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# Ab-Externo MicroShunt versus Trabeculectomy in Primary Open-Angle Glaucoma

## *Two-Year Results from a Randomized, Multicenter Study*

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***Purpose:*** To compare the effectiveness and safety of the MicroShunt (Santen Inc) versus trabeculectomy in patients with primary open-angle glaucoma (POAG).

***Design:*** Prospective, randomized, multicenter trial conducted in the United States and Europe.

***Participants:*** Adult patients (aged 40−85 years) with mild to severe POAG inadequately controlled on maximum tolerated medical therapy and intraocular pressure (IOP) $\geq$ 15 mmHg and $\leq$ 40 mmHg.

***Methods:*** Patients were randomized 3:1 to stand-alone MicroShunt implantation (n = 395) or trabeculectomy (n = 132), both augmented with mitomycin C (MMC) 0.2 mg/ml for 2 minutes.

***Main Outcome Measures:*** The primary effectiveness end point was surgical success, defined as $\geq$ 20% reduction in mean diurnal IOP from baseline with no increase in glaucoma medications. Secondary end points included changes in mean IOP and medication use from baseline and the need for postoperative interventions.

***Results:*** At 2 years, the rate of surgical success was lower in the MicroShunt group than in the trabeculectomy group (50.6% vs. 64.4%, $P = 0.005$). Mean diurnal IOP was reduced from 21.1 $\pm$ 4.9 mmHg at baseline to 13.9 $\pm$ 3.9 mmHg at 24 months in the MicroShunt group and from 21.1 $\pm$ 5.0 mmHg at baseline to 10.7 $\pm$ 3.7 mmHg at 24 months in the trabeculectomy group ($P < 0.001$ compared with baseline in both groups). Mean medication use decreased from 3.1 to 0.9 in the MicroShunt group and from 2.9 to 0.4 in the trabeculectomy group ($P < 0.001$ compared with baseline in both groups). Adverse events at 2 years were generally similar in the 2 groups, except that hypotony was more common in eyes undergoing trabeculectomy (51.1% vs. 30.9%, $P < 0.001$). Repositioning or explantation of the implant occurred in 6.8% of MicroShunt patients. The majority of these patients had device removal at the time of subsequent glaucoma surgery. Vision-threatening complications were uncommon in both groups.

***Conclusion:*** At 2 years, both the MicroShunt and trabeculectomy provided significant reductions in IOP and medication use, with trabeculectomy continuing to have greater surgical success.

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Since its description in 1968, the Cairns-type trabeculectomy has been the clinical standard for surgical reduction of intraocular pressure (IOP) in eyes with glaucoma.[1] Based on its efficacy, trabeculectomy is the preferred procedure in eyes with advanced glaucoma or very low interventional IOP.[2-5] However, its safety profile—with potentially sight-threatening complications, including bleb leaks, choroidal effusions, hypotony maculopathy, and blebitis/endophthalmitis—may limit its value in eyes with more modest therapeutic goals.[4,6] Trabeculectomy also requires a high level of surgeon skill and experience to appropriately manage a delicate series of operative and postoperative manipulations and adjustments. The advent of a family of procedures collectively referred to as "micro-invasive glaucoma surgery" (MIGS) has expanded the indications for surgical intervention in eyes with glaucoma. The MIGS family includes procedures that shunt aqueous humor across the trabecular meshwork to Schlemm's canal or the suprachoroidal space. Some of these procedures require the implantation of a permanent device, whereas



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others are limited to the incision or excision of various ocular tissues.[7-11] In general, MIGS procedures have a more favorable safety profile compared with trabeculectomy, but with lower efficacy. Thus, canal-based MIGS procedures may be viable options for patients who would benefit from surgical IOP reduction but whose more modest therapeutic goals may not justify the risks of trabeculectomy.[7-11]

The MicroShunt (Santen Inc) is an implantable device, measuring 8.5 mm in length and 0.35 mm in width, with a lumen diameter of 70 μm and a pair of 0.375-mm fins for intrascleral fixation. The tube length and lumen diameter were selected to accommodate sloughed endothelial cells (40−50 μm) while providing sufficient resistance to limit pressure reduction and minimize the risk of hypotony.[12] The MicroShunt is implanted subconjunctivally via an ab-externo approach and provides filtration from the anterior chamber to the subconjunctival space without the need for scleral flap formation, sclerostomy, or iridectomy.

This 2-year trial compared the effectiveness and safety of the MicroShunt with trabeculectomy in patients with uncontrolled primary open-angle glaucoma (POAG), using maximal tolerated medical therapy, in the United States and Europe. Interim 1-year results of this trial have been reported.[13] The present study describes the 2-year results of this trial.

