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Original Paper

A Nonrandomized, Open-Label, Multicenter, Phase 4 Pilot Study on the Effect and Safety of ILUVIEN® in Chronic Diabetic Macular Edema Patients Considered Insufficiently Responsive to Available Therapies (RESPOND)

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Abstract
Purpose: The aim of this study was to assess the effectiveness and safety of ILUVIEN® in patients with chronic diabetic macular edema (DME) who were insufficiently responsive to prior therapies. **Methods:** This is a prospective, nonrandomized, multicenter, open-label, phase 4 pilot study assessing the effectiveness and safety of ILUVIEN® involving 12 patients insufficiently responsive to available therapies. Assessments were performed at screening, baseline, week 1, and months 1, 3, 6, 9, and 12. Demographics, medical/ophthalmic history, prior laser, anti-VEGF, and steroid treatments, and lab tests were recorded at screening. A complete ophthalmic examination and SD-OCT were performed at screening and at all follow-up visits. **Results:** The patients showed improvements in best-corrected visual acuity (+3.7 letters), with greater improvement among pseudophakic patients (+6.8 letters) compared with phakic patients (−2.5 letters) 12 months after ILUVIEN®. The mean central subfield thickness decrease from baseline to month 12 was statistically significant, with a rapid reduction in the first week. Regarding safety, only 2 patients showed an intraocular pressure (IOP) increase over 25 mm Hg during the study, and the rise in IOP was well managed with eye drops only. **Conclusions:** This prospective and pilot study suggests that ILUVIEN® is safe and may be considered effective for chronic DME patients insufficiently responsive to other available therapies as it showed a rapid and sustained improvement of macular edema obtained after treatment with ILUVIEN®.

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Introduction

Diabetes is expected to affect almost 642 million people worldwide in 2040 and likely to lead to large increases in the rates of complications related to diabetes, including diabetic retinopathy (DR) and diabetic macular edema

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(DME) [1, 2]. Globally, nearly 93 million people currently have DR, 17 million have proliferative DR, 21 million have DME, and 28 million are living with a vision-threatening form of the disease [3].

DME remains a major cause of vision loss in patients with diabetes. Its pathogenesis is complex and multifactorial, largely caused by a change in the permeability across the blood-retinal barrier (BRB) as a result of hyperglycemia [4]. BRB breakdown allows the leakage of fluid and small and large molecules across the compromised BRB, causing macular edema [5].

At early disease stages, vascular endothelial growth factor (VEGF) is primarily responsible for retinal changes, owing to its overexpression. VEGF inhibitor therapies are currently used as treatment options in DME [5, 6]. Within the past few years, VEGF inhibitors, such as ranibizumab, aflibercept, and bevacizumab (used off-label) have been part of the therapeutic arsenal of ophthalmologists for treating DME. However, it is estimated that up to 40% of patients are insufficiently responsive to anti-VEGF intravitreal therapy and other treatment options are necessary in these cases. It is well established that inflammation has an important role in the pathophysiology of DME, and intravitreal steroids, such as triamcinolone acetonide, and more recently intravitreal steroid drug delivery systems like fluocinolone acetonide (FAc; ILUVIEN®, Alimera Sciences Inc., Atlanta, GA, USA) and dexamethasone (Ozurdex®, Allergan Inc., Irvine, CA, USA) have been successfully used in the treatment of visual impairment due to DME [7, 8].

Recent studies focused on patients with chronic DME demonstrated that there are numerous inflammatory cascades due to chronic microglia activation resulting from retinal damage that leads to cytokine production by retinal cells in the eye [6]. At this stage, VEGF is likely no longer primarily responsible for the biochemical and physiological changes in the eyes and anti-VEGF agents are consequently less effective. Due to their multifactorial mode of action, steroids are probably most effective at this stage [6].

Whilst an intravitreal bolus injection of a steroid into the eye provides a rapid (pulse) release of the active drug with a short-term pharmacological effect, repeated injections are necessary [9, 10]. In contrast, a single injection of ILUVIEN® provides a sustained, low-dose delivery of FAc for up to 36 months [11, 12], avoiding the need for frequent injections and requiring only routine assessments (e.g., intraocular pressure, IOP, and cataract formation) [13].

