

# Intraocular Pressure in Patients With Uveitis Treated With Fluocinolone Acetonide Implants

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**Objective:** To report the incidence and management of elevated intraocular pressure (IOP) in patients with uveitis treated with the fluocinolone acetonide (FA) intravitreal implant.

**Design:** Pooled data from 3 multicenter, double-masked, randomized, controlled, phase 2b/3 clinical trials evaluating the safety and efficacy of the 0.59-mg or 2.1-mg FA intravitreal implant or standard therapy were analyzed.

**Results:** During the 3-year follow-up, 71.0% of implanted eyes had an IOP increase of 10 mm Hg or more than baseline and 55.1%, 24.7%, and 6.2% of eyes reached an IOP of 30 mm Hg or more, 40 mm Hg or more, and 50 mm Hg or more, respectively. Topical IOP-lowering medication was

administered in 74.8% of implanted eyes, and IOP-lowering surgeries, most of which were trabeculectomies (76.2%), were performed on 36.6% of implanted eyes. Intraocular pressure-lowering surgeries were considered a success (postoperative IOP of 6-21 mm Hg with or without additional IOP-lowering medication) in 85.1% of eyes at 1 year. The rate of hypotony (IOP  $\leq$  5 mm Hg) following IOP-lowering surgery (42.5%) was not different from that of implanted eyes not subjected to surgery (35.4%) ( $P = .09$ ).

**Conclusion:** Elevated IOP is a significant complication with the FA intravitreal implant but may be controlled with medication and surgery.

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THE INCIDENCE OF UVEITIS IN the United States is estimated to be 200 cases per 100 000 people per year and mostly affects adults aged 20 to 50 years.<sup>1</sup> Topical, intraocular, and systemic administration of corticosteroids are commonly used treatments,<sup>2</sup> while immunomodulators and targeted biological agents are increasingly used as corticosteroid-sparing therapies. The 0.59-mg fluocinolone acetonide (FA) intravitreal implant (Retisert; Bausch & Lomb, Rochester, New York) is the first and, currently the only, sustained-release intraocular implant approved by the US Food and Drug Administration for the treatment of noninfectious posterior uveitis. The FA intravitreal implant provides sustained release of drug for approximately 2 and a half years and significantly reduces uveitis recurrence, improves visual acuity (VA), and decreases the need for adjunctive therapy; however, elevated intraocular pressure (IOP) is a common adverse event.<sup>3</sup>

Elevated IOP following treatment with corticosteroids is often controlled by topical pressure-lowering medication.<sup>4,5</sup> When elevated IOP cannot be controlled phar-

macologically, IOP-lowering surgery is usually performed.<sup>6,7</sup> Intraocular pressure-lowering surgical options include trabeculectomy, which can be performed in a variety of ways,<sup>8</sup> and the placement of glaucoma drainage devices.<sup>9,10</sup> Selective laser trabeculoplasty has also been used in a small case series of patients.<sup>11</sup>

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We present the emergence of elevated IOP as an adverse event secondary to the use of the FA intravitreal implant for the treatment of patients with noninfectious posterior uveitis. In this analysis, we pooled data related to IOP from 3 clinical trials evaluating the efficacy and safety of the FA intravitreal implant. Treatments for controlling IOP and outcomes of IOP management with nonsurgical and surgical interventions are reviewed.

## METHODS

### STUDIES

Data from 3 phase 2b/3, prospective, randomized, multicenter clinical trials evaluating the

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safety and efficacy of the 0.59-mg FA intravitreal implant (Reisert) and the 2.1-mg FA intravitreal implant over a 3-year period in eyes with noninfectious posterior uveitis were pooled to characterize the incidence of elevated IOP and its management. Eyes implanted with either a 0.59-mg (n=294) or a 2.1-mg (n=290) FA implant are included in the current analysis.

Study BLP 415-001 (ClinicalTrials.gov Identifier: NCT00407082) was a 3-year, double-masked, randomized, multicenter, controlled, phase 2b/3 safety and efficacy trial of 278 patients undergoing treatment with the FA intravitreal implant. The study was carried out at 27 sites in the United States (26) and Singapore (1), and 2 doses of the FA implant (0.59 mg and 2.1 mg) were compared. Study BLP 415-002 (ClinicalTrials.gov Identifier: NCT00468871) was a 3-year, randomized, multicenter, phase 2b/3 study of 146 patients with noninfectious posterior uveitis comparing the safety and efficacy of the 0.59-mg FA intravitreal implant with standard of care treatment. Standard of care therapy consisted of 0.2 mg/kg/d or more of prednisolone equivalent (or  $\geq 10$  mg/d for patients weighing more than 50 kg) if steroids were given alone or 0.1 mg/kg/d or more of prednisolone equivalent if steroids were given with immunosuppressive agents. After 6 months, if the disease was controlled, treatment doses were tapered according to each investigative site's standard guidelines. The study was carried out at 43 sites in Europe, Israel, and Saudi Arabia. BLP 415-004 (ClinicalTrials.gov Identifier: NCT00456482) was a 3-year, double-masked, randomized, multicenter, controlled, phase 2b/3 safety and efficacy study evaluating 2 doses (0.59 mg and 2.1 mg) of the FA intravitreal implant in 239 patients. The study was carried out at 19 sites in the United States, Canada, China, India, Australia, and the Philippine Islands. Prior to enrollment, patients were stratified according to their use of systemic or local therapy, such as corticosteroids or other immunosuppressive drugs.

In all 3 studies, ophthalmic examinations, including IOP measurements, were conducted on days 1 and 2 and at weeks 1, 4, 8, 12, 18, 24, 30, 34, and 52. After the 1-year visit, follow-up visits were at 3-month intervals for an additional 2 years. Visual field measurements were conducted at baseline and at selected visits in the postimplantation follow-up.

## FA INTRAVITREAL IMPLANT

The design and implantation technique of the FA intravitreal implant have been described in detail elsewhere.<sup>12</sup> Briefly, the implant is generally placed in the inferonasal or inferotemporal quadrant. A conjunctival peritomy is fashioned, followed by a 3- to 3.5-mm sclerotomy parallel to and 3.5 to 4 mm posterior to the limbus. Care is taken to ensure that the incision is through the choroid. A limited vitrectomy is performed, and the implant is sutured in place with an 8-0 polypropylene suture. The sclera is closed with an 8-0 or 9-0 polypropylene suture, and after verifying implant location, the conjunctiva is closed.

The FA implant contains FA in a polymeric delivery system and is designed to provide controlled drug release for approximately 2 and a half years.<sup>13</sup> The intravitreal implant studied contained either 0.59 mg or 2.1 mg of FA.