## Methods

This was a prospective, single-masked, randomized, multicenter, noninferiority trial conducted at 24 sites in the United States and 5 sites in Europe. The study was conducted in accordance with the tenets of the Declaration of Helsinki, as well as all applicable local regulations.[14] The study protocol was approved by all relevant ethics boards, and all subjects provided written informed consent to participate. The trial was registered at ClinicalTrials.gov (NCT01881425).

The study design, eligibility criteria, treatments, and surgical details have been reported previously.[13] Briefly, this trial enrolled patients aged 40 to 85 years with mild to severe POAG (visual field mean deviation −3.0 decibels or worse) with IOP ≥ 15 mmHg and ≤ 40 mmHg, inadequately controlled on maximal tolerated medical therapy. Key exclusion criteria included secondary glaucoma, vision level of no light perception, prior ocular surgery involving the conjunctiva, and the requirement for general anesthesia for the study procedure. Only 1 eye was enrolled per patient. Eligible subjects were randomly assigned 3:1 to undergo MicroShunt implantation or trabeculectomy; unequal allocation was deemed applicable to this confirmatory trial, because it allowed recruitment of a sufficient number of eyes in the treatment arm to detect rare adverse events. Both procedures were augmented with mitomycin C (MMC) 0.2 mg/ml applied for 2 minutes via saturated sponges on bare sclera. For the MicroShunt procedure, a 1-mm double-step knife was used to fashion a narrow scleral track with a wider scleral pocket at its distal end. The device was threaded through the track and the fins tucked into the pocket. Flow of aqueous humor from the anterior chamber was confirmed, and Tenon's capsule and conjunctiva were sutured in watertight closure. Fornix-based trabeculectomy was performed in standard fashion with watertight closure of Tenon's capsule and conjunctiva.

Patients were evaluated at 1 day, 1 and 4 weeks, and 3, 6, 12, 18, and 24 months after surgery. Parameters measured included best-corrected visual acuity (BCVA), IOP by Goldmann tonometry (mean of 2 readings within 2 mmHg or 3 readings if the difference was > 2 mmHg), medication use, and complications. The trial protocol specified that the window for year 1 (12 month) visits was on study days 330 to 420 and the window for year 2 (24 month) visits was on study days 690 to 780. At baseline and months 12 and 24, diurnal IOP was assessed at 9 AM, 12 PM, and 4 PM. Before randomization, an interventional IOP (above which an IOP-lowering intervention would be applied) was set for each eye as either 21 mmHg or preoperative IOP if it was < 21 mmHg or as an IOP selected by the investigator based on individual risk factors. Interventions included laser suture lysis, needling, and laser disruption of outflow obstruction; medications were generally initiated only after unsuccessful attempt at these procedural interventions, unless such attempts were believed unlikely to achieve interventional IOP.

Efficacy was analyzed in the intent-to-treat population (all randomized subjects) with the baseline-observation-carried-forward approach to imputation of missing data for the primary effectiveness end point, defined as a ≥ 20% reduction from baseline in mean diurnal IOP at the month 24 visit without increasing the number of preoperative IOP-lowering medications, consistent with guidelines set by the World Glaucoma Association.[15] End point failures included loss of light perception at 2 consecutive visits, IOP < 6 mmHg at 2 consecutive visits after month 3, incisional or laser reoperation (except for suture lysis, needling, or laser removal of outflow obstruction) for complications or inadequate IOP control, and the need for oral carbonic anhydrase inhibitors for IOP control. A Farrington-Manning test was used to construct 95% confidence intervals (CIs) around the difference in success rates between treatment groups. Farrington-Manning tests were performed to test for non-inferiority, and Wald-type tests were performed to test the equality of rates. Time to first failure was assessed using Kaplan−Meier survival analysis with treatments compared using the log-rank test. Prespecified subgroup analyses in patients with baseline mean diurnal IOP < 18, 18 to < 21, and ≥ 21 mmHg were conducted.

Secondary effectiveness end points included mean diurnal IOP change at month 24 and the need for postoperative interventions by month 24. Mean diurnal IOP change was evaluated using a mixed-effects model for repeated measures with Hochberg step-up adjusted *P* values based on a 2.5 mmHg noninferiority margin (as in the Tube Versus Trabeculectomy study).[16] The mean number of glaucoma medications required at each visit was an exploratory efficacy end point.

The proportions of eyes in each group requiring interventions through month 24 and the incidence of specific qualifying reoperations (bleb revision, repositioning or removal of implant, resuturing scleral flap, trabeculectomy, glaucoma drainage device, and iridotomy/iridectomy) were compared using Wald-type 2-sample proportions tests for the equality of rates.

