Expert Opinion

Iluvien™: a new sustained delivery technology for posterior eye disease

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Iluvien™ (fluocinolone acetonide intravitreal insert, Alimera Sciences, Inc.), a novel injectable intravitreal insert, is being studied to deliver a very low dose of a corticosteroid to the retina for up to 3 years as a treatment for diabetic macular edema. Using a proprietary 25-gauge injector system, an ophthalmologist injects the Iluvien insert, which uses the Medidur™ (Alimera Sciences, Inc.) technology, into the vitreous through a minimally invasive procedure in an out-patient setting. The placement of the device in the inferior vitreous has the potential to maximize drug at the retina while reducing exposure of the anterior chamber. Phase III studies are underway to test the safety and efficacy of Iluvien. This article offers a specific review of the Iluvien technology rather than an overview of the various intravitreal methods of treating posterior eye disease.

Keywords: diabetic macular edema, fluocinolone acetonide, intravitreal, sustained delivery

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1. Introduction

Fueled by an aging population and a rapid increase of obesity, diabetes has reached epidemic proportions worldwide. Each year, another 7 million people develop diabetes. In 2007, 246 million people worldwide had diabetes. In 2025, that figure is projected to be 380 million, an increase of 55% [1].

Diabetic macular edema (DME) is part of the spectrum of findings associated with diabetic retinopathy and results from the hyperglycemic state and other metabolic changes. DME is characterized by the accumulation of extracellular fluid in the retina, which occurs after breakdown of the blood–retinal barrier due to dilated hyperpermeable capillaries and microaneurysms [2-4]. The mechanism of breakdown of the blood retinal barriers is likely to involve changes to the tight junction proteins, and VEGF has been implicated as a significant mediator in that process by numerous studies [1-9]. VEGF is an inflammatory cytokine that is released in the eye in response to hypoxia [6].

2. Treatments for diabetic macular edema

There are no approved drug therapies for DME in Europe or the US. The primary treatments are laser photocoagulation and vitrectomy; however, neither treatment is effective for all patients, and physicians are looking for new treatment options. One of those treatments may be Iluvien™ (fluocinolone acetonide [FA] intravitreal insert, 0.18 mg, Alimera Sciences, Inc.), a novel injectable intravitreal insert, is being studied to deliver a very low dose of a corticosteroid to the retina for up to 3 years as a treatment for diabetic macular edema. While this article does touch on various methods of treating posterior eye disease, it is intended to provide a specific review of the Iluvien technology rather than a general overview of the intravitreal treatments.

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2.1 Current surgical interventions

Laser photocoagulation is the current standard of treatment for DME, and it has been shown to reduce the incidence of moderate visual loss [1]. Photocoagulation is used to seal leaking microaneurysms and has been shown to reduce the risk of vision loss in 60% of patients with proliferative diabetic retinopathy and 50% of those with DME [1,2]. However, < 3% of patients experienced a three-line improvement in visual acuity during 1 – 3 years of follow up [4]. Photocoagulation can also have serious side effects, including pain during treatment, short- and long-term visual loss, restriction of the visual fields and night blindness [6,10].

Vitrectomy, which involves the removal of the vitreous and its replacement with a fluid or gas, is indicated when there are vitreous hemorrhage and tractional retinal detachment [1,2]. This may be of value in the treatment of DME that results from the traction of the vitreous on the macula. Retrospective studies have suggested that 38 – 100% of eyes that underwent vitrectomy for DME showed improved visual acuity [7]. However, vitrectomy can accelerate cataract formation and can cause retinal detachment and endophthalmitis [2].

2.2 Current pharmacotherapy for diabetic macular edema

Due to the absence of alternative drug treatments, drugs that are not approved for DME are being used extensively based only on perceived efficacy and small preliminary studies [11]. Anti-VEGF intravitreal injections, such as pegaptanib, ranibizumab and bevacizumab, have been studied for the off-label treatment of DME [6]. These drugs have previously proved successful in slowing the formation of subretinal fluid and the growth of new vessels in patients with age-related macular degeneration [1]. Findings from various studies suggest that intravitreal injections of these drugs may significantly improve visual acuity, decrease central retinal thickness, and resolve leakage of neovascularization [8,9].

Although triamcinolone acetonide (TA) has not been approved by the FDA for the treatment of DME, 90% of retinal physicians reported that they use TA for some patients with DME [11]. The injection of a suspension of TA suppresses inflammation, reduces vascular leakage, and inhibits fibrovascular proliferation [1]. A 2-year study has demonstrated that intravitreal injections of TA improve visual acuity and reduce macular thickness, even in patients with refractory DME [12].

