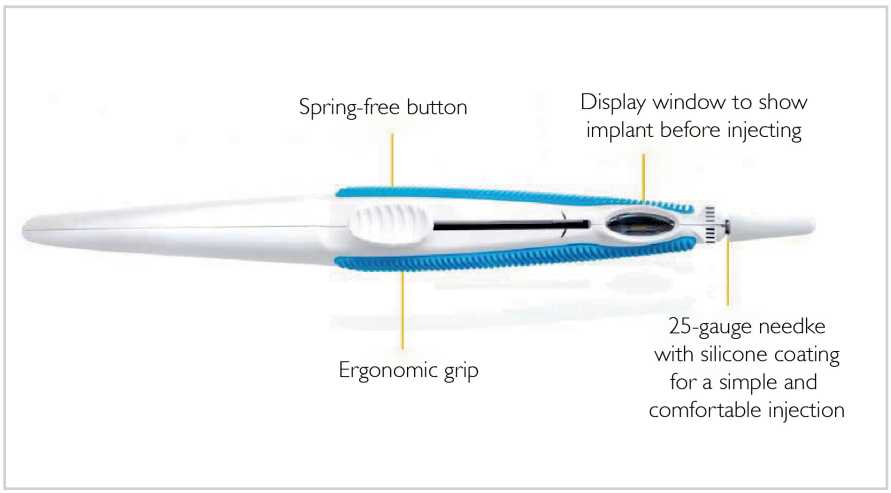


Figure 12. ILUVIEN device applicator has been custom-designed for ILUVIEN placement in the posterior of the eye.

Part V: ILUVIEN Unleashed

The Retro-IDEAL study

Albert Augustin

We are familiar with the correlation between glycaemia and retinal inflammation (38), and between retinal inflammation and progression of DR and DME (39). Steroid-mediated control of inflammation should benefit DME – but how do steroid implants perform in the real world? Retro-IDEAL (Sidebar) examined this issue.

Retro-IDEAL conclusions:

- ILUVIEN effectively resolves edema over 36-month periods.
- No additional safety signals were seen compared to the FAME RCTs. .
- Supplementary treatments were needed in ~31 percent of cases.

Retro-IDEAL study population (40)

- Retrospective study of ILUVIEN-treated DME patients
- 16 sites in Germany
- 63 patients, 81 eyes (diagnosed with DME)
- Mean age 68 ± 10.4 years
- Type 1 diabetes: 27.2 percent, type 2: 70.4 percent
- Diabetes duration ~20 years, DME duration ~4 years
- pre-ILUVIEN
- Preceding treatments (in the 12 months pre-FAc implantation): 92.5 percent laser, 97.5 percent ranibizumab injection.
- All patients had insufficient response to previous treatment, and 32 percent had no visual acuity improvement from previous therapy

Retro-IDEAL Outcomes

Safety

- IOP: controlled in 100 percent of patients: 3/81 eyes required surgery (comparable to FAME)
- Cataract: 17 phakic eyes needed surgery (comparable to FAME)

Effectiveness

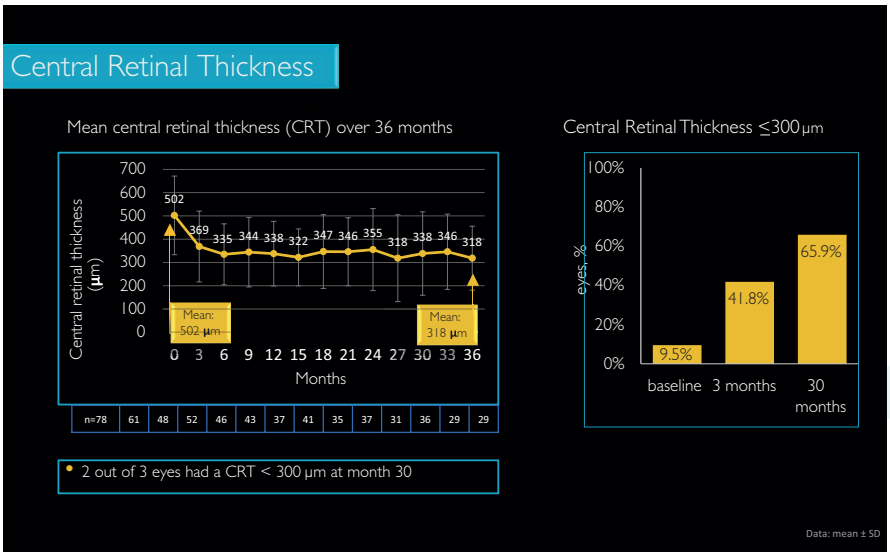
- Function: Mean visual acuity increase = +5.4 letters at month 30 (similar gains reported at months 12 and 24, i.e. improvements are sustained to month 30), and 2.7 letters at month 36