Safety was analyzed in the safety population, consisting of all subjects who underwent surgery. Prespecified safety end points included the occurrence of adverse events, development of cataract as assessed using the Lens Opacities Classification System, Version III in phakic eyes, time for postoperative BCVA to return to baseline, and change in endothelial cell density. Endothelial cell density was measured using a Konan specular microscope, with all measurements performed at the endothelial cell density Corneal Image Analysis Reading Center at the Department of Ophthalmology and Visual Sciences at Case Western Reserve University School of Medicine.[13]

Sample size calculations were based on a Z-test with normal distribution approximation and assuming an annual dropout rate of 6%.[13] A sample size of 514 patients was calculated for the primary effectiveness end point assuming a month 12 IOP success rate of 0.74, a 1-sided significance level of 0.025, 90% statistical power, and a noninferiority margin of 0.15 (15%).

## Results

### Subject Disposition and Demographics

The intent-to-treat population included 527 subjects who were randomized to treatment with the MicroShunt (n = 395) or trabeculectomy (n = 132) (Fig 1). Of these, all but 1 patient randomized to trabeculectomy (who required general anesthesia and was thus ineligible) underwent the assigned study procedure and comprised the safety population. By the end of the second year of the study, 9 subjects (7 in the MicroShunt and 2 in the trabeculectomy group) were lost to follow-up, and 25 subjects (18 in the MicroShunt group and 7 in the trabeculectomy group) discontinued the study. Of the 18 patients in the MicroShunt group who discontinued, 5 died, 3 discontinued due to adverse events, 8 withdrew consent, and 2 were withdrawn by the investigator. Of the 7 patients in the trabeculectomy group who discontinued, 1 died, 4 withdrew consent, 1 was withdrawn by the investigator, and 1 had been enrolled after closure of the study enrollment window. Small proportions of patients visited at times outside the prespecified follow-up times. Specifically, of the 527 randomized patients, only 11 (2.1%) visited outside the 12-month window of 330 to 420 days and only 8 (1.5%) visited outside the 24-month window of 690 to 780 days. The demographic and ocular characteristics of the study population are shown in Table 1. Baseline characteristics were similar in the 2 groups except for ethnicity, with a higher proportion of Black subjects in the MicroShunt group than in the trabeculectomy group (18.0% vs. 8.3%, $P = 0.04$).

### Primary Effectiveness End Point

Surgical success (≥ 20% reduction in IOP from baseline with no increase in the number of glaucoma medications) was observed in 50.6% of subjects in the MicroShunt group and 64.4% in the trabeculectomy group ($P = 0.005$) (Fig 2A). Subgroup analysis showed that at year 2, the between-group difference in surgical success in eyes with baseline IOP < 18 mmHg was −12.8% (95% CI, −29.5 to 4.0; $P = 0.141$; Fig 2B); in eyes with IOP ≥ 18 mmHg but < 21 mmHg, this difference was −22.2% (95% CI, −41.7 to −2.8, $P = 0.012$; Fig 2C); and in eyes with IOP ≥ 21 mmHg, this difference was −11.5% (95% CI, −26.4 to 3.3; $P = 0.114$; Fig 2D). The time to first failure in each group is shown in Figure 3. Median survival times could not be determined, because less than 50% of the eyes in each group had failed by study end. The nature of failures is shown in Table 2. Failure to achieve an IOP reduction of ≥ 20% from baseline was the most common reason for failure in the MicroShunt group, whereas persistent hypotony was the leading cause of failure in the trabeculectomy group.

### Secondary Effectiveness End Points

Mean IOP by treatment group at each study time point is shown in Figure 4. Mean IOP was higher in eyes in the trabeculectomy compared with the MicroShunt group during the first postoperative week, indicative of tight closure of the scleral flap and subsequent suture lysis after day 7. From month 3 onward, mean IOP was lower in the trabeculectomy group, by approximately 3 mmHg, at each time point through the end of the study. Mean IOP from month 3 to year 2 was approximately 14 mmHg in eyes in the MicroShunt group and approximately 11 mmHg in eyes in the trabeculectomy group.

Glaucoma medication use at baseline and months 12, 18, and 24 is shown in Figure 5A. Mean medication use was reduced from 3.1 ± 1.0 at baseline to 0.9 ± 1.3 at month 24 in MicroShunt-treated eyes and from 2.9 ± 0.9 to 0.4 ± 0.9 in trabeculectomy-treated eyes ($P < 0.001$ compared with baseline in both groups). The proportions of eyes that were medication-free at 12, 18, and 24 months are shown in Figure 5B. At month 24, 61.1% of eyes in the MicroShunt group and 79.8% of eyes in the trabeculectomy group were medication-free.

To assess regional differences, outcomes were compared in the United States and the European Union. The baseline demographic and clinical characteristics were well matched across groups by location and intervention (Table S3, available at www.aaojournal.org). Surgical success rates were higher in the European Union than in the United States (Fig S6, available at www.aaojournal.org). Patients in the United States who underwent MicroShunt implantation and trabeculectomy had mean diurnal IOPs of 21.1 ± 5.1 mmHg and 21.2 ± 5.2 mmHg, respectively, at baseline, decreasing to 14.1 ± 4.1 mmHg and 10.6 ± 3.7 mmHg, respectively, at 2 years ($P < 0.001$ compared with baseline in both groups). The differences in mean changes from baseline were −6.4 ± 5.8 mmHg in the MicroShunt group and −10.1 ± 5.5 mmHg in the trabeculectomy group, with the between-group difference being statistically significant ($P < 0.001$).

