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Singer MA, Wykoff CC, Riemann CD, et al. Fluocinolone acetonide implant as a baseline therapy for diabetic macular edema: results from the randomized phase 4 NEW DAY study. *Ophthalmology*. 2026:S0161-6420(26)00206-X. doi:10.1016/j.ophtha.2026.03.019

Alimera Sciences, an ANI Pharmaceuticals, Inc. company, is the NDA holder of ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg.

Please note that some of the information about ILUVIEN described in this journal article may not be consistent with the FDA-approved Prescribing Information.

ILUVIEN is a corticosteroid indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.
- ILUVIEN is contraindicated in patients with glaucoma who have cup to disc ratios of greater than 0.8.
- ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

- **Intravitreal Injection-related Effects:** Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Patients should be monitored following the intravitreal injection. Patients may experience temporary blurred vision after injection of the implant.
- **Intraocular Pressure (IOP) Increase:** Prolonged use of corticosteroids may result in the development of glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be routinely monitored during the course of the treatment.
- **Cataracts:** The use of corticosteroids may result in posterior subcapsular cataract formation.
- **Delayed Corneal Wound Healing:** The use of corticosteroids after cataract surgery may delay healing and increase the incidence of bleb formation.
- **Corneal and Scleral Melting:** Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of ophthalmic corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation of the globe.
- **Bacterial Infections:** Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. Acute purulent or parasitic infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.
- **Viral Infections:** Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

Please see additional Important Safety Information on back and accompanying full Prescribing Information.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

- **Fungal Infections:** Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.
- **Risk of Implant Migration:** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

Diabetic Macular Edema

Ocular adverse reactions reported by greater than or equal to 1% of patients in the two combined 3-year clinical trials following injection of ILUVIEN for diabetic macular edema include: cataract (82%), myodesopsia (21%), eye pain (15%), conjunctival hemorrhage (13%), posterior capsule opacification (9%), eye irritation (8%), vitreous detachment (7%), conjunctivitis (4%), corneal oedema (4%), foreign body sensation in eyes (3%), eye pruritus (3%), ocular hyperaemia (3%), optic atrophy (2%), ocular discomfort (2%), photophobia (2%), retinal exudates (2%), anterior chamber cell (2%), and eye discharge (2%). Non-ocular adverse reactions reported by greater than or equal to 5% of patients include: anemia (11%), headache (9%), renal failure (9%), and pneumonia (7%)

Increased Intraocular Pressure: IOP elevation greater than or equal to 10 mm Hg from baseline at any visit was seen in 34% of ILUVIEN patients versus 10% of sham patients. IOP elevation greater than or equal to 30 mm Hg was seen in 20% of ILUVIEN patients versus 4% of sham patients. 38% of the patients who received ILUVIEN were subsequently treated with IOP-lowering medications during the study versus 14% of sham patients. 5% of the patients who received ILUVIEN needed surgical intervention for elevated IOP versus 1% of sham patients

Cataracts and Cataract Surgery: The incidence of cataract development in patients who had a phakic study eye was higher in the ILUVIEN group (82%) compared with sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the ILUVIEN group and 19 months in the sham group. Among these patients, 80% of ILUVIEN subjects versus 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (median month 15 for both ILUVIEN group and for sham) of the studies.

Financial Disclosures

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Sincerely,

ANI Pharmaceuticals, Inc.

Scan the QR code to view the
NEW DAY Study published in *Ophthalmology*:

Alimera was acquired by ANI Pharmaceuticals, Inc. on September 16, 2024.

Please see the accompanying full Prescribing Information.

ani Pharmaceuticals, Inc.

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Fluocinolone Acetonide Implant as a Baseline Therapy for Diabetic Macular Edema

Results from the Randomized Phase 4 NEW DAY Study

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Purpose: The NEW DAY (ClinicalTrials.gov identifier, NCT04469595) study assessed the efficacy and safety of the fluocinolone acetonide (FAc; 0.19 mg) intravitreal implant as baseline therapy in diabetic macular edema (DME).

Design: Prospective, randomized, single-masked, active-controlled, multicenter, 18-month, phase 4 study.

Participants: Adults with type 1 or 2 diabetes and center-involving DME confirmed by central subfield thickness (CST).

Methods: Treatment regimens were FAc implant followed by rescue supplemental injections of aflibercept if needed (2 mg/0.05 ml) for 17 months versus aflibercept loading dose (2 mg every 4 weeks for 5 consecutive doses) followed by rescue supplemental injections of aflibercept if needed (2 mg/0.05 ml) for 13 months.

Main Outcome Measures: The primary end point was mean rescue supplemental injections of aflibercept needed during the study by treatment group. Additional outcomes included time to first rescue supplemental injection, best-corrected visual acuity (BCVA), CST, rates of cataract procedures, and increases in intraocular pressure (IOP).

Results: Five hundred seventeen participants were screened, and 306 participants randomized. Mean (standard deviation [SD]) rescue supplemental injections were 2.4 (3.2) with FAc and 2.5 (3.1) with aflibercept ($P = 0.76$; primary end point). Counting both protocol-mandated and rescue supplemental injections, the FAc group received fewer injections compared with the aflibercept group (mean [SD], 3.4 [3.2] vs. 7.2 [3.4] injections; nominal $P < 0.001$). Time to first rescue supplemental injection was longer with FAc than with aflibercept (mean [SD], 185.4 [97.9] days vs. 132.8 [94.0] days; nominal $P < 0.001$). Proportions of participants who did not receive rescue supplemental injections were similar (32.5% vs. 30.3%; nominal $P = 0.68$). Mean change in BCVA was similar between groups (1.8 letters vs. 5.5 letters; nominal $P = 0.08$), as was the change in CST (mean [SD], −119 [112] μm vs. −114 [103] μm; nominal $P = 0.71$). In the FAc group, 27.9% underwent a cataract procedure versus 6.6% in the aflibercept group. Increased IOP occurred in 15.6% and 3.3% of participants in the FAc and aflibercept groups, respectively.

Conclusions: Although the primary end point of rescue supplemental injection superiority was not met, FAc-treated participants achieved similar visual and anatomic improvements as those receiving aflibercept with fewer than half the number of total injections throughout the study. Safety data results were consistent with previous FAc implant studies.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology 2026;133:837-851 Published by Elsevier Inc. on behalf of American Academy of Ophthalmology, Inc.*

Supplemental material available at www.aaojournal.org.

The prevalence of diabetes mellitus is rising worldwide, with an estimated incidence of approximately 529 million patients in 2021 increasing to 783 million patients in 2045, approximately 1 in 4 of whom will develop diabetic retinopathy (DR).[1–3] The likelihood of patients with DR developing diabetic macular edema (DME) is roughly 7%, with untreated DME leading to impaired vision and blindness.[4] With rising longevity, it is estimated that DME lifetime risk will increase to 25% to 30%.[5]

The pathophysiologic features of DR and DME historically have been considered a consequence of retinal microangiopathy and neovascularization driven by ischemia and hypoxia, as well as the result of chronic inflammation and overproduction of vascular endothelial growth factor (VEGF).[6] However, many other factors contribute to the pathogenesis of DR and DME, including retinal neurodegeneration, advanced glycation end product formation, and oxidative stress, which precede the earliest

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manifestation of DR vasculopathy.[7,8] In DR and DME, the release of cytokines activates microglia, which in turn amplify inflammatory signaling through astrocytes and Müller glial cells, resulting in microvascular dysfunction and aberrant angiogenesis.[9,10] Hypoxia and inflammation in the retina increase the production of VEGF, which may result in pathogenic neovascularization and increased endothelial permeability.[8]

The most commonly used pharmacologic treatments for DME include anti-VEGF agents and corticosteroids. Intravitreal injections of anti-VEGF therapies reduce edema and neovascularization in the retina; however, frequent injections and close monitoring can place a high burden on patients, leading to reduced adherence to treatment over time.[5,11] In addition, sole inhibition of VEGF does not address other pathophysiologic pathways of DME, such as upregulated inflammatory cascades. Many patients are not fully responsive to anti-VEGF therapy, characterized by persistent macular thickening.[12–14] In the DRCR.net Protocol T trial, although eyes received 3 to 6 consecutive monthly anti-VEGF injections, between one-third and two-thirds of eyes demonstrated persistent DME after 6 months; among these eyes, 60% to 71% required rescue laser treatment at 1 year.[13] Although high adherence rates have been observed in pivotal trials of intravitreal anti-VEGF for DME,[15,16] these are not replicated in the clinical setting, where patients attend fewer clinic visits and receive fewer injections[17] and have higher discontinuation rates, even with an extended anti-VEGF treatment interval.[18] These missed visits have been associated with worse visual outcomes.[17]

As an alternative therapeutic option, corticosteroids offer the potential of increasing treatment-free intervals and demonstrate suppression of chronic hyperglycemia-triggered inflammation by reducing the production of VEGF and inflammatory cytokines.[19,20] However, the use of corticosteroids can be associated with increased progression of cataracts and elevated ocular hypertension.[19–21]

The fluocinolone acetonide (FAc) 0.19-mg intravitreal implant (ILUVIEN) is a corticosteroid approved by the United States Food and Drug Administration for the treatment of DME in patients who previously were treated with a course of corticosteroids and did not show a clinically significant rise in intraocular pressure (IOP).[22] The FAc 0.19-mg implant is a sustained-release intravitreal drug-delivery system that is designed to deliver a continuous low dose (0.2 μg/day) of FAc in the vitreous humor for up to 36 months.[23] The ability of the FAc implant to be formulated with low-dose corticosteroid may mitigate some risks of steroid-related adverse events (AEs) compared with higher-dose implants.[24]

The efficacy and safety of the FAc implant have been demonstrated in several clinical studies. The phase 3 Fluocinolone Acetonide in Diabetic Macular Edema (FAME) studies were randomized, masked, sham-injection-controlled, parallel-group, multicenter studies that demonstrated the long-term efficacy and safety of the FAc implant in patients with persistent DME despite 1 or more macular laser treatment(s).[25] Twenty-eight percent of participants who received the FAc implant achieved 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS)-letter improvements from baseline compared with 19% of participants who received a sham injection. Although FAc implants can lead to elevated IOP,[25] a post hoc analysis of FAME found that participants who previously tolerated an ocular steroid before enrollment without an uncontrolled rise in IOP did not require IOP-lowering surgery after receiving the FAc 0.2-μg/day implant.[26]

Clinical trials and observational clinical evidence indicate that patients benefit most from FAc implants when used in the early stages of DME. In the United States Retrospective Chart Review in Patients Receiving ILUVIEN (USER) study, patients with better visual acuity (20/40 or better) showed the greatest reduction in treatment burden when treated with the FAc implant,[27] with a significant reduction in retinal thickness fluctuations.[28] The phase 4 IOP Signals Associated with ILUVIEN (PALADIN) study was a 3-year, phase 4, nonrandomized, open-label observational study that focused on safety outcomes in participants treated for DME and further validated the findings of USER.[29,30] In the PALADIN study, best-corrected visual acuity (BCVA) was increased significantly by +4.5 letters, with 68% of eyes receiving 0 to 2 yearly treatments in the 36 months after FAc implant insertion, compared with a loss of −6.4 letters with 75% of eyes receiving 3 or more yearly treatments during the 36 months before FAc implantation.[31] Retinal thickness variability was reduced significantly at all time points after FAc implantation, and better control of edema was correlated with better visual outcomes. Importantly, all patients in the PALADIN study previously had tolerated a corticosteroid without a clinically significant IOP rise, in line with the United States FAc implant label for DME[22]; under these label-compliant conditions, mean IOP remained stable and manageable, and no new safety signals were identified.[29–31]

The NEW DAY study is a prospective, phase 4 trial that compared the FAc 0.19-mg implant with an anti-VEGF (aflibercept 2 mg) treatment as a baseline therapy for the treatment of DME in participants whose eyes were treatment-naive or nearly naive for DME (Fig 1). The aim was to characterize the safety, effectiveness, and injection burden of the FAc implant when used as baseline therapy, with rescue supplemental injection(s) of aflibercept if needed, in a multicenter clinical setting.

