

# LONG-TERM EFFICACY OF FLUOCINOLONE IN EYES WITH IRIS–LENS DIAPHRAGM DISRUPTION AND PCME WITH MEDICATION FIXED IN THE SCLERA (MEFISTO)

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**Purpose:** The aim of our prospective off-label, interventional clinical trial was to evaluate the efficacy and safety of the fluocinolone-loop-anchoring technique over two years in eyes with iris–lens diaphragm disruption and pseudophakic cystoid macular edema.

**Methods:** In 10 eyes, scleral fixation of fluocinolone implant was performed. Main outcome measures were the development of best-corrected visual acuity (BCVA), central retinal thickness over 24 months, and general safety of the procedure.

**Results:** A significant improvement to  $0.57 \pm 0.38$  log MAR (Snellen 20/80) (range 0–1.30) was observed ( $P = 0.003$ ) at 1 month. Further improvement to  $0.45 \pm 0.36$  log MAR (Snellen 20/60) was observed until month 18 ( $P = 0.081$ ). Mean central retinal thickness decreased by 22% from  $601.6 \pm 235.5 \mu\text{m}$  to  $449.1 \pm 128.9 \mu\text{m}$  at 1 month. In one patient, the implant has to be removed at Month 7 because of elevated intraocular pressure and one patient after globe rupture had a retinal redetachment at Month 4.

**Conclusion:** In this study, we showed that the treatment of recalcitrant pseudophakic cystoid macular edema with scleral fixated fluocinolone implant in eyes with disruption of the iris–lens diaphragm provides good anatomical and functional results with a reasonable safety profile over 24 months in eyes where pseudophakic cystoid macular edema is otherwise difficult to treat and often left untreated.

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It is well known that eyes that have undergone complicated cataract surgery, posterior capsule rupture, or eyes after trauma have an increased risk for pseudophakic cystoid macular edema (PCME), and therefore require an effective and safe approach with a low risk of further complications such as intraocular pressure (IOP) increase.<sup>1</sup>

The use of topical or intravitreal medication with steroids and nonsteroidal antiinflammatory drugs has been proven to address recalcitrant PCME, also in vitrectomized eyes, but the problem is the need for a sustainable medical treatment in the long-term.<sup>2,3</sup>

Therefore, the use of intravitreal steroid implants (IVSIs) such as dexamethasone implant (Ozurdex) or fluocinolone implant (Iluvien) seems to be a reasonable approach. IVSI has been proven to be of long-term

benefit for patients with diabetic macular edema, but also for patients with PCME or Irvine–Gass syndrome.<sup>4–6</sup>

At the same time, eyes with disrupted anterior–posterior segment border are also at highest risk to develop complications in migration of an IVSI into the anterior chamber, which can lead to severe corneal decompensation through mechanical and possibly toxic effects.<sup>7,8</sup>

Therefore, the scleral fixation of IVSI is a reasonable and potentially reversible approach for those eyes. The fixation of dexamethasone implant (Ozurdex) has been described, but the efficacy of the treatment is shorter than in fluocinolone implant and biodegradation of the dexamethasone implant may lead to loosening of the scleral fixation with time and nevertheless migration of the implant.<sup>9</sup>

The scleral fixation of fluocinolone implant (Iluvien) in eyes with severe iris–lens diaphragm disruption and recalcitrant PCME by means of a novel technique (“FLAT”—the fluocinolone-loop-anchoring technique) has been proven to be technically feasible and safe for those challenging and complex eyes.<sup>10,11</sup>

The aim of this single-center, prospective, off-label, interventional clinical trial was to determine the long-term clinical efficacy and safety of fluocinolone in eyes with severe iris–lens diaphragm disruption and recalcitrant PCME with scleral fixation in a larger cohort.

## Methods

For this single-center, prospective, interventional clinical trial, 10 eyes were included at our retinal disease clinic of the eye hospital of the Ludwig Maximilian University, Munich, Germany.

Inclusion criteria were recurrence of PCME with previous dexamethasone implant-related problems, previous migration of dexamethasone implant or aphakic macular edema with a high risk of IVSI migration into the anterior chamber due to disrupted anterior–posterior segment border after complicated cataract surgery or trauma. Further inclusion criteria were a central retinal thickness (CRT) of more than 400  $\mu\text{m}$ .