In comparison, patients in the European Union who underwent MicroShunt implantation and trabeculectomy had mean diurnal IOPs of 20.6 ± 3.4 mmHg and 20.3 ± 3.7 mmHg, respectively, at baseline, decreasing to 13.3 ± 2.8 mmHg and 11.5 ± 3.7 mmHg, respectively, at 2 years ($P < 0.001$ compared with baseline in both groups). The differences in mean changes from baseline were −7.1 ± 3.6 mmHg in the MicroShunt group and −8.3 ± 5.4 mmHg in the trabeculectomy group, with the between-group difference not being statistically significant ($P = 0.296$). Within the United States, the percentages of patients who were medication-free were 60.8% in the MicroShunt group and 81.5% in the trabeculectomy group. In the European Union, the corresponding figures were 63.2% and 68.8%, respectively.

Patients with low baseline IOP (< 18 mmHg) were compared in the MicroShunt (n = 119) and trabeculectomy (n = 45) groups. The demographic and clinical characteristics of these 2 groups were similar (Table 4). Mean diurnal IOP ± standard deviation in the MicroShunt and trabeculectomy groups were 16.4 ± 0.9 mmHg and 16.6 ± 0.9 mmHg, respectively, at baseline, decreasing to 12.9 ± 3.2 mmHg and 10.6 ± 4.3 mmHg, respectively, at 2 years ($P < 0.001$ compared with baseline in both groups), with 66.1% and 69.8%, respectively, being medication-free at 2 years. The composite primary end point of surgical success was achieved by 36.1% of patients in the MicroShunt group and 48.9% in the trabeculectomy group (noninferiority $P = 0.398$). Rates of postoperative interventions and postoperative adverse events did not differ significantly in these 2 groups.

### Safety

Table 5 shows the frequency and nature of adverse events, each of which occurred in > 5% of subjects in either group through 2 years. The most common adverse event in both the MicroShunt and trabeculectomy groups was increased IOP requiring treatment (56.2% vs. 55.7%; $P = 0.924$). Hypotony, defined as IOP < 6 mmHg at any time point, was significantly more

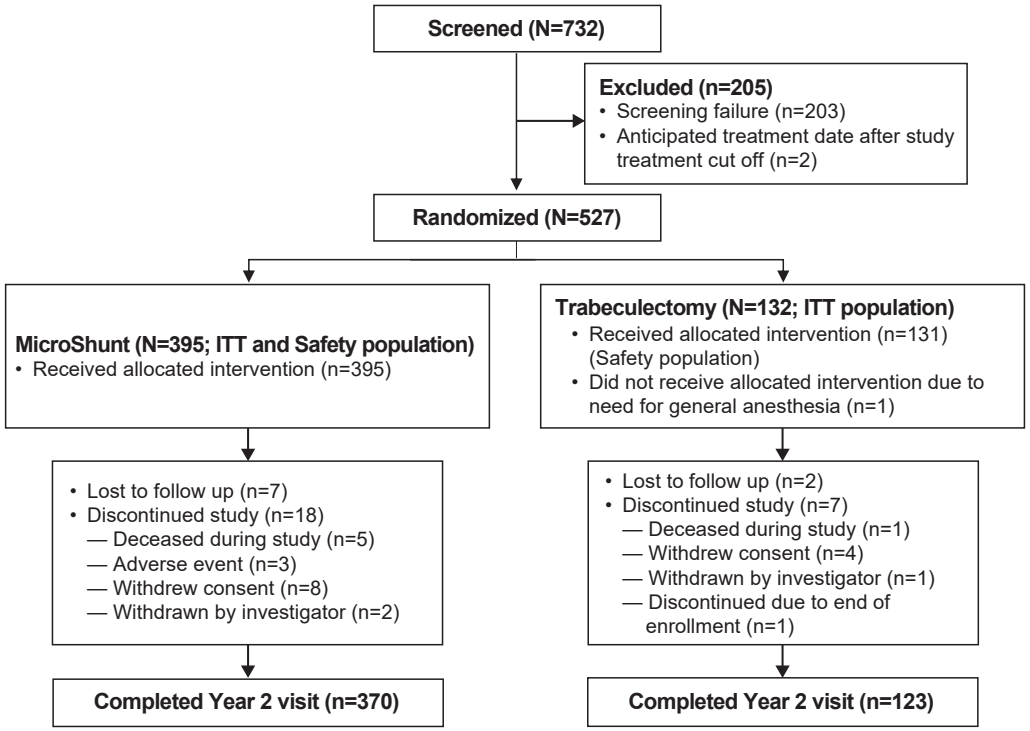


**Figure 1.** Consolidated Standards of Reporting Trials (CONSORT) diagram showing the disposition of study subjects. ITT = intent-to-treat.

