

# Sustained Delivery Fluocinolone Acetonide Vitreous Inserts Provide Benefit for at Least 3 Years in Patients with Diabetic Macular Edema

Peter A. Campochiaro, MD,<sup>1</sup> David M. Brown, MD,<sup>2</sup> Andrew Pearson, MD,<sup>3</sup> Sanford Chen, MD,<sup>4</sup> David Boyer, MD,<sup>5</sup> Jose Ruiz-Moreno, MD,<sup>6</sup> Bruce Garretson, MD,<sup>7</sup> Amod Gupta, MD,<sup>8</sup> Seenu M. Hariprasad, MD,<sup>9</sup> Clare Bailey, MD,<sup>10</sup> Elias Reichel, MD,<sup>11</sup> Gisele Soubrane, MD,<sup>12</sup> Barry Kapik, MS,<sup>13</sup> Kathleen Billman, BS,<sup>13</sup> Frances E. Kane, PhD,<sup>13</sup> Kenneth Green, PhD,<sup>13</sup> for the FAME Study Group\*

**Objective:** To assess long-term efficacy and safety of intravitreal inserts releasing 0.2  $\mu\text{g}/\text{d}$  (low dose) or 0.5  $\mu\text{g}/\text{d}$  (high dose) fluocinolone acetonide (FAC) in patients with diabetic macular edema (DME).

**Design:** Two randomized, sham injection-controlled, double-masked, multicenter clinical trials.

**Participants:** Subjects with persistent DME despite  $\geq 1$  macular laser treatment were randomized 1:2:2 to sham injection (n = 185), low-dose insert (n = 375), or high-dose insert (n = 393).

**Methods:** Subjects received study drug or sham injection and after 6 weeks were eligible for rescue laser. Based on retreatment criteria, additional study drug or sham injections could be given after 1 year.

**Main Outcome Measures:** Percentage of patients with improvement of  $\geq 15$  letters from baseline. Secondary outcomes included other parameters of visual function and foveal thickness.

**Results:** At month 36, the percentage of patients who gained  $\geq 15$  in letter score using the last observation carried forward method was 28.7% (low dose) and 27.8% (high dose) in the FAC insert groups compared with 18.9% ( $P = 0.018$ ) in the sham group, and considering only those patients still in the trial at month 36, it was 33.0% (low dose) and 31.9% (high dose) compared with 21.4% in the sham group ( $P = 0.030$ ). Preplanned subgroup analysis demonstrated a doubling of benefit compared with sham injections in patients who reported duration of DME  $\geq 3$  years at baseline; the percentage who gained  $\geq 15$  in letter score at month 36 was 34.0% (low dose;  $P < 0.001$ ) or 28.8% (high dose;  $P = 0.002$ ) compared with 13.4% (sham). An improvement  $\geq 2$  steps in the Early Treatment Diabetic Retinopathy Study retinopathy scale occurred in 13.7% (low dose) and 10.1% (high dose) compared with 8.9% in the sham group. Almost all phakic patients in the FAC insert groups developed cataract, but their visual benefit after cataract surgery was similar to that in pseudophakic patients. The incidence of incisional glaucoma surgery at month 36 was 4.8% in the low-dose group and 8.1% in the high-dose insert group.

**Conclusions:** In patients with DME FAC inserts provide substantial visual benefit for up to 3 years and would provide a valuable addition to the options available for patients with DME.

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\*Group members listed online (available at <http://aaojournal.org>).

Diabetic macular edema (DME) is a prevalent cause of vision loss that is difficult to manage because of its chronicity. Therapeutic agents that provide sustained benefit are needed. Fluocinolone acetonide (FAC) intravitreal inserts are nonbiodegradable cylindrical tubes (3.5 $\times$ 0.37 mm) of polymer loaded with FAC that are inserted into the vitreous cavity through a 25-gauge needle in an outpatient setting. Inserts that release either 0.5 or 0.2  $\mu\text{g}/\text{d}$  of FAC in vitro provide excellent sustained delivery of FAC in the eye.<sup>1</sup> The Fluocinolone Acetonide for Diabetic Macular Edema (FAME) Studies demonstrated substantial visual benefit 2

years after initiation of treatment with FAC inserts in patients with DME and met the primary endpoint.<sup>2</sup> Twenty-eight percent of DME patients treated with 0.5 or 0.2  $\mu\text{g}/\text{d}$  FAC inserts had an improvement in best-corrected visual acuity (BCVA) letter score  $\geq 15$  compared with 16% in the sham group. Benefit occurred surprisingly early with significant improvement compared with sham at 3 weeks and all subsequent time points. The mean improvement from baseline in BCVA letter score at month 24 was 4.4 and 5.4 in the low- and high-dose groups compared with 1.7 in the sham group ( $P = 0.02$  and 0.016). At all time points

compared with sham, there was significantly more improvement in foveal thickness (FTH), the thickness of the retina in the center of the fovea. Subjects requiring cataract surgery were more common in the insert groups and their visual benefit was similar to subjects who were pseudophakic at baseline. The biggest concern was steroid-induced ocular hypertension, but there was a clear dose effect because through month 24, 3.7% of patients in the low-dose insert group required incisional surgery compared with 7.6% in the high-dose insert group. Thus, efficacy was similar with the 2 inserts, but safety was better for the low-dose insert, favoring its use in clinical care. Follow-up continued after the 2-year primary endpoint and herein we report the 3-year results of the FAME studies.