Exclusion criteria were single eye condition or uncontrolled glaucoma.

For sample size calculation, we opted a power of 80% with a type I error rate of 5%. The calculation was based on the reduction of CRT in patients with diabetic macular edema according to a recent study.<sup>12</sup>

For a mean reduction of CRT from 600  $\mu\text{m}$  to 450  $\mu\text{m}$  and an SD of 135  $\mu\text{m}$ , a sample size of seven patients was calculated.

At baseline, and at all follow-up visits, the patients underwent a full clinical examination, including best-corrected visual acuity (BCVA), measurement of the IOP, and spectral domain optic coherence tomography (Spectralis OCT, Heidelberg Engineering GmbH, Heidelberg, Germany). Photo documentation of the anterior segment and posterior segment with Optos ultra-widfield camera (Optos, Inc, Marlborough, MA) were performed 3 monthly.

The surgical procedure of scleral fixation of the fluocinolone acetonide implant (Iluvien, Alimera Sciences Inc, Alpharetta, GA) was performed under local anesthesia with retrobulbar injection of lidocaine or sub-tenon anesthesia according to the protocol of the FLAT-technique that has been described before.<sup>10</sup>

The FLAT-technique consists of preparing the implant with a 10.0 Prolene suture and creating a knot with two loops. This allows handling of the thread-fixed implant within the following procedure. The fluocinolone implant is then inserted through a 1.5-mm sclerotomy at 3, 5 mm into the eye. By cautiously pushing the two loops with a flat-headed lens nucleus rotator, the implant is prevented to slip from the fixated suture while being inserted into the vitreous. Thereafter, the same thread is used to close the sclerotomy.

The patients underwent follow-up visits at week 2, and then monthly until Month 12, then 3 monthly following a standardized protocol until Month 24.

Main outcome measure was the development of BCVA and CRT from baseline to Month 24.

Study-specific adverse events such as migration of the implant or rise of IOP have been checked and documented at every follow-up visit.

Included patients signed written informed consent before the surgery for this off-label surgical procedure and off-label use of fluocinolone implant and gave consent to publication of their deidentified data and obtained eye images.

This prospective interventional clinical trial was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. It has undergone ethics approval by the institutional review board and is registered at the DRKS (Registration No. DRKS00020282).

## Statistical Analysis

All data were collected in an MS-Excel 2013 spreadsheet (Microsoft Corporation, Redmond, WA) and analyzed using the Statistical Package for Social Sciences version 24 for Windows (SPSS/IBM, New York, NY). Normal distribution was checked with Kolmogorov–Smirnov one sample test. Parametric and nonparametric tests were used for comparisons of the

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same variable between the different follow-up time points. Box-plots were used to visualize the development of BCVA and CRT over the follow-up period. Kaplan–Meier curve was obtained for assessment of recurrence rate over the follow-up period. To avoid false-positive results because of CRT fluctuations, recurrence was defined as increase of more than 20% of the CRT in comparison to the last two follow-up examinations.

**Results**

*Baseline Characteristics*

This study comprised 10 eyes of 10 patients over a follow-up period of 24 months. Three patients were women and seven men. The mean age was 66 years (46–82 years, SD 12 years). Most eyes (7 patients) had a history of complicated cataract surgery, whereas two eyes were aphakic after severe trauma and globe rupture (one had scleral fixated IOL at Month 4) and one eye was an aphakic nanophthalmus after complicated cataract surgery. The overall baseline characteristics, previous surgeries, BCVA, CRT, and IOP at baseline are shown in Table 1.

*Visual Acuity*

Mean BCVA at baseline was generally poor ( $1.00 \pm 0.55$ ; range 0.2–2.00 Log MAR, Snellen, 20/200). One month after the implantation, a statistically significant improvement to  $0.57 \pm 0.38$  log MAR (Snellen 20/80) (range 0–1.30) was observed ( $P = 0.003$ , paired *t*-test).