frequent in the trabeculectomy group than in the MicroShunt group (51.1% vs. 30.9%; $P < 0.001$). Surgical failure due to hypotony (IOP < 6 mmHg at 2 consecutive visits) also occurred more often in the trabeculectomy group (15.2% vs. 3.8% $P < 0.001$). Hypotony maculopathy was detected in 0.5% of MicroShunt-treated and 1.5% of trabeculectomy-treated eyes. Endothelial cell density decreased significantly in both groups over 2 years ($P < 0.001$), with mean reductions of 7.7% in the

Table 1. Baseline Demographic and Ocular Characteristics of the Patients Included in the Study

| | MicroShunt (Santen Inc.) Group (n = 395) | Trabeculectomy Group (n = 132) | P Value |
|---|---|---|---|
| Mean ± SD age, yrs | 66.4 ± 9.3 | 67.8 ± 9.3 | 0.14 |
| Male, n (%) | 181 (45.8) | 73 (55.3) | 0.06 |
| Race, n (%) | | | 0.04 |
| White | 311 (78.7) | 113 (85.6) | |
| Black/African American | 71 (18.0) | 11 (8.3) | |
| Asian | 10 (2.5) | 6 (4.5) | |
| Other | 3 (0.8) | 2 (1.5) | |
| Lens status, n (%) | | | 0.26 |
| Phakic | 227 (57.5) | 76 (57.6) | |
| Pseudophakic | 168 (42.5) | 56 (42.4) | |
| Baseline IOP, n (%) | | | |
| < 18 mmHg | 119 (30.1) | 45 (34.1) | 0.40 |
| ≥ 18 and < 21 mmHg | 116 (29.4) | 31 (23.5) | |
| ≥ 21 mmHg | 160 (40.5) | 56 (42.4) | |
| Mean ± SD IOP, mmHg | 21.1 ± 4.9 | 21.1 ± 5.0 | 0.99 |
| Mean ± SD number of glaucoma medications | 3.1 ± 1.0 | 2.9 ± 0.9 | 0.31 |
| Mean ± SD Humphrey VF MD, dB | −12.3 ± 7.0 | −12.4 ± 7.1 | 0.88 |
| Glaucoma severity classification, n (%) | | | 0.37 |
| Early (−3.00 dB to −6.00 dB) | 84 (21.3) | 30 (22.7) | |
| Moderate (−6.01 dB to −12.00 dB) | 134 (33.9) | 46 (34.8) | |
| Advanced (−12.01 dB to −20.00 dB) | 119 (30.1) | 33 (25.0) | |
| Severe (≤−20.01 dB) | 58 (14.7) | 22 (16.7) | |

dB = decibels; IOP = intraocular pressure; MD = mean deviation; SD = standard deviation; VF = visual field.