## Methods

The FAME A and B studies were performed under a single protocol as randomized, double-masked, sham injection-controlled, parallel-group, multicenter studies conducted over a 36-month period. The first, FAME A, was conducted at 49 sites in the United States, Canada, 4 countries in the European Union, and India; FAME B was conducted at 52 sites in the United States, India, and 3 countries in the European Union. The studies adhered to the guidelines of the Declaration of Helsinki and the protocol and consent form were approved by each institution's governing Institutional Review Board/Ethics Committee. Each subject provided written informed consent. The studies are registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) under the identifier NCT00344968 (accessed June 26, 2006).

## Study Population

Consenting subjects with DME were screened by measuring BCVA by the protocol described in the Early Treatment Diabetic Retinopathy Study (ETDRS)<sup>3</sup> and FTH (center point thickness) using the Fast Macular Scan protocol on a Stratus 3 optical coherence tomography instrument (Carl Zeiss Meditec, Dublin, CA). Subjects were eligible if they had FTH  $\geq 250$   $\mu\text{m}$  despite  $\geq 1$  prior focal/grid macular laser photocoagulation treatment and BCVA in ETDRS letter score between 19 and 68 (20/50–20/400). Enrollment was stratified by baseline BCVA ( $\leq 49$  letter score [20/100],  $>49$  letter score). Patients were excluded if they had glaucoma, ocular hypertension, intraocular pressure (IOP)  $>21$ , or if they were on IOP-lowering drops. Detailed inclusion and exclusion criteria (Appendix 1, available at <http://aaojournal.org>) have been previously reported.<sup>2</sup> A total of 956 subjects were randomized in a 2:2:1 ratio to 0.2  $\mu\text{g}/\text{d}$  FAc intravitreal insert, 0.5  $\mu\text{g}/\text{d}$  FAc intravitreal insert, or sham injection. The assigned treatment was administered to only 1 eye referred to as the "study" eye. Standard procedures were used for injections.

## Clinical Assessments

There were  $\geq 16$  study visits over a 3-year treatment period, including screening, baseline, 1 week, 3 weeks, 6 weeks, and 3 months after initial study treatment, and every 3 months thereafter. Study assessments included BCVA (ETDRS charts at 4 m or electronic visual acuity tester at 3 m), time-domain optical coherence tomography, fluorescein angiography, fundus photography, adverse event, and concomitant medications. Patients were allowed to receive rescue focal/grid laser for persistent edema any time after the week 6 assessment and subsequently treatments were allowed as frequently as every 3 months for persistent or recurrent

DME. Subjects were eligible for retreatment with their initially assigned study drug after month 12 if they experienced loss of  $\geq 5$  letters in BCVA or an increase in FTH  $\geq 50$   $\mu\text{m}$  compared with the subject's best status during the previous 12 months. In the event of retreatment, there were 2 posttreatment visits at 1 day and 1 week. Although treatment with nonprotocol therapies was discouraged, subjects who were treated with other therapies were retained in the study.

## Primary Analysis

Data were analyzed by one of the authors (B.K.) with expertise in biostatistics. Pair-wise comparisons to sham treatment were made using a Cochran-Mantel-Haenszel chi-square test stratified by baseline visual acuity strata. A Hochberg-Bonferroni correction was used to adjust for multiple comparisons against the control. An intent to treat population is presented in which all patients randomized are included and missing data are imputed by the method of last observation carried forward.