Best-corrected visual acuity remained stable over Month 3 and 6. A further improvement to  $0.45 \pm 0.36$  log MAR (Snellen 20/60) was observed at Month 9 up to Month 18 ( $P = 0.081$ , paired *t*-test). However, BCVA slightly decreased to  $0.56 \pm 0.41$  log MAR (Snellen 20/80) at the last follow-up 24 months after implantation ( $P = 0.088$ , paired *t*-test). Nevertheless, 24 months after the implantation, BCVA was comparable to 1 month postoperatively ( $P = 0.410$ , paired *t*-test). With exception of Patient 2, BCVA improved significantly in all other study subjects over the complete follow-up period of 24 months (Figure 1).

*Central Retinal Thickness*

Mean CRT decreased by almost 22% from  $601.6 \pm 235.5 \mu\text{m}$  (range: 403–1203  $\mu\text{m}$ ) to  $449.1 \pm 128.9 \mu\text{m}$  (range: 331–768  $\mu\text{m}$ ) within the first month. A further decrease to  $418.6 \pm 157.5 \mu\text{m}$  (252–808  $\mu\text{m}$ ) was observed after 3 months. Thereafter, CRT remained mainly stable, showing only small changes.

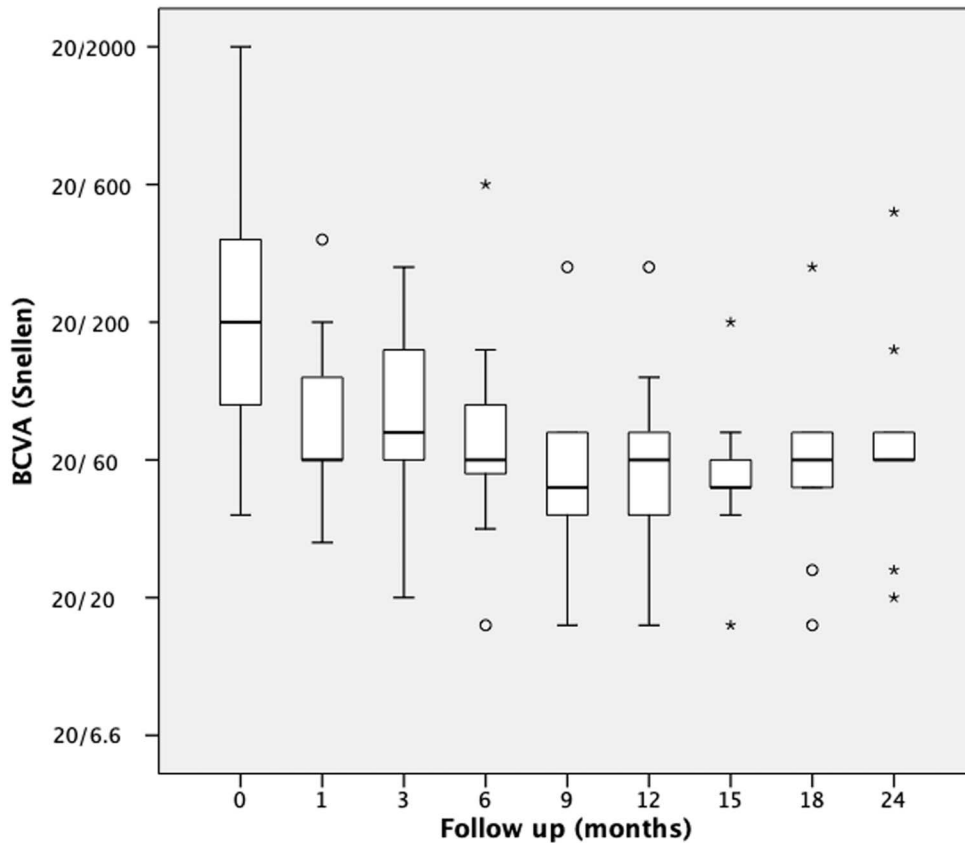
After the initial significant CRT reduction at Month 3, a further CRT decrease to  $373.1 \pm 71 \mu\text{m}$  (range: 287–516  $\mu\text{m}$ ) was observed between Month 3 and Month 12. Although fluctuations were individually observed, no further significant changes of mean CRT were observed up to Month 24 (CRT:  $386.3 \pm 73 \mu\text{m}$ ; range: 283–502  $\mu\text{m}$ ;  $P = 0.435$ ) (Figure 2). Example of a patient and optic coherence tomography scans are shown in Figure 3.