TA may be more effective than anti-VEGF drugs in treating DME. A recent study demonstrated that a single injection of TA was associated with a greater reduction in central macular thickness in patients with refractory diffuse DME compared with a single injection of bevacizumab in the short term [13]. This may be the result of simultaneously interfering with VEGF through multiple pathways.

Injections of TA are, however, limited by the time-dependent nature of their benefits and the variable duration of their effect [7,8]. In some patients, recurrence of DME symptoms can come as early as 2 weeks after injection, while in other patients, recurrence comes later [7]. The effect of TA injections typically lasts 3 – 6 months [12].

Clinically, intravitreal injections have a risk of serious complications: endophthalmitis, retinal detachment, iritis, uveitis, ocular hypertension, intraocular hemorrhage and hypotony [1,6,14]. Administration of corticosteroids by many routes may result in cataract formation and elevated intraocular pressure (IOP).

3. Optimizing corticosteroid therapy for diabetic macular edema

3.1 Rationale

The use of corticosteroids suppresses inflammation and reduces damage to the blood–retinal barrier [15]. Because DME is primarily a vascular disease with some aspects of chronic inflammation, these effects suggest that the use of corticosteroids may be an excellent therapeutic strategy.

Recent work has demonstrated that the affinity of different corticosteroids for the glucocorticoid receptor varies and that the relative potency of corticosteroids in dermatological preparations is not necessarily predictive of the potency when the drugs are administered intravitreally. This has been demonstrated by the finding that FA and TA have greater affinity for the receptor (by more than an order of magnitude) than dexamethasone [16]. Longer-term sustained-delivery formulations may be feasible with FA or TA, as less of the drug will be required than for a less potent drug.

In designing corticosteroid therapy for DME there are several issues to consider. Perhaps the most limiting problem of corticosteroid use in the eye is the potential for adverse effects in the anterior segment, such as elevated intraocular pressure and cataracts. A delivery system that minimizes exposure of the anterior segment to the drug might provide significant advantages. New formulations would ideally minimize the number of injections to reduce the risks of infection and retinal detachments while providing consistent long-term delivery. A brief summary of other technologies under development for the delivery of glucocorticoids to the retina is provided in Section 7.

3.2 Retisert

As FA has been in use for many years as a dermal product, its pharmacology, systemic metabolism and elimination are well established. FA has already been formulated in a sustained-delivery device, Retisert® (Bausch and Lomb, Inc.). This surgically implanted device was developed by Control Delivery Systems, Inc. (now pSivida Limited) and is marketed for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. It has not been submitted to the FDA for use in DME. The device consists of FA coated with silicone and polyvinyl attached to a 5.5-mm silicone suture tab that is surgically implanted in