This investigator-driven clinical trial is the first real-life clinical experience with ILUVIEN® in Portugal and will assess the effectiveness and safety of the ILUVIEN® intravitreal implant in chronic DME patients considered insufficiently responsive to available therapies.

Materials and Methods

Study Design
This is a prospective, nonrandomized, multicenter, open-label phase 4 pilot study. Twelve patients were enrolled at 4 Portuguese sites: 1 site with 4 patients, 2 sites with 3 patients, and 1 site with 2 patients. Men and women aged ≥18 years with chronic DME, defined as persistent macular edema for more than 1 year in the study eye, considered insufficiently responsive to other previous treatments, including at least 3 anti-VEGF injections in the last 6 months, were included. Further inclusion requirements were: mean central foveal thickness at baseline (central subfield thickness; CST) ≥290 μm in women and ≥305 μm in men with Zeiss Cirrus or ≥305 μm in women and ≥320 μm in men with Heidelberg Spectralis in the study eye, as measured using SD-OCT (spectral domain optical coherence tomography); vision impairment (20/50 to 20/400 using Snellen visual acuity equivalent) related to DME, and the investigator's opinion that a further visual improvement is possible.

Exclusion criteria in the study eye included: IOP >21 mm Hg at screening; history of a rise in IOP >25 mm Hg following treatment with an intravitreal steroid; use of ≥2 active agents as IOP-lowering medications to control IOP at screening; previous vitreomacular traction in DME and opaque media; severe proliferative DR requiring pan retinal photocoagulation; diagnosis of angiographic central macular ischemia; previous pan retinal photocoagulation or cataract surgery in the 3 months prior to the screening visit; contraindications according to the current Summary of Product Characteristics [14]; the presence of preexisting glaucoma; active or suspected ocular or periocular infection, and hypersensitivity to the active agent or to 1 of the excipients [14]. Pregnant or breastfeeding women and women of child-bearing potential not using a highly effective method of birth control were also excluded.

This study was designed, implemented, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC) and with the ethical principles laid down in the Declaration of Helsinki.

Eligible patients only participated in the study after providing approved written informed consent. The study was registered with EudraCT (No. 2014-003491-23) and it was conducted from October 2014 to July 2016.

Study Treatment
The ILUVIEN® implant is an injectable intraocular sustained-release drug delivery system for FAc preloaded into a single use sterile applicator. Each implant contains 190 μg of FAc as the active ingredient within a 3.5-mm-long cylindrical polyimide tube with an internal diameter of 0.37 mm. The implant is to be injected through the pars plana into the vitreous using a 25-G needle.

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All patients received the ILUVIEN® 190-μg intravitreal implant in an applicator (releasing 0.2 μg of FAc per day) at the inclusion visit. The implant was administered by injection according to the method of administration defined in the summary of product characteristics [14]. Only 1 eye of each patient was treated with ILUVIEN®. In case of bilateral DME, the fellow eye received ocular treatments according to the standard clinical practice.

Outcomes

The defined study outcomes were:
- changes in best-corrected visual acuity (BCVA) from baseline to month 12;
- changes in central retinal thickness assessed using spectral domain optical coherence tomography (SD-OCT) from baseline to month 12;
- adverse events, namely cataract and elevated IOP.

Visits and Assessments

This 12-month study included 8 visits. After informed consent was obtained and, prior to enrolment, the patients were evaluated to determine eligibility. Patient assessments were performed at screening, baseline, week 1, and months 1, 3, 6, 9, and 12 to assess the effectiveness and safety of ILUVIEN®. The following were recorded at the screening visit: demographics, diabetes history, diagnosis of DME, medical/ophthalmic history, prior laser, anti-VEGF, and steroids treatments, and lab tests. The following assessments were performed at the screening visit and at all follow-up visits: an ophthalmic examination consisting of BCVA (using Early Treatment Diabetic Retinopathy Study, ETDRS, charts), IOP, CST, and macular volume (MV) using SD-OCT, corneal thickness (via spectral SD-OCT), slit lamp examination, ophthalmoscopy, fundus photography, lens status, and DR severity. Concomitant medications, ocular procedures, and adverse events were recorded during the follow-up visits.