Methods

Study Design

The NEW DAY study was a randomized, single-masked, active-controlled, parallel-group, multicenter study (ClinicalTrials.gov identifier, NCT04469595) conducted at 42 sites in the United States. This study was sponsored by Alimera (acquired by ANI Pharmaceuticals, Inc, in 2024) and was conducted according to the ethical principles defined in the Declaration of Helsinki and Good Clinical Practice guidelines, as described by the International Council for Harmonisation. Sterling Institutional Review Board

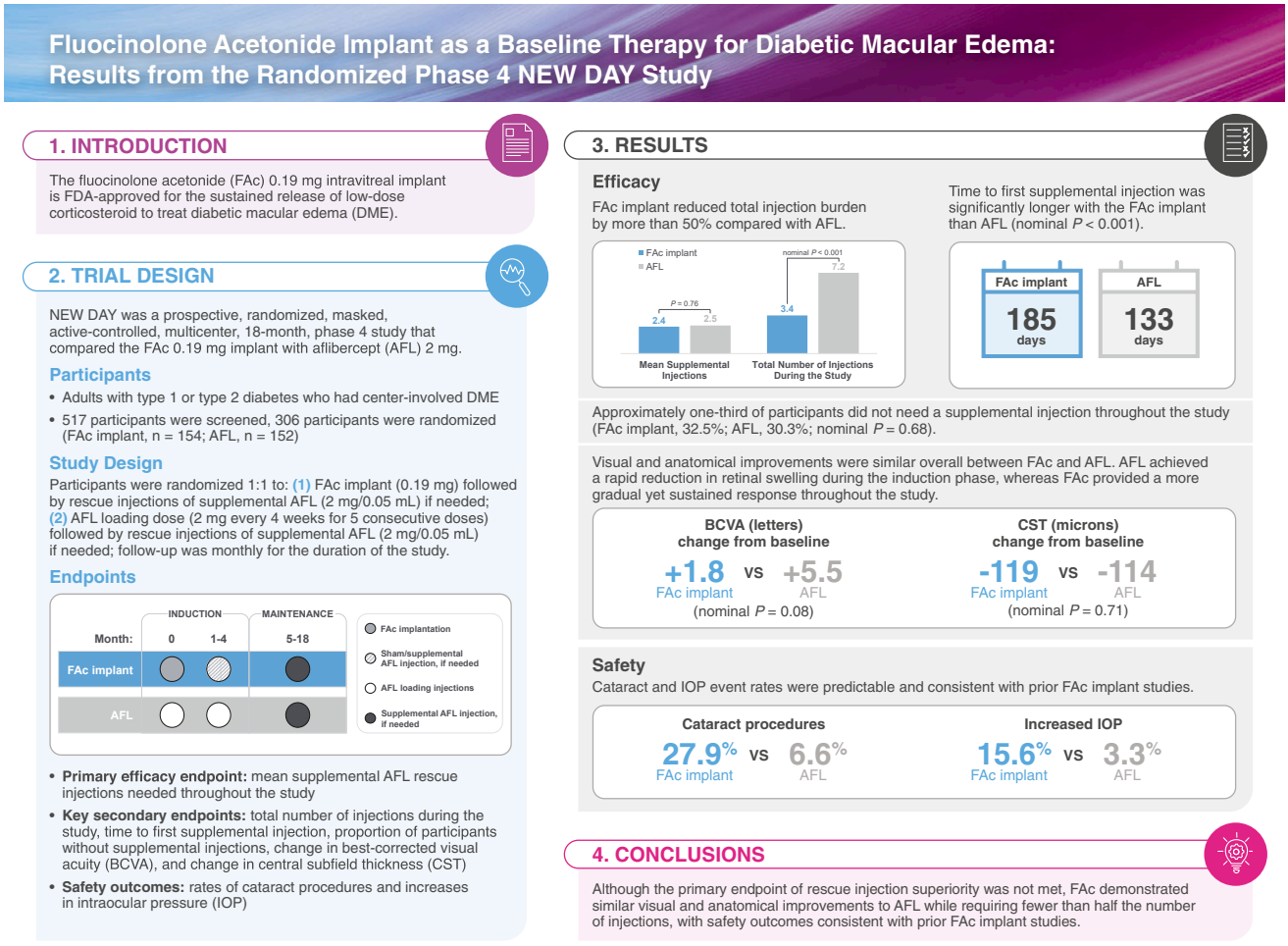

Figure 1. Graphical abstract of the NEW DAY study. FDA = United States Food and Drug Administration.

served as the central IRB for the study. Baylor College of Medicine and Kaiser Permanente Research were the only sites that did not use the central IRB and instead followed their respective institutional IRBs. Participants provided written informed consent.

NEW DAY was designed to assess the efficacy of the FAc implant as a baseline therapy to treat center-involving DME (Fig 2). Participants enrolled in the study had treatment-naive DME or did not receive more than 1 ranibizumab or

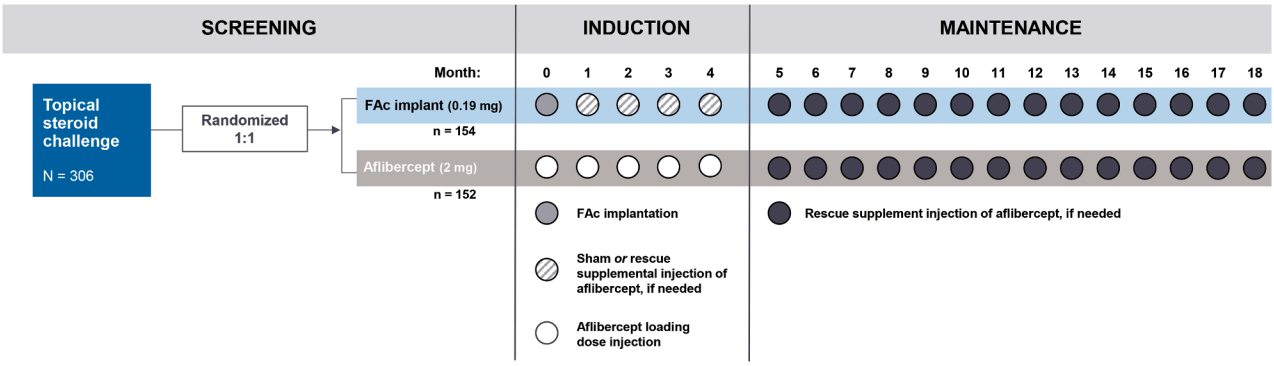

Figure 2. Diagram showing NEW DAY study design, including screening and 1:1 randomization to fluocinolone acetonide (FAc) implant (0.19 mg; n = 154) or aflibercept (2 mg; n = 152) arms. Participants received either 1 intravitreal FAc implant (plus supplemental rescue aflibercept injection if needed) or 5 intravitreal injections of aflibercept during the induction phase (months 0–4). All participants were eligible for rescue supplemental injection with aflibercept during the maintenance period (months 5–18).

bevacizumab intravitreal DME treatment for the preceding 12 months, as documented in the participants' medical records. Participants treated for DME for more than 12 months previously received 4 or fewer intravitreal anti-VEGF injections. Eligible participants were 18 years of age or older with a confirmed diagnosis of center-involving DME and had a BCVA of 80 or fewer ETDRS letters and 35 or more ETDRS letters in the study eye (Snellen equivalent, 20/25−20/200). Participants were excluded if they had a medical history of proliferative diabetic retinopathy (PDR) or were at high risk of PDR developing. During each study visit, images for Diabetic Retinopathy Severity Scale (DRSS) analysis were acquired. At the end of the study, the images were graded by a central examiner and were assigned a DRSS score. Complete study eligibility criteria are provided in Appendix 1 (available at www.aaojournal.org). Eligible participants underwent a steroid challenge with topical difluprednate eye drops (1 drop given 4 times daily for at least 2 weeks before the baseline visit), with eligibility confirmed by IOP readings at baseline. Participants who experienced an IOP of 25 mmHg or more or an increase of 8 mmHg or more from screening at the baseline visit were excluded from the study.

The treatment groups compared in NEW DAY were those who received the FAc implant (0.19 mg), followed by rescue supplemental injection(s) of aflibercept if needed (2 mg/0.05 ml) for 17 months, and those who received an intravitreal aflibercept loading regimen (2-mg intravitreal injection every 4 weeks for 5 consecutive doses), followed by rescue injection(s) of supplemental aflibercept if needed (2 mg/0.05 ml) for 13 months (Fig 2). Certified ophthalmic technicians, masked to treatment assignments, conducted ETDRS BCVA testing and optical coherence tomography (OCT) and recorded results in the electronic data capture (EDC) system.

The study consisted of screening, induction therapy, and maintenance therapy periods (Fig 2). Screening was conducted 15 to 21 days before the baseline visit. Participants meeting the eligibility criteria began a minimum 2-week steroid challenge with self-administered difluprednate eye drops before the baseline visit, as described above. Participants who did not successfully meet the steroid challenge criteria were excluded from the study. During screening visits, investigators selected the study eye of each participant with the worst BCVA. When both eyes had the same BCVA, investigator discretion was used.

Participants were randomized 1:1 to the FAc implant or aflibercept groups as determined by an EDC system. Treatment assignment was stratified by baseline BCVA and lens status (phakic vs. pseudophakic) to ensure balanced enrollment to treatment groups. Participants were masked to treatment assignments. Investigators treating the participants were not masked to treatment assignments; however, examiners performing the BCVA and OCT tests were masked to treatment assignments and whether rescue supplemental treatment was recommended by the treatment algorithm. Participants assigned to the FAc implant group received sham injections at visits 3 through 6 of the induction period (corresponding to study months 1−4) to maintain masking, unless rescue supplemental treatment was required.

Participants received the intravitreal FAc implant or first dose of aflibercept on visit 2 (study month 0) and were monitored on site for immediate side effects, per site standard procedure. Participants returned monthly for 4 additional visits and further aflibercept loading or sham injections. During each visit, OCT and BCVA testing were performed to determine whether rescue supplemental therapy criteria were met. Surveillance, maintenance therapy, and possible rescue supplemental injections occurred monthly from study months 2 through 18 for the FAc group and from study months 6 through 18 for the aflibercept group. Maintenance therapy visits and rescue supplemental treatments (when needed) continued through study month 18, unless the investigator decided to stop therapy for safety or a requirement for treatments not allowed by the protocol. The study monitor was contacted before deviation from the rescue supplemental injection protocol or discontinuing study drug in any participant. During the maintenance therapy period, participants reported to the site monthly for safety and efficacy evaluations; those who met the criteria for rescue supplemental therapy received intravitreal aflibercept.

The need for rescue supplemental aflibercept in both treatment groups was determined by the EDC system using criteria based on BCVA and central subfield thickness (CST). The criteria for rescue supplemental therapy were based on the period of the study (induction or maintenance). In the induction period (FAc group only), the criteria to receive rescue supplemental therapy were: (1) CST worsening of more than 10% from previous visit attributable to DME and a BCVA loss of 5 or more letters at the visit compared with the previous visit also attributable to DME, (2) a BCVA loss of 10 or more letters compared with the previous visit attributable to DME, or (3) a BCVA loss of 5 or more letters at 2 consecutive visits compared with the previous visit attributable to DME. In the maintenance period for either group, the criteria for rescue supplemental therapy were: (1) CST of more than 400 μm, (2) CST of more than 320 μm and a BCVA loss of 5 or more letters compared with the previous visit attributable to DME, (3) a BCVA loss of 10 or more letters compared with the previous visit attributable to DME, or (4) a BCVA loss of 5 or more letters at 2 consecutive visits compared with the previous visit attributable to DME.

Study Participants

The intention-to-treat (ITT) population included all participants enrolled and randomized to any treatment. The safety analysis population included all randomized participants.

Demographics and Baseline Disease Characteristics

Demographic and medical history information were compiled for the ITT population and the safety population, respectively. These summaries included age, sex, race, ethnicity, and baseline DME status, as well as other relevant medical history. Medical history was summarized separately by baseline medical history and concomitant illness, where baseline medical history was defined as conditions that stopped before the screening visit, and concomitant illness was defined as conditions that were ongoing at screening visit. Intraocular pressure-lowering medications also were summarized separately by prior medication and concomitant medication. Prior medication was defined as medication that was no longer being taken by the first dose of study medication. Concomitant medication was defined as any medication that started before the first dose of study medication, but was ongoing, or any medication that was started on or after the first dose of study medication.

Outcomes

The primary efficacy end point was the mean total number of rescue supplemental aflibercept injections needed during the study by treatment group. Key secondary efficacy end points included time to rescue supplemental injections during the study, proportion of participants who did not require any rescue supplemental therapy during the study, proportion of participants with 5-letter,

10-letter, and 15-letter ETDRS gains from baseline at month 18, mean change from baseline and area under the curve (AUC) in BCVA, and mean change from baseline and AUC in CST. Post hoc end points included DRSS and retinal nerve fiber layer thickness (RNFLT) from baseline. Both the primary and secondary efficacy end points were assessed in the ITT population. The safety end points included the incidence and severity of treatment-related AEs and were determined in the safety population. Additional safety end points included rate of laser procedures or incisional IOP-lowering surgeries, new or worsening of preexisting cataracts, and rate and timing of cataract procedures in participants with phakia. The incidence of increases in IOP and number of medicines used to control IOP also were assessed and included evaluation of IOP of 25 mmHg or more, 35 mmHg or more, and 10 mmHg or more from baseline.