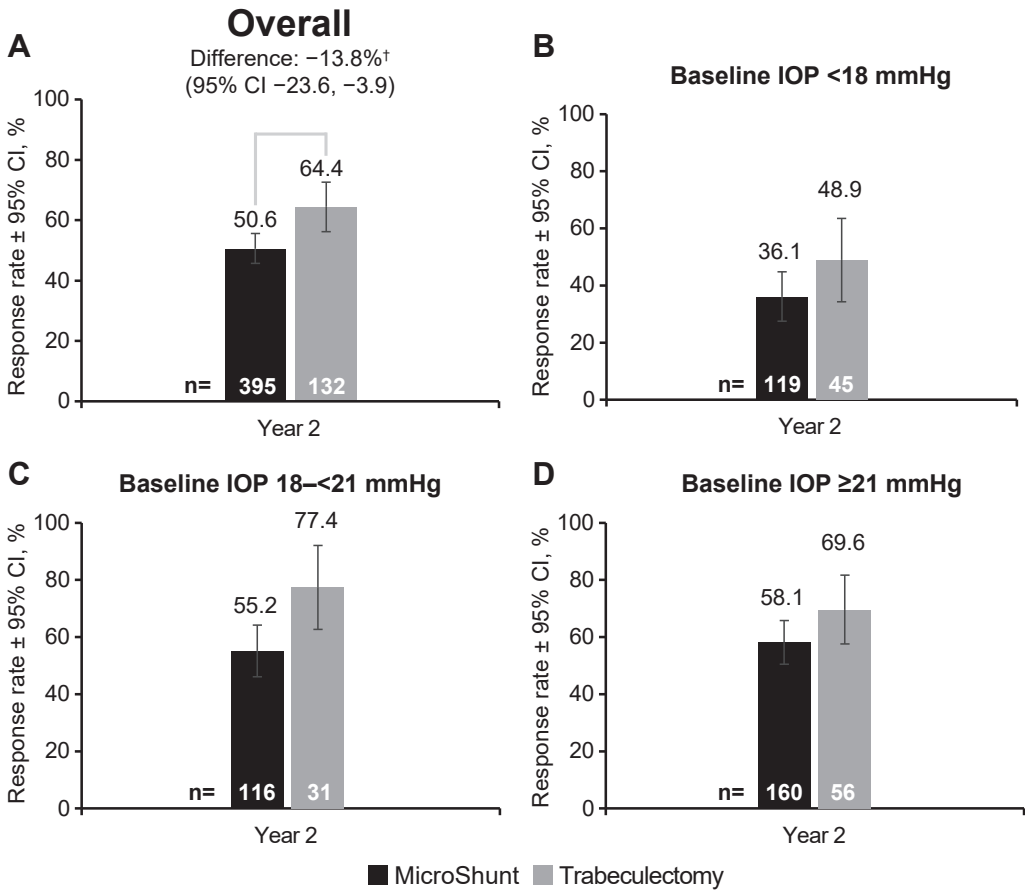


**Figure 2.** Comparisons of surgical success rates at 24 months in the **(A)** overall MicroShunt (Santen Inc.) and trabeculectomy groups, and in subgroups of patients with baseline intraocular pressure (IOP) **(B)** < 18 mmHg, **(C)** 18 to < 21 mmHg, and **(D)** ≥ 21 mmHg. Success was defined as a ≥ 20% reduction in IOP from baseline with no increase in the number of glaucoma medications and no criteria for failure met. Results were determined on the basis of multiple imputation, with *P* values calculated by 2-sample proportion Wald-type tests. CI = confidence interval.

MicroShunt group and 9.6% in the trabeculectomy group ($P = 0.242$) (Fig 7). No cases of endophthalmitis occurred in either group.

Mean BCVA was modestly reduced (by ~5 ETDRS letters) at month 1 in both groups and returned to preoperative values (within 1−3 letters) by month 3 in both groups. Rates of lens opacity

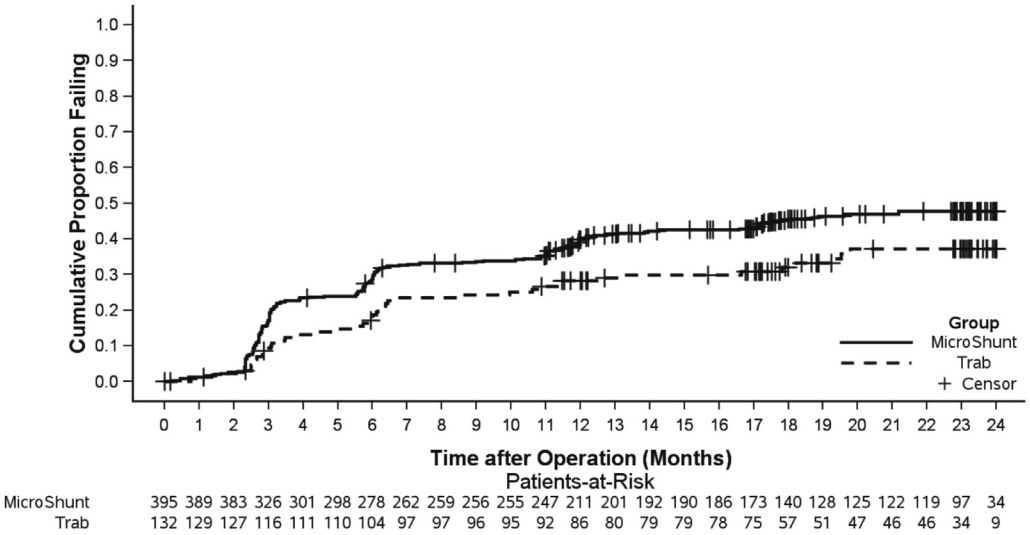


**Figure 3.** Kaplan−Meier analysis of time to first failure in the MicroShunt and trabeculectomy groups through 2 years.

Table 2. Reasons for Surgical Failure at 2 Years in > 5% of Patients in the MicroShunt and Trabeculectomy Groups in the Intent-to-Treat Population

| | MicroShunt Group (n = 395), n (%) | Trabeculectomy Group (n = 132), n (%) | P Value |
|---|---|---|---|
| IOP reduction < 20% from baseline | 116 (29.4) | 12 (9.1) | <0.001 |
| IOP < 6 mmHg at 2 consecutive visits | 15 (3.8) | 20 (15.2) | <0.001 |
| Qualifying reoperation* in the study eye | 74 (18.7) | 14 (10.6) | 0.014 |
| Other glaucoma surgery to reduce IOP | 41 (10.4) | 5 (3.8) | 0.004 |

IOP = intraocular pressure.
All surgical failures are shown. A total of 45 subjects are listed in more than 1 category due to concurrent failures.
*Qualifying reoperations include trabeculectomy, placement of a drainage device, bleb revision (other than needling), explantation or repositioning of the MicroShunt, iridotomy/iridectomy, or resuturing of the scleral flap.