Supplementary treatment:

- 69.1 percent of patients required no additional treatment

Eyes, %	Retro-IDEAL (n=81)	FAME (0.2 mcg/day; n=375)
IOP-elevation ≥30 mmHg	12.3%	18.4%-
IOP-lowering meds after ILUVIEN	27.2%	38.4%
Cataract extraction	88.2%	80%
Visual acuity, letters	+2.7#	+5.3

Figure 13. Comparing retro-IDEAL with FAME. Retro-IDEAL revealed no additional safety features; #, VA results similar to FAME at month 30, with differences potentially explicable by variation between patient populations (40).



Sheffield Centre audit of ILUVIEN – European real-world experience

Fahd Quhill

Diseases driven by multiple mediators may need therapies with multiple actions; inflammation-driven DME cannot be managed with anti-VEGF alone. ILUVIEN looks like a rational choice: how does it perform in clinical practice?

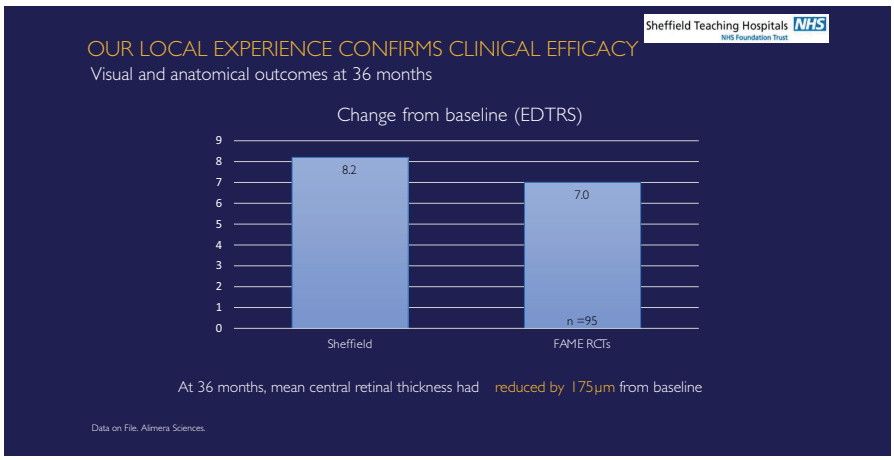


Figure 14. Patient Record Review: ILUVIEN visual and anatomical outcomes at 36 months.

Patient Record Review: study population

- Retrospective review of electronic patient records
- 22 patients (26 consecutive eyes) from first cohort treated for DME in Sheffield, UK
- 36-month follow-up
- Mean age ~68y
- Mean duration diabetes: ~20y
- 100 percent pseudophakic
- VA, ETDRS letters: ~40
- Previous treatments (macular laser, anti-VEGF, triamcilinone injections) ineffective

Patient Record Review: study outcomes

Safety

- IOP: All effects manageable; 30-40 percent patients required IOP-lowering medication, one required surgery

Effectiveness

- VA: Mean VA improvement: eight letters (similar to FAME pseudophakic results); 34 percent patients improved by 15 letters
- Anatomy: CRT decreased by mean of 175 microns

Supplementary treatments

- 60-70 percent patients required no additional therapies.

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UK MEDISOFT audit study of ILUVIEN

Fahd Quhill

To assess real-world ILUVIEN outcomes in patients with persistent or recurrent DME, we undertook an audit of UK electronic medical records in 14 UK NHS centers, using the Medisoft audit tool. Unlike FAME, the study included patients with very poor and relatively good vision. ILUVIEN effectively resolves edema over 36-month periods.

Audit conclusions

- ILUVIEN real-world UK outcomes are generally good (41), and reflect the FAME study results (Figures 15, 16).
- Tangible effect on quality of life – over 31 percent of patients could resume driving!