Overall, in our cohort, CRT showed fluctuations in three patients during the follow-up period. However, only in one of these three patients, a persisting increase

Table 1. Patients’ Baseline Characteristics

Pat. No.	Diagnosis	Previous Complication	Fixation of IOL	Vitrectomy	Number of Previous Intraocular Surgery	BCVA logMAR Baseline (Snellen)	CRT $\mu\text{m}$ Baseline	IOP mmHg Baseline
1	Compl. Cat. Surg.	AC implant	Sclera	Ant.vitr.	22	1.00 (20/200)	528	15.00
2	Globe rupture, severe trauma	Aphakic condition	Sclera (later)	ppv	2	2.00 (20/1,000)	576	7.00
3	Compl. Cat. Surg.	AC implant	Iris	ppv	5	1.50 (20/600)	410	16.00
4	Compl. Cat. Surg.	Aphakic condition	n.a.	ppv	7	1.30 (20/400)	603	14.00
5	Compl. Cat. Surg.; IOL luxation	AC implant	Iris	ppv	4	0.20 (20/30)	536	17.00
6	Compl. Cat. Surg.	AC implant	Sclera	ppv	3	0.30 (20/40)	553	14.00
7	Compl. Cat. Surg. IOL dislocation	AC implant	Iris	Ant.vitr.	4	0.70 (20/100)	403	11.00
8	Luxated IOL	AC implant	Iris	ppv	6	1.30 (20/400)	1,203	12.00
9	Compl. Cat. Surg.	Endophthalmitis	Sulcus	ppv	2	1.00 (20/200)	758	16.00
10	Severe trauma	Aphakic, CB detachment	n.a.	ppv	16	0.70 (20/100)	446	4.00

The table shows patients’ baseline characteristics before the study procedure. Compl. Cat. Surg., history of complicated cataract surgery; AC implant, previous migration of steroid implant into the anterior chamber; BCVA in log MAR; CRT, CRT in  $\mu\text{m}$ ; IOP, IOP in mmHg.



**Fig. 1.** Development of best-corrected visual acuity (BCVA) from baseline to Month 24.

of CRT was observed initially after 18 months and further after 24 months, reflecting a low recurrence rate after 24 months. Figure 4 shows the Kaplan–Meier curve for recurrence rate over the follow-up period.

*Intraocular Pressure*

Mean IOP did not change significantly during the follow-up period. Preoperatively, mean IOP was  $12.6 \pm 4.2$  mmHg, at 12 months  $14.3 \pm 3.4$  mmHg, and at Month 24  $13.4 \pm 3.0$  mmHg. Increased IOP was observed in three of the treated patients during the 24 months follow-up. Of those, two patients had raised IOP within the first month. In two of the three patients, normalization of IOP was possible with implant reposition or topical antiglaucomatous treatment, and in one patient, removal of the implant was necessary.

*Adverse Events/Safety*

The overall safety of the procedure was good in most of the 10 patients, with only mild complaints of dry eye symptoms or discomfort within the first 4 weeks after the surgery in nine of 10 patients with spontaneous resolution in all cases.

There were no complications directly related to the insertion and retention of the implant because of a