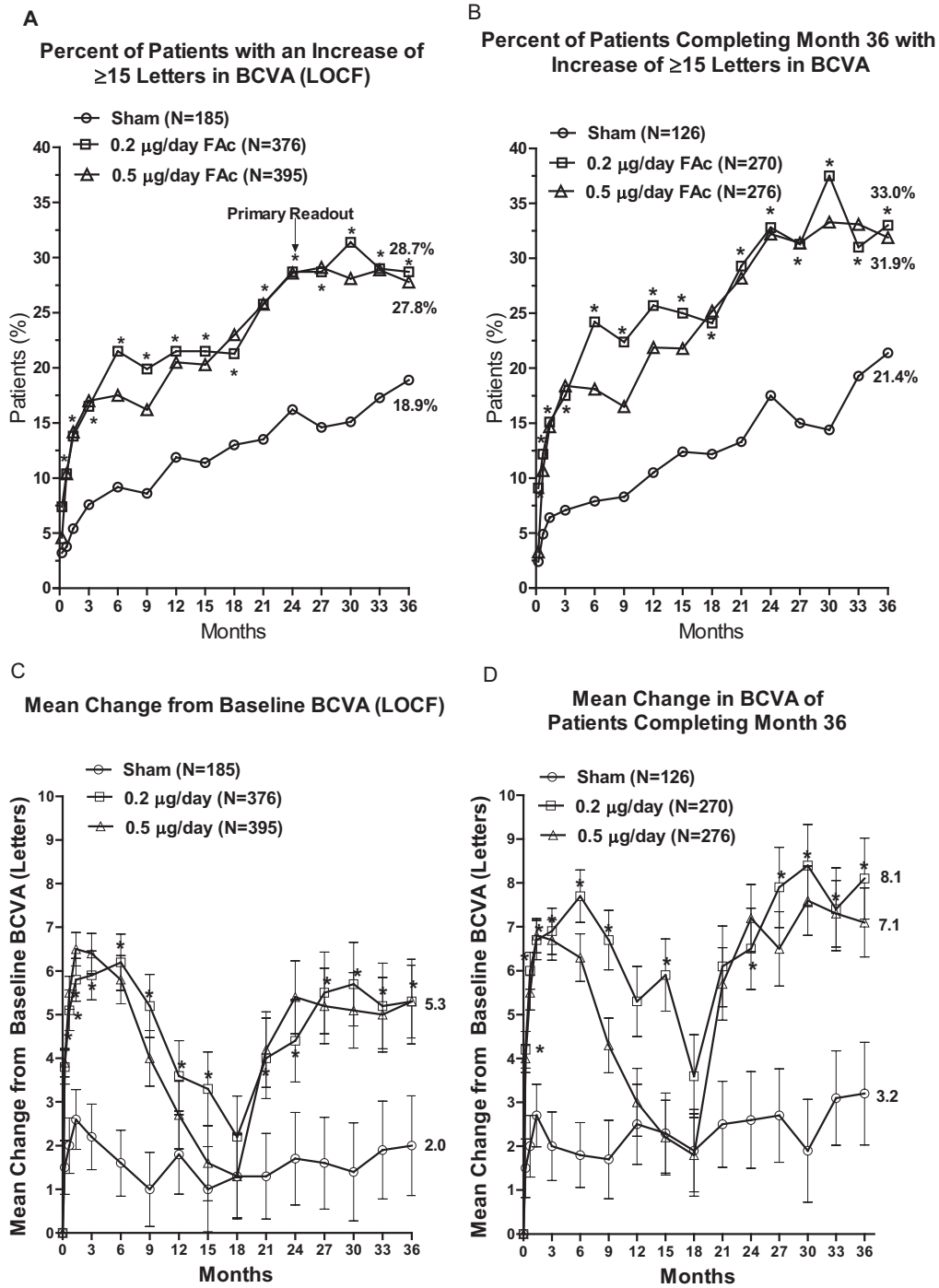
## Results

### Baseline Characteristics and Patient Disposition

There were no imbalances at baseline with respect to age, race, the mean duration of diabetes (range, 16.1–17.1 years), the mean duration of DME (range, 3.5–3.9 years), mean BCVA (range, 52.9–54.7 ETDRS visual acuity score), or FTH (range, 451.3–485.1  $\mu\text{m}$ ). The percentage of patients who failed to remain in the study until the month 24 primary endpoint was 19.0% in the high-dose group, 19.9% in the low-dose group, and 22.7% in the sham group, and the percentage that exited before the month 36 visit was 29.4%, 27.1%, and 31.9%, respectively. Typical of long duration studies, the most common reasons for exit from the study were withdrawal of consent (6.8%, 8.2%, and 7.6% in the high-dose, low-dose, and sham groups, respectively), death (7.8%, 7.2%, and 5.9%, respectively), or an adverse event (3.8%, 1.1%, and 2.7%, respectively).

### Effect of Inserts on Visual Acuity

Analysis of all patients that entered the study using last observation carried forward showed that the percentage of patients with improvement in BCVA letter score  $\geq 15$  at month 36 was 28.7% (low dose) and 27.8% (high dose) of patients in the FAc insert groups compared with 18.9% in the sham group ( $P = 0.018$  for difference between low-dose FAc insert and sham; Fig 1A). To better understand the durability of a treatment, it is important to examine outcomes at month 36 for those patients who were still in the study; 33.0% (low dose) and 31.9% (high dose) of patients in the FAc insert groups compared with 21.4% in the sham group gained  $\geq 15$  in letter score ( $P = 0.030$  for difference between low dose FAc insert and sham; Fig 1B). For all patients enrolled using last observation carried forward, the mean improvement from baseline BCVA letter score at month 36 was 5.3 in the 2 insert groups compared with 2.0 in the sham group ( $P \leq 0.018$ ; Fig 1C). For patients who remained in the trial through month 36, the mean improvement from baseline BCVA letter score at month 36 was 8.1 (low dose) and 7.1 (high dose) compared with 3.1 for the sham group ( $P = 0.007$  for difference between low dose and sham). The dip in mean BCVA in the 2 insert groups between months 9 and 18 was because of cataract progression, and the improvement between months 18 and 24 was due to cataract surgery in a substantial number of patients as previously shown.<sup>2</sup> Forty-eight patients in the low dose FAc group who were phakic at baseline had not had



**Figure 1.** Vision outcomes through 36 months in patients with diabetic macular edema (DME) treated with 0.2 or 0.5  $\mu\text{g/d}$  fluocinolone acetonide (FAc) inserts versus sham injection. **A**, Percentage of all enrolled patients who gained  $\geq 15$  letters using last observation carried forward (LOCF) is shown at time points between baseline and month 36.  $*P \leq 0.0491$  for difference between 0.2  $\mu\text{g/d}$  FAc insert and sham by Cochran-Mantel-Haenszel chi-square test stratified by baseline best-corrected visual acuity (BCVA). **B**, Percentage of patients who gained  $\geq 15$  letters is shown for only those patients who remained in the trial through month 36.  $*P \leq 0.0491$  for difference between 0.2  $\mu\text{g/d}$  FAc insert and sham by Cochran-Mantel-Haenszel chi-square test stratified by BCVA. **C**, The mean change ( $\pm$  standard error of the mean) from baseline BCVA is shown for all enrolled patients using last observation carried forward.  $*P \leq 0.0491$  for difference between 0.2  $\mu\text{g/d}$  FAc insert and sham by analysis of variance model with treatment and baseline BCVA strata as fixed effects. **D**, Mean ( $\pm$  standard error of the mean) change from baseline BCVA is shown for patients who remained in the trial through month 36.  $*P \leq 0.0491$  for difference between 0.2  $\mu\text{g/d}$  FAc insert and sham by analysis of variance model with treatment and baseline BCVA strata as fixed effects.

cataract surgery by month 36 and their mean change in BCVA letter score was  $-6$ .