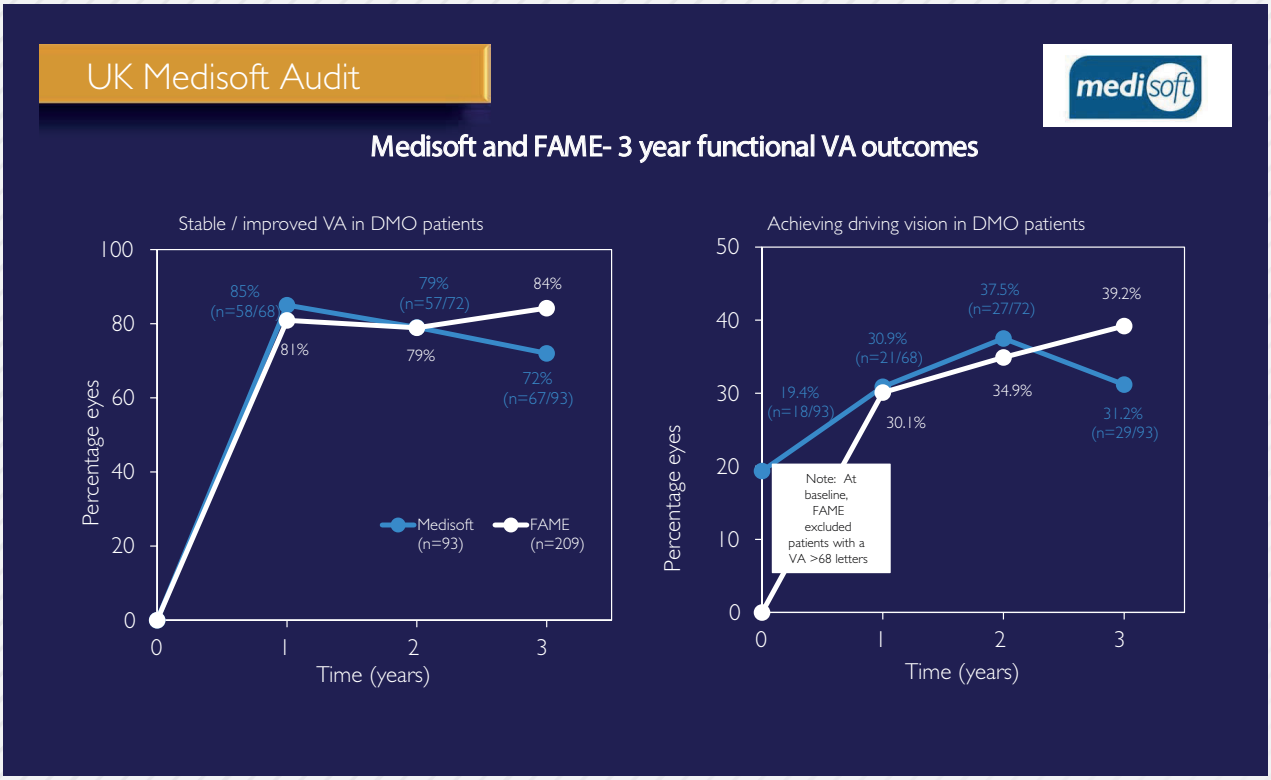

Figure 15. Three-year IOP changes – Medisoft and FAME studies.

UK MEDISOFT study: baseline

- 85 patients, 93 eyes
- Mean age ~66 y
- ~84 percent pseudophakic
- Previous therapy 87 percent (mainly anti-VEGF)
- Baseline VA ~54 letters), IOP 16 mmHg, CRT ~490 microns

UK MEDISOFT audit study: outcomes

Safety

- IOP: ~32 percent showed increase of >=10 mmHg; ~31 percent required IOP-lowering medication, 1.1 percent (1/93) required trabeculoplasty, and 3.3 percent (3/93) required IOP-lowering surgery

Effectiveness

- VA: 72 percent stable / improved

ICE-UK study

Fahd Quhill

The ICE-UK retrospective study was undertaken to investigate outcomes when ILUVIEN is used as a second-line agent (42).

ICE-UK study: fellow eye comparison (43)

- 12 months prior: VA declined in study eye, despite receiving multiple DME therapies, and remained stable in fellow eye
- 12 months post: Study eye VA and CRT improved markedly, with CRT values being similar to those of the fellow eye; during this period, there was a marked decline in the use of other DME therapies. In the fellow eye, however, VA continued to decline.
- Conclude: Patients' vision declines pre-ILUVIEN but improves over the 12-month post-implantation period.
- CRT significantly improves after implantation.

IRISS study

Fahd Quhill

The ILUVIEN registry safety study, IRISS, has released interim data for 593 eyes (563 patients) (44).

IRISS Conclusions

- No additional safety concerns compared with FAME
- VA improvements are similar to FAME and persist over three years
- In patients with persistent or recurrent DME, those with shorter-standing DME had better outcomes than patients with longer-standing DME (Figure 16).