Statistical Analysis

The sample size was determined based on the primary efficacy end point of differences in injection frequency between the treatment arms. Calculations were based on the following assumptions: a 1:1 randomization, 90% power, a type 1 error of 0.05, standard deviation (SD) of 5, and a 20% reduction in supplemental injections. The sample size provides 90% power to detect a 20% reduction in supplemental injections in the experimental arm. Although all secondary end points were prespecified and were included intentionally in the original protocol to explore the clinical impact of each therapeutic arm, the study was not powered for any additional outcomes beyond the primary end point, and no formal hypothesis testing or multiplicity adjustments have been performed for any of these additional outcomes. The primary and secondary efficacy analyses included all randomized participants (ITT population). In addition to *P* values for statistical tests, the estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between the 2 treatment groups; *P* values for all secondary and post hoc outcomes are nominal and are intended for descriptive purposes only. All 95% CIs were 2-sided.

Results

Participants

This randomized, masked, active-controlled, parallel-group, multicenter study was conducted from August 2020 through January 2025 at 42 sites in the United States. Of 517 individuals who were screened, 306 participants (306 eyes) were randomized for treatment (FAc implant, n = 154; aflibercept, n = 152) and comprised the ITT and safety populations; 211 participants did not pass the screening process, most commonly because of a lack of DME confirmation or CST of less than 350 μm (n = 88) and BCVA outside the required range (n = 33), with additional reasons including systemic conditions, ocular history, and other factors. Among those randomized, 19.5% (n = 30) discontinued early in the FAc implant group and 22.4% (n = 34) discontinued early in the aflibercept group; the most frequent reason for early discontinuation was loss to follow-up (FAc implant, 46.7% [n = 14]; aflibercept, 29.4% [n = 10]; Fig 3). Protocol deviations also are provided in Table S1 (available at www.aaojournal.org).

Baseline demographic and clinical characteristics generally were balanced between treatment groups (Table 1)[32]: mean age, 61.4 years; 37.3% female; and 80.5% White. Participants had a baseline mean BCVA of 66.0 ETDRS letters (Snellen equivalent, 20/50) and a mean CST of 461 μm. Mean IOP was 17.2 mmHg, with almost all patients (99.7%) not receiving IOP-lowering medication.

Efficacy Outcomes

Rescue Supplemental Injections. The primary efficacy end point, the mean ± SD total number of rescue supplemental aflibercept injections needed during the study in the ITT population (Table 2), was similar between the FAc and aflibercept groups (2.4 ± 3.2 vs. 2.5 ± 3.1 rescue supplemental injections, respectively; $P = 0.76$). With the inclusion of the protocol-mandated FAc or aflibercept injections during the induction period (1 FAc implant injection excluding sham injections and 5 aflibercept injections), the mean overall number of injections was fewer in the FAc group compared with the aflibercept group (3.4 ± 3.2 vs. 7.2 ± 3.4, respectively; nominal $P < 0.001$). The mean ± SD time from the last protocol-mandated injection (month 1 for FAc, month 5 for aflibercept) to the first rescue supplemental injection was longer with the FAc implant than aflibercept (185.4 ± 97.9 days vs. 132.8 ± 94.0 days; nominal $P < 0.001$). The proportion of participants who did not require rescue supplemental injections over the course of the study was similar between both groups (FAc, 32.5%; aflibercept, 30.3%; nominal $P = 0.68$).

Visual Acuity Outcomes. Visual functional outcomes were comparable between both groups over 18 months. No difference was found in mean ± SD change from baseline in ETDRS letters in participants receiving FAc and aflibercept (1.8 ± 20.0 letters and 5.5 ± 10.8 letters, respectively), with a group difference of 3.7 ± 16.2 letters (95% CI, −7.8 to 0.4 letters; nominal $P = 0.08$; Fig 4A). Accordingly, at month 18, no difference was found in the proportion of participants with ETDRS gains of 5 letters, 10 letters, and 15 letters between the FAc and aflibercept groups (41.0% vs. 49.6% [nominal $P = 0.18$], 23.0% vs. 29.9% [nominal $P = 0.22$], and 11.5% vs. 10.3% [nominal $P = 0.76$], respectively). No differences were found in the AUC of BCVA over the course of the study between groups. The mean ± SD AUC of BCVA was 33 628 ± 10 420 for participants receiving FAc and 33 893 ± 23 130 for participants receiving aflibercept, with an observed difference of −265 ± 17 777 (95% CI, −4320 to 3790; nominal $P = 0.90$). During the induction period (months 0–4), the AUC of BCVA was not different between groups: 8033 ± 1745 with FAc and 8358 ± 1542 with aflibercept, with an observed difference of −325 ± 1650 (95% CI, −701 to 52; nominal $P = 0.09$). During the maintenance period (months 5–18), the AUC of BCVA was lower in the FAc group compared with the aflibercept group: 24 341 ± 7823 with FAc and 26 430 ± 7054 with aflibercept, with an observed difference of −2089 ± 7462 (95% CI, −3840 to −339; nominal $P = 0.02$).

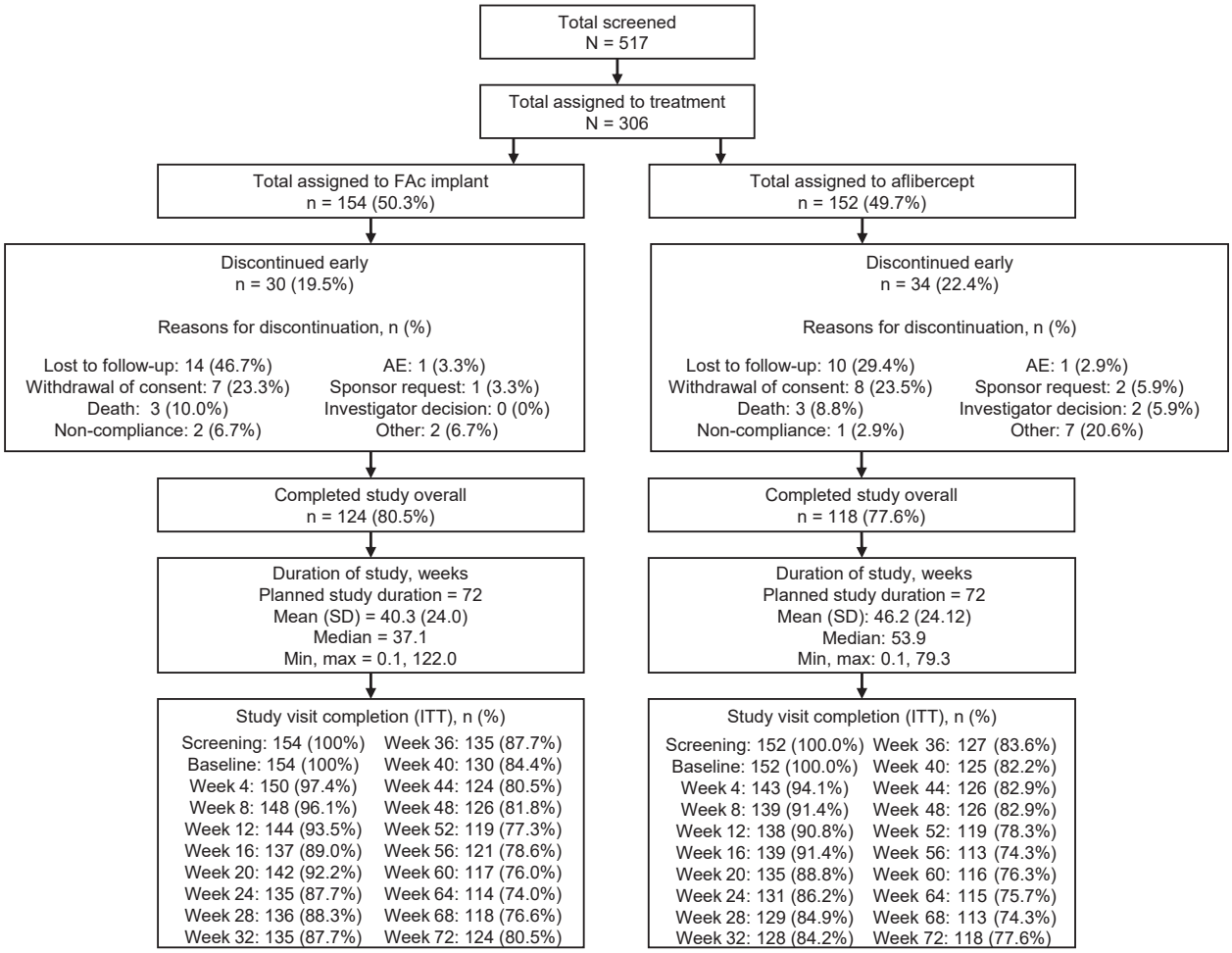

Figure 3. Flow diagram showing participant disposition. A total of 517 participants were screened, and 306 participants were assigned to treatment (fluocinolone acetonide [FAc] implant, n = 154; aflibercept, n = 152). Reasons for early discontinuation and study visit completion rates are summarized. AE = adverse event; ITT = intention-to-treat; max = maximum; min = minimum; SD = standard deviation.

When considering lens status, the participants in the FAc group who were pseudophakic demonstrated the greatest numerical increase in BCVA (10.3 letters) compared with those in the FAc group who were phakic (−8.0 letters) and those who were pseudophakic or phakic in the aflibercept group (6.7 letters and 5.0 letters, respectively). Among participants who were pseudophakic at month 18, the mean change from baseline in BCVA was numerically greater between the FAc and aflibercept groups (10.3 ± 10.8 letters vs. 6.7 ± 15.3 letters), with an overall difference of 3.6 ± 12.5 letters (95% CI, −1.7 to 9.0 letters; nominal $P = 0.18$). Among participants who were phakic at 18 months, a difference was found in the mean change from baseline in BCVA between the FAc and aflibercept groups (−8.0 ± 23.4 letters vs. 5.0 ± 8.6 letters), with a difference favoring aflibercept over FAc of 13.1 ± 16.2 letters (95% CI, 18.6−7.6 letters; nominal $P < 0.001$; Fig 4B).

Anatomic Outcomes. The mean ± SD change from baseline in CST at month 18 (Fig 5) was similar between the FAc and aflibercept groups (−119 ± 112 μm vs. −114 ± 103 μm, respectively), with a group difference of 5 ± 108 μm (95% CI, −33 to 22 μm; nominal $P = 0.71$). No difference was found in the mean ± SD AUC of CST over 18 months between FAc and aflibercept: 173 624 ± 58 613 with FAc versus 167 776 ± 99 348 with aflibercept, with an observed difference of 5848 ± 81 029 (95% CI, −12 635 to 24 330; nominal $P = 0.53$). During the induction period (months 0−4), the AUC of CST was numerically improved in the aflibercept group compared with the FAc group: 44 886 ± 12 645 with FAc and 42 821 ± 9232 with aflibercept, with an observed difference of 2065 ± 11 117 (95% CI, −470 to 4601; nominal $P = 0.11$). Conversely, during the maintenance period (months 5−18), the AUC of CST was improved numerically in the FAc group versus the aflibercept group: 120 882 ± 42 830 with FAc and 128 352 ± 36 487 with aflibercept, with an observed difference of −7470 ± 39 898 (95% CI, −16 830 to 1889; nominal $P = 0.117$). No difference in mean ± SD RNFLT was found between FAc and aflibercept at baseline