A final BCVA of  $\geq 20/40$  is an excellent outcome because it allows for high-level functioning including reading and driving, even if the other eye has severe visual impairment. This outcome was attained at month 36 in 35.1% and 34.9% of patients in the FAc insert groups compared with 26.5% in the sham group (Fig 1D; sham vs low dose [ $P = 0.016$ ]; sham vs high dose [ $P = 0.005$ ] by Cochran-Mantel-Haenszel chi-square test stratified by baseline visual acuity).

## Assessment of Macular Edema by Optical Coherence Tomography

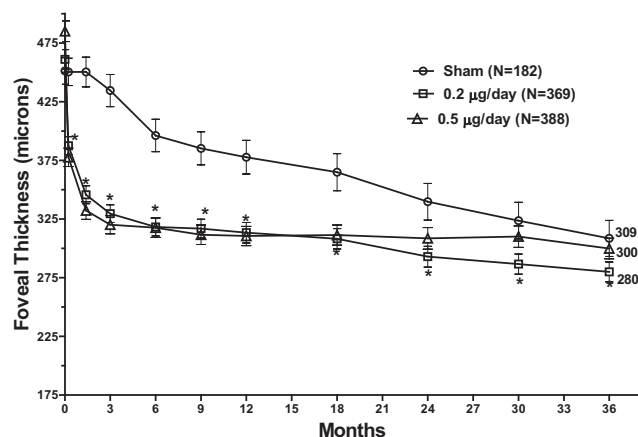
At baseline the mean FTH was 451, 461, and 485  $\mu\text{m}$  in the sham, low-dose, and high-dose groups, respectively, indicating relatively severe edema. There was a rapid reduction in mean FTH in the 2 FAc insert groups, which was significant as early as week 1 and at week 6 it was  $< 350$   $\mu\text{m}$  in both groups compared with 450  $\mu\text{m}$  in the sham group (Fig 2). At month 6, it was 318  $\mu\text{m}$  in the FAc insert groups and 396  $\mu\text{m}$  in the sham group. After month 6, there was gradual reduction in all 3 groups. At month 24, the mean FTH was significantly lower in the FAc groups (low dose, 293  $\mu\text{m}$  [ $P = 0.005$ ]; high dose, 308  $\mu\text{m}$  [ $P < 0.001$ ]) compared with the sham group (340  $\mu\text{m}$ ). Between months 24 and 36, mean FTH declined slightly in all groups, but more so in the sham group (309  $\mu\text{m}$ ) compared with the low-dose (280  $\mu\text{m}$ ) and high-dose (300  $\mu\text{m}$ ) groups, so that there were no longer any significant differences at month 36.

## Subgroup Analysis

To determine if some patients had an expanded benefit-to-risk ratio, the effect of duration of DME on visual outcomes, a pre-planned subgroup analysis, was explored. The median duration of DME reported by patients at baseline was 3 years; therefore, outcomes were assessed in patients with duration of DME at

baseline  $< 3$  years (short duration) versus  $\geq 3$  years (long duration). At month 36 in the integrated FAME studies, the percent of long duration DME patients who gained  $\geq 15$  in letter score was 13.4% in the sham group compared with 34.0% (low dose;  $P < 0.001$ ) and 28.8% (high dose;  $P = 0.002$ ) in the FAc insert groups (Fig 3A). A high percentage of patients with DME for  $< 3$  years who were in the FAc insert groups gained  $\geq 15$  in letter score (low dose, 22.3%; high dose, 26.4%), but that was also the case for the sham group (27.8%) and the difference was not significant (Fig 3B). This differential treatment effect in long and short duration DME patients at month 36 was replicated in the 2 independent FAME studies. In FAME A (Fig 3C), the percentage of patients with DME  $\geq 3$  years who gained  $\geq 15$  in letter score was 13.6% in the sham group compared with 31.8% in the low-dose insert group ( $P = 0.010$ ), whereas the percentage of patients with DME  $< 3$  years who gained  $\geq 15$  in letter score was 28.6% in the sham group compared with 24.1% in the low-dose insert group. In FAME B (Fig 3D), the percentage of patients with DME  $\geq 3$  years who gained  $\geq 15$  in letter score was 13.2% in the sham group compared with 36.4% in the low-dose insert group ( $P = 0.004$ ), whereas the percentage of patients with DME  $< 3$  years who gained  $\geq 15$  in letter score was 27.0% in the sham group compared with 20.7% in the low-dose insert group.

Peak efficacy occurred at month 30, when the percentage of patients with long duration DME who gained  $\geq 15$  in letter score in the integrated FAME analysis was 10.7% (sham) compared with 37.8% (low dose,  $P < 0.001$ ) and 30.2% (high dose,  $P < 0.001$ ). For those patients who were still in the study at month 36, the percentage of long duration DME patients who gained  $\geq 15$  in letter score was 16.0% (sham) compared with 38.9% (low dose,  $P < 0.001$ ) or 32.9% (high dose,  $P = 0.008$ ). The mean change in BCVA letter score between baseline and month 36 in long duration DME subjects was 1.8 (sham) compared with 7.6 (low dose,  $P = 0.004$ ) or 6.2 (high dose,  $P = 0.024$ ). In patients with long duration DME, the striking difference in VA outcomes between FAc insert-treated patients and sham-treated patients was not accompanied by a difference in reduction in FTH; there was a substantial reduction in FTH in both the sham and FAc insert groups at month 36 and the difference was not significant (Fig 4).