Figure 16. Mean visual acuity and change in acuity over time. With earlier administration of ILUVIEN, better VA outcomes were observed in the short-standing DME group.

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ICE-UK National Audit: study

- Retrospective observational study at 13 UK hospitals
- 208 treated eyes
- One-year follow-up and one-year pre-ILUVIEN history

Outcomes

Safety

- IOP: managed effectively by medication (only 2 required surgery (42))

Effectiveness

- VA: Median VA was 52 letters at implant, improving to 55.0 letters at 12 months post-implant. 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 (42).
- Anatomy: CRT improved over 12 months post-ILUVIEN

Supplementary therapies

- Additional DME treatments were used in 30 percent of treated eyes during the 12-month follow-up period; 20 percent of patients required anti-VEGF injections after ILUVIEN, compared with 82 percent pre-implantation

IRISS study population

- 31 sites in UK, 11 in Germany, five in Portugal
- 593 eyes
- Mean age: 67.5 years
- 82.6 percent pseudophakic
- Mean IOP 15.6 mmHg (5.2. percent patients had IOP >21 mmHg – an exclusion criterion in the FAME studies)
- Mean DME duration 4.5 years
- Previous treatment: 99 percent (mostly anti-VEGF)

Outcomes:

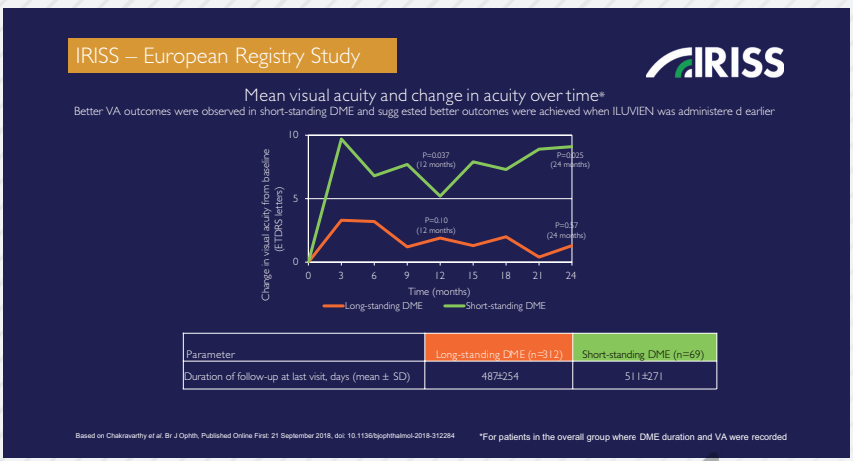
Effectiveness

- VA: Gain of 1.9 letters in longer-standing DME and 7.2 letters in short-standing DME

Safety

- IOP: IOP-lowering medication required by up to 23.7 percent of patients (this is the value in the long-standing DME group, and is the higher value of the two groups); very low incidence of surgery

Supplementary treatments: ~70 percent patients required no additional therapy after ILUVIEN



US real-world studies: PALADIN and USER

Antonio Cutino

The US ILUVIEN label does not require patients to have insufficient response to available therapies; the idea is that prior steroid outcomes will help us select patients likely to respond well to ILUVIEN. Has this worked in practice? The USER retrospective chart review and PALADIN (Phase 4 IOP Signals Associated with ILUVIEN) prospective Phase IV study address this question.

Overall conclusions

We have gathered real-world data from different studies in many different countries; what have we learnt? Firstly, it is clear that clinical practice outcomes reflect those of the FAME study. This is despite real-world patients differing significantly from FAME patients – they are older, have longer-duration DME, and have had many more prior DME therapies than the patients in the FAME studies.

Thus, real-world data from over 18,000 patients show no additional safety concerns as compared with the FAME trial; when increases in IOP are seen (as in IRISS, for example), they are small and similar to those seen in studies of other steroid treatments. In fact, the cumulative rate of non-pharmacological IOP interventions, such as incisional surgery and trabeculoplasty, is only 0.6 percent. Even if we assume a degree of under-reporting, this is a significant finding and is, at the least, in line with the FAME trial.

Similarly, efficacy results from the FAME trial are mirrored by real-world data, both in terms of visual acuity improvements and reductions in CRT. Especially gratifying are the reports of significant numbers of patients maintaining or regaining VA levels sufficient for driving.

