

## **Preliminary evaluation of YUTIQ (fluocinolone acetonide intravitreal implant 0.18 mg) in posterior uveitis**

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### **Abstract**

Uveitis is a major cause of ocular morbidity, potentially leading to significant visual impairment. The recent adoption of alternative drug delivery options has led to the development of new sustained-delivery corticosteroid systems, able to manage successfully chronic non-infectious posterior uveitis. The treatment goal is to target the site of inflammation with low dose of corticosteroids, delivered over an extended period of time, to minimize the cumulative damage resulting from repeated recurrences, reducing both injections frequency and ocular side effects. This article will review the pharmacology and preliminary clinical data of the 0.18 mg fluocinolone acetonide intravitreal implant (Yutiq), to show its efficacy and safety in the treatment of non-infectious posterior uveitis.

### **Keywords**

Fluocinolone acetonide, Yutiq, intravitreal corticosteroid implant, sustained-release drug delivery system, non-infectious uveitis, posterior uveitis.

## Background

Uveitis encompasses a group of sight-threatening inflammatory ocular diseases, including multiple, heterogeneous, infectious and non-infectious, clinical entities. It constitutes a major cause of ocular morbidity, that can lead to significant visual impairment if not treated properly.<sup>1</sup> It is estimated that uveitis is responsible for 5-10% of visual impairment worldwide and that up to 35% of patients with uveitis suffer from significant visual loss to legal blindness.<sup>1,2,3,4</sup> The typical course of Non-infectious Posterior Uveitis (NIPU) is characterized by recurrences, with each flare of inflammation potentially leading to incremental visual loss. To limit sight-threatening complications, good control of inflammation and prevention of recurrences is therefore necessary.

Systemic corticosteroids are the mainstay of treatment for NIPU. However, despite providing control of inflammation, long term use of high dose corticosteroids can be associated with both systemic and ocular side effects. In order to reduce steroid complications and improve corticosteroid safety and tolerability, new intraocular drug delivery systems have been recently developed. Intraocular administration of therapeutic agents provides high concentrations of the drug at the site of inflammation, reducing systemic exposure. The intravitreal route of administration coupled with recent design of corticosteroid implants, providing a long local sustained release of the drug at the site of inflammation, has reduced the need for repeated intravitreal injections, necessary to maintain the local anti-inflammatory effect.

Currently, different slow-release, sustained-delivery corticosteroid systems have been approved for the treatment of NIPU with different efficacy and safety profiles.

In 2005, the surgically implanted fluocinolone acetonide (FA) intravitreal implant 0.59 mg (Retisert, Bausch + Lomb/Valeant, Bridgewater, NJ, US) was approved in the USA. The Retisert implant is a non biodegradable device surgically implanted in the vitreous cavity through a pars plana incision. The device provides sustained delivery of 0.59 mg FA with initial release rate of approximately 0.6 µg/day, which decreases over the 1st month to a steady rate of 0.3–0.4 µg per day.<sup>5</sup> The steroid implant was designed to release the drug for between 30 and 36 months and has been demonstrated to control intraocular inflammation effectively in chronic non infectious uveitis affecting the posterior segment of the eye.<sup>6</sup>

In 2011, Ozurdex (Allergan, Irvine, CA), an injectable 0.7-mg dexamethasone-containing intravitreal insert, was approved by the U. S. Food and Drug Administration (FDA) for use in the treatment of adult patients with inflammation of the posterior segment of the eye presenting as non-infectious uveitis. It is delivered intravitreally with a 22-gauge applicator through a shelved injection technique to ensure a self-sealing wound.

A single dexamethasone implant significantly improves intraocular inflammation and visual acuity, enabling an extended release over a 6-month period.<sup>7,8</sup>

In 2018, Yutiq (EyePoint Pharmaceuticals, Inc., Watertown, MA, US), a sterile non-bioerodible intravitreal implant containing 0.18 mg FA, was approved by the U. S. FDA, based on clinical data from two randomized, sham injection-controlled, double-masked phase 3 clinical trials.<sup>9,10</sup> It releases the drug at an initial rate of 0.25 µg/day in a 36-month sustained-release drug delivery system. Yutiq was designed to improve on the performance of Retisert to deliver a lower dose of corticosteroid to the retina with fewer adverse events, i.e. increased intraocular pressure (IOP) and cataract, reducing patient inconvenience and side effects associated with application methods. Moreover, the long lasting effect decreases the dosing frequency.<sup>11</sup> Yutiq, is nearly identical to Iluvien (Alimera Sciences, Inc., Alpharetta, GA, US), an intravitreal insert currently approved in the United States and Europe for the treatment of diabetic macular edema. Yutiq contains 0.18 mg of FA compared to Iluvien which has 0.19 mg of FA. Both drugs are sterile sustained release non-bioerodible intravitreal implants designed to release drug for up to 3 years. This article will focus on updated data related to pharmacokinetics and pharmacodynamics as well as clinical data on to the use of the Yutiq sustained-release device.