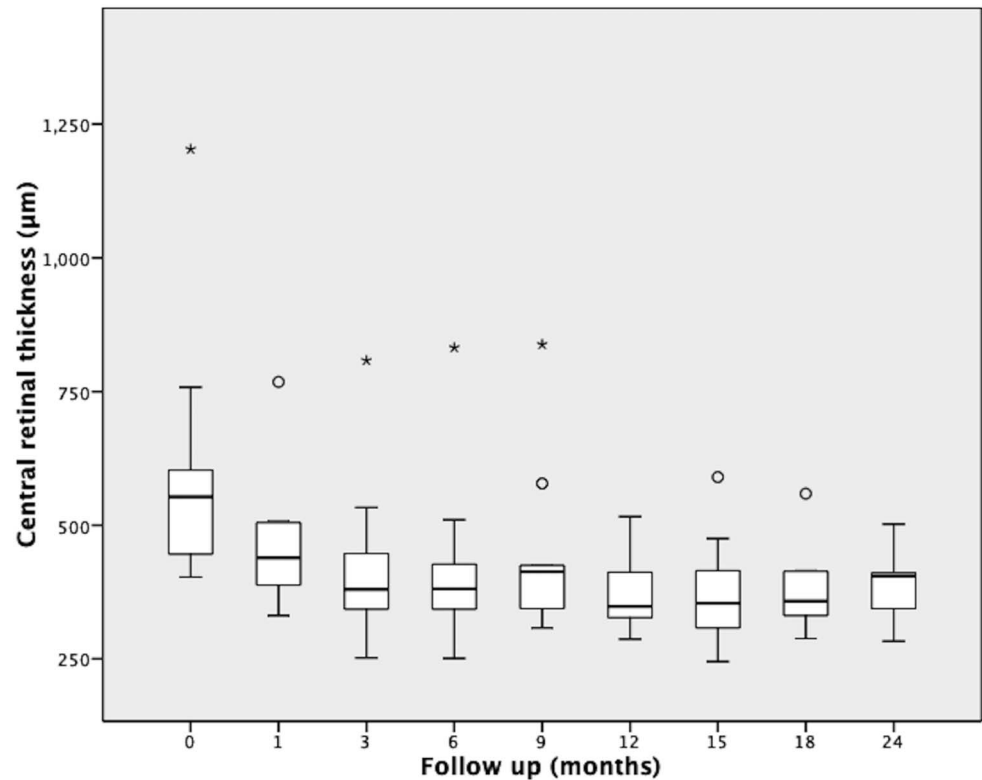
strictly standardized procedure protocol. During the follow-up, no dislocation of the implant was observed.

Direct complications related to the fluocinolone implant and leading to surgical treatment were observed in two patients (Patient 5 and 10).

In one patient who experienced IOP increase in the first 2 weeks after implantation, the implant was repositioned posteriorly at Week 2, because it was considered to have been induced mechanically. Thereafter IOP stabilized without any medication up to Month 6 (Patient 10). Of note, this patient had a severely traumatized eye with convulsion of the ciliary body and preexisting ocular hypotony. However, an increase of IOP thereafter required a topical therapy only. In another patient (Patient 7), IOP increased 10 months after the implantation, but remained under control with topical antiglaucomatous agents.

One further patient required oral medication for IOP control (Patient 5) at Month 1. Because of persistent, uncontrolled IOP under local and systemic medication, a glaucoma surgery was necessary at Month 5 (XEN gel implant, Pharm Allergan). Nevertheless, IOP persisted above 30 mmHg and 2 months later, the fluocinolone implant was removed, with immediate IOP normalization without any further antiglaucomatous treatment within 5 days. As expected, a

**Fig. 2.** Development of CRT from baseline to Month 24.



recurrence of PCME occurred 2 months after fluocinolone implant removal and was further treated with anti-VEGF agents.

Two other surgical interventions were mostly associated with the underlying disease that caused PCME.

In a patient with a history of severe globe rupture, aphakia, and previous vitrectomy, a new rhegmatogenous retinal redetachment occurred 4 months after implantation and was therefore treated with revitrectomy and gas tamponade. However, because of persisting hypotony revitrectomy with silicon oil filling was necessary during later follow-up.

The other patient (Patient 3) had to undergo Descemet membrane endothelial keratoplasty (DMEK) because of worsening of preexisting corneal decompensation at Month 14. In this patient, corneal damage was caused by previous migration of a dexamethasone implant into the anterior chamber before inclusion in the study.