However, the real-world data has also generated new insights: sub-group analysis indicates patients with short-standing DME achieve better VA outcomes, potentially with fewer IOP-related adverse events. This may be because eyes with longer-standing disease accumulate more damage during treatment with ineffective drugs. Similarly, US data show that the subgroup of patients with better baseline VA enjoy a reduced post-ILUVIEN treatment burden compared with those with worse baseline vision. The FAME trial did not reveal these clinical insights, because it focused on a single objective – to examine outcomes in patients with persistent or recurrent DME. By contrast, real-world data are providing new clinical insights that will help physicians to better manage their patients.

The implications? Clearly, the sum of evidence suggests that switching suboptimally responsive patients from anti-VEGF to ILUVIEN should be done as early as possible. Fortunately, this will be facilitated by the ability to identify anti-VEGF non-responders within three months of treatment initiation. At the same time, many patients will welcome moving from monthly intravitreal injections to three-yearly implantations.

PALADIN: Study and 12-month outcomes

- 41 US study locations
- 153 patients, 201 eyes
- Eligibility per US label indicated 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.
- Objective: study IOP data at three years post-ILUVIEN (2020)

Safety
- IOP: No significant change in mean IOP post-ILUVIEN

Effectiveness
- VA: Stabilized in patients with better vision (-~3 letters); improved (+~7 letters) in patients with poorer vision
- CRT: Reduced from ~400 microns to 344 microns at one year (doubled the percentage of patients with retinal thickness of 300 microns or less)

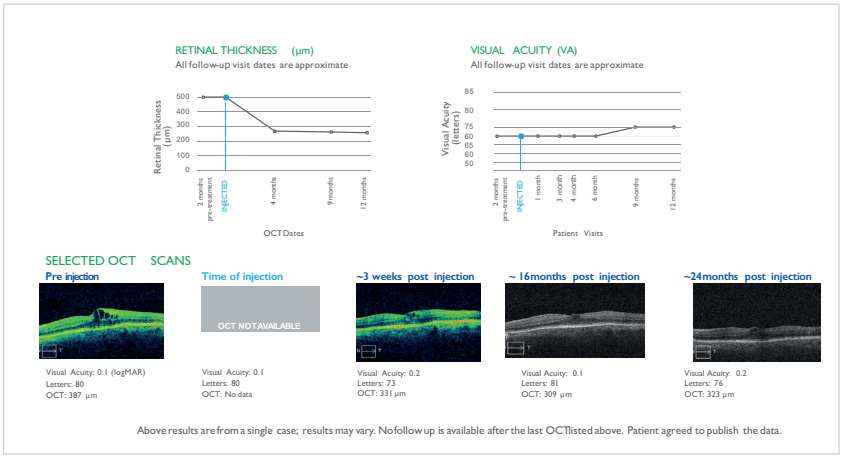
Supplementary treatments: Post-ILUVIEN, patients with better vision required an additional treatment every ~10 months; those with poor baseline vision (less than 20/40) required one additional treatment every ~7 months

PALADIN conclusions
- Retinal normalization (drying) is not a transient post-implantation effect; but is maintained over time, giving photoreceptors the best chance of recovery.
- Manageable safety profile in line with RCTs and real world data in the rest of the world.

"If the anti-VEGF response is insufficient to manage edema, the edema is unlikely to be VEGF-mediated – so we need to suppress other mediators." – Fahd Quhill.

Patient case: Holistic approach to DME: ILUVIEN as first-line therapy?

Vasant Raman, Royal Eye Infirmary, University Hospital, Plymouth



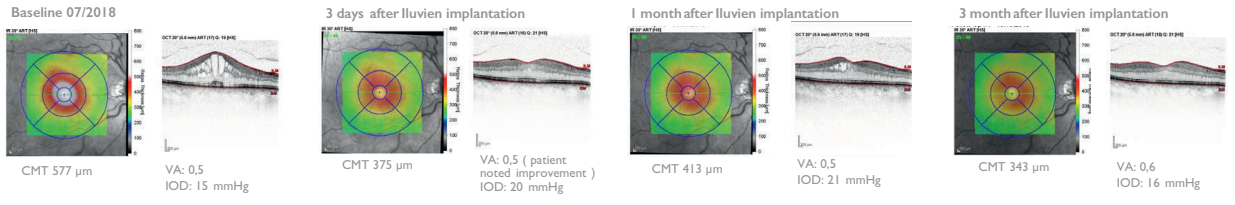
Above results are from a single case; results may vary. No follow up is available after the last OCT listed above. Patient agreed to publish the data.

