Title

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Authors

Brandt, James D
Sall, Kenneth
DuBiner, Harvey
et al.

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Six-Month Intraocular Pressure Reduction with a Topical Bimatoprost Ocular Insert

Results of a Phase II Randomized Controlled Study

James D. Brandt, MD,[1] Kenneth Sall, MD,[2] Harvey DuBiner, MD,[3] Robert Benza, MD,[4] Yair Alster, MD,[5] Gary Walker, PhD,[5] Charles P. Semba, MD[5]

Purpose: Improving adherence to manage elevated intraocular pressure (IOP) remains an unmet need. A topical bimatoprost ocular insert was compared with twice-daily timolol eye drops in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) treated for 6 months.

Design: Parallel-arm, multicenter, double-masked, randomized, controlled trial.

Participants: One hundred thirty adult OAG or OHT patients.

Methods: Eligible patients were randomized 1:1 to receive a bimatoprost insert plus artificial tears twice daily or a placebo insert plus timolol (0.5% solution) twice daily for 6 months after a screening washout period. Diurnal IOP measurements (at 0, 2, and 8 hours) were obtained at baseline; weeks 2, 6, and 12; and months 4, 5, and 6. Key eligibility included washout IOP of 23 mmHg or more at time 0, IOP of 20 mmHg or more at 2 and 8 hours, and IOP of 34 mmHg or less at all time points; no prior incisional surgery for OAG or OHT; and no known nonresponders to prostaglandins.

Main Outcome Measures: The primary efficacy end point examined the difference in mean change from baseline in diurnal IOPs (point estimate, 95% confidence interval) across 9 coprimary end points at weeks 2, 6, and 12 comparing the bimatoprost arm with the timolol arm using a noninferiority margin of 1.5 mmHg. Secondary end points were diurnal IOP measurements at months 4, 5, and 6 and adverse events (AEs).

Results: A mean reduction from baseline IOP of −3.2 to −6.4 mmHg was observed for the bimatoprost group compared with −4.2 to −6.4 mmHg for the timolol group over 6 months. The study met the noninferiority definition at 2 of 9 time points but was underpowered for the observed treatment effect. Adverse events were consistent with bimatoprost or timolol exposure; no unexpected ocular AEs were observed. Primary retention rate of the insert was 88.5% of patients at 6 months.

Conclusions: Clinically relevant reduction in mean IOP was observed over 6 months with a bimatoprost ocular insert and seems to be safe and well tolerated. The topically applied bimatoprost insert may provide an alternative to daily eye drops to improve adherence, consistency of delivery, and reduction of elevated IOP. *Ophthalmology 2016;123:1685-1694 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental video is available at www.aaojournal.org.

Glaucoma is a leading cause of irreversible vision loss worldwide, and reduction of elevated intraocular pressure (IOP) is the only proven treatment to slow or halt progression of the disease[1]; however, a common problem in disease management is low patient adherence to ocular medication administration.[2,3] Factors contributing to the lack of compliance include forgetfulness, cost of medications, poor understanding of glaucoma, difficulty with drop self-administration, and difficulty with medication schedule.[4] Lack of adherence has been shown to correlate with the progression of vision loss.[5] Even in the setting of good patient adherence, inefficient self-administration of eye drops (e.g., too many drops instilled or mistargeted drops) may lead to an extended period of no treatment before refilling of the prescription. An unmet need exists for sustained delivery of ocular hypotensive medications to improve adherence and persistence as an alternative to daily eye drops in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT).

We describe a simple and novel sustained-release bimatoprost ocular insert that is applied topically to the ocular surface by a physician and allows continuous drug delivery for up to 6 months per application of the insert. Previous exploratory, phase I dose-finding safety studies in OAG and OHT patients whose disease was well controlled with topical monotherapy demonstrated that the bimatoprost insert can sustain an IOP reduction of 20% or more (4−6 mmHg) compared with washout baseline IOP for up to 6 months; however, these open-label studies were neither randomized nor controlled (Goldberg I, et al. Poster P0390,

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American Academy of Ophthalmology annual meeting, 2014; Goldberg I, et al. Poster P-S-04, World Glaucoma Congress meeting, 2015). The safety profile was consistent with bimatoprost exposure (e.g., mild conjunctival hyperemia), and the ocular insert seemed to be well tolerated. The purpose of this study was to assess the relative efficacy and safety of a bimatoprost insert compared with twice-daily timolol 0.5% ophthalmic solution in patients with OAG or OHT treated for 6 months in a multicenter, randomized, double-masked, randomized, controlled study.

Methods

Study Design

This was a phase II, prospective, randomized, double-masked, active-controlled, parallel-arm study conducted at 10 sites in the United States (Appendix 1). The study lasted approximately 7 months and consisted of 2 periods: screening (day −35±7 days to day 0) and treatment (day 0 to 6 months). A total of 8 study visits were scheduled: 2 during screening (visits 1 and 2) and 6 during treatment (weeks 2, 6, and 12 and months 4, 5, and 6). The first patient was enrolled in October 2013 and the last patient completed the study in November 2014.

The study was conducted in accordance with the International Conference of Harmonization guidelines (E6) of Good Clinical Practice and the tenets of the Declaration of Helsinki and is registered at ClinicalTrials.gov (identifier, NCT01915940). Written informed consent was obtained before patient enrollment, and the study was reviewed and approved by an investigational review board.

Investigational Ocular Inserts

Description. The bimatoprost insert is a preservative-free ocular ring containing 13 mg bimatoprost mixed into a silicone matrix placed over an inner polypropylene support structure and is manufactured in diameters ranging from 24 to 29 mm (Fig 1). Drug release is based on passive, concentration gradient−driven molecular diffusion of the drugs through the silicone matrix into the tear film. The release rate of bimatoprost into the tear film is determined by the physical properties of the silicone, the surface area of the silicone−drug matrix, and the concentration of the bimatoprost in the silicone−drug matrix. The elution profile of the bimatoprost insert is a continuous monotonically declining dose that elutes a higher dose of bimatoprost at day 0 (day of insertion) than at day 180 (day of removal). Over the range of 6 months (180 days), the bimatoprost insert elutes a descending dose of bimatoprost of approximately 35 μg/day at day 0 to 6 μg/day at day 180, and a total dose of approximately 2.5 mg bimatoprost (data on file). By comparison, topical bimatoprost 0.03% (Lumigan; Allergan, Inc, Irvine, CA.) is approved as a once-daily eye drop with a concentration of approximately 9 μg/day (total dose, approximately 1.6 mg over 180 days). Bimatoprost was selected as the active drug product for this program based on manufacturability and efficacy of the drop formulation; formulation testing supports that travoprost or latanoprost also can be incorporated into the silicone matrix without difficulty.