## EFFICACY

The primary efficacy outcome in all trials was the recurrence of uveitis, while VA was a secondary efficacy outcome. These outcomes were monitored in each trial for more than 3 years but are not the focus of the current analysis. The 34-week recurrence rate and within-patient comparison of VA from study BLP 415-001 have been reported previously,<sup>3</sup> while 3-year efficacy and safety results of that study and the efficacy and safety

results of study BLP 415-002 are the subject of separate articles.

Three-year uveitis recurrence rates and VA data from the 3 trials were pooled in the current analysis. In all 3 studies, a recurrence was defined as any 1 of the following: (1) 2-step or more increase in the number of anterior chamber cells compared with baseline, (2) 2-step or more increase in vitreous haze compared with baseline, (3) deterioration of at least 0.30 logarithm of the minimum angle of resolution (logMAR) in VA from screening/baseline without an obvious alternate etiology, or (4) ocular inflammation that, in the opinion of the investigator, required initiation or modification of therapy. Visual acuity was assessed (and recorded in logMAR units) using the standard Early Treatment Diabetic Retinopathy Study (ETDRS) procedure adapted for the Age-Related Eye Disease Study (AREDS).<sup>14</sup> Visual acuity improvement was defined as a gain of at least 3 lines, whereas stabilization was defined as a change of fewer than 3 lines from baseline VA.

## ELEVATED IOP AND MANAGEMENT

Goldmann applanation tonometry was used to measure IOP. The mean of 3 measurements in each eye was recorded as the IOP. Intraocular pressure measurements were not corrected for central corneal thickness. In eyes with elevated IOP, topical IOP-lowering medication was used as first-line treatment. Topical IOP-lowering medications included all classes of drugs currently approved by local agencies, with the choice of medication at the discretion of the investigator. The use of any IOP-lowering medications was recorded at every study visit. If IOP-lowering medications did not adequately control IOP, IOP-lowering surgeries were performed. Surgical interventions for IOP management were chosen, in most cases, by glaucoma specialists and were recorded throughout each study. These included trabeculectomies, glaucoma drainage devices, and cyclophotocoagulation. There were no criteria specified for the initiation of IOP-lowering surgery or choice of surgery; these were at the discretion of the clinician.

Complete success of IOP-lowering surgery was defined as postoperative IOP of 6 to 21 mm Hg that did not require additional IOP-lowering medications to stay within this range. Qualified success of IOP-lowering surgery was defined as postoperative IOP of 6 to 21 mm Hg that required additional IOP-lowering medications to stay within this range.

## STATISTICAL ANALYSIS

Statistical analysis included descriptive statistics (frequencies and percentages for discrete measures) to determine the incidence of events, such as the need for IOP-lowering medications or surgical procedures performed for IOP management, as well as continuous descriptive statistics (sample size, mean, standard deviation, minimum, and maximum) for measures of logMAR VA and IOP (millimeters of mercury). In addition, Kaplan-Meier analyses were performed to determine the time from implantation to any interventions for IOP management, with log-rank statistics to determine statistically significant differences in the time to event between implant groups.

The mean changes in VA and IOP from preoperative to postoperative visits were analyzed using paired *t* tests. The difference in the mean changes in VA and IOP from preoperative to postoperative visits between implant doses and between eyes treated with drainage devices and eyes treated with trabeculectomies were analyzed using pooled-variance *t* test methods when heterogeneity was not statistically significant (assessed through folded *F* test method,  $P > .05$ ) and using Satterthwaite *t* test estimates when heterogeneity was statistically sig-

**Table 1. Patient Baseline Characteristics**

Parameter	All Patients	Subgroups of All Patients	
		Patients Requiring IOP-Lowering Surgery <sup>a</sup>	Patients Not Requiring IOP-Lowering Surgery <sup>a</sup>
Age, y, mean ± SD (range)	41.4 ± 14.2 (7.0-92.0)	38.5 ± 13.9 (7.0-80.0)	44.3 ± 14.5 (8.0-92.0)
Ethnicity, No. (%)			
White	297 (50.9)	114 (38.4)	183 (61.6)
African American	56 (9.6)	11 (19.64)	45 (80.4)
Asian	188 (32.2)	75 (39.9)	113 (60.1)
Hispanic	25 (4.3)	7 (28.0)	18 (72.0)
Other	17 (2.9)	7 (41.2)	10 (58.8)
Sex, No. (%)			
M	216 (37.0)	103 (47.7)	113 (52.3)
F	368 (63.0)	111 (30.2)	257 (69.8)

Abbreviation: IOP, intraocular pressure.

<sup>a</sup>Ethnicity and sex data are within-group percentages.

**Table 2. Intraocular Pressure-Lowering Therapy by Drug Class**

Medication Class	No. (%)
β-Adrenergic antagonists	222 (50.8)
α-Adrenergic agonists	88 (20.1)
Prostaglandin analogues	22 (5.0)
Carbonic anhydrase inhibitors	
Topical	14 (3.2)
Oral	1 (0.2)
Miotics	4 (0.9)
Combination drugs	
Dorzolamide hydrochloride/timolol maleate	84 (19.2)
Latanoprost/timolol maleate	2 (0.4)
Total medication use, No./Total No. (%)	437/584 (74.8)

nificant ( $P \leq .05$ ). Hypotony rates between subjects with or without IOP-lowering surgeries were assessed using Pearson  $\chi^2$  statistics. Because these analyses were exploratory, all results with  $P$  values  $< .05$  were considered statistically significant.

## RESULTS

### PATIENTS

All eyes (584) implanted with either the 0.59-mg FA implant ( $n=294$ ) or the 2.1-mg FA implant ( $n=290$ ) were included in this analysis. The mean patient age was 41.4 years (range, 7-92 years), 63% were female, and half of the patients were white. Baseline characteristics of all the patients who received implants in this pooled analysis are presented in **Table 1** as well as the characteristics of those patients who required IOP-lowering surgery and those who did not. While data regarding the etiology of uveitis were not collected in all 3 studies, most patients had idiopathic uveitis.

### FA INTRAVITREAL IMPLANT EFFICACY

Pooled efficacy results for the FA intravitreal implant are presented in the eTable (available at <http://www>

.archophthalmol.com). The uveitis recurrence rate in implanted eyes was significantly reduced compared with pre-implantation rates. Uveitis recurrence rates at 3 years postimplantation for the 0.59-mg FA implant, the 2.1-mg FA implant, and both doses combined were 19.1%, 38.3%, and 28.6%, respectively, while the recurrence rate in fellow eyes without an implant was 55.8%, 57.8%, and 56.8%, respectively. Visual acuity was stabilized or improved in 86.8%, 81.0%, and 84.0% of implanted eyes in the 0.59-mg implant group, the 2.1-mg implant group, and both dose groups combined, respectively, vs 83.4%, 86.0%, and 84.6% of fellow eyes, respectively, at 3 years postimplantation.