(Lens Opacities Classification System, Version III) in phakic eyes at 2 years, defined as postoperative lens opacity or worsening of preexisting lens opacity, were similar in the MicroShunt (41.1% [78/190]) and trabeculectomy (47.6% [30/63]) groups ($P = 0.361$). Cataract surgery through month 24 was performed in 7.6% of eyes in the MicroShunt group and 13.0% of eyes in the trabeculectomy group ($P = 0.095$).

Through 2 years of follow-up, a higher percentage of MicroShunt-treated patients than trabeculectomy-treated patients required bleb needling with an antifibrotic agent (most commonly MMC) (24.8% vs. 9.1%; $P < 0.001$). Of these eyes that underwent needling, 21.4% and 25% from the MicroShunt and trabeculectomy groups, respectively, were needled more than once.

Qualifying reoperations for complications or inadequate IOP control (Table 6) were more common in the MicroShunt group than in the trabeculectomy group (18.7% vs. 10.6%; $P = 0.014$). Bleb revision with opening of the conjunctiva was the most common procedure in both groups (10.1% vs. 7.6%). Nineteen patients (4.8%) required MicroShunt explantation, including 4 for device-related reasons/complications. Of these 4 patients, 2 experienced anterior migration of the implant, requiring device removal due to endothelial concerns; 1 underwent explantation due to persistent hypotony, and 1 underwent explantation due to device-associated erosion of the conjunctiva. The other 15 patients underwent MicroShunt removal at the time of subsequent glaucoma surgery. Eight additional patients (2.0%) required MicroShunt repositioning at the time of open revision.

## Discussion

The results of this 2-year prospective, randomized trial comparing the effectiveness and safety of the MicroShunt versus trabeculectomy in eyes with medically uncontrolled POAG showed that IOP reduction and surgical success rates were statistically greater in the trabeculectomy group, similar to the results observed after 1 year.[13] The rates of surgical success, defined as a ≥ 20% reduction in baseline IOP without an increase in the number of glaucoma medications, at 2 years were 64.4% in the trabeculectomy group (72.7% at year 1) and 50.6% (53.9% at year 1) in the MicroShunt group. These rates are generally consistent with studies reporting the outcomes of these 2 procedures individually.[17-24] Several retrospective, multicenter studies

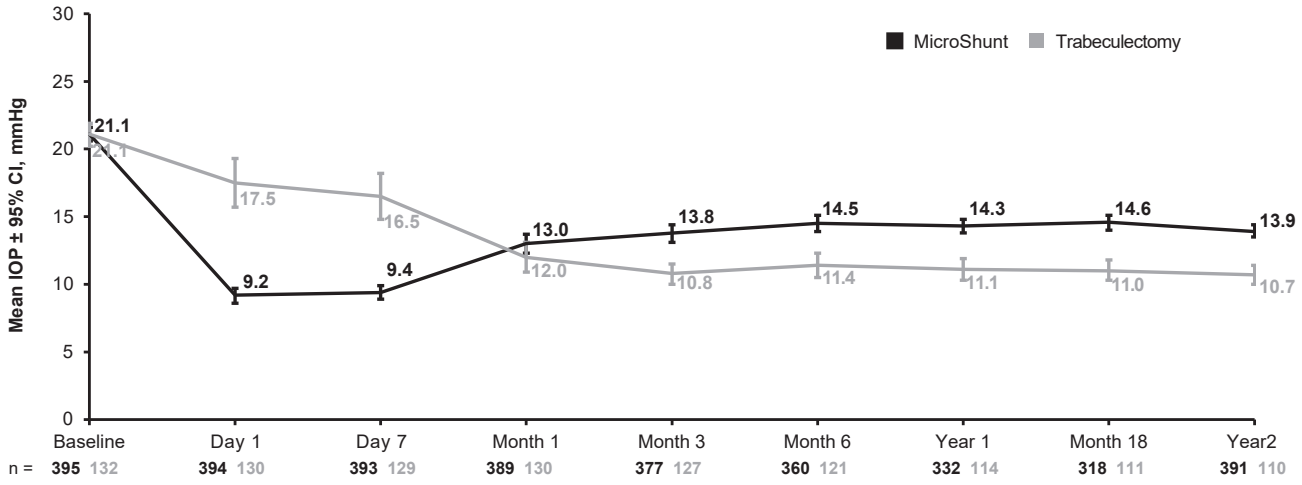


**Figure 4.** Mean intraocular pressure (IOP) in the MicroShunt and trabeculectomy groups at each study time point. Mean diurnal IOP was measured at baseline and Year 1 by taking standard IOP measurements at 9:00 AM ± 1.5 hours, 12:00 PM ± 1 hour, and 4:00 PM ± 2 hours. The 3 standard IOP measurements were used to determine the mean diurnal IOP; standard IOP was defined as the mean of 2 readings within 2 mmHg of each other or the median of 3 readings if > 2 mmHg apart; based on multiple imputation. Data presented for the ITT population. CI = confidence interval; ITT = intention-to-treat.