## **Pharmacology**

Fluocinolone acetonide ((6a,11b, 16a)-6,9-difluoro-11,21-dihydroxy-16,17-[(1- methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione) is a medium potency synthetic fluorinated glucocorticoid, used for the past several years as a derma anti-inflammatory product.

**Pharmacokinetics** FA is a corticosteroid with low solubility in aqueous solution, leading steroids to be released over a much longer time period and achieving high concentrations in the posterior segment with very low systemic absorption.<sup>12,13</sup> Preclinical studies evaluated ocular and systemic pharmacokinetics of FA using FA intravitreal implant in pigmented rabbits.<sup>13,14</sup> The results demonstrated that the 0.2 µg/day FA intravitreal implant delivers consistent low levels of drug to ocular tissue for 24 months with no quantifiable systemic exposure.<sup>14</sup> The concentration of FA was measured by a validated liquid chromatography-mass spectrometry/mass spectrometry method both in plasma and ocular tissues at various points of time through the 24-month period. The level of FA was below the quantifiable limit (200 pg/mL) in all plasma samples. Consequently, no further pharmacokinetic analysis was performed. Following the administration of the 0.2 µg/day FA implant, the levels of the drug hit a peak in most tissues at day 2 or 8, reached approximate steady state levels by month 3 and gradually decreased over the 2 year period. The highest levels of FA were

observed in the choroid/retinal pigment epithelium, followed by retina or iris/ciliary body and lens, whereas the lowest levels were detectable in vitreous and aqueous humor. FA levels in aqueous accounts for slightly 2 ng/ml for approximately 3 months, followed by steady-state levels between 1.0 and 0.5 ng/ml through 36 months.<sup>15</sup> Levels of FA in vitreous are limited by its hydrophobic nature in a primarily hydrophilic medium. Tissue distribution of FA demonstrates that the drug diffuses through the vitreous in the retina and other ocular tissues and the insert effectively delivers the drug to the target tissues for posterior uveitis. FA was still present in the vitreous, choroid/retinal pigment epithelium, lens and iris/ciliary body at 24 months. The elimination half lives in the tissues for which it was measurable were greater than 83 days.

### **Clinical efficacy**

The clinical efficacy of Yutiq in the treatment of NIPU has been evaluated in two randomized, sham injection-controlled, double-masked phase 3 clinical trials with patient follow-up continuing for three years (ClinicalTrials.gov identifiers: NCT01694186 and NCT02746991).<sup>16,17</sup> Across the two trials, 282 subjects were enrolled and included in the intent-to-treat populations and safety populations. Of these, 188 subjects were randomized to the drug treatment group and 94 subjects were randomized to sham injection group. Patients with non-infectious uveitis affecting the posterior segment of at least 1 eye for a minimum of 1 year were included in the studies. During the year before the enrolment they had experienced at least 2 different relapses of intraocular inflammation, requiring systemic steroids or immunosuppressive agents or local steroid therapy, or had been treated with systemic medications for a minimum of 3 months or with at least 2 local steroid injections. The primary outcome, which was performed on the intent-to-treat population, was to assess any difference in the frequency of recurrences of uveitis by month 6 between the study groups. Secondary end points were related to treatment-group comparisons through 12 months of relapse rate, cumulative number of reactivations, time to first recurrence, best corrected visual acuity (BCVA) modification from baseline, resolution of intraretinal fluid and number of additional treatments required. Pooled 6-month results from the two trials showed improvements in the rate of uveitis recurrence (26.6% versus 73.4%;  $p < 0.001$ ) and visual acuity (mean change: +6.0 versus +4.4 letters) in implanted eyes compared with sham-treated eyes.<sup>9</sup>

The prespecified primary outcome end point (6-month analyses) and 12-month results of one of the two phase 3 controlled studies have just been published by Jaffe et al. (clinicaltrials.gov identifier, NCT01694186).<sup>10</sup> One hundred twenty-nine participants with recurrent NIPU were included and assigned randomly to FA insert ( $n=87$ ) or sham injection ( $n=42$ ). The uveitis recurrence rates in FA insert eyes and sham injection eyes were 28% and 91% at 6 months and 38% and 98% at 12 months, respectively. The recurrence rates were significantly

lower ( $P < 0.001$ ) in the FA insert group compared to the sham injection group. The median time to first recurrence was 378.0 days for FA insert eyes and 70.5 days for sham injection eyes. Fewer recurrences per study eye (mean, 0.7 vs. 2.5), lower incidence of 15-letter or more decrease in BCVA (14% vs. 31%), reduced systemic, corticosteroid or immunosuppressant, (19% vs. 40%) and local, intraocular or periocular, (7% vs. 62%) uveitis adjunctive treatments were observed in FA insert eyes vs. sham, respectively. A total of 71% of FA insert and 48% of sham injection study eyes with macular edema reported at baseline had no intraretinal fluid reported at 12 months. At baseline, the mean central subfield thickness (CST) was  $368.0 \pm 145.0 \mu\text{m}$  and  $369.5 \pm 165.4 \mu\text{m}$  for FA insert eyes and sham injection group, respectively. At 12 months, CST decreased to  $285.5 \pm 75.6 \mu\text{m}$  and  $303.7 \pm 113.1 \mu\text{m}$  for FA insert and sham injection study eyes, respectively. Vitreous haze stabilized or improved at a higher rate in the FA insert group compared to the sham injection group, and the same results were observed for the improvement of anterior chamber cell counts.<sup>18,19</sup> Table 1 summarizes study results.