Table 1. Demographics and Baseline Disease Characteristics

Variable	FAc Implant (n = 154)	Aflibercept (n = 152)	Overall (N = 306)
Age (yrs)			
No. of participants	154	152	306
Mean (SD)	61.0 (8.1)	61.8 (9.1)	61.4 (8.6)
Median	61.0	61.5	61.0
Min, max	38, 84	36, 86	36, 86
Sex			
Female	54 (35.1)	60 (39.5)	114 (37.3)
Male	100 (64.9)	92 (60.5)	192 (62.7)
Race			
No. of participants	152	151	303
American Indian or Alaska Native	3 (2.0)	3 (2.0)	6 (2.0)
Asian	5 (3.3)	1 (0.7)	6 (2.0)
Black or African American	21 (13.8)	16 (10.6)	37 (12.2)
Native Hawaiian/other Pacific Islander	1 (0.7)	0 (0.0)	1 (0.3)
White	117 (77.0)	127 (84.1)	244 (80.5)
Other	5 (3.3)	4 (2.6)	9 (3.0)
Ethnicity			
Hispanic or Latino	38 (24.7)	38 (25.0)	76 (24.8)
Not Hispanic or Latino	114 (74.0)	111 (73.0)	225 (73.5)
Not reported	2 (1.3)	2 (1.3)	4 (1.3)
Unknown	0	1 (0.7)	1 (0.3)
Baseline BCVA, ETDRS letters			
No. of participants	153	152	305
Mean (SD)	66.2 (11.2)	65.7 (11.3)	66.0 (11.2)
Mean Snellen equivalent*	20/50	20/50	20/50
Median	69.0	68.0	68.0
Min, max	30, 86	28, 92	28, 92
Baseline median IOP (mmHg)			
No. of participants	154	152	306
Mean (SD)	17.2 (3.1)	17.2 (3.4)	17.2 (3.3)
Median	17.0	18.0	17.0
Min, max	9, 26	7, 24	7, 26
Baseline RNFLT (μm)			
No. of participants	143	146	289
Mean (SD)	102 (22)	100 (23)	101 (22)
Median	99	97	98
Min, max	12, 189	12, 180	12, 189
Baseline CST (μm)			
No. of participants	154	152	306
Mean (SD)	457 (113)	466 (112)	461 (112)
Median	416	432	425
Min, max	324, 1009	280, 897	280, 1009
Lens status			
Phakic	96 (62)	106 (70)	202 (66)
Pseudophakic	58 (38)	46 (30)	104 (34)
Baseline DRSS score			
No. of participants	148	139	287
No DR	0	1 (0.7)	1 (0.3)
Mild NPDR	16 (10.8)	15 (10.8)	31 (10.8)
Moderate NPDR	22 (14.9)	22 (15.8)	44 (15.3)
Moderately severe NPDR	67 (45.3)	48 (34.5)	115 (40.1)
Severe NPDR	30 (20.3)	42 (30.2)	72 (25.1)
Mild PDR	7 (4.7)	5 (3.6)	12 (4.2)
Moderate PDR	4 (2.7)	4 (2.9)	8 (2.8)
High-risk PDR	2 (1.4)	2 (1.4)	4 (1.4)
IOP-lowering medications			
No. of participants	154	152	306
Yes	0	1 (0.7)	1 (0.3)
No	154 (100)	151 (99.3)	305 (99.7)

BCVA = best-corrected visual acuity; CST = central subfield thickness; DR = diabetic retinopathy; DRSS = Diabetic Retinopathy Severity Scale; ETDRS = Early Treatment Diabetic Retinopathy Study; FAc = fluocinolone acetonide; IOP = intraocular pressure; max = maximum; min = minimum; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; RNFLT = retinal nerve fiber layer thickness; SD = standard deviation.

Data are presented as no. (%) unless otherwise indicated.

*Mean Snellen equivalent was calculated according to AMA Network.[32]

Table 2. Rescue Supplemental Injections Needed During the Study

Variable	Fluocinolone Acetonide Implant (n = 154)	Aflibercept (n = 152)	Observed Difference (SD), 95% CI	P Value
No. of rescue supplemental injections				
No.	154	152	−0.1 (3.1), −0.8 to 0.6	0.76*
Mean (SD)	2.4 (3.2)	2.5 (3.1)		
Median (min, max)	1.0 (0, 13)	1.5 (0, 13)		
No. of protocol-mandated plus rescue supplemental injections needed during the study				
No.	154	152	−3.8 (3.3), −4.5 to −3.0	< 0.001*,†
Mean (SD)	3.4 (3.2)	7.2 (3.4)		
Median (min, max)	2.0 (1, 14)	6.0 (1, 18)		
Time to first rescue supplemental injection since last injection in induction period, days				
No.	101	103	52.6 (96.0), 26.1−79.1	< 0.001*,†
Mean (SD)	185.4 (97.9)	132.8 (94.0)		
Median (min, max)	156.0 (29, 511)	107.0 (25, 398)		
Proportion of participants who received no rescue supplemental injections				
No. (%)	50 (32.5)	46 (30.3)	—	0.68§
95% CI‡	25.6−40.2	23.5−38.0		

— = not applicable; CI = confidence interval; max = maximum; min = minimum; SD = standard deviation.
*Generated from a 2-sided independent pooled *t* test with an α level of 0.05.
†All *P* values were nominal for secondary and post hoc efficacy end points.
‡95% Wilson CI.
§*P* value generated from the likelihood ratio chi-square test.

(102.0 ± 21.7 μm vs. 100.2 ± 23.0 μm, respectively; nominal $P = 0.56$) or at month 18 (91.3 ± 21.3 μm vs. 89.8 ± 14.3 μm, respectively; nominal $P = 0.48$).

Throughout the study, DRSS distribution was similar between the FAc and aflibercept groups. In participants receiving the FAc implant, no change in the proportion of participants by DRSS severity was noted at baseline compared with month 18 (no difference among DRSS scale categories). No change was noted in the proportion of participants with PDR (mild to advanced) from baseline to month 18 within either group.

Safety. Safety findings were consistent with the known profiles of FAc and aflibercept. Treatment-emergent AEs (TEAEs) were reported in 88.3% of FAc-treated participants and in 75.7% of aflibercept-treated participants; treatment-related TEAEs occurred in 40.9% and 3.3%, respectively (Table 3). Serious TEAEs were reported in 24.7% of FAc-treated participants and 30.3% of aflibercept-treated participants, with no serious treatment-related TEAEs reported in either group. No retinal detachments were found in either treatment group; 1 TEAE, a case of endophthalmitis, was reported in the aflibercept group over the course of the study.

As expected, cataract-related TEAEs were more frequent with FAc than with aflibercept (53.9% vs. 24.3%) among all participants in the safety analysis population (Table S2, available at www.aaojournal.org); among participants who were phakic at baseline, new cataracts or worsening of preexisting cataracts in the study eye were more frequent with FAc than with aflibercept (29.9% vs. 0.7%). Accordingly, rates of cataract surgery in the study eye were higher with FAc than with aflibercept (27.9% vs. 6.6%; Table S2).

Intraocular pressure-related events were more frequent in participants receiving FAc than in those receiving aflibercept (Table 4): any IOP increase event occurred in 15.6% versus 3.3%; an IOP increase of 10 mmHg or more occurred in 2.6% versus 0.7%; an IOP increase of 25 mmHg or more occurred in 11.0% versus 2.6%; and an IOP increase of 35 mmHg or more occurred in 1.9% versus 0%, respectively. Although no participants in the FAc group and 1 participant (0.7%) in the aflibercept group reported administration of IOP-lowering medication at baseline (Table 1), the proportion of participants who received any IOP-lowering medications over the course of the study were 16.9% versus 3.9% for the FAc and aflibercept groups, respectively. Laser procedures were performed in 1.3% and 0.7% of participants in the FAc and aflibercept groups, respectively. Three participants (1.9%) in the FAc group and no participants in the aflibercept group underwent incisional surgery (Table 4).

Discussion

The NEW DAY study was designed to address a persistent gap between durable disease control and injection burden in DME. The NEW DAY randomized trial assessed the FAc implant as baseline therapy with aflibercept as rescue supplemental therapy, head-to-head with aflibercept monotherapy, and demonstrated that FAc reduces overall injection burden while producing similar visual acuity and anatomic outcomes in patients with DME. Although the primary end point (superiority of the mean number of rescue supplemental aflibercept injections) was not achieved, no difference was found in the number of rescue supplemental injections received between groups after induction therapy. The primary end point was calculated after completion of the protocol-mandated 5-month loading period in the aflibercept group, or 1 month after FAc

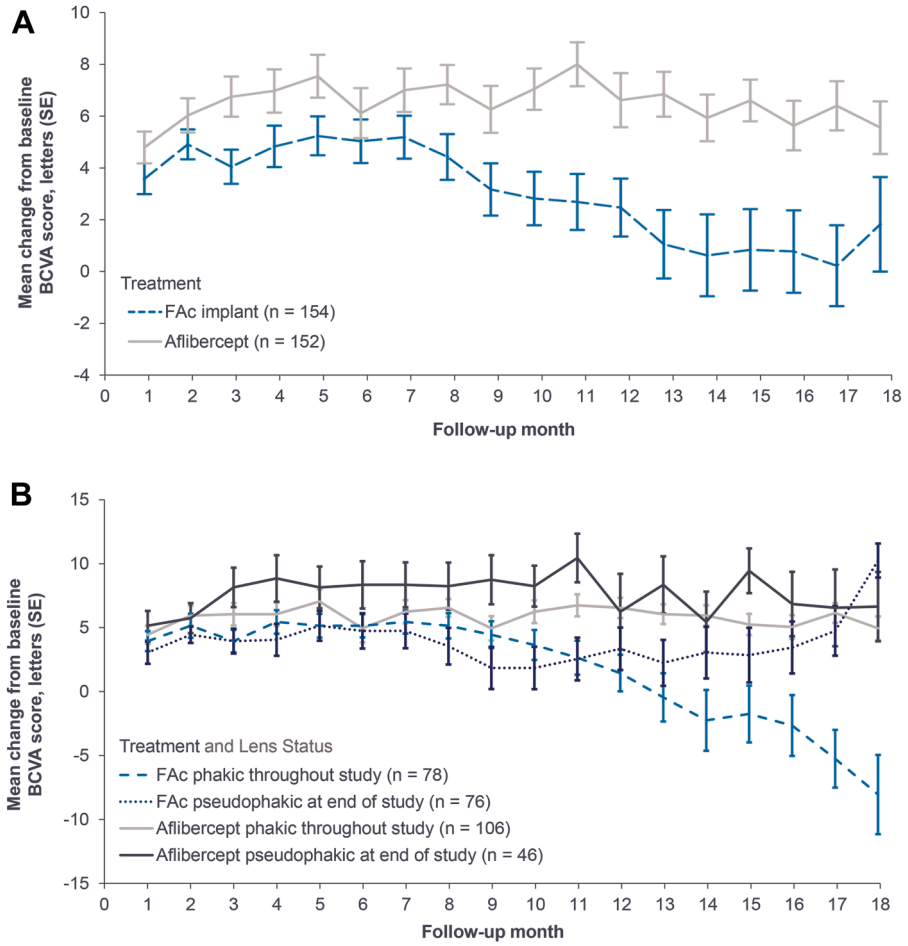

Figure 4. Graphs showing best-corrected visual acuity (BCVA) score over 18 months. **A**, Mean change from baseline in BCVA (Early Treatment Diabetic Retinopathy Study letters) through month 18 in the intention-to-treat population comparing fluocinolone acetonide (FAc) (n = 154) versus aflibercept (n = 152). Mean BCVA change was similar between treatment groups, with no statistically significant difference at month 18 (nominal $P = 0.18$). **B**, Mean change from baseline in BCVA through month 18 by lens status in eyes that remained phakic throughout follow-up (FAc, n = 78; aflibercept, n = 106) and eyes that were pseudophakic by month 18 (FAc, n = 76; aflibercept, n = 46). Across subgroups, visual acuity outcomes generally were comparable; numerically, the greatest improvement was observed in pseudophakic eyes in the FAc group compared with those in the FAc group that were phakic. SE = standard error.

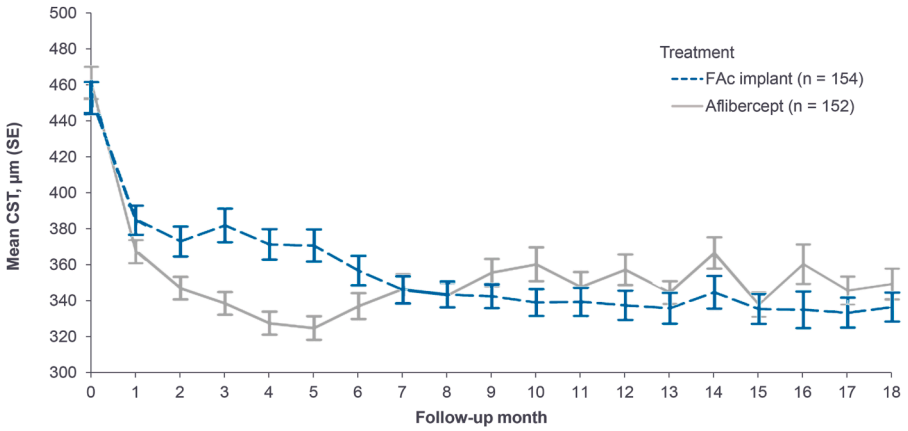

Figure 5. Graph showing mean central subfield thickness (CST) over 18 months in the ITT population comparing fluocinolone acetonide (FAc; n = 154) versus aflibercept (n = 152). Both groups demonstrated sustained CST reductions over 18 months, with similar anatomic outcomes at month 18 (mean change, −119 µm with FAc vs. −114 µm with aflibercept; nominal $P = 0.71$). SE = standard error.