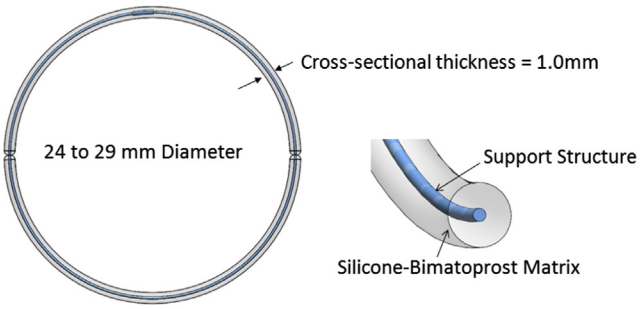

Figure 1. Schematic of a bimatoprost ocular insert. The soft ring-shaped insert is constructed of a bimatoprost and silicone-matrix polymer and is placed on top of the ocular surface. *Right*, The insert maintains its radial integrity because of its internal polypropylene support structure.

Method of Placement. To provide a custom fit, the investigator measured the intercanthal distance to select the appropriate diameter insert. After administration of an optional drop of anesthetic agent, the investigator gently manually retracted the eyelids and placed the ocular insert in the upper and lower fornices (Fig 2). A scleral depressor was used at the discretion of the physician (Video 1, available at www.aaojournal.org).

Method of Removal. The ocular insert is removed by gentle manually retracting the lower eyelid, allowing exposure of the bottom portion of the ocular insert. The exposed ring then is grasped with the fingers and pulled from the upper fornix.

Study Protocol

Screening and Eligibility. At visit 1 (day −35±7 days), after obtaining informed consent, data were collected by study personnel; these included demographic data, medical and medication history, and inclusion and exclusion evaluation. A summary of the study schema and visits is provided in Figure 3. Inclusion criteria included a diagnosis of either OAG or OHT controlled with monotherapy with IOP-lowering topical medication, or, if not medicated, likely to be controlled with monotherapy; ability to discontinue ocular hypotensive treatment for the required washout period of 4 to 6 weeks; best-corrected visual acuity equivalent to 20/80 or better in both eyes; stable visual fields in the opinion of the investigator; and corneal thickness between 490 and 620 μm. Exclusion criteria included known nonresponders or any contraindication to prostaglandin analogs (PGAs) or timolol, current treatment for glaucoma with fixed-combination medications or oral drug, use of intravitreal or peribulbar injection of depot steroid or placement of an intravitreal steroid implant within the 6 months before the screening date, cup-to-disc ratio of more than 0.8, severe central visual field loss with a sensitivity of 10 dB or less in 2 or more of the 4 points closest to the point of fixation, history of any incisional surgery for glaucoma or corneal refractive surgery, patients who required contact lens use during the study period, and patients with current punctal occlusion.

Participants meeting all eligibility criteria at visit 1 were fitted with an open-label nonmedicated (placebo) ocular insert in both eyes that was worn during the entire screening washout period to assess comfort and proper fitting of the insert before consideration for investigational treatment. At visit 2, screening procedures were repeated. Qualifying patients had to demonstrate the following IOP requirements: mean IOP for each eye of 23 mmHg or more and 34 mmHg or less at 0 hours, 20 mmHg or more and 34 mmHg or less at 2 hours, and 20 mmHg or more and 34 mmHg or less at 8 hours; and intereye IOP difference of 5.0 mmHg or less at the 0-, 2-, and 8-hour measurements. After removal of the placebo inserts, eligible patients were randomized to 1 of 2 treatment groups in a 1:1 ratio: a bimatoprost insert in both eyes plus daily unpreserved artificial tears twice daily (morning and evening; Refresh Classic; Allergan, Inc.) or a placebo insert in both eyes plus daily unpreserved timolol 0.5% ophthalmic solution twice daily (morning and evening; Valeant Ophthalmics, Bridgewater, NJ). Use of artificial tears was required for patients assigned to the bimatoprost insert to preserve masking (double-dummy design).

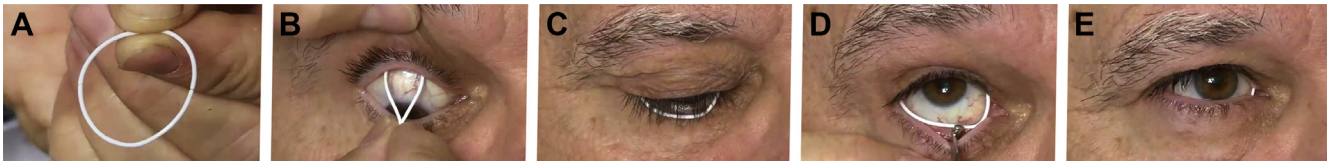

Figure 2. Photographs showing the method of placement of a bimatoprost ocular insert. **A**, The upper lid is retracted manually and the insert is placed in upper fornix by the physician. After (**B**) placement of the top half of the insert in the upper fornix, (**C**) the lower lid margin is retracted gently either manually or with a scleral depressor (**D**) to seat the bottom half of insert into the lower fornix. **E**, Insert in situ with a small portion of the insert visible in the medial canthus.

Participants returned to the study sites for diurnal IOP measurements (0, 2, and 8 hours) at weeks 2, 6, and 12 and at months 4, 5, and 6. After the 0-hour IOP measurement, patients were instructed to self-administer their assigned morning dose of the study eye drop so that 100% adherence to eye drop medication was achieved at the 2- and 8-hour measurements.

Study Masking. The treating physician, study and site personnel, and participants were masked to treatment assignment. The ocular inserts were identical, and the topical eye drops were in similar unmarked unit dose vials. Participants were randomized and assigned study kits through a web-based electronic data capture system. An unmasked independent statistician generated the patient randomization and randomized kit lists.