Statistical Analysis

All of the effectiveness variables were analyzed using the intent-to-treat data set for patients who had a valid baseline assessment. The variables for assessing effectiveness included BCVA in ETDRS letters and retinal thickness parameters assessed using SD-OCT (i.e., CST and MV). The observed change from baseline values for each variable were summarized descriptively (mean ± SD) or by the frequency distribution assessed at each visit.

Safety analyses were performed by evaluating ocular adverse events, BCVA, IOP, hemoglobin A_{1c}, slit lamp exams, ophthalmoscopy, and concomitant ocular medications and therapies. Systemic safety was assessed by evaluating nonocular adverse events, and concomitant nonocular medications and therapies. The nonparametric Wilcoxon signed-rank test was used to assess differences between screening and month 12, and the nonparametric Wilcoxon-Mann-Whitney test was used to assess differences between phakic and pseudophakic patients. For continuous variables, such as IOP, the observed and change from baseline values were summarized descriptively (mean ± SD) at each visit. Categorical variables were summarized by counts and percentages. A p value <0.05 was considered to be statistically significant. Statistical analyses were performed on Stata version 12.1 (StataCorp LP, College Station, TX, USA).

Table 1. Demographics and baseline characteristics of the study patients and eyes

Characteristics	
Patients	12
Gender	
Male	8 (66.7)
Female	4 (33.3)
DR severity	
None	3 (25.0)
Moderate	2 (16.7)
Severe	1 (8.3)
Proliferative	1 (8.3)
Laser	5 (41.7)
Age, years	69.6±9.3
Lens status	
Pseudophakic	8 (66.7)
Phakic	4 (33.3)
Diabetes	
Type 1	0 (0)
Type 2	12 (100)
Diabetes duration, years	19.1±11.1
DME duration, years	3.4±3.1
HbA1C, %	6.9±1.3
SBP, mm Hg	153.0±21.6
DBP, mm Hg	77.1±8.7
IOP, mm Hg	14.6±2.9
BCVA, ETDRS letters	48.8±10.9
CST, μm	650.5±140.9
MV, mm³	11.6±2.0
Previous treatments	
Laser + anti-VEGF + steroids	4 (33.3)
Laser + anti-VEGF	5 (41.7)
Anti-VEGF alone	3 (25.0)
Laser alone	0 (0.0)
Number of previous treatments	
Previous laser sessions	4.4±4.2
Previous anti-VEGF injections	4.0±2.9
Previous steroids treatments	2.0±1.4

Data are presented as n (%) or mean ± SD.

Results

Demographic Characteristics of Study Population

The demographics of 8 male and 4 female patients and baseline characteristics of the study eyes (n = 12) are described in Table 1. The mean age of the patients was 69.6 ± 9.3 years. Eight eyes were pseudophakic and 4 were phakic. At inclusion, the eyes had a mean DME duration of 3.4 ± 3.1 years, the mean BCVA was 48.8 ± 10.9 letters, and the CST was 650.5 ± 140.9 μm.

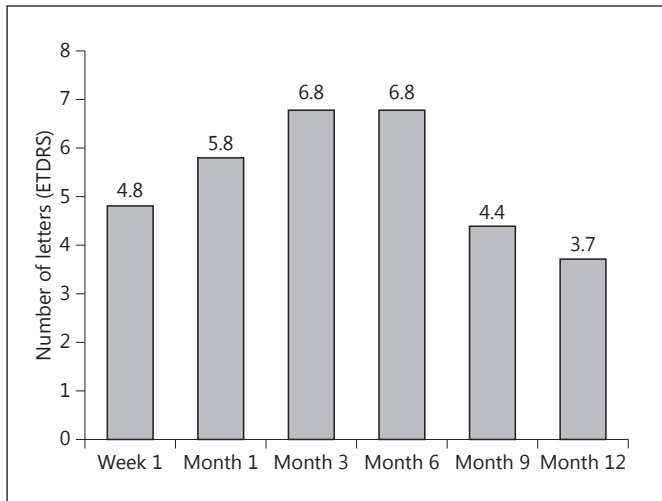All of the patients had prior anti-VEGF with a mean number of 4 injections and 75% of them had associated