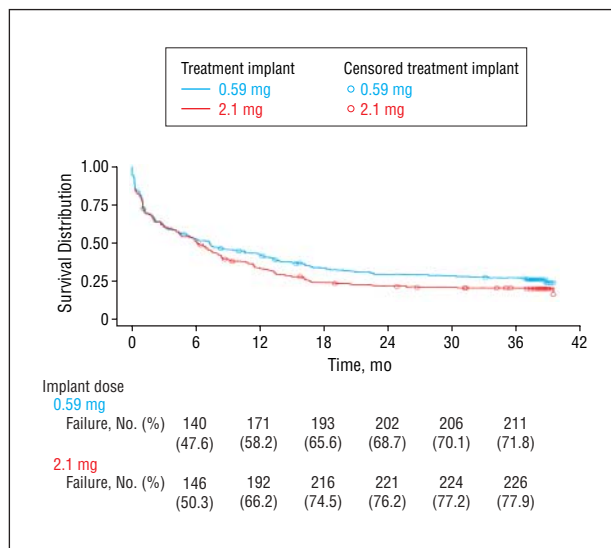
### MAGNITUDE OF AND TIME TO ELEVATED IOP

During the 3-year follow-up, 66.2% (192 of 290), 75.9% (220 of 290), and 71.0% (412 of 580) of implanted eyes reached an IOP elevation of 10 mm Hg or more from baseline (at any time) in the 0.59-mg FA implant group, the 2.1-mg FA implant group, and both dose groups combined, respectively, vs 19.8% (57 of 288), 22.5% (64 of 284), and 21.2% (121 of 572) of fellow eyes without implants, respectively.

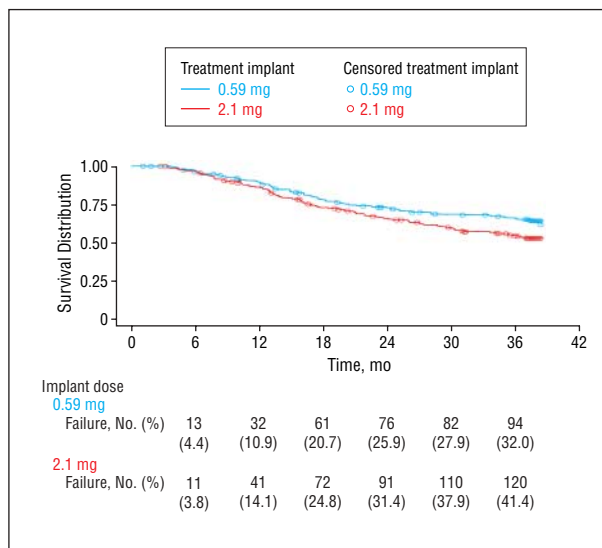
The Kaplan-Meier analyses of time from implantation to IOP of 30 mm Hg or more, 40 mm Hg or more, and 50 mm Hg or more are presented in eFigure 1 (available at <http://www.archophthalmol.com>). In the 0.59-mg implant group ( $n=293$ ), 108 (36.9%), 39 (13.3%), and 7 eyes (2.4%) at 1 year, 136 (46.4%), 54 (18.4%), and 15 eyes (5.1%) at 2 years, and 150 (51.2%), 66 (22.5%), and 18 eyes (6.1%) at 3 years postimplantation reached an IOP of 30 mm Hg or more, 40 mm Hg or more, and 50 mm Hg or more, respectively. In the 2.1-mg implant group ( $n=290$ ), 118 (40.7%), 45 (15.5%), and 10 eyes (3.4%) at 1 year, 160 (55.2%), 69 (23.8%), and 14 eyes (4.8%) at 2 years, and 171 (59.0%), 78 (26.9%), and 18 eyes (6.2%) at 3 years postimplantation reached an IOP of 30 mm Hg or more, 40 mm Hg or more, and 50 mm Hg or more, respectively. There was no significant difference in the time from implantation to IOP of 30 mm Hg or more ( $P=.07$ ), 40 mm Hg or more ( $P=.23$ ), and 50 mm Hg or more ( $P=.98$ ) in the 0.59-mg implant group vs the 2.1-mg implant group. The 25th percentile time to IOP of 30 mm Hg or more was 179 days with a 95% confidence interval (CI) of 146 to 243 days for the 0.59-mg implant group and 165 days (95% CI, 126-127) for the 2.1-mg implant group. The 25th percentile time to IOPs of 40 mm Hg or more and 50 mm Hg or more were not attained.

### TIME TO IOP-LOWERING MEDICATIONS AND IOP-LOWERING MEDICATIONS USED

Within 3 years following implantation, 437 of 584 eyes (74.8%) received IOP-lowering medication. First-line medications used are presented in **Table 2**. Kaplan-Meier analyses in **Figure 1** illustrate the time course to the initiation of IOP-lowering therapy for each implant dose, with cumulative proportions of patients at 6-month intervals requiring IOP-lowering medications included in the "Implant Dose" section. No significant differences in the



**Figure 1.** Kaplan-Meier analysis of time to intraocular pressure-lowering medication use in implanted eyes. "Implant Dose" section shows the cumulative proportions of eyes requiring intraocular pressure-lowering medication at the indicated intervals. Censored treatment includes patients removed from the at-risk population before study completion.



**Figure 2.** Kaplan-Meier analysis of time to intraocular pressure-lowering surgery in implanted eyes. "Implant Dose" section shows the cumulative proportions of eyes requiring intraocular pressure-lowering surgery at the indicated intervals. Censored treatment includes patients removed from the at-risk population before study completion.

incidence or the time course to initiation of IOP-lowering therapy were observed between the 0.59-mg and 2.1-mg implants ( $P = .12$ ). The mean  $\pm$  SD time from implantation to the initiation of IOP-lowering therapy was 409.3  $\pm$  18.7 days (both implant groups combined). Median time to initiation of IOP-lowering therapy from implantation was 197 days with a 95% CI of 166 to 232 days (both implant groups combined). The most commonly administered IOP-lowering medications included  $\beta$ -adrenergic antagonists (50.8%), followed by  $\alpha$ -adrenergic agonists (20.1%) and the fixed-dose dorzolamide hydrochloride/timolol maleate combination (19.2%).

