MODULE 10.3
Clinical Studies and Treatment Data - FAME

FAME[1]

Study Name	Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema.
Purpose of study	To compare efficacy and safety of 0.2 µg/day (low dose) or 0.5 µ g/day (high dose) fluocinolone intravitreal implants in patients with persistent DME.
Study authors	Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, Tolentino M, Gupta A, Duarte L, Madreperla S, Gonder J, Kapik B, Billman K, Kane FE, for the FAME Study Group
Published in	*Ophthalmology.* 2011;118:626-635.
Study also known as	FAME, FAMOUS
Subsequent studies	Campochiaro PA, Hafiz G, Shah SM, et al, for the FAMOUS study group. Sustained ocular delivery of fluocinolone acetonide by an intravitreal insert. ***Ophthalmology.*** 2010;117: 1393–1399. Campochiaro PA, Brown DM, Pearson A, et al. for the FAME Study Group. Sustained delivery fluocinolone acetonide vitreous inserts provide benefit for at least 3 years in patients with diabetic macular edema. ***Ophthalmology***. 2012;119:2125-2132.

Study Overview

Retisert (0.59 µg/day fluocinolone acetonide) is an extended-release product approved to treat uveitis; in an evaluation for diabetic macular edema (DME), it showed some promise,[2] but the overwhelming percentage of patients requiring cataract surgery (80%-90%) or incisional glaucoma surgery to manage intraocular pressure (IOP) (15%-20%) who needed spikes quickly ended this implant's potential. However, 0.2-µg/day (low-dose) or 0.5-µg/day (high-dose) fluocinolone acetonide encapsulated in a polymer insert has somewhat alleviated those side effect concerns by eliminating the surgical component of the Retisert implants and has shown a 15-letter improvement from baseline at 2 years in 28.7% of the low-dose group and in 28.6% of the high-dose group.[1]

The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) study group conducted 2 identical, double-masked, sham injection - controlled, parallel-group, multicenter phase 3 studies that randomized 953 patients with persistent edema despite at least 1 macular laser photocoagulation treatment to sham injection (n = 185), low-dose fluocinolone (n = 375) or high-dose fluocinolone (n = 393) for 36 months. The FAME study A was conducted at 49 sites in the United States, Canada, 4 countries in the European Union, and India. The FAME study B was conducted at 52 sites in the United States, India, and 3 countries in the European Union.[1] Subjects were eligible if they had foveal thickness of 250 µm or more despite at least 1 prior focal/grid macular laser photocoagulation treatment and best-corrected visual acuity (BCVA) in Early Treaty Diabetic Retinopathy Study (ETDRS) letter score between 19 and 68 (Snellen equivalent range, 20/50–20/400). Patients were excluded if they had glaucoma or ocular hypertension. There were 16 planned study visits over the course of the 3-year study; once patients had their initial 3-month

evaluation, study visits were every 3 months. Patients were allowed rescue therapy during the initial 6 weeks, and retreatments with laser were allowed as often as every 3 months for persistent or recurrent DME. Subjects were eligible for retreatment with the initial study drug after month 12 if they lost 5 or more letters or had a 50-µm increase in foveal thickness.[1] The primary end point was the percentage of patient with improvement in BCVA of 15 letters or more at 24 months.

There were no major differences in baseline characteristics in the 3 treatment arms in either study. About 20% in each of the fluocinolone groups and 23% of the sham group discontinued treatment. A total of 28% in each of the fluocinolone groups achieved the primary endpoint compared to 16% of the sham group (P = .002). Benefit of the implant was seen fairly quickly, with 10% in each treatment arm gaining 15 or more letters by month 1 (see Figure 1). In pseudophakic eyes, patients showed a mean increase in BCVA scores of 7 letters that remained stable through month 24; eyes that were phakic at baseline showed a mean BCVA increase of 3 letters that was stable through month 9, then decreased to a loss of 5 letters (high dose) or 9 letters (low dose) by month 24. Eyes that were phakic at baseline but underwent cataract surgery during the study time frame showed a mean improvement of 9 letters (high dose) or 7 letters (low dose) at month 24.

At baseline, all 3 treatment groups had foveal thicknesses of more than 450 µm, indicating severe edema. There was a rapid reduction in mean foveal thickness in the 2 fluocinolone groups, dropping to under 350 µm by week 6; the sham group remained at 450 µm. By month 24, the mean foveal thickness had decreased to 293 µm in the low-dose group and to 308 µm in the high-dose group, and to 340 µm in the sham group.