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Table 3. Overall Safety Summary and Ocular Treatment-Emergent Adverse Events

Variable	Fluocinolone Acetonide Implant (n = 154)	Aflibercept (n = 152)	Overall (n = 306)
Any TEAE	136 (88.3)	115 (75.7)	251 (82.0)
Treatment-related TEAEs	63 (40.9)	5 (3.3)	68 (22.2)
Serious TEAEs	38 (24.7)	46 (30.3)	84 (27.5)
Serious treatment-related TEAEs	0	0	0
Ocular TEAEs			
Eye disorders	107 (69.5)	68 (44.7)	175 (57.2)
Borderline glaucoma	1 (0.6)	0	1 (0.3)
Cataract	68 (44.2)	27 (17.8)	95 (31.0)
Cataract cortical	0 (0.0)	2 (1.3)	2 (0.7)
Cataract nuclear	8 (5.2)	2 (1.3)	10 (3.3)
Cataract subcapsular	7 (4.5)	6 (3.9)	13 (4.2)
Posterior capsule opacification	16 (10.4)	7 (4.6)	23 (7.5)
Conjunctival hemorrhage	3 (1.9)	3 (2.0)	6 (2.0)
Corneal abrasion	2 (1.3)	3 (2.0)	5 (1.6)
Endophthalmitis	0	1 (0.7)	1 (0.3)
Eye hemorrhage	0	1 (0.7)	1 (0.3)
Eye pruritus	1 (0.6)	0	1 (0.3)
Glaucoma	3 (1.9)	0	3 (1.0)
Keratitis	1 (0.6)	0	1 (0.3)
Ocular hypertension	10 (6.5)	2 (1.3)	12 (3.9)
Vitreous floaters	5 (3.2)	7 (4.6)	12 (3.9)
Infectious endophthalmitis	0	1 (0.7)	1 (0.3)
General disorders and administration-site conditions	13 (8.4)	11 (7.2)	24 (7.8)
Injection-site pain	1 (0.6)	1 (0.7)	2 (0.7)
Ocular implant exposure	1 (0.6)	0	1 (0.3)
Investigations	23 (14.9)	11 (7.2)	34 (11.1)
Intraocular pressure increased	16 (10.4)	5 (3.3)	21 (6.9)

TEAE = treatment-emergent adverse event.
Data are presented as no. (%).

implantation. This design introduced a lag that underestimated the practical injection burden of multiple injections. Furthermore, the very clinically meaningful metric of total overall injections (excluding the sham injections in the FAc group) demonstrated an approximately 50% reduction in injections in the FAc group compared with the aflibercept group (3.4 vs. 7.2 injections).

The NEW DAY study is a prospective, masked, multicenter, randomized trial that provides novel level 1 evidence of a head-to-head comparison between FAc and aflibercept as a primary treatment for DME. Although the visual and anatomic outcomes in NEW DAY were comparable among the FAc implant and aflibercept-only groups, they should be interpreted further in the context of expected cataract progression over the course of the study. In the pivotal FAME program, which evaluated participants with persistent DME despite macular laser treatment from 2007 through 2010, those receiving FAc experienced a transient mid-course dip in BCVA of approximately 4 to 5 letters that was attributed to cataract progression, with recovery after cataract surgery, whereas pseudophakic eyes showed steadier improvements.[25] Consisting of participants with treatment-naive or nearly naive DME, the NEW DAY study also exhibited this pattern, as demonstrated by the FAc group undergoing more cataract procedures by 18 months than the aflibercept group; the FAc group showed numerically better and clinically meaningful improvements in vision in pseudophakic eyes than the aflibercept group, whereas visual outcomes with aflibercept were numerically better in phakic eyes. Because many eyes remained phakic at 18 months and some had developing cataracts without surgery, short-term BCVA comparisons may underrepresent the longer-term functional potential of the FAc implant. This is also supported by previous observations.[25,29,33–35] These studies often include predominantly pseudophakic eyes at baseline or report functional recovery after cataract surgery.[25,33] In this longer-term context, noninferior BCVA outcomes of the NEW DAY study coupled with halved injection burden and equivalent CST control at 18 months are concordant with the FAc evidence base and reflect the relatively short observation window and lens status distribution. The CST trends in the NEW DAY study are consistent with evidence that FAc reduces anatomic fluctuations in DME. Post hoc analyses of the USER study demonstrated that FAc reduces long-term retinal thickness variability (RTV), and that lower RTV correlates with better BCVA and reduced yearly treatment burden.[28,36] Although RTV metrics are not reported in the current study, continued improvements in CST beyond month 5 suggest a longer time to disease control that is concordant with the RTV literature. Furthermore, in the NEW DAY study, aflibercept achieved a rapid reduction in retinal swelling during the induction phase, whereas the

Table 4. Intraocular Pressure Change and Interventional Procedures for Intraocular Pressure

Variable	Fluocinolone Acetonide Implant (n = 154)	Aflibercept (n = 152)
Participants who experienced any IOP increase event	24 (15.6)	5 (3.3)
IOP increase event description		
Change in IOP ≥ 10 mmHg from baseline	4 (2.6)	1 (0.7)
Change in IOP ≥ 25 mmHg from baseline	17 (11.0)	4 (2.6)
Change in IOP ≥ 35 mmHg from baseline	3 (1.9)	0
Conditions contributing to increased IOP		
Combined mechanism glaucoma	1 (0.6)	0
Ocular hypertension	1 (0.6)	0
Possible late steroid responder	1 (0.6)	0
Possible steroid responder	1 (0.6)	0
Primary open-angle glaucoma	1 (0.6)	1 (0.7)
Secondary glaucoma	1 (0.6)	0
Steroid responder	1 (0.6)	0
Laser procedure*	2 (1.3)	1 (0.7)
Argon laser trabeculoplasty	1 (0.6)	0
Laser peripheral iridotomy	1 (0.6)	1 (0.7)
Selective laser trabeculoplasty	1 (0.6)	0
Incisional surgery*	3 (1.9)	0
Kahook dual-blade goniotomy	1 (0.6)	0
Ahmed shunt placement	1 (0.6)	0
iTrack goniotomy	1 (0.6)	0
Participants who took any IOP-lowering medication	26 (16.9)	6 (3.9)

IOP = intraocular pressure.
Data are presented as no. (%).
*Participants could have been included in more than 1 type.

FAc implant provided a more gradual yet sustained response throughout the study.

Safety findings were aligned with established class effects, with more AEs of cataract- and IOP-related events in the FAc group, albeit with low rates of IOP procedures and no new safety signals.[26,27,29,30] Similar to previous studies, incisional IOP surgery remained uncommon in the NEW DAY study, and IOP elevations generally were predictable and typically were managed with topical medications.[25,27,29,33,34,37–39] These findings align with the pivotal FAME trials, in which dose-dependent IOP events were observed, but incisional surgery remained infrequent, in the 0.2-μg/day group (4.8% over 36 months), and with post hoc analyses showing that eyes previously tolerating steroids rarely required incisional surgeries.[25,40] Against this backdrop, the NEW DAY study adds randomized, comparator-controlled evidence that, in steroid-challenged eyes (i.e., those that did not respond to difluprednate eyedrops steroids during screening), FAc's IOP risk is low and manageable. Similar RNFLT trajectories among treatment groups suggest that, under appropriate IOP monitoring, the FAc implant does not cause additional structural optic nerve damage compared with aflibercept. Furthermore, a key strength of the novel design of NEW DAY is the description of manageable steroid responder characteristics following a steroid challenge of topical difluprednate eyedrops administered 4 times daily for at least 2 weeks before randomized intravitreal treatment.

During the NEW DAY study, endophthalmitis did not develop in any participants receiving FAc, whereas endophthalmitis did develop in 1 participant receiving aflibercept. Although the NEW DAY study was not powered to make any determinations of relative endophthalmitis risk because of its rarity, our data align with previously published safety findings.[25,29,31,33,34] Although the endophthalmitis risk generally is low with intravitreal injections (0.02%–0.06%),[41,42] halving the number of injections required with FAc may be clinically relevant while also mitigating other drawbacks associated with serial injections, including patient discomfort, inconvenience, compliance with follow-up, and other injection-related factors.

Beyond edema, the FAME program provided a rationale to explore retinopathy-level effects.[40] In a post hoc analysis, FAc slowed progression to PDR and increased the probability of a 2-step or more improvement in DRSS, particularly in eyes with more severe baseline nonproliferative diabetic retinopathy and nonperfusion.[40] As noted, cataract formation and progression are expected class effects of corticosteroids and likely contributed to the mid-course BCVA reductions observed in phakic eyes at baseline, with subsequent improvement attributable to postoperative visual recovery after cataract surgery.[26,27,29,30] Current descriptive analyses of DR severity in the NEW DAY study suggest that no large differences existed between treatment groups in terms of DRSS distribution over time. Further analyses of patient-level transitions of those treated with the FAc implant may provide insights into DR regression rates.

Although the FAc implant may be able to substantially reduce the overall number of intravitreal injections, it also introduces a corresponding need for IOP monitoring. In the NEW DAY study, participants were evaluated monthly. In

routine clinical practice, early and periodic IOP assessments are important to consider, particularly during the initial months after implantation and after any IOP elevation. However, it should be recognized that incisional procedures are required rarely for elevated IOP treatments.[29,31] These IOP risks, together with another known steroid-related risk of cataract progression,[25,43] can be discussed with patients and balanced against the potentially meaningful reductions in injection burden and overall clinic visits. Although cost-effectiveness analyses were not conducted in the current prospective study, the direct cost of the implant compared with other therapies being considered, and the associated monitoring needs, can be considered and discussed with patients when selecting DME treatment options.

Since the design and execution of the NEW DAY study, longer-acting anti-VEGF strategies with faricimab[44,45] and aflibercept 8 mg[46,47] and surgical implantation of a sustained-release ranibizumab delivery system[48,49] have been approved, and biofactory gene therapy treatments are under development.[50] The NEW DAY study does not provide specific insights into FAc implant efficacy, injection burden, and safety compared with these newer DME treatment options. Furthermore, unlike other recent studies, which included control groups with fixed dosing, the NEW DAY study included retreatment pro re nata criteria that were applied equally to both randomized groups. Although newer therapies may lower anti-VEGF injection burden, they do not diminish the unique contribution of the NEW DAY study, which provides comparator-controlled evidence that a steroid-first foundation can deliver comparable visual acuity and anatomic outcomes improvements while substantially reducing injections over 18 months. This complements extended-interval anti-VEGF approaches and, for many clinicians and patients, provides an alternative path to burden reduction that is office-based and nonsurgical.

Conclusions

The prospective, randomized, single-masked, active-controlled NEW DAY study provides robust evidence to inform the use of steroids in combination with anti-VEGF bolus rescue therapy in the management of DME. Although the study did not meet its primary end point, the FAc 0.19-mg implant provided similar improvements in visual and anatomic outcomes as aflibercept monotherapy and seemed to meaningfully reduce the total number of intravitreal injections, by more than half through 18 months. Furthermore, the time to the first rescue supplement injection seemed to be meaningfully longer with FAc compared with aflibercept monotherapy. The safety data, along with AEs of cataract and IOP outcomes, in the NEW DAY study corroborate the consistent safety profile of the FAc implant in the treatment of DME. In addition to contributing to the body of evidence supporting the use of the FAc implant in DME, the results of the NEW DAY study indicate that the FAc implant, as baseline therapy with rescue supplemental anti-VEGF therapy administered as needed, may be considered early in the management of patients with DME.

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Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. This study was conducted according to the ethical principles defined in the Declaration of Helsinki and Good Clinical Practice guidelines, as described by the International Council for Harmonisation. The study received ethics approval from appropriate regulatory authorities and Sterling Institutional Review Board; participants provided written informed consent.

No animal subjects were included in this study.