#### TIME TO IOP-LOWERING SURGERY AND SURGICAL PROCEDURES USED

Within the 3-year postimplantation period, 36.6% (214 of 584) of eyes underwent surgical intervention for IOP management. Some of these surgical procedures were performed more than 2 years postimplantation. Kaplan-Meier analysis illustrating the time course to surgical intervention for IOP management is shown in **Figure 2**, while cumulative proportions of patients requiring IOP-lowering surgery at 6-month intervals are included in the "Implant Dose" section. The mean  $\pm$  SD time from implantation to surgery for IOP management was 870.5  $\pm$  13.9 days (both implant groups combined). The 25th percentile time to initiation of IOP-lowering surgery from implantation was 581 days (95% CI, 497-693 days); the 50th percentile was not attained. Time to IOP-lowering surgery was significantly longer for the 0.59-mg implant group than the 2.1-mg implant group ( $P = .02$ ). The 25th percentile time to initiation of IOP-lowering surgery for the 0.59-mg implant group was 691 days (95% CI, 518-998 days), with a mean  $\pm$  SD time of 898.4  $\pm$  19.0 days, and the 25th percentile time to initiation of IOP-lowering surgery for the 2.1-mg implant group was 525

days (95% CI, 451-651 days), with a mean  $\pm$  SD time of 820.8  $\pm$  19.2 days.

The distribution of IOP in eyes undergoing surgery just prior to surgery was as follows: 9.8% of eyes had an IOP of 6 to 21 mm Hg, 57.9% had an IOP of 22 to 35 mm Hg, 23.8% had an IOP of 36 to 45 mm Hg, and 8.4% had an IOP of 46 mm Hg or more. Because clinicians made their decision to initiate IOP-lowering surgery based on traditional variables, including visual field test and optic nerve head findings, as well as IOP, a small percentage of eyes undergoing IOP-lowering surgery had relatively modest elevations in IOP prior to surgery.

Intraocular pressure-lowering surgeries included trabeculectomy, glaucoma drainage devices, nonpenetrating surgery, and cyclophotocoagulation. The most commonly performed procedure was trabeculectomy (163 of 214 [76.2%]), followed by implantation of a glaucoma drainage device (44 of 214 [20.6%]), as presented in **Table 3**. Of the 214 initial IOP-lowering surgeries, 86 (40.2%) were augmented by antimetabolites (84 of the augmentations occurring with trabeculectomies), and of the surgeries augmented with antimetabolites, 83 were augmented at the time of surgery or within 7 days after surgery (67 with mitomycin C and 16 with 5-fluorouracil). Three were augmented more than 7 days after the initial surgery (2 with 5-fluorouracil and 1 with mitomycin C).

Repeated IOP-lowering surgeries were required in 20 of the 163 eyes treated initially with trabeculectomy and included Ahmed (5), Baerveldt (3), and repeated trabeculectomy (12) procedures, with 1 eye requiring a third procedure (Baerveldt). Eight of the 20 eyes requiring repeated surgery received an antimetabolite as adjunct therapy to their initial trabeculectomy. One of the 17 patients undergoing an initial Baerveldt procedure required a second procedure (Ahmed) and 3 of 5 patients undergoing initial cyclophotocoagulation required a second procedure (all trabeculectomies), with 2 of those pa-

**Table 3. Intraocular Pressure–Lowering Surgical Procedures**

Procedure	No. (%)
Trabeculectomy	163 (76.2)
Augmented with antimetabolites <sup>a</sup>	84 (51.5)
Mitomycin C augmentation <sup>b</sup>	66 (78.6)
5-Fluorouracil augmentation <sup>b</sup>	18 (21.4)
Glaucoma drainage device	44 (20.6)
Ahmed <sup>a</sup>	22 (50.0)
Baerveldt <sup>a</sup>	19 (43.2)
Express <sup>a</sup>	3 (6.8)
Cyclophotocoagulation	5 (2.3)
Trans-scleral <sup>a</sup>	4 (80.0)
Endoscopic <sup>a</sup>	1 (20.0)
Nonpenetrating surgery	2 (0.9)
Viscocanalostomy	1 (0.5)
Deep sclerotomy	1 (0.5)
Total	214

<sup>a</sup>Percentages are for each group and not for all surgeries combined.

<sup>b</sup>Percentages are for each subgroup and not for all surgeries combined.

tients requiring a third procedure (repeated cyclophotocoagulation). Finally, 2 of 3 patients undergoing initial Express shunts required a second procedure (1 Ahmed and 1 trabeculectomy), and 1 of those 2 patients required a third procedure (Ahmed).

### SURGICAL OUTCOMES

Preoperative and postoperative mean IOP and VA in eyes undergoing IOP-lowering surgical interventions are presented in **Table 4** (both implant groups combined). **Figure 3** shows the proportion of eyes within defined IOP ranges prior to IOP-lowering surgery and up to 12 months postsurgery. Surgical success and qualified success rates in 3-month intervals up to 1 year following the initial IOP-lowering procedure are presented in eFigure 2 (available at <http://www.archophthalmol.com>). Complete success of IOP-lowering surgery was recorded in 48.3%, 54.1%, 51.1%, and 50.0% at 3, 6, 9, and 12 months after surgery, respectively. Qualified success occurred in 25.9%, 27.0%, 27.7%, and 35.1% of eyes at 3, 6, 9, and 12 months after surgery, respectively. Surgical success rates in eyes that were augmented with antimetabolites were similar to those in eyes that were not augmented with antimetabolites (data not shown).

Prior to IOP-lowering surgery, the mean  $\pm$  SD IOP was 32.21  $\pm$  8.96 mm Hg (both implant groups combined). Postsurgery, the mean  $\pm$  SD IOP declined to 13.44  $\pm$  7.23 mm Hg at 3 months ( $\pm$  30 days), 14.62  $\pm$  7.39 mm Hg at 6 months ( $\pm$  30 days), 14.79  $\pm$  7.48 mm Hg at 9 months ( $\pm$  30 days), and 15.87  $\pm$  8.49 mm Hg at 12 months ( $\pm$  30 days) ( $P < .01$  for all). There were no significant differences in the mean change from preoperative to postoperative IOP levels between implant doses ( $P \geq .14$ ) or between eyes treated with drainage devices and eyes treated with trabeculectomy ( $P \geq .16$ ) through 12 months. The majority of patients were in the 6 to 21 mm Hg range from 3 months after IOP-lowering surgery through 12 months postsurgery.