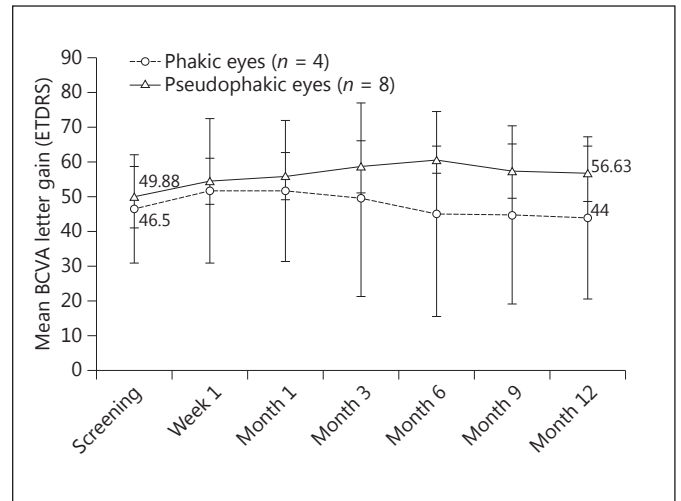**Fig. 1.** BCVA changes in all 12 patients from baseline to month 12.

Fig. 2. BCVA by lens status at screening and follow-up visits.

therapies (laser or steroids). Details for the previous treatments and the number of previous treatments are included in Table 1.

Visual Outcomes: BCVA

This study showed that a single injection of ILUVIEN® led to a BCVA improvement in 9 of the 12 patients with chronic DME who were considered insufficiently responsive to first-line therapies. Although the average BCVA difference from baseline to month 12 (+3.7 letters; Fig. 1) was not statistically significant ($p = 0.255$), there was an almost statistically significant trend for improvement among pseudophakic patients (mean difference +6.8 letters, $p = 0.058$), which was not present in phakic eyes (mean difference –2.5 letters, $p = 0.715$; Fig. 2). Pseudophakic eyes showed a BCVA improvement from baseline that reached statistical significance between week 1 and month 6 (week 1, $p = 0.019$; month 1, $p = 0.014$; month 3, $p = 0.025$; month 6, $p = 0.012$), while phakic eyes had a quick gain of 5 letters in the first week followed by a decrease of visual acuity that did not reach statistical significance (Fig. 2).

Anatomical Outcomes: CST and MV

Statistically significant improvements in the average CST (–292.83 μm, $p = 0.003$) and average MV (–1.8 mm³, $p = 0.005$) were observed in 92% of the patients from baseline to month 12. There was a significant and rapid decrease of macular edema in the first week after ILUVIEN® implant insertion, with a mean CST change of –203.3 μm, which was sustained over the 12-month follow-up (Fig. 3).

Safety

Regarding safety, no surgeries or trabeculectomies were needed to control IOP. Nevertheless, statistically significant differences were observed from baseline to month 12 for IOP ($p = 0.005$). However, only 5 patients experienced an IOP over 22 mm Hg during the study, 2 of which had an IOP over 25 mm Hg, and no subjects had an IOP over 30 mm Hg (Fig. 4). Of the 5 patients with an elevated IOP, 4 (80%) were phakic. These patients were all well controlled with eye drops. One of the patients had a worsening of preexisting cataract and underwent surgery, showing an improvement of the edema and visual acuity.

No patients were discontinued from the study. No serious adverse events relating to the study drug were reported. Regarding glycemic control, no statistically significant differences were found in hemoglobin A_{1c} levels from baseline to month 12 ($p = 0.623$).