- Patient: Female, 80 years, bilaterally pseudophakic, OS treated. Diabetic for 20 years, DME for less than two years, multiple significant co-morbidities including coronary artery disease (CAD), hyperlipidemia, hypertension, stroke, and mild cognitive effect. CRT >400 microns.
- Pre-ILUVIEN: Single anti-VEGF administration; then developed health issues (wheelchair-bound, IHD, indwelling urinary catheter), suggesting ILUVIEN would be more appropriate.
- Post-ILUVIEN: Reduced retinal edema at 3 weeks and 4 months; improved visual acuity at 16 months; no additional treatment required throughout 24-month follow-up; visual acuity maintained within five letters of baseline.
- Take-home messages: "We should take a more holistic, patient-centric view of DME treatment: consider ILUVIEN as first-line therapy in patients with issues that make anti-VEGF treatment difficult/inappropriate, or poor compliance likely."

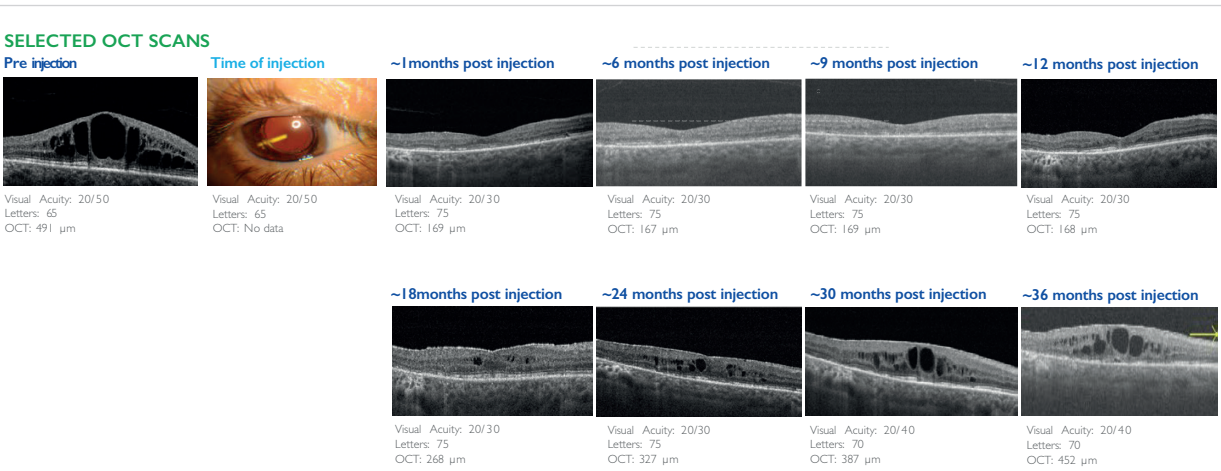
Patient case: Stroke following VEGF therapy – alternative treatment options

Tobias Duncker, Institute of Ophthalmology, Halle, Germany

- Patient: Male, 65 years, OD treated, phakic. Diabetic for 20 years, HbA1c 8.5 percent; stroke with hemiparesis one month after last anti-VEGF injection
- Pre-ILUVIEN: 15 anti-VEGF administrations
- Post-ILUVIEN: Rapid response to ILUVIEN – 200 micron decrease of CMT within three days of implantation. IOP stable without medication. Vision improved
- Take-home messages: "In patients with significant cardiovascular risk factors, I tend to switch DME patients early on to ILUVIEN, regardless of whether the patient is pseudophakic or not."



Above results are from a single case; results may vary. No follow up is available after the last OCT listed above. Patient agreed to publish the data.



Above results are from a single case; results may vary. No follow up is available after the last OCT listed above.

Patient case: Recurrent DME treated with ILUVIEN

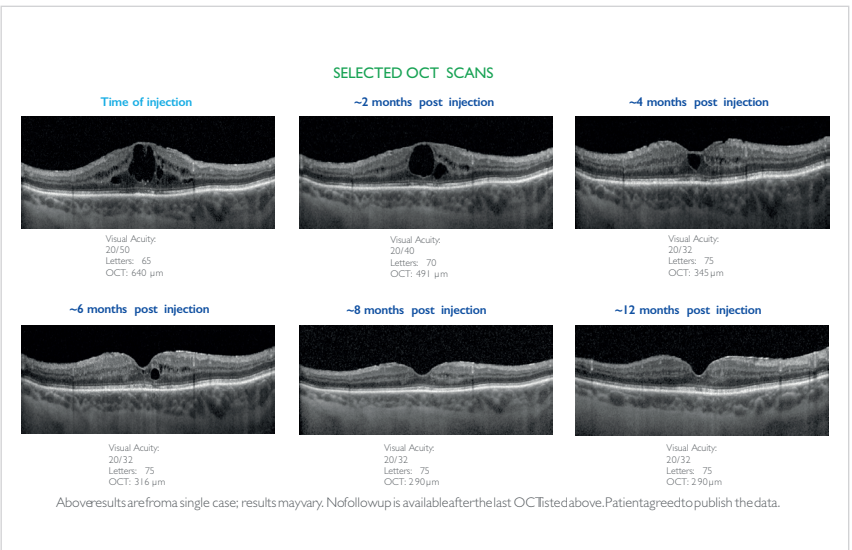
Carla Teixeira, Hospital Pedro Hispano, Matosinhos, Portugal