The nonmedicated placebo insert is identical (in physical form and color) to the bimatoprost insert, except that it contains no active drug. The artificial tears (buffered saline with polyvinyl alcohol 1.4% and povidone 0.6%) and timolol 0.5% ophthalmic solution were packaged in similar low-density polypropylene unpreserved unit doses with no identifiable markings on the ampules. Open-label use of artificial tears, as needed, was allowed for all patients during the screening and washout period.

Rescue Treatment. Rescue therapy with topical bimatoprost (Lumigan 0.01% bimatoprost ophthalmic solution; Allergan, Inc.) in one or both eyes was allowed by the study investigator for any patient with IOP meeting the following criteria at 2 consecutive visits at least 1 week apart: mean IOP more than 25 mmHg in one or both eyes at any time point on a visit day and mean IOP reduction less than 10% in one or both eyes at the same time point on a visit day compared with the IOP at the time of randomization.

Outcome Measures

Efficacy. The primary efficacy measure was mean IOP reduction from baseline measured with Goldmann applanation tonometry at 0, 2, and 8 hours at weeks 2, 6, and 12. The primary efficacy end point was the difference between the mean change in IOP for the bimatoprost insert group and the mean change in IOP for the timolol treatment group as measured from baseline (day 0) at each of the diurnal time points within the first 12 weeks.

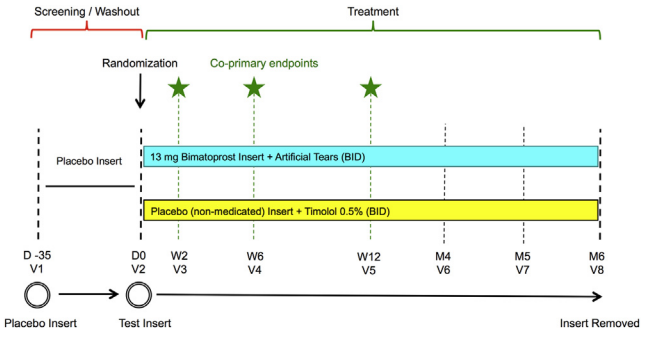

Figure 3. Study schema comparing a bimatoprost ocular insert plus artificial tears with a placebo (nonmedicated) ocular insert and timolol 0.5% ophthalmic solution for 6 months in patients with open-angle glaucoma or ocular hypertension. BID = twice daily; D0 = day 0 (baseline); M = month; V = study visit; W = week.

Safety. Safety measures included adverse events (AEs), biomicroscopy, funduscopy, visual acuity, and visual fields. Slit-lamp biomicroscopic observations for conjunctival hyperemia and eye discharge (mucus) were graded on a numerical scale from 0 to 3: 0 = none, 0.5 = trace, 1 = mild, 2 = moderate, and 3 = severe. A 2-step change from baseline was considered an ocular AE for conjunctival hyperemia or eye discharge. All AEs were classified according to the Medical Dictionary for Regulatory Activities version 16.0 (MedDRA MSSO, McLean, VA).

Participants were instructed on the care and maintenance of the ocular insert after placement by the investigator that included care when rubbing the eyes and instructions on how to retract the eyelid manually and reinsert a partially dislodged insert. For fully dislodged inserts, the participants were instructed not to reinsert the insert at home; instead, they were required to return to the clinical site for placement of a new insert.

Statistical Analysis

The primary efficacy end point consisted of mean change in IOP averaged over both eyes that was modeled using a repeated-measures analysis of covariance model with fixed effect terms for treatment group, visit, IOP at randomization, and the interaction of treatment by visit. The 0-, 2-, and 8-hour measures were assessed across visits using separate repeated-measures analysis of covariance models. The mean change in IOP for each group, the difference between the mean changes of the 2 arms (bimatoprost insert group minus timolol group), and their 2-sided 95% confidence interval (CI) was calculated using separate linear contrasts for weeks 2, 6, and 12. The hypothesis tested in the primary analysis at each of the 9 coprimary time points was based on the upper limit of the 2-sided 95% CI for the difference in the mean IOP between the 2 treatment groups at each of the 9 time points based on the following: H_0: $\mu_{Nt} - \mu_{Xt} \geq 1.5$ mmHg and H_a: $\mu_{Nt} - \mu_{Xt} < 1.5$ mmHg, where μ_{Nt} and μ_{Xt} are the mean changes in IOP for the bimatoprost insert group and the timolol group, respectively. The noninferiority hypothesis was tested at each of the 3 diurnal time points at weeks 2, 6, and 12. The bimatoprost insert treatment regimen is declared noninferior to the timolol treatment regimen if the upper limit of the 95% CI is less than 1.5 mmHg for all 9 coprimary time points.

Efficacy Analysis Population. The primary population for the test of the primary efficacy hypotheses was the full analysis set. The full analysis set included all randomized patients who completed at least 1 on-treatment study visit. The analysis of the primary efficacy outcome and the secondary efficacy outcomes was performed on the full analysis set according to the randomized treatment assignment. Sensitivity analyses included per protocol and worse eye. In the per-protocol analysis, the data from any

Table 1. Study of a Bimatoprost Ocular Insert: Patient Disposition

Status	Total Patients (n = 130)	Bimatoprost* Patients (n = 64)	Timolol† Patients (n = 66)
Patients randomized	130	64	66
Randomized and treated (ITT/safety population)	130	64	66
Randomized, treated, and completed at least 1 on-study follow-up visit (FAS population)	127	63	64
Patients receiving rescue treatment through month 6	0	0	0
Patients withdrawn from study before week 12	10 (7.7)	8 (12.5)	2 (3.0)
Decision of patient	1 (0.8)	0 (0.0)	1 (1.5)
AE	8 (6.2)	7 (10.9)	1 (1.5)
Other	1 (0.8)	1 (1.6)	0 (0.0)
Patients withdrawn from study before month 6	15 (11.5)	11 (17.2)	4 (6.1)
Decision of patient	4 (3.1)	1 (1.6)	3 (4.5)
AE	10 (7.7)	9 (14.1)	1 (1.5)
Other	1 (0.8)	1 (1.6)	0 (0.0)

AE = adverse event; FAS = full analysis set; ITT = intent to treat.
Data are no. or no. (%).
*Bimatoprost ocular insert.
†Timolol 0.5% ophthalmic solution.

insert that had dislodged fully were censored from the time the original insert was replaced.