Visual acuity was minimally impacted by IOP-lowering surgery, and in fact, a statistically significant net

gain of 1 line of vision (from logMAR 0.49 to logMAR 0.40;  $P = .02$ ) was observed 1 year postoperatively (both implant groups combined, including only subjects who had a 1-year postoperative visit). Prior to surgery, the mean  $\pm$  SD VA for all subjects who had an IOP-lowering surgery was 0.47  $\pm$  0.40 (both implant groups combined), while postsurgery, the mean  $\pm$  SD VA ranged from 0.40 to 0.47 and was significantly improved at 9 months and 12 months ( $P = .04$  and  $.02$ , respectively). There were no significant differences in the mean change from preoperative to postoperative VA between implant doses ( $P \geq .35$  for all) or between eyes treated with drainage devices and eyes treated with trabeculectomy ( $P \geq .25$  for all) through 12 months.

### IOP-LOWERING SURGERY ADVERSE EVENTS

Hypotony, defined as IOP of 5 mm Hg or lower occurring at 8 days or more after IOP-lowering surgery, developed in 42.5% (91 of 214) of eyes requiring IOP-lowering surgery. Approximately half of eyes (42 of 91 [46.0%]) with hypotony manifested more than 60 days following the initial IOP-lowering surgery, and 18% (16 of 91) developed hypotony more than 1 year following the initial surgery. In implanted eyes that did not require IOP-lowering surgery, hypotony occurred in 35.4% eyes (131 of 370). There was no significant difference in the proportion of implanted eyes that developed hypotony after IOP-lowering surgery vs those without IOP-lowering surgery ( $P = .09$ ). Of the 86 eyes that had IOP-lowering surgery augmented with antimetabolites, 37 (43.0%) developed hypotony vs 54 of 128 eyes (42.2%) not augmented with an antimetabolite.

After the first IOP-lowering surgery, hypotony (IOP  $\leq$  5 mm Hg) occurred in 36% (16 of 44) of eyes treated with shunts (glaucoma drainage devices) and in 45% (74 of 163) of eyes treated with trabeculectomy. At 3, 6, 9, and 12 months ( $\pm$  30 days) following surgery, 15.04%, 8.40%, 8.93%, and 3.19% of implanted eyes treated with trabeculectomy experienced hypotony vs 5.41%, 0%, 0%, and 5.88% of implanted eyes treated with drainage devices. Other postsurgery complications included retinal detachment (4 of 214 [1.9%]) and endophthalmitis (3 of 214 [1.4%]).

### EXPLANTS

A total of 13 patients had their implants surgically removed in an attempt to control elevated IOP. Of these patients, 8 required further intervention, 6 surgical and 2 medical, for IOP control.

### COMMENT

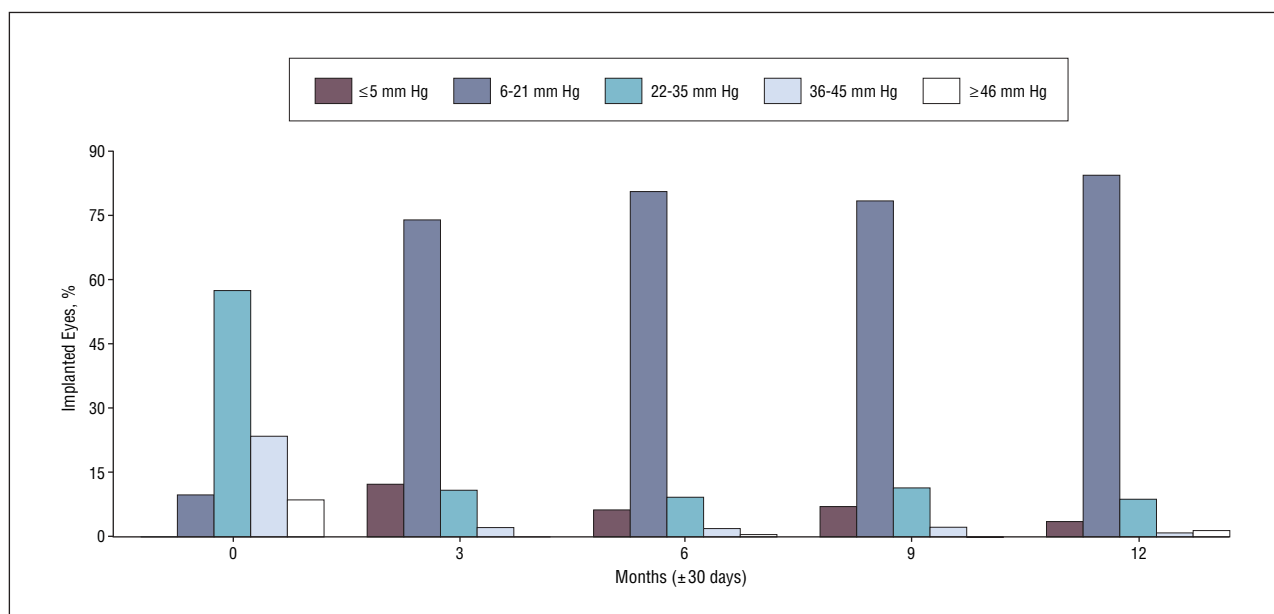
Uveitis has long been associated with elevated IOP; Georg Joseph Beer first reported this association in 1813.<sup>15</sup> Indeed, elevated IOP occurs in 8% to 26% of patients with acute uveitis and in 11% to 46% of patients with chronic uveitis, and the risk of elevated IOP has been shown to increase over time.<sup>6,16-18</sup> There are various mechanisms by which an inflammatory process can lead to elevated IOP. Alterations in aqueous composition and/or an obstructive

**Table 4. Outcomes Following Surgery for IOP Reduction**

Parameter	Time From IOP-Lowering Surgery, mean±SD			
	3 mo (± 30 d)	6 mo (± 30 d)	9 mo (± 30 d)	12 mo (± 30 d)
IOP, mm Hg				
No. of patients	174	148	137	114
Preoperative <sup>a</sup>	32.97±9.12	32.10±9.52	32.97±9.52	32.41±9.06
Postoperative	13.44±7.23	14.62±7.39	14.79±7.48	15.87±8.49
Change	-19.54±11.43	-17.48±11.43	-18.18±11.31	-16.54±11.89
P value	<.01	<.01	<.01	<.01
VA, logMAR				
No. of patients	154	132	129	111
Preoperative <sup>a</sup>	0.46±0.40	0.48±0.42	0.46±0.39	0.49±0.39
Postoperative	0.47±0.40	0.45±0.42	0.40±0.36	0.40±0.39
Change	0.01±0.36	-0.03±0.39	-0.06±0.33	-0.09±0.41
P value	.78	.40	.04	.02

Abbreviations: logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; VA, visual acuity.

<sup>a</sup>Preoperative IOP and VA represent the baseline mean value for those patients who were sampled at the indicated points.