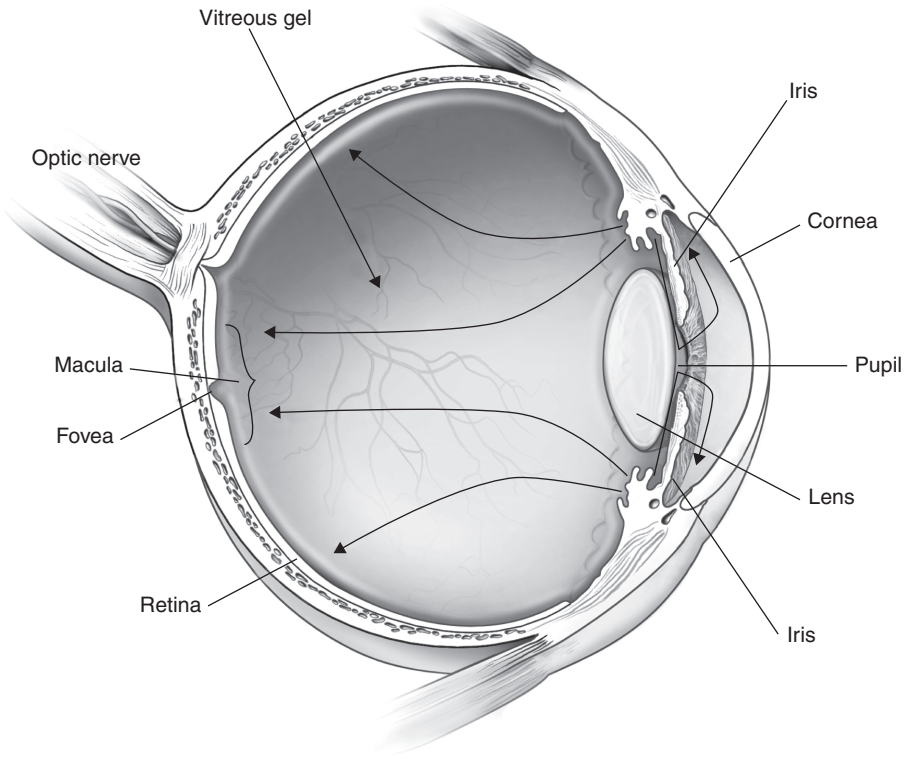

Figure 1. Fluid movement in the eye. Aqueous humor is produced by the ciliary process, migrates through the zonules to the anterior chamber and is eliminated from the eye through Schlemm's canal at the corner of the cornea and iris. Aqueous humor also migrates through the vitreous humor and is eliminated by active transport through the retinal pigment epithelium which lies under the retina.
Figure from National Eye Institute, National Institutes of Health, USA. Arrows added by authors.

the vitreous at the pars plana and releases the drug at a nominal initial rate of 0.59 µg/day (Retisert PI). This placement allows release of drug near the ciliary processes (the source of aqueous humor). A discussion of Retisert is pertinent to this article because Retisert contains the same drug in the same polymer matrix (but in a different physical device) as Iluvien.

The release kinetics and ocular drug levels of intravitreal Retisert were determined in rabbit studies with durations of 2 h, 2 weeks and 3, 6, 9 and 12 months [17]. In this study, rabbits were implanted with FA/Retisert sustained-release intravitreal systems releasing at rates of 0.5 or 2 µg/day. Drug levels in various ocular tissues were determined for up to 1 year postimplantation. FA mean values were consistent over 12 months in the range of 9 – 14.6 ng/ml and 91 – 106 ng/ml for the 0.5 and 2 µg/day implants, respectively. Aqueous humor levels were ~ 100× less than vitreous levels. Plasma levels of FA in patients treated with Retisert were below the limit of detection of 0.2 ng/ml at all times [17].

The data from the Phase III clinical studies of Retisert for the treatment of DME performed by Bausch and Lomb indicate that, after 2 and 3 years of therapy, intraocular sustained-release FA from Retisert is a more effective treatment than the current standard of care, which includes laser photocoagulation, as judged by the percentage of subjects with complete resolution of DME and by 15-letter gain in visual acuity [18-22]. The studies in uveitis indicate significant efficacy of the implant for reduction of inflammation, decreased recurrence of disease and improved vision. The adverse events common in the large DME Phase III clinical study were cataract and IOP elevation. The incidence of cataract was 95% by the end of 3 years. The incidence of IOP elevation (≥ 30 mmHg) remained stable through 3 years of treatment at ~ 35%. Despite pharmacotherapy, 28% of patients required filtration surgery to reduce IOP by the end of the third year. Approximately 5% required explantation of the Retisert device due to IOP elevation [18-22].

These results indicate that FA has a positive effect on DME; however, the side-effect profile made the Retisert delivery system less attractive for long-term treatment of DME.

3.3 Models of intravitreal drug distribution

There may be substantial variability in the local concentrations of drugs administered into the vitreous. Using a mathematical model, Friedrich *et al.* have concluded that the location of

Table 1. Rabbit ocular tissue levels after 0.59 mg Retisert implant.

Tissue assayed	Mean fluocinolone acetonide levels (ng/g or ng/ml)	
	6 months	12 months
Aqueous humor	0.21	0.19
Lens	27.87	23.72
Iris-ciliary body	35.05	13.89
Vitreous	17.10	10.72
Retina	42.28	56.01
RPE/choroid	21.93	24.88

RPE: Retinal pigment epithelium.
Data from [17].

an intravitreal injection may have a very large effect on the distribution and elimination of drugs in the vitreous. Injections of fluorescein situated near the lens resulted in > 600-fold concentrations at the lens than at the retina (peak values of 0.989 µg/ml at the retina versus 628 µg/ml at the lens [23].

A computer simulation suggests that both anterior and posterior routes of elimination are important for the drug clearance after intravitreal injection [24]. The model predicts that small molecules will be cleared by absorption into the retina or movement into the aqueous.