Safety Analysis Population. The safety population comprised all randomized patients who had a masked ocular insert placed in their eyes. The principal safety analyses were performed according to the actual treatment each patient received.

Sample Size Considerations. The sample size was based on the following assumptions: a standard deviation of 3.5 mmHg in the change in IOP for patients in each treatment group, a 1:1 randomization, a noninferiority margin of 1.5 mmHg, a treatment difference under the null hypothesis of −0.5 mmHg (e.g., the bimatoprost insert is better than timolol drops by 0.5 mmHg), a 1-sided type 1 error rate (α) of 0.025, and a dropout rate of slightly less than 20% at 12 weeks. A sample size of approximately 63 randomized (50 evaluable) patients in each group provided 81% power for testing the hypothesis based on these assumptions.

Results

Patient Disposition and Demographics

One hundred sixty-nine patients were screened and 130 patients were randomized (Table 1) to receive the 13-mg bimatoprost insert (n = 64) or timolol (n = 66). Of the 169 screened patients, 151 (89.3%) had no comfort issues with the nonmedicated insert. A total of 115 patients (88.5%) completed the study at month 6 (82.8% [n = 53] and 93.9% [n = 62] for the bimatoprost insert and timolol groups, respectively). The overall demographic characteristics were well balanced between groups with respect to age, gender, glaucoma status, central corneal thickness, and IOP at baseline; there was a slight racial imbalance, with fewer white patients in the bimatoprost group (67.2%) compared with the timolol group (80.3%; Table 2). No patients received rescue treatment during the study.

Intraocular Pressure–Lowering Efficacy

Participants receiving either a bimatoprost insert or daily timolol had clinically relevant sustained reductions in IOP compared with baseline (Table 3; Fig 4) over the 6-month study period. However, daily timolol 0.5% ophthalmic solution provided approximately 0 to 1.5 mmHg more IOP reduction compared with the bimatoprost insert.

For the primary efficacy analysis, the point estimates of the mean difference in the IOP measurements between the 2 groups were less than 1.5 mmHg at all 9 time points; however, because the upper boundary of the 95% CI exceeded the 1.5 mmHg noninferiority margin at 7 of 9 time points within the first 12 weeks, the bimatoprost insert did not meet the protocol definition of noninferiority to timolol (Fig 5). The sensitivity analyses, including the per-protocol analysis, were consistent with the primary efficacy analysis.

Retention

The primary retention rate of the ocular inserts, defined as maintenance of the insert in situ without requiring physician reintervention, was 93.1% at 12 weeks and 88.5% at 6 months overall for the combined treatment group (bimatoprost insert and placebo insert). The retention rates were similar across treatment groups: the primary retention rate at 12 weeks and 6 months was 90.6% and 87.5% for the bimatoprost group, and 93.9% and 90.9% for the placebo group of participants in both eyes. A total of 28 dislodgements were reported in 15 patients. The proportion of dislodgements was higher among men (20.8%) than women (5.2%); no other demographic trends were observed. The dislodgements were distributed relatively evenly between study days 2 and 180 after randomization. Nine patients experienced a single dislodgement; 3 patients had 2 dislodgements; 2 patients had 3 instances of dislodgement; and 1 patient experienced 7 dislodgements. Patients who had fully displaced inserts received new inserts, allowing for continuous maintenance of days on therapy. There were no cases of a lost or missing ocular insert; all inserts were fully accounted for by the investigators.

Safety

The bimatoprost insert seemed to be safe and well tolerated, and the overall safety profile was consistent with either bimatoprost or timolol exposure. The bimatoprost insert group had a higher percentage of ocular (bimatoprost, 45.3%; timolol, 34.8%) and nonocular (bimatoprost, 26.6%; timolol, 24.2%) treatment-emergent

Table 2. Study of a Bimatoprost Ocular Insert: Patient Demographics

	All Patients (n = 130)	Bimatoprost Patients (n = 64)	Timolol Patients (n = 66)
Age (yrs)			
Mean (SD)	65.6 (9.4)	64.9 (10.1)	66.3 (8.5)
Minimum–maximum	39–86	39–85	45–86
Male sex, no. (%)	53 (40.8)	31 (48.4)	22 (33.3)
Race, no. (%)			
White	96 (73.8)	43 (67.2)	53 (80.3)
Asian	5 (3.8)	3 (4.7)	2 (3.0)
Black	28 (21.5)	17 (26.6)	11 (16.7)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.8)	1 (1.6)	0 (0.0)
Glaucoma status at randomization, no. (%)			
Glaucoma	81 (62.3)	41 (64.1)	40 (60.6)
Ocular hypertension	49 (37.7)	23 (35.9)	26 (39.4)
Central corneal thickness (μm), mean (SD)	558.7 (32.5)	552.9 (31.7)	564.4 (32.5)
Duration of IOP at baseline (hours), mean ± SE			
0	—	24.99±0.29	25.34±0.29
2	—	23.65±0.31	23.75±0.28
8	—	22.95±0.29	23.16±0.29

IOP = intraocular pressure; SD = standard deviation; SE = standard error.

AEs than the timolol group. Most ocular AEs were mild to moderate in severity and resolved without sequelae.

The most common (≥5%) treatment-emergent AEs occurring in either treatment group, regardless of causality, are summarized in Table 4. The ocular AE of eye discharge (mucus) was reasonably balanced across both groups and presumably is the result of mechanical stimulation of the conjunctival goblet cells from the physical presence of the insert on the ocular surface.

There was 1 protocol-specified serious ocular AE of blurred vision resulting in 3-line or more loss in visual acuity in a patient assigned to the timolol group. The event was transient, resolved fully with no sequelae, and was reported as not being drug related. Four patients (2 in each treatment group) experienced nonocular serious AEs; none were reported as drug related and all resolved fully. These include a fall resulting in cellulitis and vascular hypertension in the bimatoprost group and drug hypersensitivity (opioid allergic reaction) and atrial fibrillation in the timolol group.

The other ocular safety parameters (best-corrected visual acuity, slit-lamp biomicroscopy results, dilated funduscopy results) were comparable between groups with the exception of higher slit-lamp-determined rates of conjunctival hyperemia in the bimatoprost group compared with the timolol group.