**Figure 3.** Proportion of eyes within a defined range of intraocular pressure before and after intraocular pressure-lowering surgery.

tion of the filtering angle by inflammatory cells and other cellular debris may result in elevated IOP.<sup>19,20</sup> Intraocular pressure may also be elevated by angle closure. This event can occur in patients with posterior synechiae, causing pupil block, or it may occur secondary to progressive formation of peripheral anterior synechiae.<sup>21</sup>

Corticosteroids, the mainstay in the treatment of uveitis, may also elevate IOP because of their impact on the trabecular meshwork, where they decrease aqueous outflow.<sup>22,23</sup> While all corticosteroid administration routes have been associated with elevated IOP,<sup>24-29</sup> local ocular administration is associated with a greater risk, and of local delivery methods, intraocular delivery carries the greatest risk.<sup>28,30-34</sup> The extent of IOP elevation depends on the potency of the corticosteroid, the dose and duration of treatment, the route of administration, and the patient's susceptibility to corticosteroid-induced ocular hypertension.<sup>35</sup> Hence, in patients with uveitis with cor-

ticosteroid treatment, elevated IOP may be the result of the corticosteroid treatment and/or the uveitis itself.

The FA intravitreal implant is approved by the Food and Drug Administration for the treatment of noninfectious posterior uveitis. Its efficacy in managing this condition has been documented<sup>3,12,36</sup> and reconfirmed in the current pooled analysis with recurrence rates, 3 years postimplantation, of 19% and 38% in the 0.59-mg and 2.1-mg implant groups, respectively, compared with 56% and 58% of fellow eyes without an implant in the 0.59-mg and 2.1-mg implant groups. However, because the active ingredient in the implant is FA, a potent corticosteroid, the adverse effect profile of the implant includes complications attributable to corticosteroids in general, including cataract and elevated IOP.

In the current pooled analysis of IOP outcomes from 3 clinical trials, approximately three-fourths of eyes with non-infectious posterior uveitis treated with an FA intravit-

real implant developed elevated IOP of 10 mm Hg or more than baseline, requiring IOP-lowering pharmacotherapy, and one-third required IOP-lowering surgery within 3 years of implantation. Few eyes required explantation. The magnitude of IOP elevation was high; approximately half of implanted eyes reached an IOP of 30 mm Hg or more and one-quarter reached an IOP of 40 mm Hg or more prior to IOP-lowering treatment. The incidence of elevated IOP with the FA intravitreal implant was higher than that of other published studies, with intraocular corticosteroid therapy (primarily intravitreal triamcinolone acetonide [IVTA]) ranging from 36.3% to 48.6% depending on the definition used for elevated IOP.<sup>12,30-34</sup> Apart from differences between triamcinolone acetonide and FA at the molecular level and consequent potency at the glucocorticoid receptor, the higher incidence of elevated IOP with the FA intravitreal implant may be related to constant exposure to corticosteroid throughout the implant's 30-month lifespan, whereas in the referenced studies, eyes were exposed to fluctuating corticosteroid levels every 3 months. Thus, following IVTA injection, triamcinolone acetonide levels are expected to peak immediately, likely to supratherapeutic levels, and decline rapidly over 3 months down to negligible levels prior to the next IVTA injection. Also, results in some of the earlier-cited references were based on a single IVTA injection with short follow-up periods. Given the delayed IOP elevation that required therapy in the current study, it is likely that the reported incidence of elevated IOP after IVTA would be considerably higher with repeated IVTA injections over a similar study period.

The most common medications used to lower IOP in the pooled analysis were  $\beta$ -adrenergic antagonists,  $\alpha$ -adrenergic agonists, and the fixed-dose combination drug dorzolamide/timolol, with a mean time to IOP-lowering medication slightly longer than a year and a median of about 200 days. It follows that most patients who develop elevated IOP will do so within the first year following implantation with the FA intravitreal implant and that the risk for increased IOP is much lower thereafter. However, patients who develop elevated IOP will need management well beyond this time frame and a considerable proportion will require IOP-lowering surgery.

When surgery was necessary to control elevated IOP, trabeculectomy was the most common surgical procedure and the mean time to surgical intervention was approximately 29 months. Surgical outcomes were favorable; in the majority of eyes, IOP ranged from 6 to 21 mm Hg from 3 months through 12 months following IOP-lowering surgery. Approximately 50% of surgeries were classified as a complete success (IOP of 6-21 mm Hg, without the use of medication) and 25% to 35%, as a qualified success (IOP of 6-21 mm Hg, with the aid of additional medication). These rates are similar to or better than other published rates in patients with uveitic glaucoma<sup>37-39</sup> and are consistent with prior analysis of surgical outcomes in study BLP 415-001.<sup>40</sup>

Hypotony was the most common postoperative complication following IOP-lowering surgery, occurring in 42.5% of eyes. The timing of the onset of hypotony in eyes that underwent IOP-lowering surgery, along with the incidence of hypotony in both eyes with and without implants without a preceding IOP-lowering sur-

gery, suggests that the implant surgery and/or the disease itself may account for some proportion of these cases of hypotony. While chronic inflammation can significantly damage the ciliary body, resulting in reduced aqueous production,<sup>41,42</sup> the hypotony in these cases cannot be attributed solely to the underlying disease process because only 14.2% of eyes without implants developed hypotony (data not shown).

Because there was no significant difference with regard to hypotony in implanted eyes receiving glaucoma drainage devices vs those receiving a trabeculectomy, either surgery may be used to manage elevated IOP. However, we recognize that further hypotony may arise once the implant has run out of FA (regardless of the surgery), at which point it will be difficult to discern whether the IOP-lowering surgery or the uveitis or both is the cause of the hypotony. On the other hand, based on the limited success of explantation to control elevated IOP (8 of 13 patients in the pooled analysis whose implants were removed required further intervention to lower their IOP), it remains to be determined to what degree hypotony occurs following implant depletion. Longer follow-up will be needed to help clarify whether the drainage implant or trabeculectomy performs better in this situation of depleted implants.

In summary, in the current pooled analysis, the incidence and magnitude of elevated IOP following treatment of patients with uveitis with the FA intravitreal implant were high but manageable with medication and IOP-lowering surgery. When surgery was required, rates of complete or qualified surgical success were high. Ultimately, the need to manage elevated IOP as an adverse event following treatment with the FA intravitreal implant should be balanced against the excellent efficacy of the FA intravitreal implant in reducing uveitis recurrence. Patients and treating physicians must be cognizant of the very real possibility of marked elevation in IOP (unlikely to resolve on its own) secondary to this implant, prepared for frequent follow-up to monitor IOP rises and/or spikes, and aware of the significant risk of requiring glaucoma surgery. Furthermore, baseline optic nerve photographs and/or imaging and visual field testing are strongly suggested so that subsequent decisions about the need for surgical intervention can be based not only on IOP but also on either an increase in cupping or visual field loss.