## Discussion

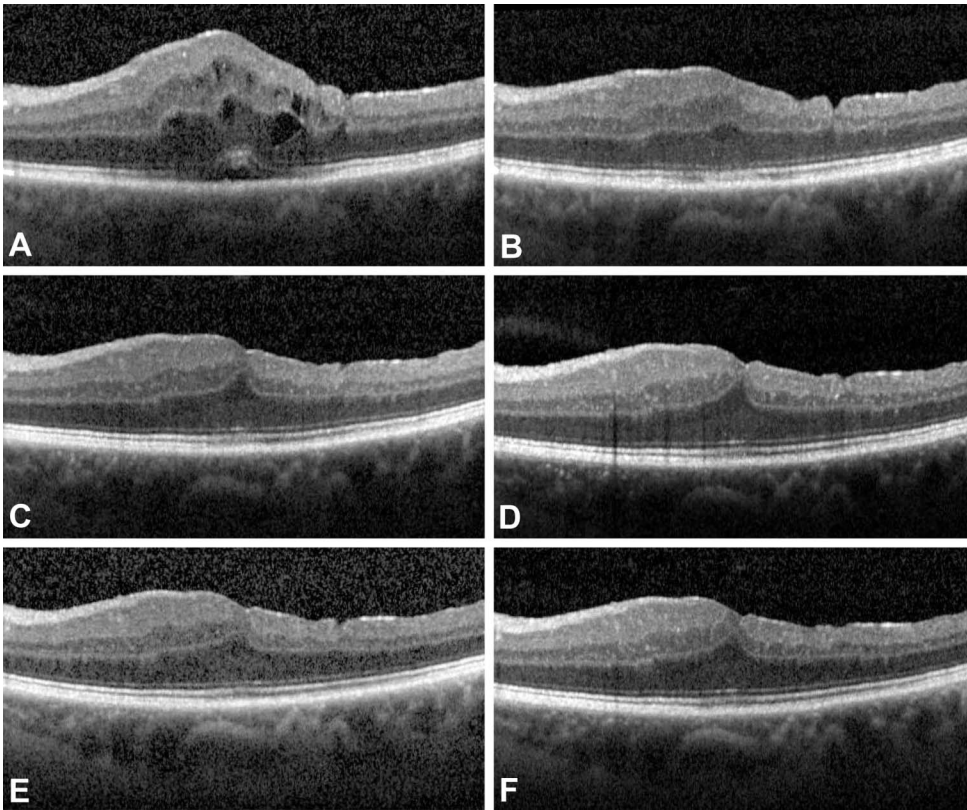
Eyes with disrupted iris–lens diaphragm after complicated cataract surgery or trauma are challenging to handle from several aspects. Although such eyes are at a high risk to develop PCME, such patients with anterior chamber IOL or aphakia are very difficult to treat with existing treatment modalities. IVSIs are a good option,

but the use of them bears a high risk of migration of the implant into the anterior chamber.<sup>6,7</sup> Because of that, many eyes with PCME are left untreated leading to visual deterioration in the long-term.

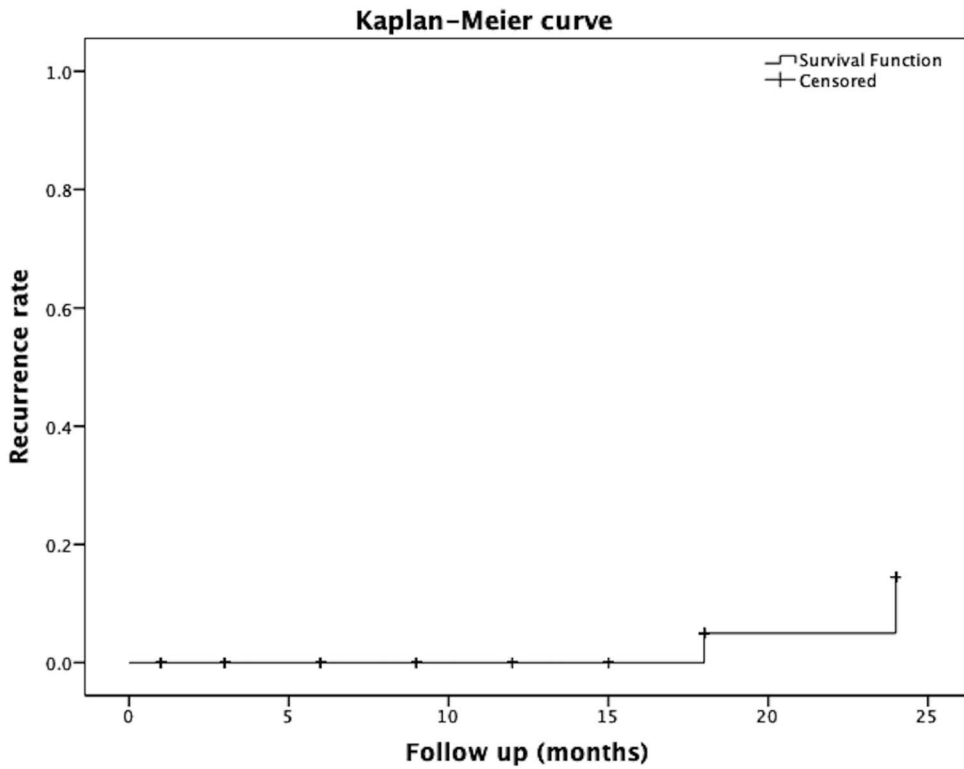
The FLAT technique with scleral fixation of fluocinolone implant previously described seems a reasonable technique that can be applied for long-term treatment of PCME in complex cases. This two-loop technique prevents the implant from slipping out of the fixated thread and can provide treatment of PCME with a long-term effect. Furthermore, because of scleral fixation with the same thread, this technique also allows for an atraumatic removal of the implant in a fish-rod-like manner, because it has become necessary in one of our patients. Therefore, this simple and novel surgical technique may be even more suitable for those severely damaged eyes, who otherwise would have a higher risk for side effects, mainly the migration of IVSI into the anterior chamber.