A total of 10 patients withdrew from the study because of treatment-emergent AEs, 9 of whom were assigned to the bimatoprost group and 1 of whom was assigned to the timolol group (Table 5). This rate of imbalance between the bimatoprost and timolol groups was similar to prior registration studies comparing the 2 agents.[6] All of the AEs resolved with no sequelae.

Discussion

To our knowledge, this is the first study to demonstrate the proof of concept that sustained reduction in IOP can be achieved nonsurgically with a topically applied drug-delivery system in patients for 6 months. Persistence and adherence with daily-administered IOP-lowering eye drops remains a significant issue for physicians managing patients with OAG and OHT.[2,3] To address the unmet medical need, we designed a simple, noninvasive, preservative-free, drug-eluting ocular insert that can be applied topically to the ocular surface by an eye care specialist and can elute

Table 3. Study of a Bimatoprost Ocular Insert: Mean Change from Baseline in Intraocular Pressure at All Time Points (Observed Data, Full Analysis Set)

	Week 2 (mmHg)			Week 6 (mmHg)			Week 12 (mmHg)		
Group	*0 Hours*	*2 Hours*	*8 Hours*	*0 Hours*	*2 Hours*	*8 Hours*	*0 Hours*	*2 Hours*	*8 Hours*
Bimatoprost	−6.40 (0.41)	−5.20 (0.34)	−4.21 (0.35)	−5.47 (0.40)	−4.70 (0.31)	−3.78 (0.34)	−5.26 (0.47)	−4.26 (0.44)	−3.99 (0.33)
Timolol	−6.30 (0.41)	−5.59 (0.41)	−4.96 (0.37)	−6.41 (0.41)	−5.40 (0.39)	−4.42 (0.39)	−6.31 (0.43)	−5.60 (0.43)	−5.19 (0.35)
	Month 4 (mmHg)			**Month 5 (mmHg)**			**Month 6 (mmHg)**		
Group	*0 Hours*	*2 Hours*	*8 Hours*	*0 Hours*	*2 Hours*	*8 Hours*	*0 Hours*	*2 Hours*	*8 Hours*
Bimatoprost	−5.14 (0.43)	−4.37 (0.38)	−3.84 (0.34)	−4.28 (0.36)	−3.87 (0.39)	−3.21 (0.34)	−4.58 (0.39)	−3.87 (0.42)	−3.25 (0.32)
Timolol	−6.29 (0.40)	−5.26 (0.41)	−5.11 (0.36)	−6.35 (0.41)	−5.45 (0.43)	−4.47 (0.38)	−5.97 (0.42)	−5.20 (0.41)	−4.24 (0.37)

Data are mean (standard error).

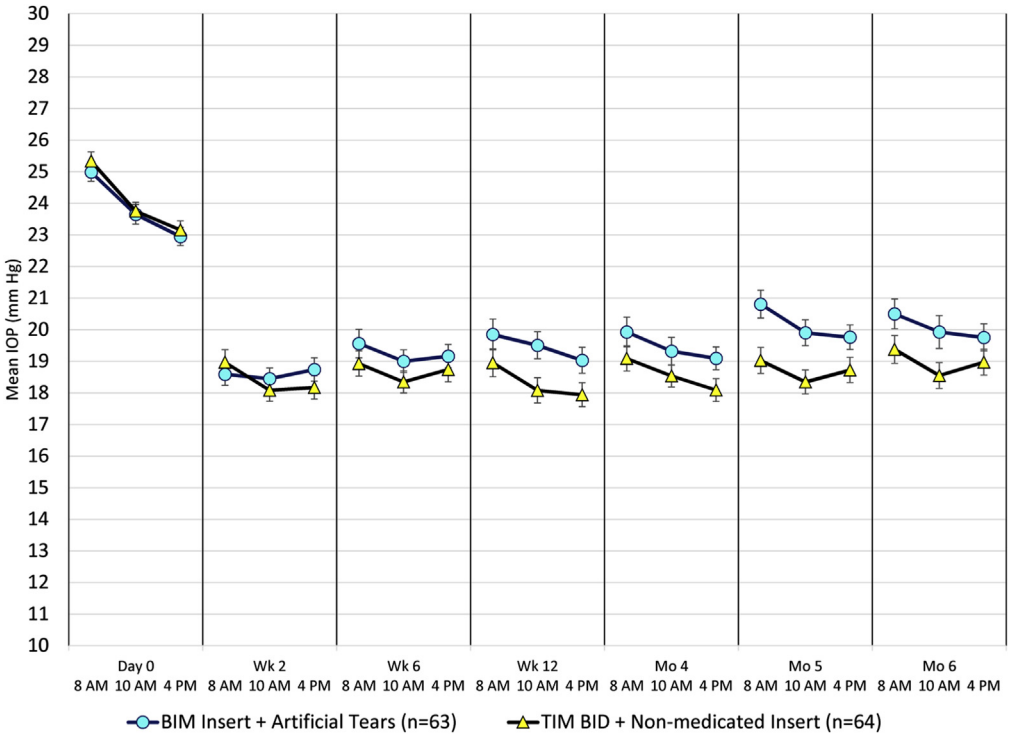

Figure 4. Graph showing the mean intraocular pressure (IOP) at each time point in a study of a bimatoprost (BIM) insert plus artificial tears compared with timolol 0.5% ophthalmic solution (TIM) and a nonmedicated insert (observed data; full analysis set population). Diurnal washout IOPs are shown at day 0 (D0) followed by diurnal IOPs at 8 AM, 10 AM, and 4 PM at weeks (Wk) 2, 6, and 12 and at months (Mo) 4, 5, and 6. BID = twice daily.

medication for up to 6 months. The intent of the insert is to provide patients and eye care specialists an alternative to daily eye drops or incisional surgery in patients with uncomplicated OAG or OHT whose disease can be controlled with monotherapy.