Author Contributions:

Conception and design: Singer, Wykoff, Riemann, Gonzalez, Weng

Analysis and interpretation: Singer, Wykoff, Riemann, Gonzalez, Weng, Alkhatib, Amarshi, Moody, Pao

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Overall responsibility: Singer, Wykoff, Riemann, Gonzalez, Weng, Alkhatib, Amarshi, Moody, Pao

Abbreviations and Acronyms:
AE = adverse event; **AUC** = area under the curve; **BCVA** = best-corrected visual acuity; **CI** = confidence interval; **CST** = central subfield thickness; **DME** = diabetic macular edema; **DR** = diabetic retinopathy; **DRSS** = Diabetic Retinopathy Severity Scale; **EDC** = electronic data capture; **ETDRS** = Early Treatment Diabetic Retinopathy Study; **FAc** = fluocinolone acetonide; **FAME** = Fluocinolone Acetonide in Diabetic Macular Edema; **IOP** = intraocular pressure; **ITT** = intention-to-treat; **OCT** = optical coherence tomography; **PALADIN** = phase 4 IOP Signals Associated with ILUVIEN; **PDR** = proliferative diabetic retinopathy; **RNFLT** = retinal nerve fiber layer thickness; **RTV** = retinal thickness variability; **SD** = standard deviation; **TEAE** = treatment-emergent adverse event; **USER** = US Retrospective Chart Review in Patients Receiving ILUVIEN; **VEGF** = vascular endothelial growth factor.

Keywords:
Aflibercept, Anti-VEGF, Diabetic macular edema, Fluocinolone acetonide, Intravitreal implant.

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ILUVIEN® safely and effectively. See full prescribing information for ILUVIEN.

ILUVIEN® (fluocinolone acetonide intravitreal implant), 0.19 mg, for intravitreal use
Initial U.S. Approval: 1963

----------RECENT MAJOR CHANGES----------
Indications and Usage, Chronic Non-Infectious Uveitis Affecting the Posterior Segment (1.2) 3/2025

----------INDICATIONS AND USAGE----------
ILUVIEN is a corticosteroid indicated for:
- the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure. (1.1)
- the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- For ophthalmic intravitreal injection. (2.1)
- The intravitreal injection procedure should be carried out under aseptic conditions. (2.2)
- Following the intravitreal injection, patients should be monitored for elevation in intraocular pressure and for endophthalmitis. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Intravitreal implant containing 0.19 mg fluocinolone acetonide in a drug delivery system. (3)

----------CONTRAINDICATIONS----------
- Ocular or Periocular Infections (4.1)
- Glaucoma (4.2)
- Hypersensitivity (4.3)

----------WARNINGS AND PRECAUTIONS----------
- Intravitreal injections have been associated with endophthalmitis, eye inflammation, increased intraocular pressure, and retinal detachments. Patients should be monitored following the injection. (5.1)
- Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity, and fields of vision. (5.2)
- Cataracts: Use of corticosteroids may result in posterior subcapsular cataract formation. (5.3)
- Delayed Healing: The use of corticosteroids after cataract surgery may delay healing and increase the incidence of bleb formation. (5.4)
- Corneal and Scleral Melting: In those diseases causing thinning of the cornea or sclera, ophthalmic corticosteroids may lead to perforation of the globe. (5.5)
- Bacterial Infections: Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated. (5.6)
- Viral Infections: Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). (5.7)
- Fungal Infections: Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. (5.8)
- Implant Migration: The implant may migrate into the anterior chamber if the posterior lens capsule is not intact. (5.9)

----------ADVERSE REACTIONS----------
The most common adverse reactions reported are cataract development and increases in intraocular pressure. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Alimera Sciences, Inc. at 1-844-445-8843 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Diabetic Macular Edema

ILUVIEN® is indicated for the treatment of diabetic macular edema (DME) in patients who have been previously treated with a course of corticosteroids and did not have a clinically significant rise in intraocular pressure.

1.2 Chronic Non-Infectious Uveitis Affecting the Posterior Segment

ILUVIEN® is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

For ophthalmic intravitreal injection.

The initial prescription and renewal of the medication order of ILUVIEN should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

2.2 Administration

The intravitreal injection procedure should be carried out under aseptic conditions, which include use of sterile gloves, a sterile drape, a sterile caliper, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum microbicide should be given prior to the injection.

The injection procedure for ILUVIEN is as follows:

1. The exterior of the tray should ***not*** be considered sterile. An assistant (non-sterile) should remove the tray from the carton and examine the tray and lid for damage. If damaged, do not use unit.

   If acceptable, the assistant should peel the lid from the tray ***without touching the interior surface***.
2. Visually check through the viewing window of the preloaded applicator to ensure that there is a drug implant inside.
3. Remove the applicator from the tray with sterile gloved hands ***touching only the sterile interior tray surface and applicator***.

   Prior to injection, the applicator tip must be kept above the horizontal plane to ensure that the implant is properly positioned within the applicator.
4. To reduce the amount of air administered with the implant, the administration procedure requires two steps. Before inserting the needle into the eye, remove the protective cap then gently push the applicator button down and slide it to the first stop (at the curved black marks alongside the button track). At the first stop, release the button and it should move to the UP position. If the button does not rise to the UP position, do not proceed with this unit.
5. Optimal placement of the implant is inferior to the optic disc and posterior to the equator of the eye. Measure 4 millimeters inferotemporal from the limbus with the aid of calipers for point of entry into the sclera.
6. Inspect the tip of the needle to ensure it is not bent.
7. Gently displace the conjunctiva so that after withdrawing the needle, the conjunctival and scleral needle entry sites will not align. Care should be taken to avoid contact between the needle and the lid margin or lashes. Insert the needle through the conjunctiva and sclera. To release the implant, while the button is in the UP position, advance the button by sliding it forward to the end of the button track and remove the needle. Note: Ensure that the button reaches the end of the track before removing the needle.
8. Remove the lid speculum and perform indirect ophthalmoscopy to verify placement of the implant, adequate central retinal artery perfusion and absence of any other complications.

Following the injection, patients should be monitored for change in intraocular pressure and for endophthalmitis. Monitoring may consist of a check for perfusion of the optic nerve head immediately after the injection, tonometry within 30 minutes following the

injection, and biomicroscopy between two and seven days following the injection. Patients should be instructed to report without delay any symptoms suggestive of endophthalmitis.

3 DOSAGE FORMS AND STRENGTHS

ILUVIEN is a non-bioerodable intravitreal implant in a drug delivery system containing 0.19 mg fluocinolone acetonide, designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day and lasting 36 months.

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

ILUVIEN is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

4.2 Glaucoma

ILUVIEN is contraindicated in patients with glaucoma, who have cup to disc ratios of greater than 0.8.

4.3 Hypersensitivity

ILUVIEN is contraindicated in patients with known hypersensitivity to any components of this product.

5 WARNINGS AND PRECAUTIONS

5.1 Intravitreal Injection-related Effects

Intravitreal injections, including those with ILUVIEN, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. For patients with non-infectious uveitis affecting the posterior segment, hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17)]*. Patients may experience temporary blurred vision after injection of the implant.

5.2 Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in the development of glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. Intraocular pressure should be routinely monitored during the course of the treatment.

5.3 Cataracts

The use of corticosteroids may result in posterior subcapsular cataract formation.

5.4 Delayed Corneal Wound Healing

The use of corticosteroids after cataract surgery may delay healing and increase the incidence of bleb formation.

5.5 Corneal and Scleral Melting

Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of ophthalmic corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation of the globe.

5.6 Bacterial Infections

Prolonged use of corticosteroids may suppress the host immune response and thus increase the hazard of secondary ocular infections. Acute purulent or parasitic infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication. If signs and symptoms fail to improve after 2 days, the patient should be reevaluated.

5.7 Viral Infections

Use of ocular corticosteroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution; frequent slit lamp microscopy is recommended.

5.8 Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local corticosteroid application. Fungus invasion should be suspected in any persistent corneal ulceration where a corticosteroid has been used or is in use. Fungal cultures should be taken when appropriate.

5.9 Risk of Implant Migration

Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions associated with ophthalmic steroids including ILUVIEN include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

Diabetic Macular Edema

ILUVIEN was studied in two multicenter, randomized, sham-controlled, double-masked trials in which patients with diabetic macular edema (DME) were treated with either ILUVIEN (n=375) or sham (n=185).

Table 1 summarizes safety data available when the last subject completed the last 36 month follow up visit for the two primary ILUVIEN trials. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry. Over the three year follow up period, approximately 75% of the ILUVIEN treated subjects received only one ILUVIEN implant.

The most common ocular (study eye) and non-ocular adverse reactions are shown in Tables 1 and 2:

Table 1: Ocular Adverse Reactions Reported by ≥1% of DME Patients and Non-ocular Adverse Reactions Reported by ≥5% of DME Patients

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Cataract[1]	192/235[2] (82%)	61/121[2] (50%)
Myodesopsia	80 (21%)	17 (9%)
Eye pain	57 (15%)	25 (14%)
Conjunctival haemorrhage	50 (13%)	21 (11%)
Posterior capsule opacification	35 (9%)	6 (3%)
Eye irritation	30 (8%)	11 (6%)
Vitreous detachment	26 (7%)	12 (7%)
Conjunctivitis	14 (4%)	5 (3%)
Corneal oedema	13 (4%)	3 (2%)
Foreign body sensation in eyes	12 (3%)	4 (2%)
Eye pruritus	10 (3%)	3 (2%)
Ocular hyperaemia	10 (3%)	3 (2%)

Adverse Reactions	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
Ocular		
Optic atrophy	9 (2%)	2 (1%)
Ocular discomfort	8 (2%)	1 (1%)
Photophobia	7 (2%)	2 (1%)
Retinal exudates	7 (2%)	0 (0%)
Anterior chamber cell	6 (2%)	1 (1%)
Eye discharge	6 (2%)	1 (1%)
Non-ocular		
Anemia	40 (11%)	10 (5%)
Headache	33 (9%)	11 (6%)
Renal Failure	32 (9%)	10 (5%)
Pneumonia	28 (7%)	8 (4%)

[1] Includes cataract, cataract nuclear, cataract subcapsular, cataract cortical and cataract diabetic in patients who were phakic at baseline. Among these patients, 80% of ILUVIEN subjects vs. 27% of sham-controlled subjects underwent cataract surgery.

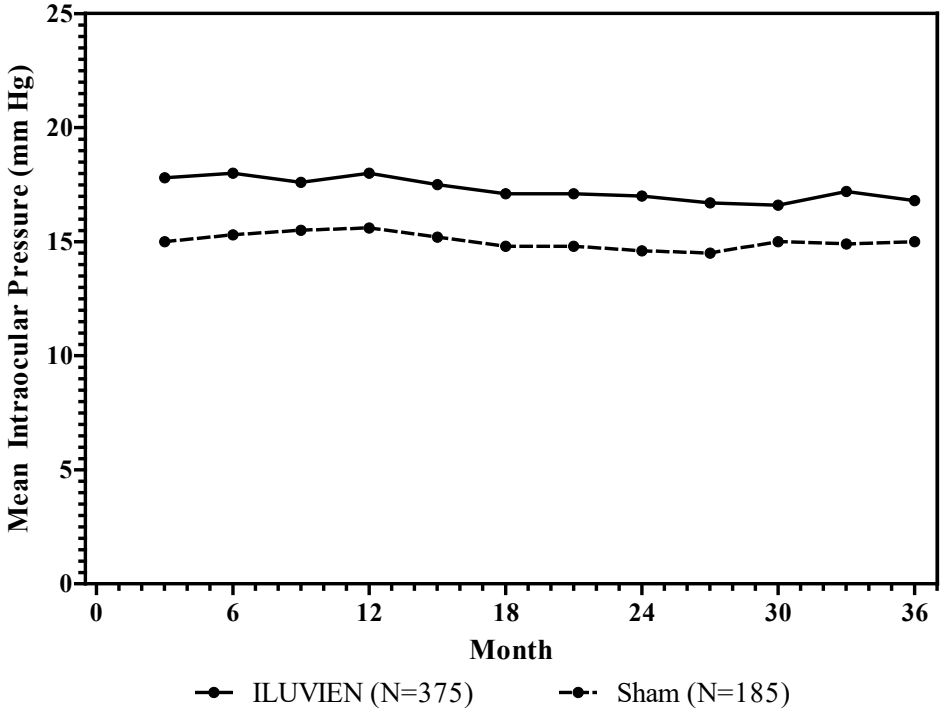
[2] 235 of the 375 ILUVIEN subjects were phakic at baseline; 121 of 185 sham-controlled subjects were phakic at baseline.