### **Safety and tolerability**

FA inserts provide steady-state aqueous levels achieved approximately 6 months after administration in the range of  $1.0 \pm 0.5 \text{ ng/ml}$  for 36 months.<sup>15</sup> The most common reported adverse effects associated with the use of intraocular steroids are cataract formation and elevated intraocular pressure (IOP).

The safety profile of Yutiq for the proposed indication is based on the data derived from the two phase 3 clinical trials. Pooled results from the trials include all clinical data collected through month 12 and through month 6 (ClinicalTrials.gov identifiers: NCT01694186 and NCT02746991, respectively).<sup>20</sup> The most frequently reported ocular treatment emergent adverse events (TEAEs) in the FA insert group for the study eye were increased IOP (27%), cataracts (16%) and reduced visual acuity (12%). The most frequently reported ocular TEAEs in the sham injection group were uveitis (30%), macular edema (19%), and increased IOP (14 % subjects). The most commonly reported severe ocular AE in the FA insert group was hypotony of the eye experienced by 3% subjects.

The 12-month results published by Jaffe et al. showed that the FA insert group had higher rates of cataract (33% vs 12%, respectively; odds ratio, 3.7;  $P < 0.01$ ).<sup>10</sup> There was a slight mean increase in IOP ( $1.3 \pm 3.57 \text{ mmHg}$ ) in insert eyes, whereas mean IOP was unchanged in sham injection eyes ( $0.2 \pm 4.17 \text{ mmHg}$ ).<sup>10</sup> In the FA insert group 48.3% and 18.4% experienced an increase in IOP of more than 5 mmHg or 12 mmHg, respectively, over baseline values compared with 33.3% and 9.5% in the sham study eyes.<sup>10</sup> However,

intraocular pressure-lowering treatment use was similar between groups (26% of FA insert study eyes and 26% of sham injection eyes).<sup>10</sup> No deaths, treatment-related study discontinuations or unanticipated safety signals were observed through 12 months.<sup>10</sup> Safety findings are summarized in Table 1.

## **Conclusion**

The treatment goals for non infectious uveitis are to induce disease quiescence and limit the recurrences of the disease, potentially leading to sight-threatening complications. The ideal treatment targets the posterior tissues of the eye and limits systemic exposure, achieving therapeutic concentration at the site of inflammation, minimizing the cumulative damage resulting from repeated recurrences. The preliminary evaluation of Yutiq shows that the device meets these goals, delivering a low long lasting FA dose to reduce both the well-known ocular side effects of corticosteroid treatment and the dosing frequency. The insert seems to provide effective control of intraocular inflammation associated with chronic non-infectious uveitis affecting the posterior segment of the eye, lowers recurrence rates, increases time to onset of recurrence and reduces the requirement for systemic rescue therapy. The FA insert application is generally well tolerated. Few adverse events associated with the treatment are consistent with the well-known effects of intravitreal corticosteroids. Real world studies as well as studies about cost-effectiveness and quality of life will be of value to provide a better assessment of the role of Yutiq in the management of chronic non-infectious posterior uveitis.

## **Executive summary**

### **Background**

- Uveitis constitutes a major cause of visual morbidity, if not treated properly.
- Systemic corticosteroids are the mainstay of treatment for NIPU; however, long-term use is associated with treatment-limiting adverse effects.
- New slow-release, sustained-delivery corticosteroid systems have been developed, to minimize the cumulative damage resulting from repeated recurrences and reduce ocular side effects of steroid treatment.
- Yutiq (0.18 mg FA) has been approved for the treatment of NIPU.

### **Clinical efficacy**

- Yutiq has been demonstrated to reduce uveitis recurrence rate. The 6-month (28% and 91%) and 12-month (38% and 98%) uveitis recurrence rates were significantly lower ( $P < 0.001$ ) with FA insert vs. sham, respectively.
- The results demonstrated efficacy of Yutiq in increasing time to onset of recurrence, reducing the requirement for systemic rescue therapy and lowering the incidence of 15-letter or more decrease in BCVA.

### **Adverse events**

- The most common reported adverse effects associated with Yutiq are cataract formation and elevated intraocular pressure.

## **Financial and competing interests disclosure**

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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