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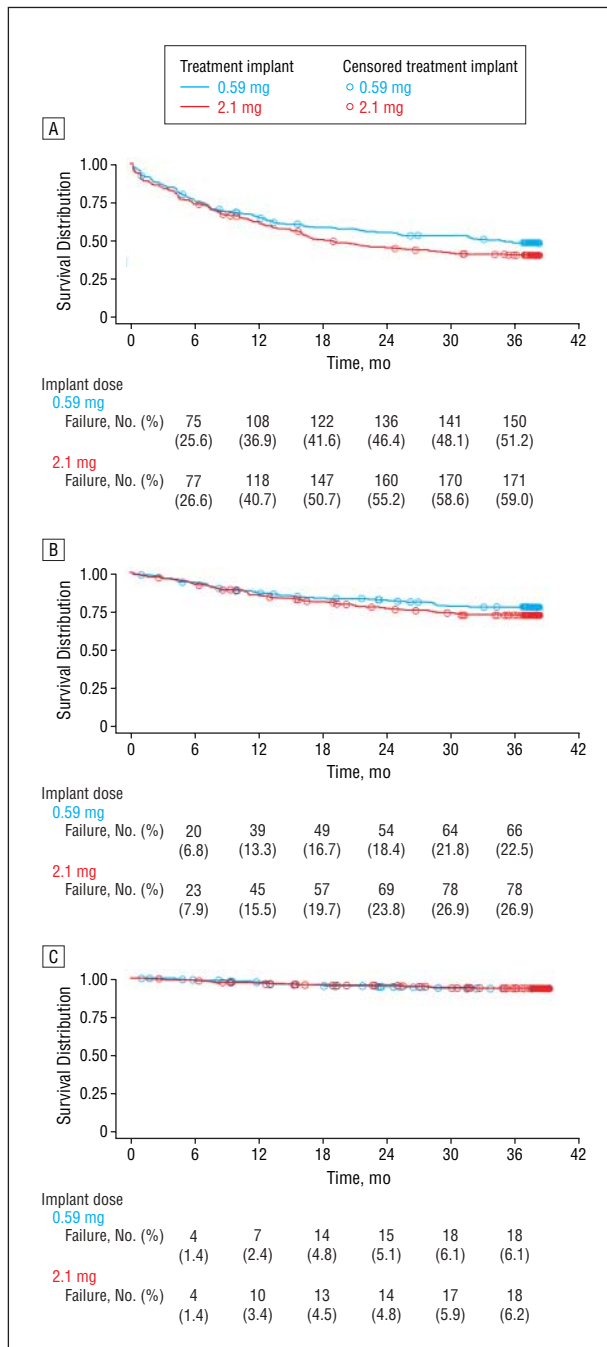
**Previous Presentations:** These data were presented in part at the American Glaucoma Society 17th Annual Meeting; March 2, 2007; San Francisco, California.

**Additional Information:** The eFigures and eTable are available at <http://www.archophthalmol.com>.

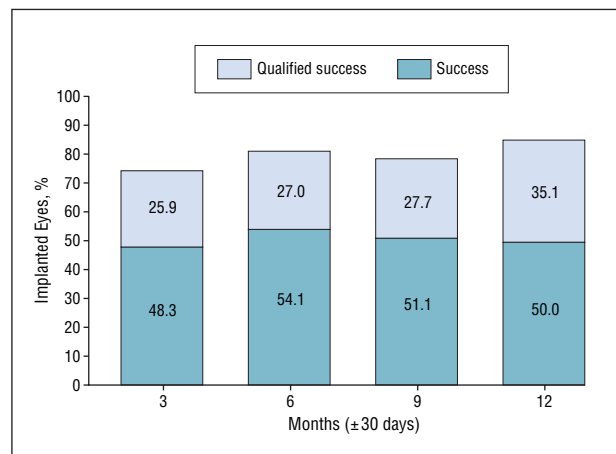
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## REFERENCES