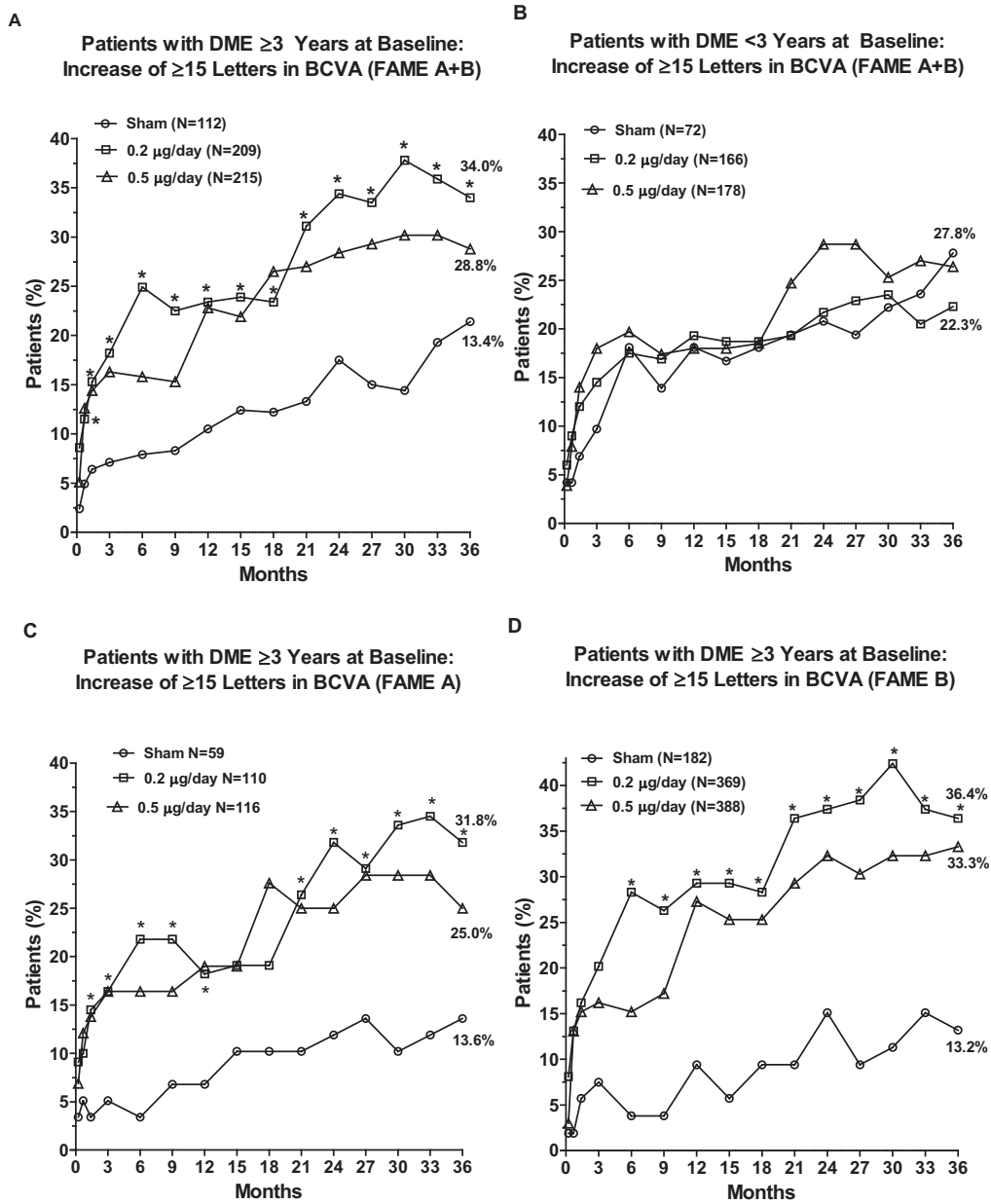
**Figure 2.** Mean foveal thickness (FTH) over time in patients with diabetic macular edema treated with fluocinolone acetonide (FAc) inserts versus sham. The curves show the mean ( $\pm$  standard error of the mean) center point thickness measured by time-domain optical coherence tomography at each time point for all patients who entered the trial using last observation carried forward. There was a rapid decline in mean FTH in the 2 insert groups compared with a gradual decline in the sham group. The FAc insert groups had a significantly lower mean FTH at month 24 compared with sham, but not at month 36.

## Repeated Study Treatments

After month 12, patients with reduced vision or increased FTH from persistent or recurrent DME were allowed to receive repeat administration of their assigned study treatment at the investigators' discretion if retreatment criteria were met. The percentage of patients that received 1, 2, or  $\geq 3$  study treatments at month 36 was 71.4, 23.8, and 4.8 in the sham group; 74.4, 21.6, and 4.0 in the low-dose group; and 70.7, 23.2, and 6.1 in the high-dose group (Table 1).

## Rescue Treatments

Focal/grid laser treatment was standard of care for DME during the study and, therefore, to enter the study, patients were required to have persistent or recurrent DME despite  $\geq 1$  macular laser treatment. In addition, after 6 weeks in the study, patients were allowed to undergo additional laser treatments, and subsequently treatments were allowed as frequently as every 3 months for persistent or recurrent DME. A significantly higher percentage of patients in the sham group (60.7%) received rescue focal grid laser than in the low-dose (40.7%) or high-dose (34.9%) FAc insert groups (Table 1). Also, a greater percentage of patients were given repeated focal/grid laser treatments in the sham group; 11.9% of patients in the sham group received  $\geq 3$  treatments during the trial compared with 6.6% and 3.3% in the low- and high-dose FAc insert groups.