Increased Intraocular Pressure (IOP) in DME Patients

Table 2: Summary of Elevated IOP Related Adverse Reactions in DME Patients

Event	ILUVIEN (N=375) n (%)	Sham (N=185) n (%)
IOP elevation ≥ 10 mmHg from Baseline	127 (34%)	18 (10%)
IOP elevation ≥ 30 mmHg	75 (20%)	8 (4%)
Any IOP-lowering medication	144 (38%)	26 (14%)
Any surgical intervention for elevated intraocular pressure	18 (5%)	1 (1%)

Figure 1: Mean IOP in DME Patients



Cataracts and Cataract Surgery in DME Patients

In the DME studies at baseline, 235 of the 375 ILUVIEN subjects were phakic; 121 of 185 sham-controlled subjects were phakic. The incidence of cataract development in patients who had a phakic study eye was higher in the ILUVIEN group (82%) compared with Sham (50%). The median time of cataract being reported as an adverse event was approximately 12 months in the ILUVIEN group and 19 months in the Sham group. Among these patients, 80% of ILUVIEN subjects vs. 27% of sham-controlled subjects underwent cataract surgery, generally within the first 18 months (Median Month 15 for both ILUVIEN group and for Sham) of the studies.

Chronic Non-Infectious Uveitis Affecting the Posterior Segment of the Eye

Studies 1 and 2 were multicenter, randomized, sham injection-controlled, double-masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either fluocinolone acetonide intravitreal implant or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with fluocinolone acetonide intravitreal implant, administered by one of two different applicators, and then received standard care for the duration of the study.

Table 3 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with fluocinolone acetonide intravitreal implant (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions in patients with non-infectious uveitis are shown in Table 3 and Table 4.

Table 3: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients with Non-Infectious Uveitis

Ocular		
ADVERSE REACTIONS	**Fluocinolone acetonide intravitreal implant (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)

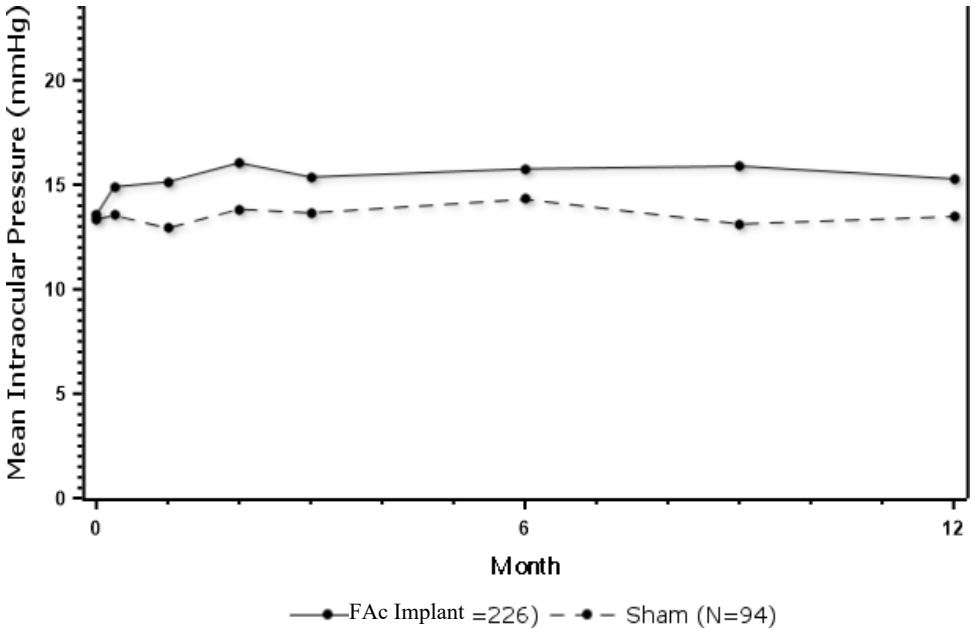
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**Fluocinolone acetonide intravitreal implant (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 fluocinolone acetonide study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 4: Summary of Elevated IOP Related Adverse Reactions in Patients with Non-Infectious Uveitis

ADVERSE REACTIONS	Fluocinolone acetonide intravitreal implant (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation $\geq$ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 2: Mean IOP in Patients with Non-Infectious Uveitis



6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of ILUVIEN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure. These reactions include reports of drug administration error and reports of the drug being ineffective.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of ILUVIEN use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with fluocinolone acetonide. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. It is not known whether ILUVIEN can cause fetal harm when administered to a pregnant women or affect reproduction capacity. ILUVIEN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

Systemically administered corticosteroids that are present in human milk can suppress growth and interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with ILUVIEN. The systemic concentration of fluocinolone acetonide following intravitreal treatment with ILUVIEN is low *[see Clinical Pharmacology (12.3)]*.

It is not known whether intravitreal treatment with ILUVIEN could result in sufficient systemic absorption to produce detectable quantities in human milk, or affect breastfed infants or milk production. Exercise caution when ILUVIEN is administered to a nursing woman.

The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for ILUVIEN and any potential adverse effects on the breastfed infant from ILUVIEN or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of ILUVIEN have not been established in pediatric patients.

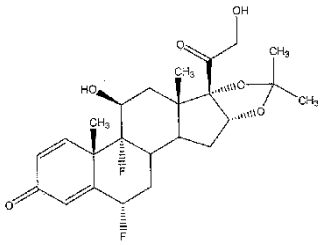
8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

ILUVIEN is a sterile non-bioerodable intravitreal implant containing 0.19 mg (190 mcg) fluocinolone acetonide in a 36-month sustained-release drug delivery system. ILUVIEN is designed to release fluocinolone acetonide at an initial rate of 0.25 mcg/day. ILUVIEN is preloaded into a single-use applicator to facilitate injection of the implant directly into the vitreous. The drug substance is a synthetic corticosteroid, fluocinolone acetonide.

The chemical name for fluocinolone acetonide is (6α,11β, 16α)-6,9-difluoro-11,21-dihydroxy-16,17-[(1-methylethylidene)bis-(oxy)]-pregna-1,4-diene-3,20-dione. Its chemical structure is:



MW 452.50; molecular formula $C_{24}H_{30}F_2O_6$

Fluocinolone acetonide is a white or almost white, microcrystalline powder, practically insoluble in water, soluble in methanol, ethanol, chloroform and acetone, and sparingly soluble in ether.

Each ILUVIEN consists of a light brown 3.5mm x 0.37mm implant containing 0.19 mg of the active ingredient fluocinolone acetonide and the following inactive ingredients: polyimide tube, polyvinyl alcohol, silicone adhesive and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Corticosteroids inhibit inflammatory responses to a variety of inciting agents including multiple inflammatory cytokines. They inhibit edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.

Corticosteroids are thought to act by inhibition of phospholipase A_2 via induction of inhibitory proteins collectively called lipocortins. It is postulated that these proteins control biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting release of the common precursor, arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2.

12.3 Pharmacokinetics

In a human pharmacokinetic study of ILUVIEN, fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all post-administration time points from Day 7 through Month 36 following intravitreal administration of a 0.2 mcg/day or 0.5 mcg/day fluocinolone acetonide insert.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to determine the carcinogenic potential or the effect on fertility of ILUVIEN.

Fluocinolone acetonide was not genotoxic *in vitro* in the Ames test (S. typhimurium and E. coli) and the mouse lymphoma TK assay, or *in vivo* in the mouse bone marrow micronucleus assay.

14 CLINICAL STUDIES

Diabetic Macular Edema

The efficacy of ILUVIEN was assessed in two three year, randomized (2:1, active: sham), multicenter, double-masked, parallel-groups studies that enrolled patients with diabetic macular edema (DME) that had previously been treated with laser photocoagulation.

The primary efficacy endpoint in both trials was the proportion of subjects in whom vision had improved by 15 letters or more from baseline after 24 months of follow-up.

Table 5: Baseline BCVA (Letters)

	Study 1		**Study 2**	
	ILUVIEN (N=190)	**Sham (N=95)**	**ILUVIEN (N=186)**	**Sham (N=90)**
Mean (SD)	53 (13)	55 (11)	53 (12)	55 (11)
Median (Range)	57 (19-75)	58 (25-69)	56 (20-70)	58 (21-68)

Table 6: Visual Acuity Outcomes at Month 24 (All randomized subjects with LOCF)

Study	**Outcomes**	**ILUVIEN**	**Sham**	**Estimated Difference (95% CI)**
1[a]	Gain of ≥15 letters in BCVA (n (%))	51 (27%)	14 (15%)	12.1% (2.6%, 21.6%)
	Loss of ≥15 letters in BCVA (n (%))	26 (14%)	5 (5%)	8.4% (1.8%, 15.1%)
	Mean change from baseline in BCVA (SD)	3.7 (18.7)	3.2 (13.1)	1.8 (-2.8, 6.3)
2[b]	Gain of ≥15 letters in BCVA (n (%))	57 (31%)	16 (18%)	13.0% (2.7%, 23.4%)
	Loss of ≥15 letters in BCVA (n (%))	22 (12%)	9 (10%)	1.8% (-5.9%, 9.6%)
	Mean change from baseline in BCVA (SD)	5.2 (18.0)	0.0 (15.6)	6.1 (1.4, 10.8)

[a]Study 1: ILUVIEN, N=190; Sham, N=95

[b]Study 2: ILUVIEN, N=186; Sham, N=90

Visual acuity outcomes by lens status (Phakic or Pseudophakic) at different visits are presented in Figure 3 and Figure 4. The occurrence of cataracts impacted visual acuity during the study. Patients who were pseudophakic at baseline achieved greater mean BCVA change from baseline at the Month 24 study visit.

Figure 3: Proportion of Subjects with >=15 Letters Improvement from Baseline BCVA in the Study Eye