1. Durrani OM, Tehrani NN, Marr JE, Moradi P, Stavrou P, Murray PI. Degree, duration, and causes of visual loss in uveitis. *Br J Ophthalmol*. 2004;88(9):1159-1162.
2. Rothova A. Corticosteroids in uveitis. *Ophthalmol Clin North Am*. 2002;15(3):389-394.
3. Jaffe GJ, Martin D, Callanan D, Pearson PA, Levy B, Comstock T. Fluocinolone acetonide implant (Retisert) for noninfectious posterior uveitis: thirty-four-week results of a multicenter randomized clinical study. *Ophthalmology*. 2006;113(6):1020-1027.
4. Fuchsjäger-Mayrl G, Markovic O, Losert D, et al. Polymorphism of the beta-2 adrenoceptor and IOP lowering potency of topical timolol in healthy subjects. *Mol Vis*. 2005;11:811-815.
5. Resch H, Garhofer G. Topical drug therapy in glaucoma. *Wien Med Wochenschr*. 2006;156(17-18):501-507.
6. Panek WC, Holland GN, Lee DA, Christensen RE. Glaucoma in patients with uveitis. *Br J Ophthalmol*. 1990;74(4):223-227.
7. Jamil AL, Mills RP. Glaucoma tube or trabeculectomy? That is the question. *Am J Ophthalmol*. 2007;143(1):141-142.
8. Simsek T, Citirik M, Batman A, Mutevelli S, Zilelioglu O. Efficacy and complications of releasable suture trabeculectomy and standard trabeculectomy. *Int Ophthalmol*. 2005;26(1-2):9-14.
9. Brasil MV, Rockwood EJ, Smith SD. Comparison of silicone and polypropylene Ahmed glaucoma valve implants. *J Glaucoma*. 2007;16(1):36-41.
10. Schwartz KS, Lee RK, Gedde SJ. Glaucoma drainage implants: a critical comparison of types. *Curr Opin Ophthalmol*. 2006;17(2):181-189.
11. Smit B. Selective laser trabeculoplasty for uncontrolled intraocular pressure after injection of triamcinolone. Paper presented at: American Glaucoma Society 17th Annual Meeting; March 3, 2007; San Francisco, CA.
12. Jaffe GJ, Ben-Nun J, Guo H, Dunn JP, Ashton P. Fluocinolone acetonide sustained drug delivery device to treat severe uveitis. *Ophthalmology*. 2000;107(11):2024-2033.
13. Retisert prescribing information. Rochester, NY: Bausch & Lomb Inc; 2005.
14. Age-Related Eye Disease Study Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report No. 8. *Arch Ophthalmol*. 2001;119(10):1417-1436.
15. Beer GJ. Die Lehre v. d. Augenkrankheiten. *Vienna*. 1813;1:633.
16. Herbert HM, Viswanathan A, Jackson H, Lightman SL. Risk factors for elevated intraocular pressure in uveitis. *J Glaucoma*. 2004;13(2):96-99.
17. Neri P, Azuara-Blanco A, Forrester JV. Incidence of glaucoma in patients with uveitis. *J Glaucoma*. 2004;13(6):461-465.
18. Takahashi T, Ohtani S, Miyata K, Miyata N, Shirato S, Mochizuki M. A clinical evaluation of uveitis-associated secondary glaucoma. *Jpn J Ophthalmol*. 2002;46(5):556-562.
19. Elliot R. *A Treatise on Glaucoma*. London, England: Oxford Medical Publications; 1918.
20. Moororthy RS, Mermoud A, Baerveldt G, Minckler DS, Lee PP, Rao NA. Glaucoma associated with uveitis. *Surv Ophthalmol*. 1997;41(5):361-394.
21. Ritch R. Pathophysiology of glaucoma in uveitis. *Trans Ophthalmol Soc UK*. 1981;101(3)(pt 3):321-324.
22. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics, I: the effect of dexamethasone in the normal eye. *Arch Ophthalmol*. 1963;70:482-491.
23. Becker B, Mills DW. Corticosteroids and intraocular pressure. *Arch Ophthalmol*. 1963;70:500-507.
24. Bernstein HN, Mills DW, Becker B. Steroid-induced elevation of intraocular pressure. *Arch Ophthalmol*. 1963;70:15-18.
25. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. *JAMA*. 1997;277(9):722-727.
26. Garrott HM, Walland MJ. Glaucoma from topical corticosteroids to the eyelids. *Clin Experiment Ophthalmol*. 2004;32(2):224-226.
27. Kalina RE. Increased intraocular pressure following subconjunctival corticosteroid administration. *Arch Ophthalmol*. 1969;81(6):788-790.
28. Singh IP, Ahmad SI, Yeh D, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. *Am J Ophthalmol*. 2004;138(2):286-287.
29. Jones R III, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Curr Opin Ophthalmol*. 2006;17(2):163-167.
30. Gualino V, Audren F, Erginay A, et al. Intraocular pressure after intravitreal triamcinolone acetonide for diabetic diffuse macular edema. Paper presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2005 Annual Meeting; May 2, 2005; Fort Lauderdale, FL.
31. Jonas JB, Degenring RF, Kreissig I, Akkoyun I, Kamppeier BA. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Ophthalmology*. 2005;112(4):593-598.
32. Kok H, Lau C, Maycock N, McCluskey P, Lightman S. Outcome of intravitreal triamcinolone in uveitis [published online ahead of print September 19, 2005]. *Ophthalmology*. 2005;112(11):1916.e1-7.
33. Ozkiris A. Intravitreal triamcinolone acetonide injection for the treatment of posterior uveitis. *Ocul Immunol Inflamm*. 2006;14(4):233-238.
34. Roth DB, Varma V, Realini T, Prenner J, Fechtner RD, Feuer WJ. Long term incidence and timing of intraocular hypertension following intravitreal triamcinolone acetonide injection. Paper presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2007 Annual Meeting; May 10, 2007; Fort Lauderdale, FL.
35. Clark A. Steroids, ocular hypertension, and glaucoma. *J Glaucoma*. 1995;4(5):354-369.
36. Jaffe GJ, McCallum RM, Branchaud B, Skalak C, Butuner Z, Ashton P. Long-term follow-up results of a pilot trial of a fluocinolone acetonide implant to treat posterior uveitis. *Ophthalmology*. 2005;112(7):1192-1198.
37. Ceballos EM, Parrish RK II, Schiffman JC. Outcome of Baerveldt glaucoma drainage implants for the treatment of uveitic glaucoma. *Ophthalmology*. 2002;109(12):2256-2260.
38. Gil-Carrasco F, Salinas-VanOrman E, Recillas-Gispert C, Paczka JA, Gilbert ME, Arellanes-Garcia L. Ahmed valve implant for uncontrolled uveitic glaucoma. *Ocul Immunol Inflamm*. 1998;6(1):27-37.
39. Molteno AC, Sayawat N, Herbison P. Otago glaucoma surgery outcome study: long-term results of uveitis with secondary glaucoma drained by Molteno implants. *Ophthalmology*. 2001;108(3):605-613.
40. Godfrey DG, Callanan DC. Incidence and treatment of steroid induced glaucoma after treatment of uveitis with the Retisert (fluocinolone acetonide) intravitreal implant. Paper presented at: American Glaucoma Society 17th Annual Meeting; March 2, 2007; San Francisco, CA.
41. da Costa DS, Lowder C, de Moraes HV Jr, Orefice F. The relationship between the length of ciliary processes as measured by ultrasound biomicroscopy and the duration, localization and severity of uveitis. *Arq Bras Oftalmol*. 2006;69(3):383-388.
42. Windisch BK, Iliev ME. Treatment of uveitis-associated refractory ocular hypotony with topical ibopamine. *Klin Monatsbl Augenheilkd*. 2006;223(5):422-424.



**eFigure 1.** Kaplan-Meier analysis of time from implantation to intraocular pressure of 30 mm Hg or more (A), 40 mm Hg or more (B), and 50 mm Hg or more (C) in the implant groups. “Implant Dose” sections show cumulative proportions over time. Censored treatment includes patients removed from the at-risk population before study completion.



**eFigure 2.** Surgical success (postoperative intraocular pressure [IOP] 6-21 mm Hg, not necessitating additional IOP-lowering medications) and qualified success (postoperative IOP 6-21 mm Hg, necessitating additional IOP-lowering medications) at specific points following surgery in patients for whom follow-up data were available.

**eTable. Fluocinolone Acetonide Intravitreal Implant Pooled Efficacy Results**

Implant Dose	No./Total No. (%)				
	Recurrence Rate at 3 Years		Visual Acuity at 3 Years		
	Implanted Eye <sup>a</sup>	Fellow Eye	Stabilized	Improved	Total
0.59 mg	56/293 (19.1)	163/292 (55.8)	160/258 (62.0)	64/258 (24.8)	224/258 (86.8)
2.1 mg	111/290 (38.3)	166/287 (57.8)	149/247 (60.3)	51/247 (20.6)	200/247 (81.0)
Both doses	167/583 (28.6)	329/579 (56.8)	309/505 (61.2)	115/505 (22.8)	424/505 (84.0)

<sup>a</sup>In patients with bilateral disease, the more severely affected eye was implanted.