The primary objective of this study was to evaluate whether sustained reduction in IOP can be achieved with a bimatoprost insert compared with twice-daily timolol 0.5% ophthalmic solution in a population of OAG and OHT patients. The results demonstrated that a clinically relevant sustained reduction in IOP of approximately 4 to 6 mmHg (≥20% reduction compared with washout baseline) for 6 months can be achieved with the bimatoprost insert, with no patients receiving rescue therapy. In OHT patients observed in the Ocular Hypertension Treatment Study, a 20% lowering of IOP reduced the conversion rate to OAG by half.[7]

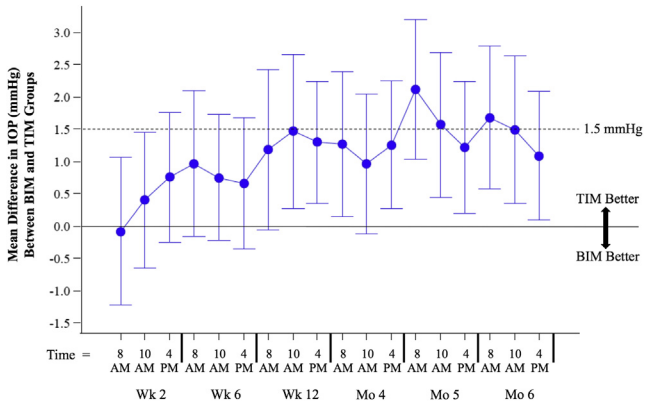

Figure 5. Graph showing the mean difference (point estimates and 95% confidence intervals) in intraocular pressure (IOP) at all diurnal time points comparing the bimatoprost (BIM) group with the timolol (TIM) group in a study of a BIM ocular insert (repeated-measures analysis of covariance, full analysis set population) through 6 months (Mo). The dashed line represents the noninferiority boundary of 1.5 mmHg. Wk = week.

The overall primary ocular retention rate was high at 93.1% and 88.5% of patients at 3 and 6 months, respectively. The comfort profile was acceptable in nearly 90% of patients during the initial screening and washout period using a nonmedicated insert; those participants who experienced insert-related discomfort typically elected to discontinue within the first few days of wear. The bimatoprost insert seems to be safe, with an AE and tolerability profile similar to that of bimatoprost 0.03% ophthalmic solution (e.g., mild to moderate conjunctival hyperemia and ocular pruritus).[6,8] All participants in whom an insert dislodged fully were aware of the dislodgement and returned promptly to the clinic for a new insert and therapy continuation.

The observation that the IOP-lowering profile of the bimatoprost insert is slightly less effective relative to the predicted IOP reduction of a once-daily administered 0.01% or 0.03% bimatoprost drop is not wholly unexpected. Prostaglandin analogs have a known U-shaped dosing frequency response curve—that is, there is less effective IOP lowering with increasing dosing frequency[6]—and this phenomenon is observed across all approved PGAs

Table 4. Study of a Bimatoprost Ocular Insert: Safety Summary

	All Patients (n = 130)	Bimatoprost Patients (n = 64)	Timolol Patients (n = 66)
Ocular TEAE			
Patients with any ocular TEAE	52 (40.0)	29 (45.3)	23 (34.8)
Ocular TEAE ≥5%			
Eye discharge	19 (14.6)	10 (15.6)	9 (13.6)
Conjunctival hyperemia	12 (9.2)	9 (14.1)	3 (4.5)
Punctate keratitis	12 (9.2)	8 (12.5)	4 (6.1)
Eye pruritus	9 (6.9)	7 (10.9)	2 (3.0)
Ocular discomfort	6 (4.6)	4 (6.3)	2 (3.0)
Nonocular TEAE			
Patients with any nonocular TEAE	33 (25.4)	17 (26.6)	16 (24.2)
Nonocular TEAEs ≥5%			
Upper respiratory tract infection	8 (6.2)	3 (4.7)	5 (7.6)
SAEs			
Ocular SAE*			
Vision blurred	1 (0.8)	0 (0)	1 (1.5)
Nonocular SAE			
Hypertension (vascular)†	1 (0.8)	1 (1.6)	0 (0)
Fall/cellulitis‡	1 (0.8)	1 (1.6)	0 (0)
Drug hypersensitivity§	1 (0.8)	0 (0)	1 (1.5)
Atrial fibrillation	1 (0.8)	0 (0)	1 (1.5)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Data are no. (%).
*Protocol-specified ocular SAE; fully resolved.
†Patient had new-onset uncontrolled systemic hypertension; fully resolved.
‡Patient was hospitalized for a fall, and cellulitis of the lower extremity developed; fully resolved.
§Patient experienced an allergic response to opioid analgesics after an orthopedic procedure; fully resolved.

available in the United States.[9–11] This atypical dose response of PGAs was reported first with latanoprost in 1998, for which receptor subsensitivity was proposed; however, the exact mechanism remains poorly understood.[12] The paradoxical IOP-lowering PGA effect relative to timolol also has been observed in emerging clinical data using drug-eluting punctal plugs delivering either latanoprost[13] or travoprost.[14] Attempts to overcome this atypical pharmacodynamic profile have led to alternative investigational approaches through direct intracameral injection of sustained-release PGAs (Lewis RA, et al. Poster P00093, American Academy of Ophthalmology annual meeting, 2015). The intracameral route potentially allows for lower drug loads and elution rates compared with topical approaches that require higher drug loading to drive passive diffusion of the active molecule across the cornea. However, it is likely that regardless of approach (e.g., intracameral, punctal plug, ocular inserts), all sustained-release platforms using PGAs will have similar long-term efficacy profiles because of the clinical observation of agonist desensitization.[12] To address this, we will be exploring the feasibility of ocular inserts containing fixed combinations of drugs as a means to improve further IOP lowering.

Table 5. Study of a Bimatoprost Ocular Insert: Patient Discontinuations Because of Adverse Events

	Treatment Group	Day of Withdrawal*
Ocular TEAE (n = 8)		
Patient A: punctate keratitis, lacrimation increased, eye pruritus, eye discharge	Bimatoprost	12
Patient B: punctate keratitis	Bimatoprost	18
Patient C: corneal defect†	Bimatoprost	24
Patient D: conjunctivitis	Bimatoprost	40
Patient E: photophobia	Bimatoprost	52
Patient F: eyelid ptosis	Bimatoprost	58
Patient G: ocular discomfort	Bimatoprost	121
Patient H: vision blurred	Bimatoprost	148
Nonocular TEAE (n = 2)		
Patient I: dyspnea, bradycardia, dizziness	Timolol	9
Patient J: fatigue	Bimatoprost	43

TEAE = treatment-emergent adverse event.
*Days after randomization.
†Patient had a corneal abrasion caused by the eye dropper bottle tip.