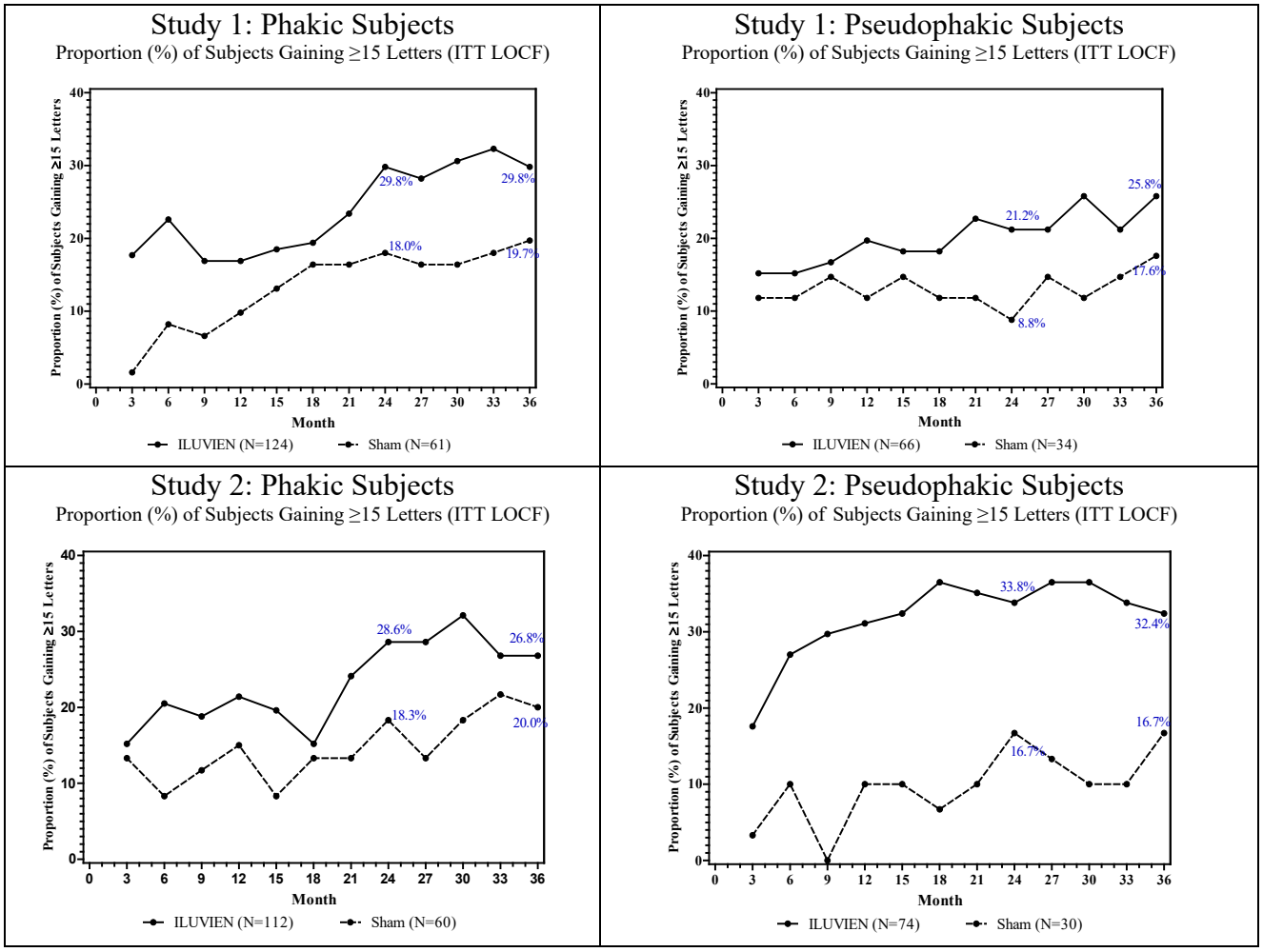
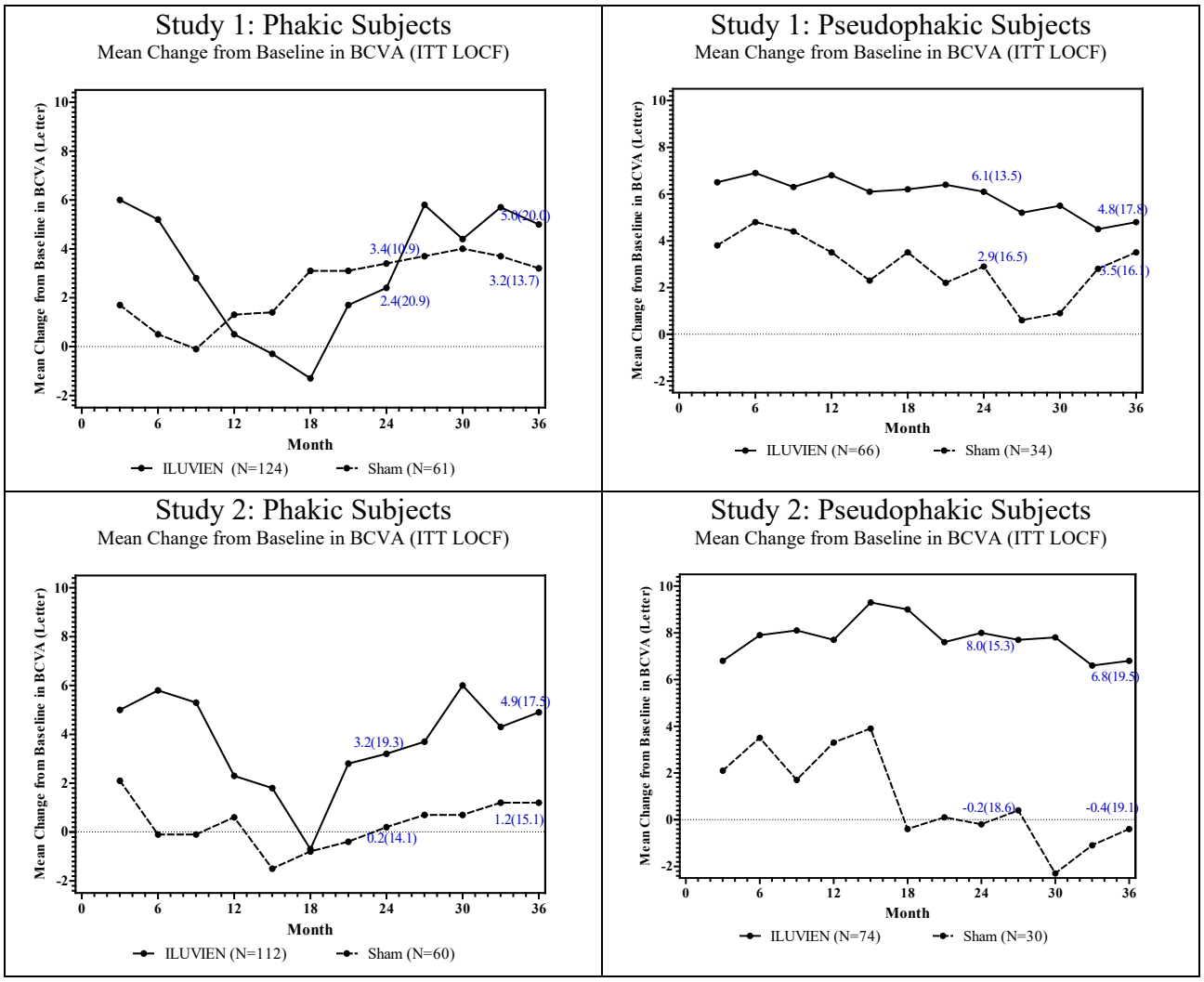


Figure 4: Mean BCVA Change from Baseline



The BCVA outcomes for the Pseudophakic and Phakic subgroups from Studies 1 and 2 at Month 24 are presented in Table 7.

Table 7: Visual Acuity outcomes at Month 24 (Subgroup for pooled data with LOCF)

Lens Status	Outcomes	ILUVIEN	Sham	Estimated Difference (95% CI)
[a]Pseudophakic	Gain of ≥15 letters in BCVA (n (%))	39 (28%)	8 (13%)	15.4% (4.4%, 26.3%)
	Loss of ≥15 letters in BCVA (n (%))	7 (5%)	7 (11%)	-5.9% (-14.4%, 2.5%)
	Mean change from baseline in BCVA (SD)	7.1 (14.5)	1.5 (17.4)	5.6 (0.7, 10.6)
[b]Phakic	Gain of ≥15 letters in BCVA (n (%))	69 (29%)	22 (18%)	11.1% (2.1%, 20.1%)
	Loss of ≥15 letters in BCVA (n (%))	41 (17%)	7 (6%)	11.6% (5.2%, 18%)
	Mean change from baseline in BCVA (SD)	2.8 (20.1)	1.8 (12.6)	1 (-2.5 ,4.4)

[a]Pseudophakic : ILUVIEN, N=140; Sham, N=64

[b]Phakic: ILUVIEN, N=236; Sham, N=121

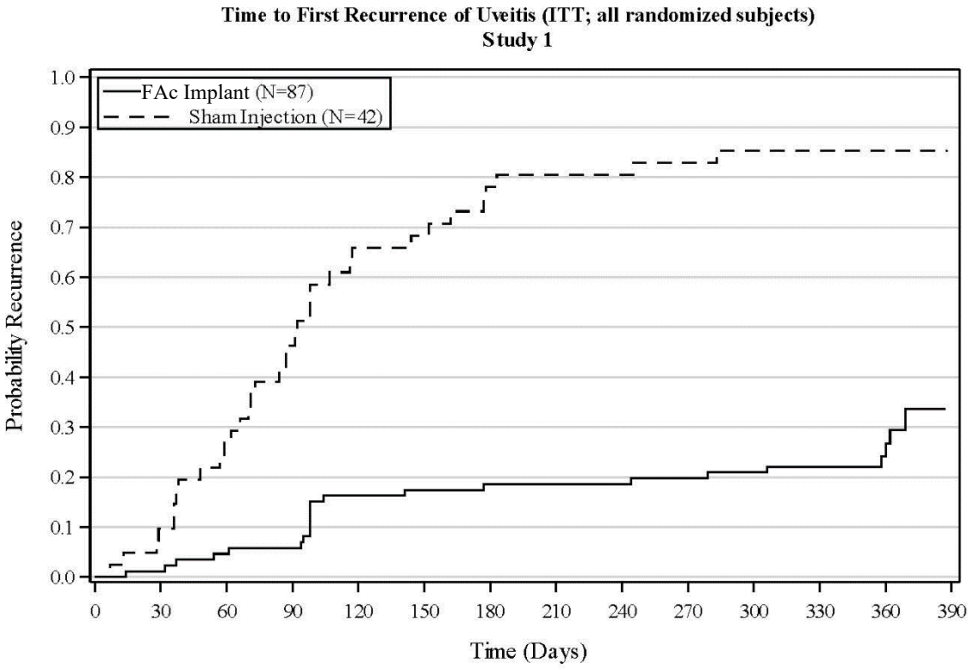
Chronic Non-Infectious Uveitis Affecting the Posterior Segment

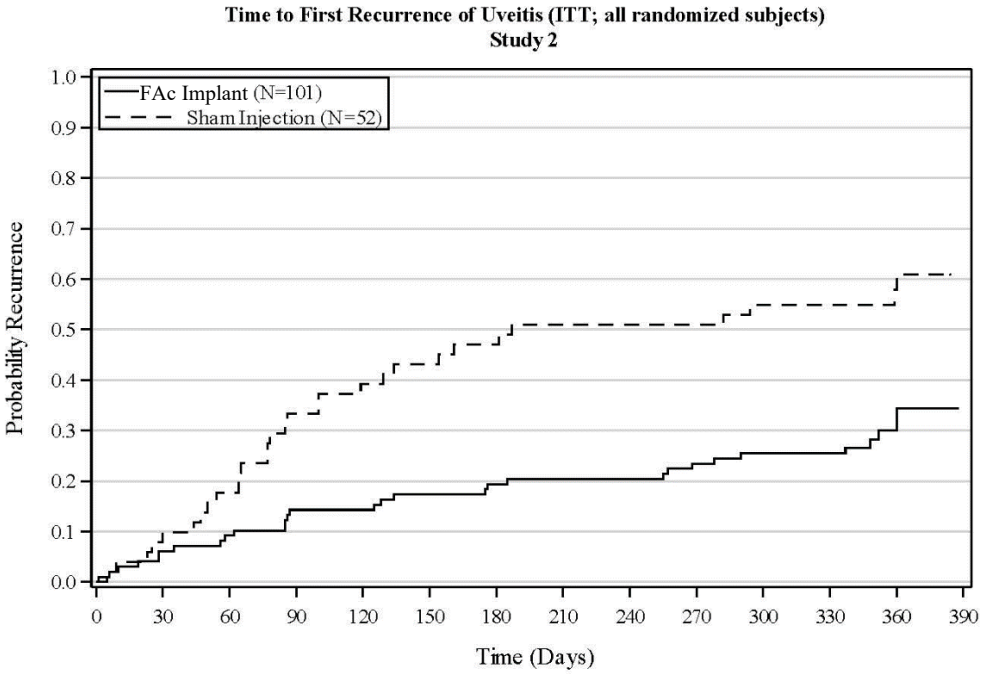
The efficacy of fluocinolone acetonide intravitreal implant was assessed in two randomized (2:1, fluocinolone acetonide intravitreal implant: sham-injection), multi-center, double-masked, parallel-groups studies (NCT #01694186 and #02746991) that enrolled patients with non-infectious uveitis affecting the posterior segment of the eye. The primary efficacy endpoint in both trials was the proportion of patients who experienced a recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence of uveitis was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis or the need for rescue medications.

Table 8: Efficacy Results of Recurrence of Uveitis in Randomized Study Eyes

	Study 1		**Study 2**	
	FAc Implant	**Sham**	**FAc Implant**	**Sham**
	N = 87	**N = 42**	**N = 101**	**N = 52**
Eyes with recurrence within 6 months, n (%)	**16 (18%)**	**33 (79%)**	**22 (22%)**	**28 (54%)**
Difference (95% CI) in recurrence rates	**60% (41%, 73%)**		**32% (15%, 48%)**	
P-value	< 0.01		< 0.01	
Eyes with recurrence within 12 months, n (%)	**24 (28%)**	**36 (86%)**	**33 (33%)**	**31 (60%)**
Difference (95% CI) in recurrence rates	**58% (40%, 70%)**		**27% (9%, 43%)**	

Figure 5: Time to First Recurrence of Uveitis (ITT: All Randomized Patients)





16 HOW SUPPLIED/STORAGE AND HANDLING

ILUVIEN® (fluocinolone acetonide intravitreal implant) 0.19 mg is supplied in a sterile, single-use preloaded applicator with a 25-gauge needle, packaged in a tray sealed with a lid inside a carton.

NDC 68611-190-02

Storage: Store at 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Steroid-related Effects
Advise patients that a cataract may occur after treatment with ILUVIEN**.** If this occurs, advise patients that their vision will decrease, and they will need an operation to remove the cataract and restore their vision.

Advise patients that they may develop increased intraocular pressure with ILUVIEN treatment, and the increased IOP may need to be managed with eye drops, or surgery.

When to Seek Physician Advice
Advise patients that in the days following intravitreal injection of ILUVIEN, patients are at risk for potential complications including in particular, but not limited to, the development of endophthalmitis or elevated intraocular pressure.

Advise patients that if the eye becomes red, sensitive to light, painful, or develops a change in vision, they should seek immediate care from an ophthalmologist.

Driving and Using Machines
Inform patients that they may experience temporary blurred vision after injection of the implant. Advise patients not to drive or use machines until this has been resolved.

Manufactured for:
Alimera Sciences, Inc.
Baudette, MN 56623

Patented.

alimera