**Figure 3.** Subgroup analysis: Visual outcome in patients with diabetic macular edema (DME) ≥3 versus <3 years at baseline. **A**, In patients from both Fluocinolone Acetonide for Macular Edema (FAME A + B) trials who had DME ≥3 years at baseline, the percentage who gained ≥15 letters from baseline was significantly greater for those treated with fluocinolone acetonide (FAc) inserts compared with sham-treated patients. \* $P \leq 0.0491$  for difference between 0.2 µg/d FAc insert and sham by Cochran-Mantel-Haenszel chi-square test stratified by baseline best-corrected visual acuity (BCVA). **B**, In patients from both FAME trials who had DME ≤3 years at baseline, the percentage that gained ≥15 letters from baseline was not significantly different in those treated with FAc inserts compared with sham-treated patients. The results shown in **(A)** were also seen in each of the independent clinical trials, FAME A **(C)** and FAME B **(D)**.

During the period this trial was carried out, intraocular injections of anti-vascular endothelial growth factor (VEGF) agents (ranibizumab, bevacizumab, or pegaptanib) or triamcinolone acetonide were not approved for patients with DME; therefore, none were allowable rescue treatments. However, when a patient is not experiencing improvement in a study eye, investigators feel obligated to consider all possibilities, including exiting patients from a trial to administer alternative unproven treatments. In the FAME studies, when investigators felt additional treatment choices were necessary, it was not required that the patient exit the study. Use of

these off-protocol treatments occurred in a greater percentage of patients in the sham group (33.0%) than the low-dose (15.2%) or high-dose (16.3%) FAc insert groups. Table 1 shows the percentage of patients who received intravitreal or periocular corticosteroid, an anti-VEGF agent, or any other treatment (primarily vitrectomy) and, because some patients received >1 type of treatment, the total percentages are greater than that listed previously. Because focal/grid laser treatments and other treatments were much more common in the sham group and were administered at the discretion of the masked investigators based on their

perceived clinical need, they did not contribute to the greater benefit seen in the 2 FAc insert groups compared with sham.

### Improvement in Diabetic Retinopathy

Masked grading of the severity of diabetic retinopathy by the reading center (Fig 5) indicated that the percentage of patients with  $\geq 2$  step improvement on the ETDRS Retinopathy Eye Scale at month 36 was smaller in the sham treatment group (8.9%) than the low-dose group (13.7%); the high-dose group was similar to the sham (10.1%). The explanation for this finding may be that the high-dose insert released for approximately 24 months, whereas the low-dose insert released for 36 months and the protocol did not permit retreatment after month 33.

### Adverse Events

The most common study eye adverse event was cataract, which was listed as an adverse event in 42.7% of the low-dose group, 51.7% of the high-dose group, and 9.7% of the sham group; this

Table 1. Study Treatments, Rescue Laser Treatments, and Off-protocol Treatments through Month 36

	Control (n = 112)	0.2 $\mu\text{g/d}$ FAc (n = 209)	0.5 $\mu\text{g/d}$ FAc (n = 215)
Study treatments (sham injection or ILUVIEN device), %			
1	66.1	76.1	68.8
2	27.7	18.7	24.2
$\geq 3$	6.3	5.3	7.0
Rescue laser treatments (at masked physician's discretion after week 6)			
Patients, n (%)	68 (60.7)	85 (40.7)	75 (34.9)
P value	—	0.003	<0.001
Off-protocol treatments			
Any, n (%)	39 (34.8)	28 (13.4)	34 (15.8)
P value	—	<0.001	<0.001
IVTA	27 (24.1)	17 (8.1)	16 (7.4)
P value	—	<0.001	<0.001
Anti-VEGF	17 (15.2)	7 (3.3)	11 (5.1)
P value	—	<0.001	0.002

Statistical comparisons were made between each fluocinolone acetonide (FAc) insert group and the sham group by analysis of variance. FAc = fluocinolone acetonide; IVTA = intravitreal triamcinolone acetonide; VEGF = vascular endothelial growth factor.

constituted 81.7%, 88.7%, and 50.7% of the patients in each of the groups that had not had cataract surgery in the study eye at baseline (Table 2). The median time for cataract reported as an adverse event was month 12 and the median time for cataract surgery was 18 months. Of those patients who were phakic at baseline, cataract surgery was performed in 80.0% (low dose) and 87.2% (high dose) of patients in the FAc insert groups compared with 27.3% in the sham group. Overall, IOP-related adverse events were more frequent in the FAc insert groups than in the sham group (low dose, 37.1%; high dose, 45.5%; sham, 11.9%; Table 2).