Scleral fixation of IVSIs has been described for dexamethasone implant and for fluocinolone implant before.<sup>8–10</sup> Nevertheless, the biodegradation of the dexamethasone implant may result in a loosening of fixation with possible migration into the anterior chamber or parts of the implant accompanied by severe, although mostly reversible corneal complications.<sup>7</sup>

Furthermore, the duration of treatment efficacy is longer with fluocinolone than with the dexamethasone



**Fig. 3.** Patient example: Optical coherence tomography scans of a 74-year-old female patient with recalcitrant PCME in the left eye after complicated cataract surgery and secondary IOL implantation (A) before the treatment with fluocinolone implant, (B) at Month 1, (C) at Month 3, and (D) at Month 6, (E) at Month 12, and (F) at Month 24 of the study. Visual acuity increased from 0.3 log MAR (Snellen 20/40) to 0.00 log MAR (Snellen 20/20).



**Fig. 4.** Kaplan-Meier curve for recurrence rate over the follow-up period.

implant. This means a lower treatment burden and less visits, which may result in an overall lower cost at the long-term. Because all included patients had multiple previous surgeries, a long-term stabilization with only one minimal-invasive procedure and a long-acting steroid seems to be the best approach.

This is the first prospective study to report the functional and visual long-term outcomes of this technique in complex cases and the complications over a follow-up period of two years. This study enrolled very complex cases with recurrent PCME that was not responding to other treatments or made repeated treatments with other medical agents inevitable. Therefore, initial visual acuity in our population was poor. Overall, mean BCVA showed a significant improvement within the first month that remained up to the last follow-up visit. In accordance with this finding, mean CRT reduced in average over 150  $\mu\text{m}$  within the first month and further 30  $\mu\text{m}$  by the third month. Despite the observed individual fluctuations in three patients, a recurrence with a persisting increase of PCME was observed only in one patient 18 months after the injection. These findings support a sustaining effect of fluocinolone implant over 24 months in our cohort. Surgical removal of the implant because of raised IOP was necessary only in one patient, despite previous glaucoma surgery and treatment with anti-glaucomatous drugs.

Because the efficacy of dexamethasone implant (Ozurdex) dissipates after 3 to 4 months as it has been shown for diabetic macular edema, the need for a longer acting treatment in these complex study eyes is reasonable.<sup>13</sup> Furthermore, a recent study could confirm the reduction of CRT fluctuations with fluocinolone implant in diabetic macular edema patients in the long-term.<sup>14</sup> This may support the fact that in our study there is a second decrease from Month 3 onward, which is not observed in a treatment using a shorter acting agent.

The main limitation of our study is the small number of subjects. Furthermore, despite the monthly follow-up, no imaging of the position of the implant was obtained in these cases. Nevertheless, the eyes included in this study are very complex and rare cases and therefore a heterogeneous entity difficult to evaluate. To our knowledge, ours is the first prospective clinical trial in this complex patient group with monthly visits and a close record of all possible adverse events of medication in the diagnosis PCME and of the procedure itself.

In summary, our results confirmed the overall long-term benefit and safety of scleral fixation of fluocinolone implant in eyes with iris–lens diaphragm disruption and recurrent PCME, because these eyes would otherwise have been left untreated and resulted in a poor visual prognosis.

**Key words:** fluocinolone implant, cystoid macular edema, scleral fixation, iris–lens diaphragm disruption.

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