- Patient: Female, 63 years, RE treated, pseudophakic. Diabetic for 26 years, DME for 10 years. No co-morbidities
- Pre-ILUVIEN: Four anti-VEGF administrations, five corticosteroid administrations, three focal grid laser treatments, six PRP treatments.
- Post-ILUVIEN: Reduced retinal edema and improved visual acuity within one month. No additional intravitreal treatment needed for 36 months
- Take-home messages: "Patient responded very well to ILUVIEN; DME was controlled for three years without additional treatment."

Patient case: Treatment of persistent / recurrent DME

Francesco Bandello, University Vita Salute San Rafaelle, Milan

- Patient: Female, 63 years, RE Patient: Female, 68 years, RE treated, pseudophakic. Diabetic for 15 years, proliferative D for six years, DME for five years. Hypertension (well-controlled).
- Pre-ILUVIEN: 15 anti-VEGF administrations (poor visual gain), three DEX implants (good response), one focal grid laser, one PRP treatment
- Post-ILUVIEN: Reduction of macular edema from month 3 sustained throughout follow-up; regression at year 1. VA improved at 3 months; further improvement at month 6, sustained at month 12. No additional treatment required for one-year post-ILUVIEN
- Take-home messages: "The patient's edema has been controlled for one year without the need for other treatment; impressive improvement in quality of life."



Above results are from a single case; results may vary. No follow up is available after the last OCT listed above. Patient agreed to publish the data.

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Prescribing Information UK. ILUVIEN 190 micrograms intravitreal implant in applicator. Refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** Intravitreal implant in applicator. Each implant contains 190 micrograms of fluocinolone acetonide. Light brown coloured cylinder, approximately 3.5mm x 0.37mm in size. Implant applicator with 25 gauge needle. **Indication:** ILUVIEN is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies. **Dosage and method of administration:** The recommended dose is one ILUVIEN implant in the affected eye. Administration in both eyes concurrently is not recommended. Each ILUVIEN implant releases fluocinolone acetonide for up to 36 months. An additional implant may be administered after 12 months if the patient experiences decreased vision or an increase in retinal thickness secondary to recurrent or worsening diabetic macular oedema. Retreatments should not be administered unless the potential benefits outweigh the risks. Only patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema should be treated with ILUVIEN. *Children under 18*: No relevant use. *Special populations:* No dosage adjustments are necessary in elderly patients, or those with renal or hepatic impairment. *Method of Administration:* ILUVIEN should be administered by an ophthalmologist experienced in intravitreal injections. *Educational Guidance:* Prior to administering ILUVIEN, physicians should familiarise themselves with the ILUVIEN Administration Guide. **Contraindications:** The presence of pre-existing glaucoma or active or suspected ocular or periocular infection including most viral diseases of the cornea and conjunctiva, including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections, and fungal diseases. Hypersensitivity to the active substance or to any of the excipients. **Special warnings and precautions:** Intravitreal injections have been associated with endophthalmitis, elevation in intraocular pressure, retinal detachments and vitreous haemorrhages or detachments. Patients should be instructed to report without delay any symptoms suggestive of endophthalmitis. Patient monitoring within two to seven days following the injection may permit early identification and treatment of ocular infection, increase in intraocular pressure or other complication. It is recommended that intraocular pressure be monitored at least quarterly thereafter. Use of intravitreal corticosteroids may cause cataracts, increased intraocular pressure, glaucoma and may increase the risk of secondary infections. The safety and efficacy of ILUVIEN administered to both eyes concurrently have not been studied. It is recommended that an implant is not administered to both eyes at the same visit. Concurrent treatment of both eyes is not recommended until the patient's systemic and ocular response to the first implant is known. There is a potential for implants to migrate into the anterior chamber, especially in patients with posterior capsular abnormalities, such as tears. This should be taken into consideration when examining patients complaining of visual disturbance after treatment. **Interactions:** No interaction studies with other medicinal products have been performed. **Pregnancy and lactation:** There are no adequate data from the use of intravitreal administered fluocinolone acetonide in pregnant women. As a precautionary measure it is preferable to avoid the use of ILUVIEN during pregnancy. Although systemic exposure of fluocinolone is very low, a risk benefit decision should be made prior to use of ILUVIEN during breast-feeding. **Driving and using machines:** ILUVIEN has minor influence on the ability to drive and use machines. Patients may experience temporarily reduced vision after administration of ILUVIEN and should refrain from driving or using machines until this has resolved. **Undesirable effects:** *Very common (>1/10):* cataract