Discussion

The purpose of this study was to monitor safety and effectiveness in real-life chronic DME patients considered insufficiently responsive to available therapies. The study population included patients with a mean DME duration of 3.4 years who had undergone at least 3 anti-
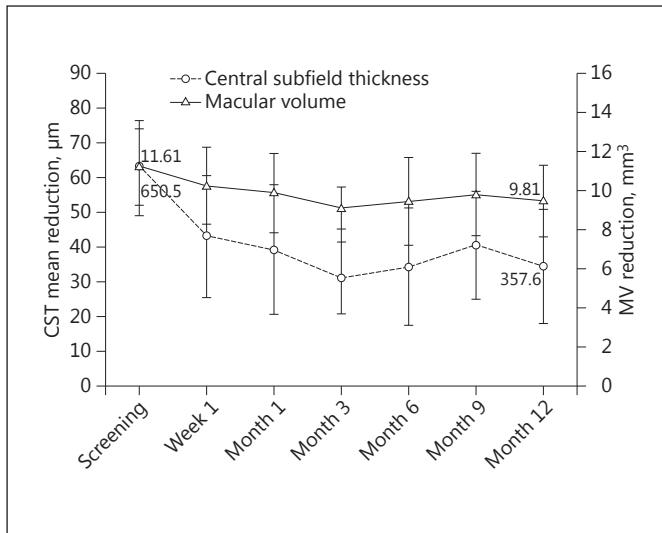
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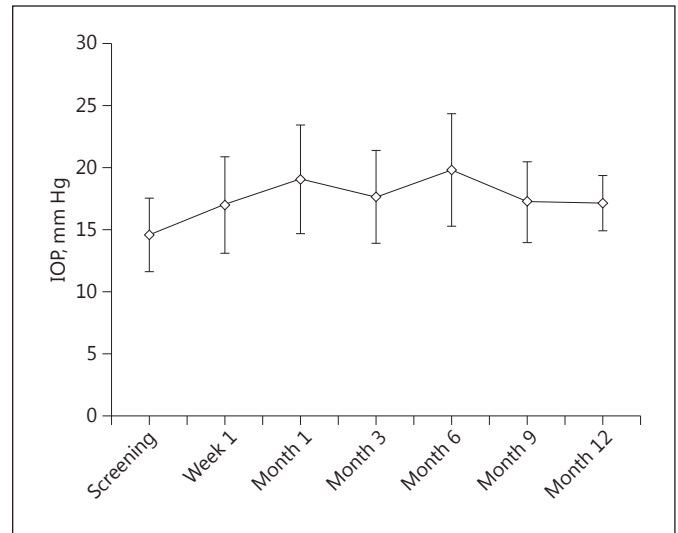**Fig. 3.** CST and MV at screening and follow-up visits.

Fig. 4. Mean IOP at screening and follow-up visits.

VEGF injections in the last 6 months. Prior to treatment with ILUVIEN®, 4 patients/eyes had been previously treated with laser, anti-VEGF, and steroids, 5 patients had been previously treated with laser and anti-VEGF, and 3 patients had been previously treated with only anti-VEGF. Indeed, patients initially treated with anti-VEGF and/or steroids had not been assessed in the Fluocinolone Acetonide for Macular Edema (FAME) studies (phase III trials of the efficacy and safety of ILUVIEN® in DME patients) [13]. In comparison with the FAME studies, the patients included in this study had worse baseline characteristics, including diabetes duration, baseline BCVA, and baseline CST.

In our study, 9 eyes had DR reported at baseline with different grades of severity. Recent data show that ILUVIEN® slows the development of both proliferative and nonproliferative DR [15].

At baseline, the mean BCVA was 48.8 ± 10.9 letters, demonstrating significant vision impairment related to DME. Ten patients maintained or improved their BCVA scores from baseline to month 12. The mean improvement of BCVA letter score was +3.7 at 12 months. This modest mean improvement of BCVA may be attributed to the development and/or worsening of cataract observed from month 6, where the mean BCVA gain was +6.8. Although the average BCVA difference from baseline to month 12 was not statistically significant, there was an almost statistically significant trend for improvement among pseudophakic patients (mean difference +6.8 let-

ters, $p = 0.058$), which was not present in phakic eyes (mean difference −2.5 letters, $p = 0.715$). Pseudophakic eyes showed a BCVA improvement that reached statistical significance between week 1 and month 6, while phakic eyes had a quick gain of 5 letters in the first week followed by a progressive decrease of visual acuity, probably due to cataract progression, which did not reach statistical significance. In FAME, the median time for cataract to be reported as an adverse event was 12 months and the median time for cataract surgery was 18 months [13]. Another possible cause for poor visual acuity improvement was the microstructural and nonreversible lesions in retinal layers after chronic and long-standing edema in the patients enrolled [16]. This would suggest the benefit of an early use of ILUVIEN®, as has already been described [17].