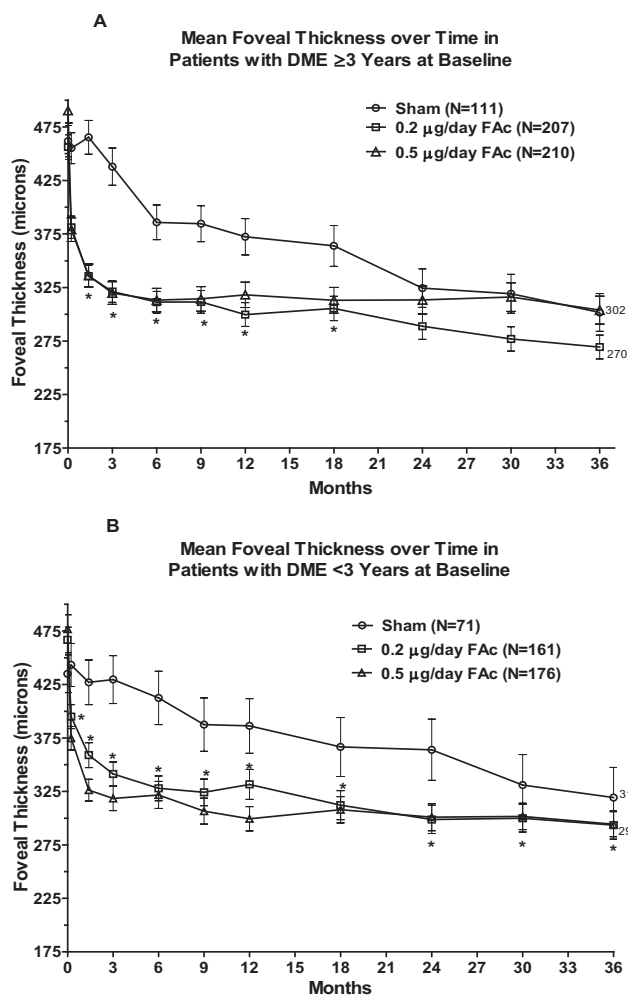


Figure 4. Subgroup analysis: Anatomic outcome in patients with diabetic macular edema (DME)  $\geq 3$  versus  $< 3$  years at baseline. In the combined Fluocinolone Acetonide for Macular Edema (FAME) A and B population, there was similar anatomic outcome in patients who had DME  $\geq 3$  (A) versus  $< 3$  years at baseline (B).

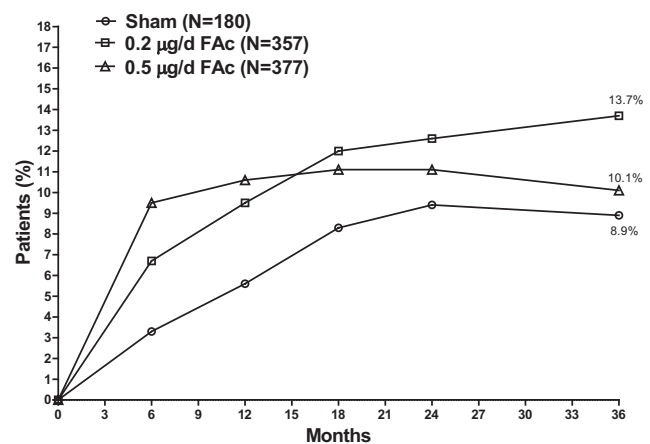


Figure 5. The percentage of patients with  $\geq 2$ -step improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) diabetic retinopathy severity score. The percentage of patients who improved by  $\geq 2$  steps in the ETDRS diabetic retinopathy severity score at month 36 was greater in patients treated with 0.2  $\mu\text{g/d}$  fluocinolone acetonide inserts compared with sham-treated patients.

Table 2. Cataract- and Intraocular Pressure (IOP)-Related Adverse Events

Phakic Patients, % (Study Eye)	Control (n = 121)	0.2 $\mu$ g/d FAc (n = 235)	0.5 $\mu$ g/d FAc (n = 265)
Cataract-related events			
Cataract considered an AE	50.4	81.7	88.7
Cataract extraction	27.3	80.0	87.2
Subjects, % (Study Eye)	Control (n = 185)	0.2 $\mu$ g/d FAc (n = 375)	0.5 $\mu$ g/d FAc (n = 393)
IOP-related events			
AE of increased IOP	11.9	37.1	45.5
Any IOP-lowering meds*	14.1	38.4	47.3
Trabeculectomy	0.0	1.3	2.5
Incisional glaucoma surgery	0.5	4.8	8.1

AE = adverse event; FAc = fluocinolone acetonide.  
The percentage of patients in each treatment group with the listed adverse events is listed.  
\*For a minimum of 7 days.

When increased IOP is severe, prolonged, and unresponsive to pharmacologic treatments, laser trabeculectomy or incisional IOP-lowering surgery are undertaken. Laser trabeculectomy was done in 2.5% of the high-dose group, 1.3% of the low-dose group, and 0% of the sham group. Incisional IOP-lowering surgery was done in 8.1% of the high-dose group, 4.8% of the low-dose group, and 0.5% of the sham group.

## Discussion

The primary outcome was met in both FAME trials. The integrated dataset showed that 28% of patients treated with a low- or high-dose FAc insert had an improvement of  $\geq 15$  in BCVA letter score at month 24 compared with 16% in the sham injection group. Continued follow-up has shown that those excellent results are maintained through at least 3 years, with roughly 28% of patients in the FAc insert groups still showing improvement of  $\geq 15$  in BCVA letter score. Approximately 30% of patients in each of the 3 groups dropped out of the study before the 36-month time point, which is typical for long duration studies. If only data from patients who remained in the study through month 36 are considered, 32% to 33% of patients in the FAc insert groups showed improvement of  $\geq 15$  in BCVA letter score and 71% to 74% of patients had only 1 insertion. This indicates superb treatment durability.