operation, cataract, increased intraocular pressure; *Common (>1/100 to <1/10):* glaucoma, trabeculectomy, eye pain, vitreous haemorrhage, conjunctival haemorrhage, blurred vision, glaucoma surgery, reduced visual acuity, vitrectomy, trabeculoplasty, vitreous floaters; *Uncommon (>1/1,000 to <1/100):* endophthalmitis, headache, retinal vascular occlusion, optic nerve disorder, maculopathy, optic atrophy, conjunctival ulcer, iris neovascularisation, retinal exudates, vitreous degeneration, vitreous detachment, posterior capsule opacification, iris adhesions, ocular hyperaemia, sclera thinning, removal of extruded implant from sclera, eye discharge, eye pruritus, extrusion of implant, implant in line of sight, procedural complication, procedural pain, device dislocation. Consult the SmPC for full details of undesirable effects. **Overdose:** No case of overdose has been reported. **Legal classification:** POM. **Pack size and NHS list price:** £5,500.00 (ex VAT) for each ILUVIEN 190 micrograms intravitreal implant in applicator. **Marketing Authorisation number:** PL 41472/0001. **Marketing Authorisation Holder:** Alimera Sciences Limited, Royal Pavilion, Wellesley Road, Aldershot, Hampshire, GU11 1PZ, United Kingdom. **Date of preparation of PI:** October 2015.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Alimera Sciences Limited (telephone: 0800 148 8274) pvalimerasciences@alimerasciences.com

For medical enquiries please email:
medicalinformation@alimerasciences.com

Prescribing Information Ireland. ILUVIEN® 190 micrograms intravitreal implant in applicator. Refer to the Summary of Product Characteristics (SmPC) before prescribing. **Presentation:** intravitreal implant in applicator. Each implant contains 190 micrograms of fluocinolone acetonide. Light brown coloured cylinder, approximately 3.5mm x 0.37mm in size. Implant applicator with 25 gauge needle. Indication: ILUVIEN is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to available therapies. **Dosage and method of administration:** The recommended dose is one ILUVIEN implant in the affected eye. Administration in both eyes concurrently is not recommended. Each ILUVIEN implant releases fluocinolone acetonide for up to 36 months. 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Patients may experience temporarily reduced vision after administration of ILUVIEN and should refrain from driving or using machines until this has resolved. **Undesirable effects:** Very common (≥1/10): cataract operation, cataract, increased intraocular pressure; Common (≥1/100 to <1/10): glaucoma, trabeculectomy, eye pain, vitreous haemorrhage, conjunctival haemorrhage, blurred vision, glaucoma surgery, reduced visual acuity, vitrectomy, trabeculoplasty, vitreous floaters; Uncommon (≥1/1,000 to <1/100): endophthalmitis, headache, retinal vascular occlusion, optic nerve disorder, maculopathy, optic atrophy, conjunctival ulcer, iris neovascularisation, retinal exudates, vitreous degeneration, vitreous detachment, posterior capsule opacification, iris adhesions, ocular hyperaemia, sclera thinning, removal of extruded implant from sclera, eye discharge, eye pruritus, extrusion of implant, implant in line of sight, procedural complication, procedural pain, device dislocation. Consult the SmPC for full details of undesirable effects. **Overdose:** No case of overdose has been reported. **Legal classification:** Product subject to prescription which may not be renewed (A). Supply through pharmacies only. **Pack size:** One single use applicator. Marketing Authorisation number: PA1953/001/001. **Marketing Authorisation Holder:** Alimera Sciences Limited, Royal Pavilion, Wellesley Road, Aldershot, Hampshire, GU11 1PZ, United Kingdom. **Date of preparation of the PI:** November 2015

Reporting suspected adverse events is important. It allows continued monitoring of the benefit/ risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2 Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www. hpra.ie; E-mail: medsafety@hpra.ie Adverse events should also be reported to Alimera Sciences Limited (telephone 1800932379) pvalimerasciences@alimerasciences.com

For medical enquiries please email:
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