In the subgroup analysis, pseudophakic patients had a higher mean letter gain of +6.8 letters than the phakic patients at 12 months. Cataract development and/or worsening occurred at the expected rate in phakic patients treated with ILUVIEN®, as this is a known effect of intravitreal steroid therapies [18]. The only case of cataract extraction performed in our study showed improvement of the macular edema and visual acuity. In fact, it has been discussed that a low dose of a steroid, such as ILUVIEN®, is beneficial during and after cataract surgery in eyes with DME due to its protective effect [18]. Results from a phase 4 study with ILUVIEN® in DME reported by Massin et al. [17] showed a benefit in BCVA and anatomical im-

provements, which were consistent with our study. The mean improvement of BCVA letter score (excluding values postrescue) at 1 year was +4.9 in patients who had received previous treatment in the study eye with laser photocoagulation for DME and no previous treatment with intraocular anti-VEGF therapy, and +4.4 in patients previously treated in the study eye with laser photocoagulation for DME (including focal/grid and pan-retinal) and with a past history of ≥3 monthly anti-VEGF treatments. This last parameter was +8.2 in pseudophakic patients.

At baseline, the mean CST and MV in our patient population were 650.5 ± 140.9 µm and 11.6 ± 2.0 mm³, respectively, confirming the insufficient DME response to prior therapies. In our study, there was a rapid reduction in mean CST, which was significant as early as week 1 with a gradual and sustained reduction over the 12-month follow-up period. The mean decrease of CST and MV was –292.83 µm and –1.8 mm³ respectively, at month 12, both of which were statistically significant. Given the anticipated poor potential for visual acuity gain due to chronic retinal lesions, the reduction in CST should be considered the best indicator of the efficacy of the treatment. Therefore, even in chronic and long-standing edema the anatomic results are very good evidence of the efficacy of long-acting steroids like ILUVIEN®. In the study by Massin et al. [17], at month 1 the mean decrease of CST was –239 µm in the group of patients that had received previous treatment in the study eye with laser photocoagulation and no previous anti-VEGF therapy, and was –147 µm in the group of patients previously treated with laser photocoagulation and anti-VEGF injections. This decrease was also rapid and a significant benefit on macular edema was obtained as early as 1 week after the injection of the study drug.

Although there was a statistically significant increase in IOP from baseline to month 12, ILUVIEN® appeared to be safe and well tolerated in all patients of our study. In the FAME study, 37.1% of patients had IOP reported as an adverse event and 38.4% of patients receiving ILUVIEN® received IOP-lowering medication [13]. In our study, IOP over 22 mm Hg was reported as an adverse event in 5 out of 12 patients. The IOP rise was well controlled with topical medication only. Of the 5 patients with an elevated IOP, only 2 experienced an IOP over 25 mm Hg, and none had an IOP over 30 mm Hg.

Our results are comparable with real-world data from Portugal, where other studies [19–21] have shown a sustained improvement in visual acuity and significant decrease in retinal thickness in DME patients with an insuf-

ficient response to prior treatments. The IOP was manageable and may not be considered a problem as long as patients are correctly monitored and managed for treatment. The reduced number of patients included in this exploratory study is, however, a clear limitation and the lack of visual acuity analysis postcataract surgery did not allow the full assessment of the visual efficacy of ILUVIEN®.

In conclusion, in this population with chronic DME a rapid and sustained improvement of macular edema was obtained after treatment with the ILUVIEN® intravitreal implant. This study showed that patients with chronic DME considered insufficiently responsive to available therapies experienced improvements in BCVA (+3.7 letters), with a greater BCVA improvement among pseudophakic patients (+6.8 letters) at 12 months after ILUVIEN® injection.

The decrease in the mean CST from baseline to month 12 was statistically significant, with a rapid reduction of the mean CST in the first week, which is anatomic evidence of the efficacy of the treatment. Regarding safety, only 2 patients showed an IOP increase over 25 mm Hg during the study, and only eye drops were used to control the IOP. This prospective, nonrandomized, multicenter, open-label, phase 4 pilot study suggests that ILUVIEN® is safe and may be considered effective for chronic DME patients considered insufficiently responsive to available therapies.

Disclosure Statement

João Figueira and José Henriques are consultants for Alimera Sciences, Alcon, Allergan, Bayer and Novartis. Miguel Amaro is a consultant for Allergan and Bayer. Vítor Rosas is a consultant for Allergan, Bayer, and Novartis. José Cunha-Vaz is a consultant for Alimera Sciences, Allergan, Bayer, Gene Signal, Novartis, Pfizer, Precision Ocular Ltd., Roche, Sanofi-Aventis, Vifor Pharma, and Carl Zeiss Meditec.

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