Animal data from two drug delivery systems, Posurdex® (dexamethasone intravitreal insert, Allergan, Inc.) and Retisert, support the concept that a drug released from a point in the posterior segment of the eye creates a gradient between the anterior and posterior segments by taking advantage of the convection currents that exist in the vitreous. Fluid from the posterior vitreous is actively removed by the retinal pigment epithelial cells, creating a 'current' towards the retina [25,26]. At the same time, fluid is leaving the front of posterior chamber through the canal of Schlemm by way of the anterior chamber (see **Figure 1**).

Ocular pharmacokinetic data from rabbits has been published for Retisert [17]. In this study, the device was implanted in the eye and tissues were collected at various times over 12 months. The FA levels in the tissues were determined and are shown in **Table 1**. It is interesting to note that the posterior segment drug concentrations are > 10-fold higher than the anterior segment drug concentrations. The levels in the aqueous humor were < 1/250 of those in the retina. Importantly, the drug gradient persisted over the 12-month period [17].

Posurdex is the second delivery system for which data have been presented that support the gradient concept [27]. Welty *et al.* have reported that the dexamethasone concentrations in both vitrectomized and non-vitrectomized eyes were similar with the Posurdex delivery technology. The concentration decreased as the distance from the device increased such that proximal retina > distal retina > vitreous > iris-ciliarybody > aqueous humor [27].

Lee *et al.* used the Retisert drug distribution results from Driot and developed a pharmacokinetic model to simulate drug distribution [28]. This model indicates that with a more posterior location of the device, the levels in the retina are increased, while those in the anterior chamber are decreased. They hypothesize that moving Retisert 4 mm posteriorly would result in at least a four-fold reduction in anterior chamber drug exposure. The authors suggest that by leveraging vitreous convection currents the potential exists to minimize the side effects of glucocorticoids for DME [28].

From these theoretical models and animal experiments, these authors speculate that the two key factors in leveraging vitreous fluid dynamics to improve corticosteroid treatment of the retina are the point of release and the dose released. The modeling predicts that delivering ≤ 0.59 µg/day at the equator, will result in near-zero anterior chamber exposure. Furthermore, minimizing the 'burst' and daily release has the potential to improve the safety profile by ensuring that the fluid dynamics are not overcome [28].

4. Iluvien intravitreal insert

4.1 Device description

Alimera Sciences, Inc. has licensed the Medidur™ FA Insert, a new technology that is designed to improve on the performance of Retisert. This miniaturized injectable intravitreal insert, which will be marketed as Iluvien, delivers the lowest dose currently under investigation of corticosteroid to the retina. The high dose of Iluvien (0.5 µg/day) is designed to release drug over an 18- to 24-month period and the low dose (0.2 µg/day) is designed to release drug over a 24- to 30-month period. The therapeutic effectiveness of Iluvien for diabetic macular edema will be determined in human clinical trials. Using a proprietary 25-gauge injector system, an ophthalmologist injects the Iluvien insert into the vitreous during an in-office procedure that takes minutes and does not require any sutures (see **Figures 2 – 4**) [29].

The hypothesis that the Iluvien insert will be effective for DME is based on the Phase III clinical trials performed with Retisert. In these studies, significant numbers of DME patients receiving FA (0.59 µg/day) had a three-line improvement in visual acuity, as well as a corresponding anatomic improvement [29]. The Iluvien insert relies on improved technology by virtue of its smaller size, thus eliminating the need for surgical implantation in the operating room and allowing the placement of the insert in a more posterior location in the eye. As a result of the vitreous fluid dynamics, the ratio of anterior to posterior tissue levels is predicted to be smaller. The differences in the two versions are presented in **Table 2**.

4.2 *In vitro* performance

Initial *in vitro* release rates of ~ 0.5 µg/day and 0.2 µg/day steadily dropped after 6 months to ~ 0.2 µg/day and

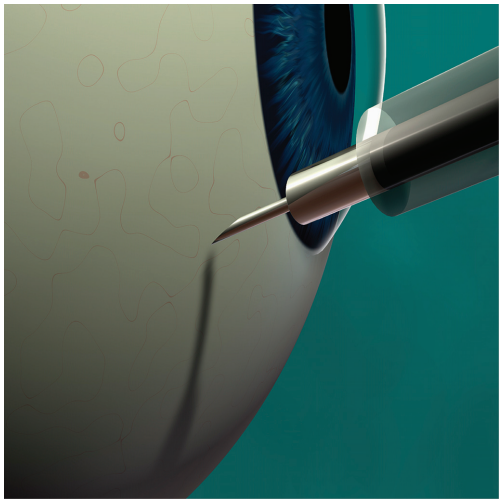

Figure 2. Site of insertion of injector.