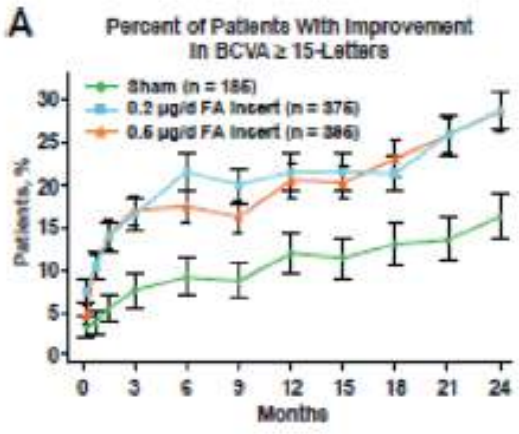
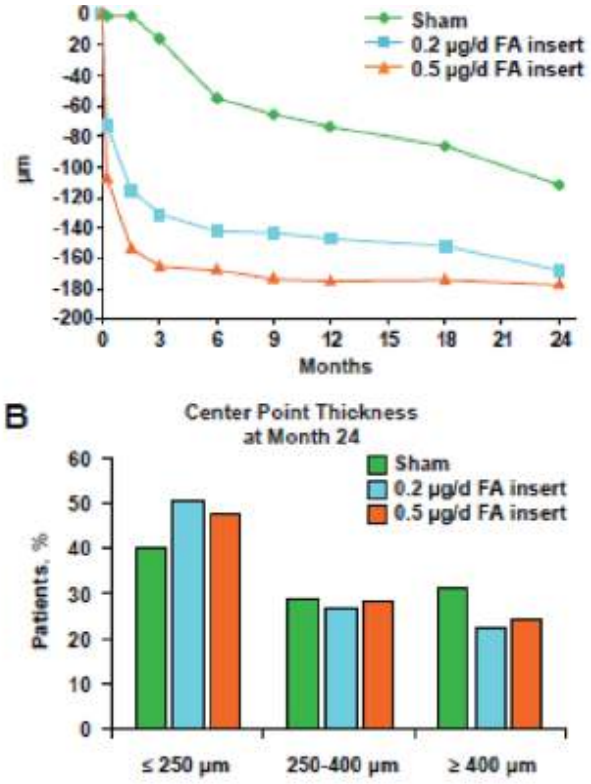


Figure 1: Percentage of patients with improvement in BCVA of at least 15 letters.

The study authors stated that a foveal thickness of 250 µm or less is "considered an excellent anatomic outcome," and this was achieved by 51% in the low-dose group, 47% in the high-dose group, and 40% in the sham group. See Figures 2 and 3.[1]



Figures 2 and 3.[1] Mean change from baseline in center point thickness (A) and at month 24 (B).

About one-fifth of groups received a second treatment with the implant during the study, and fewer than 1% in the fluocinolone groups underwent 4 treatments during the course of the study (compared to 1.6% in the sham group).[1] Additionally, cataract surgery in the eyes that were phakic at baseline occurred in 74.9% of the low-dose group, 84.5% of the high-dose group, and 23.1% of the sham group.[1] Laser trabeculectomy was necessary to manage intraocular pressure (IOP) elevations in 2.3% of the high-dose group, 0.8% of the low-dose group, and 0% in the sham group; incisional surgery was necessary to manage IOP in 8.1% of the high-dose group, 3.7% of the low-dose group, and 0.5% of the sham group.[1]

Study Implications

Iluvien took a considerable amount of time to gain US regulatory approval. The FDA issued a Complete Response Letter for fluocinolone acetonide in October 2013, stating that the New Drug Application could not be approved in its present form. The FDA indicated results from a new clinical trial would need to be submitted along with at least 12

months of follow-up for all enrolled patients. Alimera Sciences filed with the FDA for the fourth time in March 2014 with a safety update, and the FDA approved the implant in 2014 for treatment every 36 months.[3]

Although 31% and 33% of the fluocinolone groups achieved a BCVA of 20/40 or better in the study eye by month 24, 14% ended up with a BCVA of 20/200 (considered legally blind). FAME demonstrated the first pharmacologic treatment for DME that exerts a therapeutic effect for a prolonged period, but the side effect profile cannot be ignored. Because the visual outcomes were similar in patients who underwent cataract surgery during the study compared with those whose eyes were pseudophakic at study enrollment, there is a possibility that the insert may prevent cataract surgery - related worsening of DME, but more work is needed before a definitive assessment can be made.

Further, the mean ETDRS letter score gain was 4.4 and 5.4 in the low- and high-dose group, respectively, which equates to about 1 line of vision. Compared to other DME treatments, this is not particularly persuasive, although the treatment burden is considerably less. Additionally, this study reported the highest levels of incisional surgery (3.7% risk) of any of the corticosteroids being evaluated for DME; it is highly recommended patients be carefully monitored during the first few months to determine if there is a corresponding IOP increase. "If a way can be devised to identify patients at risk for severe glaucoma from sustained-delivery of low-dose FA, this would provide a helpful guide in devising a management plan for individual patients with DME," the authors wrote. In the US there is extremely limited real-world experience with the insert because the manufacturer only launched it in late February 2015.

Take-Home Points

- Both low-dose and high-dose fluocinolone acetonide performed better than sham in patients with persistent edema. The insert is approved for 36-month dosing.
- Mean ETDRS letter score gain at 24 months was 4.4 in the low-dose group and 5.4 in the high-dose group.
- Foveal thickness improved to 293 µm in the low-dose group, to 308 µm in the high-dose group, and to 340 µm in the sham group by month 24.
- 51% in the low-dose group, 47% in the high-dose group, and 40% in the sham group achieved a foveal thickness of 250 µm or less by month 24.
- Phakic patients will develop an accelerated cataract, and 3.7% of patients required incisional glaucoma surgery.

References

1. Campochiaro PA, Brown DM, Pearson A, et al. Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. *Ophthalmology.* 2011;118(4):626-635.e2.

2. Pearson PA, Comstock TL, Ip M, et al. Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. *Ophthalmology.* 2011;118(8):1580-1587.

3. Iluvien [package insert]. Atlanta, GA: Alimera Sciences Inc, 2014.