In a preplanned subgroup analysis, the effect of duration of DME on visual outcome was assessed. The median duration of DME for patients who entered the FAME study was 3 years. The relative benefit compared with the sham group was markedly better for those patients with duration of DME  $\geq 3$  years than those with DME  $< 3$  years. This suggests that patients with persistent DME who tend to respond poorly to many treatments, including focal/grid laser photocoagulation, respond well to administration of a FAc insert. The reason sustained delivery of FAc continues to provide benefit despite chronicity of edema is uncertain,

but 1 possibility is that chronic edema may exacerbate inflammation in diabetic retinas. The diabetic state itself promotes inflammation in the retina, but the long-term presence of serum proteins and other serum components in edematous retina is likely to exacerbate inflammation. Inflammation is accompanied by bystander damage to retinal neurons and the exacerbation of inflammation in persistent DME may cause it to exceed a critical threshold resulting in retinal cell death and loss of vision. Sustained delivery of FAc may reduce inflammation below the critical threshold and hence preserve vision. It is likely that such a trophic effect plays a role in the enhanced efficacy of FAc inserts in persistent DME, because when the anatomic outcome was compared between the control and FAc treated groups at month 36, there was no significant difference. This suggests that, in patients having longer-duration DME, simply addressing the anatomic distortion of the retina does not provide maximum benefit; it is also important to address inflammation. The reduction in inflammation may also contribute to regression in retinopathy grade seen in patients treated with FAc inserts and provides another important benefit of this treatment.

These excellent results occurred despite a high incidence of cataract requiring surgery in patients who received an FAc insert. Patients in the FAc groups who required cataract surgery had a mean improvement in BCVA letter score of 7, an equally good outcome as those patients who were pseudophakic at baseline (mean improvement of 6). This suggests that, although patients who developed cataract experienced a transient reduction in vision, their long-term outcome was not compromised. Forty-eight patients in the low-dose FAc group who were phakic at baseline had not had cataract surgery by month 36 and their mean change in BCVA letter score was  $-6$ . It is likely that cataract is a major contributor to this reduced vision and that if these patients had undergone cataract surgery, 36-month visual outcomes would be even better in the FAc implant groups.

The most important side effect of FAc inserts is increased IOP. The percentage of patients that required incisional glaucoma surgery was 0.8% at month 12, 3.4% at month 24, and 4.8% at month 36 for the low-dose insert. The reduction in glaucoma surgeries from 2.6% in year 2 to 1.2% in year 3 is reassuring. It is also reassuring that, in the low-dose insert group, the visual outcome was equally good in patients who required glaucoma surgery as those who did not.

The decision regarding the use of any treatment hinges on the benefit/risk ratio. Through 3 years of follow-up, it is clear that low-dose FAc inserts provide substantial benefit to patients with DME. The maximum benefit is at 30 months, but it is also impressive at 3 years, with 75% of patients requiring only 1 insert to obtain that benefit. In addition, FAc inserts cause regression of diabetic retinopathy grade, which is likely to have long-term benefits. The relative benefits are doubled in patients with long-duration, persistent DME. This is balanced against a 4.8% risk of ocular hypertension requiring incisional surgery over 3 years.

From the phase III data reported for anti-VEGF agents in DME populations that include up to 30% treatment-naive patients, intraocular injections of anti-VEGF agents provide

excellent outcomes with small risks of endophthalmitis and ocular hypertension.<sup>4</sup> Focal/grid laser photocoagulation provides modest benefit with low risk. In patients with short duration DME, it would be reasonable to initiate treatment with anti-VEGF injections and when frequent injections are required, consider focal/grid laser photocoagulation to reduce dependence on injections. If there is a poor response to anti-VEGF injections and focal/grid laser and/or an unsustainable treatment burden, which varies from patient to patient depending upon particular life circumstances, then an FAc insert would be a valuable and welcome addition to the treatment regimen. In patients with persistent DME, the relative benefits of FAc inserts would make it reasonable to consider FAc inserts earlier in the treatment regimen because there seems to be functional benefit that is out of proportion to the anatomic benefit. The bar for addition of FAc inserts to the treatment regimen is likely to be set particularly low in vitrectomized eyes with persistent DME despite focal/grid laser and eyes with DME that have a functioning glaucoma filter in place. Furthermore, development of a screening test that identifies patients at risk for steroid-induced ocular hypertension would identify a population of patients with a major increase in the benefit/risk ratio of FAc inserts. Thus, FAc inserts should provide a

valuable addition to the treatment options for patients with DME.

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## Footnotes and Financial Disclosures

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<sup>1</sup> Wilmer Eye Institute, Baltimore, Maryland.

<sup>2</sup> Vitreoretinal Consultants, Houston, Texas.

<sup>3</sup> Department of Ophthalmology and Visual Sciences, University of Kentucky, Lexington, Kentucky.

<sup>4</sup> Orange County Retina Medical Group, Santa Ana, California.

<sup>5</sup> Retina Vitreous Associates Medical Group, Beverly Hills, California.

<sup>6</sup> Institut Oflalmologico Alicante, Spain.

<sup>7</sup> Royal Oak Associates, Royal Oak, Michigan.

<sup>8</sup> Post-Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India.

<sup>9</sup> Department of Ophthalmology, University of Chicago, Chicago, Illinois.

<sup>10</sup> Bristol Eye Hospital, Bristol, UK.

<sup>11</sup> Tufts Medical Center Hospital, Boston, Massachusetts.

<sup>12</sup> Intercommunal Hospital of Creteil, Creteil, France.

<sup>13</sup> Alimera Sciences, Atlanta, Georgia.

\*The complete list of FAME Study Group is available at <http://aaajournal.org>.

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Frances Kane: Employee, stock options — Alimera Sciences

Barry Kapik: Employee, stock options — Alimera Sciences.

Andrew Pearson: Consultant — Alimera Sciences; stock options — pSividia.

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Correspondence:

Peter A. Campochiaro, MD, Maumenee 719, The Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287-9277. E-mail: [pcampo@jhmi.edu](mailto:pcampo@jhmi.edu).