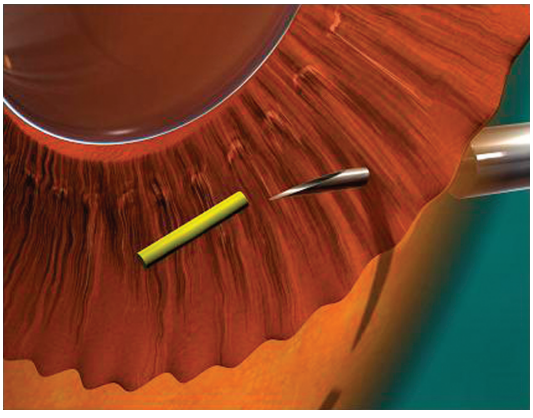

Figure 3. Interior eye view of the delivery of the Iluvien insert via the pars plana.

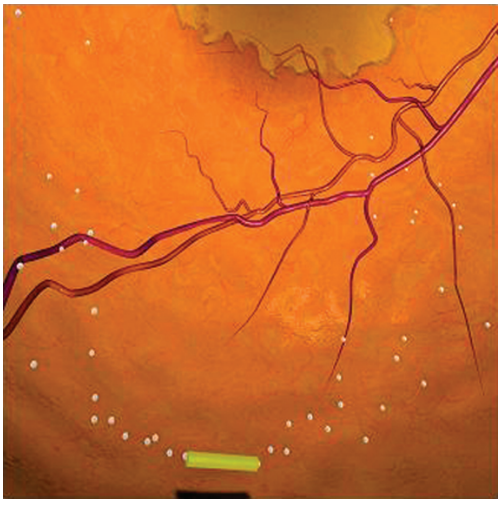

Figure 4. Location of Iluvien insert in inferior vitreous.

0.14 µg/day, respectively. At 18 months, the release rates were similar for both doses (~ 0.15 µg/day).

The insert has polyvinyl alcohol (and for the 0.2 µg/day, silicone bioadhesive) endcaps designed to regulate the drug release rate. Based on the DME data for Retisert, it is believed that the efficacy of 0.5 µg/day is supported in this indication. It is not known if a lower dose may also be efficacious, with potentially fewer side effects; therefore, a dose of 0.2 µg/day, which is currently the lowest daily delivered dose of a glucocorticoid, is also being evaluated. The Iluvien device releases the FA in a nearly zero-order manner, with a slightly higher initial release, which stabilizes to a long-term stable release (see **Figure 5**). Iluvien inserts are not bioerodible and are expected to remain in the eye permanently. In the ongoing Phase III studies, patients may receive as many as three inserts over the life of the study.

4.3 Development status of Iluvien

The FAME™ Study (Fluocinolone Acetonide in Diabetic Macular Edema), comprising a pair of Phase III clinical trials, was launched in September 2005. A total of 956 subjects were enrolled at > 100 study centers in the US, Canada, Europe and India, and randomized to one of three treatment schedules in a ratio of 2:2:1. The 24-month readout is expected during the fourth quarter of 2009, and confirmatory analysis will take place at month 36. During 2008, updates will be provided on an open-label, pharmacokinetic trial studying the same doses and same patient population as the FAME trial. Additional studies are underway or planned for other potential applications in the treatment of exudative age-related macular degeneration, geographic atrophy and retinal vein occlusion.

5. Conclusions

Diabetes and its ocular complications, diabetic retinopathy and DME, are a growing problem worldwide, and successful treatments are urgently needed. By employing an understanding of the eye's fluid dynamics, the Iluvien intravitreal insert combines a potent corticosteroid with the Medidur delivery platform, which may improve the treatment of DME.

6. Expert opinion

Clearly, patients and physicians need better methods for the delivery of drugs into the eye, especially for the treatment of retinal diseases. The delivery of a potent corticosteroid to the macula has the potential to reduce macular edema and retinal neovascularization, the two sight-threatening aspects of diabetic retinopathy. Immediate-release corticosteroids have been used for the treatment of DME, but side effects of increased intraocular pressure and cataract limit their use. The development of strategies to leverage the physiologic currents in the vitreous may achieve therapeutic doses at the

Table 2. Comparison of Retisert and Iluvien.