Although the bimatoprost insert was not noninferior to daily timolol eye drops in this study, the point estimate of the mean difference in IOP between the bimatoprost insert and timolol was less than the 1.5-mmHg noninferiority margin at all diurnal time points within the first 12 weeks. Because the CI is influenced by the sample size, it is anticipated that in a larger, adequately powered phase III study of similar design the noninferiority margin would be met in most time points for the traditional IOP assessments within the first 12 weeks. Regardless, the intent of the ocular insert is to provide consistent pharmacologic treatment for patients who otherwise would not be taking any medication because of poor adherence, and a 20% or more reduction

with consistent IOP control may be sufficient in many patients with uncomplicated OAG or OHT. Whether daily-administered artificial tears influenced the efficacy profile of the bimatoprost insert is not known. Given the short residence time of artificial tears on the ocular surface, we do not believe this was a confounding factor; however, long-term safety studies are being conducted without concomitant artificial tears (for up to 13 months) to help provide additional information.

It is unlikely that the results of our study were the consequence of insufficient drug loads delivered to the ocular surface. The total drug dose delivered by the bimatoprost insert is higher than the total dose delivered by once-daily drops of a 0.03% bimatoprost ophthalmic solution over a 6-month period; therefore, daily administration of 0.01% or 0.03% bimatoprost ophthalmic solution delivers approximately 3 to 9 μg/day, whereas the bimatoprost insert elutes a steadily declining dose of bimatoprost ranging from approximately 35 μg/day to 6 μg/day at 6 months based on in vitro assays. The day-to-day variance of drug concentration in the tear film in vivo has not yet been investigated. There is no evidence of bimatoprost accumulation in the systemic circulation when wearing the bimatoprost inserts in both eyes; plasma concentrations of bimatoprost are less than concentrations of detection after 7 days (lower limit of quantitation, 0.0250 ng/ml; data on file).

The bimatoprost insert seems to be safe and well tolerated. The most frequently reported AEs were within expectations for either bimatoprost or timolol drug exposure, and there were no unanticipated ocular AEs. The observed conjunctival hyperemia rates with the bimatoprost insert (14.1%) are lower than with topical bimatoprost ophthalmic solution (25%–45%).[9] There were no reported cases of localized hyperemia (i.e., ring-like hyperemic circles on the ocular surface in patients receiving the bimatoprost insert), local conjunctival changes (e.g., granulomatous inflammation), localized infection, or drug-related serious AEs. The most frequently reported ocular AE of eye discharge (i.e., mucus) was relatively balanced across both study arms and is consistent with earlier clinical studies using the ocular insert (Goldberg I. Poster P0390, American Academy of Ophthalmology annual meeting, 2014; Goldberg I. Poster P-S-094, World Glaucoma Congress meeting, 2015). Typically, the mucus was noted on waking as a small quantity of crusting in the canthal region; no special treatment was required. We speculate that the conjunctival surface in direct contact with the insert may stimulate goblet cells to produce additional mucin during normal lid motion. The proportion of patients discontinuing study participation through 6 months of treatment because of ocular AEs in the bimatoprost group (14.1%) was similar to published rates observed in pooled phase III registrational studies of 0.03% bimatoprost ophthalmic solution (14.5%) versus timolol.[8]

The overall bilateral primary retention rate of the ocular inserts of nearly 90% of patients at 6 months represents a significant advance in the evolution of sustained-release ocular inserts. The reason for the disproportionately higher rate of dislodgement in men (20.8%) compared with women (5.2%) observed in this study is unclear, and ongoing long-term studies will help to clarify whether true gender-related factors exist. Participants were aware of all insert dislodgements and returned promptly to the physician to have a new insert placed so that treatment continued. In 1974, the Food and Drug Administration approved an ocular insert (Ocusert; Alza, Inc., Palo Alto, CA) consisting of a reservoir containing a pilocarpine solution that eluted drug through a semipermeable membrane and provided treatment for up to 7 days.[15] The insert was inserted in the lower lid cul-de-sac, but the insert was not widely used in practice because of its high rates of dislodgement, patient discomfort, short elution period, and side effects associated with pilocarpine; the product was eventually removed from the United States market by the manufacturer.[16]

The simplicity, comfort, and high retention rate of the bimatoprost insert may have broader drug-delivery applications beyond monotherapy for OAG and OHT. The large surface area of the inserts allows loading of a combination of ocular hypotensive agents (e.g., bimatoprost plus timolol). Other applications of a so-called dropless delivery platform of the ocular insert include pharmacologic therapies for dry eye disease, ocular allergy, and postoperative inflammation, all of which are under development. Additional studies to characterize further the performance, durability, and safety profile of the bimatoprost insert include a formal dose-ranging study evaluating a 2.2-mg and 13-mg bimatoprost insert followed by a 9-month open-label safety study; other studies under consideration include nocturnal IOP evaluation, impression cytologic analysis to evaluate the conjunctival surface, and corneal specular endothelial microscopy.

Limitations of this study include the double-dummy design (masked investigational insert and a masked investigational eye drop) in which all study participants consented and agreed to be fully adherent to a daily regimen of either twice-daily artificial tears or timolol 0.5% ophthalmic solution, whereas the intent of the insert is to help patients who are nonadherent with a daily regimen of eye drops. However, a regimented dosing schedule requiring high patient compliance is required for all Food and Drug Administration registrational studies for which a comparison with eye drops is used as a control. A real-world long-term observational registry can be accomplished only after the product is approved and available to physicians and patients. With respect to the control eye drops, for the past 2 decades the regulatory benchmark for approval of new glaucoma agents in the United States has been comparison with twice-daily administered 0.5% timolol drops. At this time, there is no precedent (or requirement) for approval of a sustained-release product based on head-to-head comparison with a PGA drop. Future studies comparing the bimatoprost insert with topically administered bimatoprost drops are anticipated. The second limitation is that the insertion of a new medicated insert at 6 months was not evaluated, nor was a shorter 3-month cycle explored. Patients completing this study were eligible to participate in an open-label single-arm bimatoprost insert safety study for 13 months of additional treatment (2 cycles: first a 7-month cycle followed by a 6-month cycle), and the study is ongoing. A 6-month dosing profile was engineered based on physician feedback regarding practice patterns that would allow OHT patients to

be seen every 6 months and OAG patients to be monitored every 3 months. Finally, longer-term studies of a high-risk (low-adherence) population will be required to demonstrate the full usefulness of our ocular drug-delivery system in preserving visual fields, but such studies will require several years of follow-up and currently are not feasible at this stage of development.