	Retisert®	Iluvien™
Fluocinolone acetonide	590 µg	180 µg
Nominal initial target release rate	0.6 µg/day	0.5 µg or 0.2 µg/day
Microcrystalline cellulose	Present	Not present
Magnesium stearate	Present	Not present
Silicone adhesive	Present	Not present for 0.5 level, present for 0.2 level
Polyvinyl acetate	Present	Present
Size of product	Approx. 5 mm × 3 mm × 2 mm	Cylindrical 3.5 mm × 0.37 mm
Administration method	Surgical implantation with suture tab	Injection through 25-gauge needle

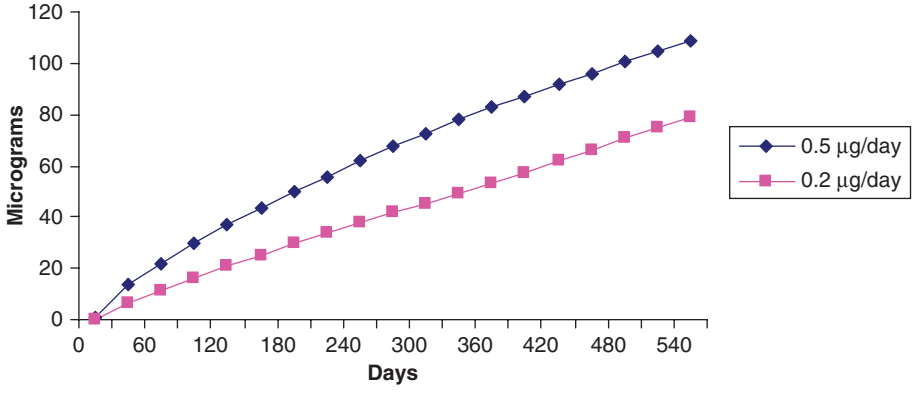

Figure 5. *In vitro* average cumulative fluocinolone acetonide release rate of two doses of Iluvien™ inserts.

Table 3. Comparison of intravitreal glucocorticoid products.

Agent	Total dose (daily release)	Procedure	Duration
Posurdex®	750 µg dexamethasone (estimated ~ 6.25 µg/day)	Injectable	~ 4 months
IVTA (Triesence™, Trivaris™)	4 mg TA (unknown)	Injectable	~ 3 months
Retisert®	500 µg FA (0.59 µg/day)	Incision and suture	2.5 years
Iluvien™	180 µg (0.5 µg or 0.2 µg/day)	Injectable	Up to 3 years
I-Vation™	Dose 925 µg TA	Incision with scleral implantation	Up to 2 years

FA: Fluocinolone acetonide; TA: Triamcinolone acetonide.

retina and reduce the exposure to the trabecular meshwork and lens. These strategies may also reduce the number of intravitreal injections and their attendant risks. Current clinical trials will determine if the risks and benefits of more persistent drug treatment may reduce long-term vision loss and progression of diabetic retinopathy. Reducing the number of treatment appointments may be important for patients with DME, many of whom are under 65 and still working. The burden of frequent injections on physicians and the healthcare system in general may also be reduced.

Iluvien is poised to be the first sustained-delivery corticosteroid to be submitted to health authorities in the US and European Union for the treatment of DME.

7. Alternative novel technologies for corticosteroid delivery to the retina

The products in use (intravitreal triamcinolone acetonide [IVTA]) or in development for which information is available are described in **Table 3**.

IVTA generally requires multiple intravitreal injections to maintain a therapeutic effect. No standard regimen has been developed; however, the duration of effect typically reported appears to be ~ 3 months. The sustained-delivery devices, Retisert and Iluvien, provide the benefit of less frequent administration; however, Retisert requires a surgical procedure, whereas Iluvien is injectable. The creation of a self-sealing wound for delivery of Iluvien is expected to provide greater safety and ease of delivery than the surgical approach of Retisert. Some of the complications of Retisert (endophthalmitis, hypotony) may be eliminated, as many of these were thought to be due to implant extrusion or suture erosion, which will not occur with the injectable implant. In addition, the low-dose Iluvien device (0.2 µg/day) delivers the lowest daily and total dose of any of the sustained-delivery devices in development. While the I-Vation™ (SurModics, Inc.) implant is reported to have a duration of release > 1 year, the procedure for implantation is unique to ophthalmology due to the 'screw'-like nature of the device, which is inserted into the eye by twisting the device through the pars plana.

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Declaration of interest

F Kane, A Cutino and K Green are employees of, and J Burdan's medical writing services were paid for by, Alimera Sciences, Inc.

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