In conclusion, a randomized clinical phase II trial using a novel bimatoprost ocular insert demonstrated that a clinically relevant reduction in IOP (4−6 mmHg) can be achieved and sustained for 6 months. The bimatoprost insert seems to be safe and well tolerated, with excellent primary retention rates. Larger confirmatory phase III studies are planned.

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[1] Department of Ophthalmology & Vision Science, University of California, Davis, Sacramento, California.

[2] Sall Research Medical Center, Artesia, California.

[3] Clayton Eye Center, Morrow, Georgia.

[4] Apex Eye, Cincinnati, Ohio.

[5] ForSight VISION5, Inc., Menlo Park, California.

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Y.A.: Cofounder and Equity owner − ForSight VISION5, Inc. (Menlo Park, CA).

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Author Contributions:

Conception and design: Brandt, Alster, Walker, Semba

Analysis and interpretation: Brandt, Walker, Semba

Data collection: Brandt, Sall, DuBiner, Benza,

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Overall responsibility: Brandt, Walker, Semba

Appendix 1. The Bimatoprost Ocular Insert Study Group

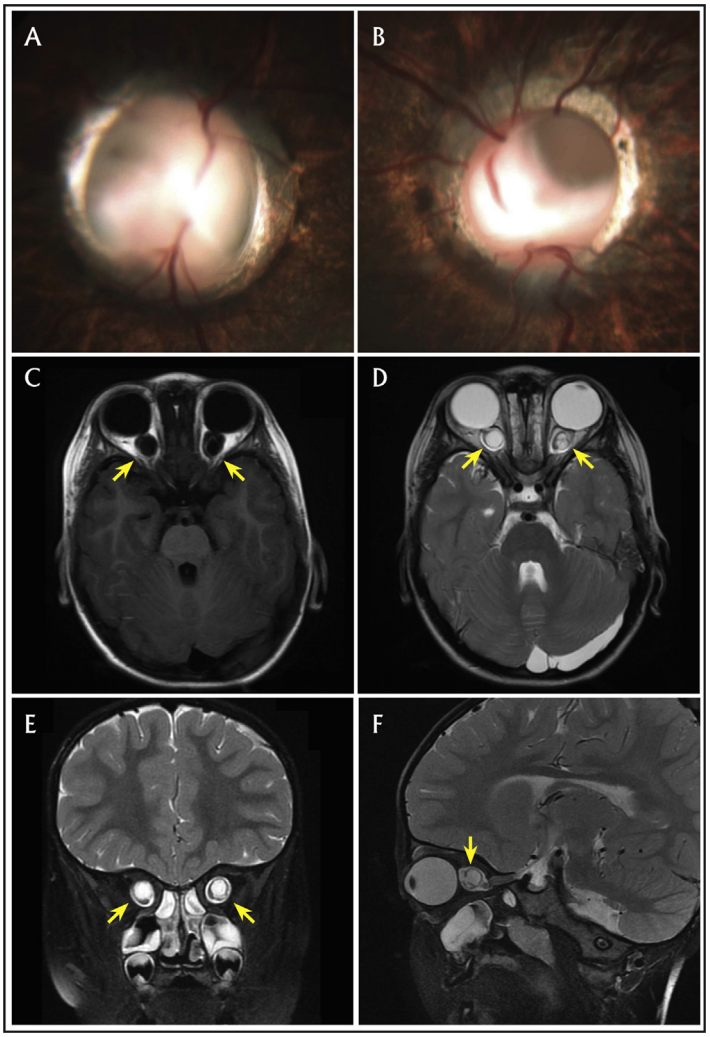
Principal Investigator: James D. Brandt, MD (University of California, Davis, Davis, CA).

Investigators: Robert Benza, MD (Apex Eye, Cincinnati, OH); Donald Budenz, MD (University of North Carolina, Chapel Hill, NC); Douglas Day, MD (Coastal Research Associates, Atlanta, GA); Harvey DuBiner, MD (Clayton Eye Center, Morrow, GA); Brian Flowers, MD (Ophthalmology Associates, PC, Fort Worth, TX); Steven Lee, MD (Ophthalmology Consultants, Saint Louis, MO); Quang Nguyen, MD (Scripps Clinic, La Jolla, CA); Kenneth Sall, MD (Sall Research Medical Center, Artesia, CA); David Wirta, MD (Aesthetic Eyecare Institute, Newport Beach, CA).

Abbreviations and Acronyms:
AE = adverse event; **CI** = confidence interval; **IOP** = intraocular pressure; **OAG** = open-angle glaucoma; **OHT** = ocular hypertension; **PGA** = prostaglandin analog.

Correspondence:
James D. Brandt, MD, Department of Ophthalmology & Vision Science, University of California, Davis, 4860 Y Street, Suite 2400, Sacramento, CA 95817-2307. E-mail: jdbrandt@ucdavis.edu.

Pictures & Perspectives



Bilateral Isolated Optic Nerve Colobomatous Cysts

A 3-year-old boy, with normal developmental milestones, presented with diminution of vision in both eyes. The visual acuity was 20/100 and 20/200 in right and left eye respectively. The child had bilateral high myopia (−12.25 SE) with V-pattern exotropia. Fundus examination showed optic disc excavation with peripapillary atrophy in both eyes (**A**, **B**). Magnetic resonance imaging showed well circumscribed, nonenhancing cystic lesions in the proximal portion of both the optic nerves, as seen on T1 and T2-weighted axial (**C**, **D**), coronal and sagittal (**E**, **F**) scans, with no associated anomalies (**C-F**, *arrows* indicate the positions of the anomaly). A diagnosis of bilateral isolated colobomatous optic nerve cysts was made.

Anjali Chandrasekharan, MS
Uppal Gandhi, DNB
Preeti Patil Chhablani, DNB

Department of Pediatric Ophthalmology and Neuro-ophthalmology, Jasti V Ramanamma Children's Eye Care Center, L. V. Prasad Eye Institute, Hyderabad, India