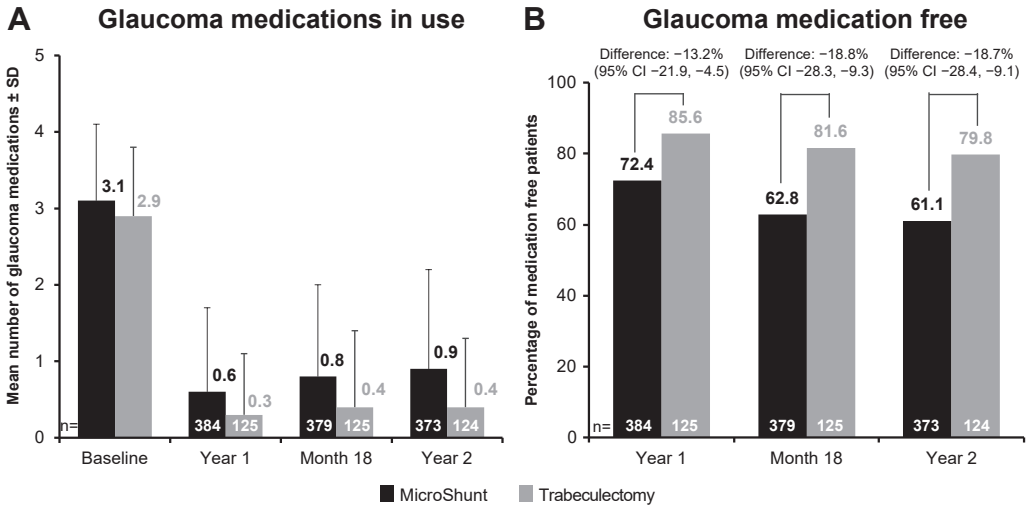


**Figure 5.** Medication use **(A)** and the proportions of medication-free eyes **(B)** at key time points in the MicroShunt and trabeculectomy groups. Data presented for the ITT population. CI = confidence interval; ITT = intention-to-treat; SD = standard deviation.

have reported that the 1-year overall success rates of the MicroShunt ranged from 59% to 74%, depending on the definition of success.[17-19] A prospective multicenter study reported that the 1-year overall success rate of the MicroShunt was 78%,[20] whereas retrospective single-center studies have reported overall success rates (with or without medication) of 79% at both 1 year and 2 years.[21] The success rates of trabeculectomy at 1 and 3 years were 87% and 79%, respectively, in the Tube Versus Trabeculectomy trial,[22,23] and 92% and 67%, respectively, in the Primary Tube Versus Trabeculectomy trial.[4,24] A post hoc analysis of the data from the present study stratified patients into tertiles based on baseline IOP. The greatest difference in surgical success between the MicroShunt and trabeculectomy groups was found in patients with a baseline pressure between 18 and 21 mmHg (Fig 2). Patients with a low baseline IOP (< 18 mmHg) were least likely to achieve surgical success in either group, with only 36.1% of patients in the MicroShunt group and 48.9% of patients in the trabeculectomy group meeting the primary end point. Inability to safely titrate the IOP to a low number with either procedure may have contributed to the relatively high rate of failure with both procedures in this subset of patients.

A variety of factors account for differences in surgical success when comparing studies, including but not limited to the definition of success, patient demographics and characteristics, surgeon experience and skill, and fixed parameters of the procedure itself. When performing microshunting procedures, pharmacologic inhibition of postoperative fibrosis is critical to achieving and maintaining optimal IOP lowering,[8] because the device dimensions limit flow and there are no other ways to

Table 5. Cumulative Postoperative Adverse Events and Other Safety Outcomes Occurring at Year 2 in > 5% of the Safety Population of the MicroShunt or Trabeculectomy Group

| Outcome | MicroShunt Group (n = 395), n (%) | Trabeculectomy Group (n = 131), n (%) | *P* Value |
|---|---|---|---|
| Increased IOP requiring treatment | 222 (56.2) | 73 (55.7) | 0.924 |
| Hypotony (IOP <6 mmHg at any time) | 122 (30.9) | 67 (51.1) | <0.0001 |
| Worsening of VF MD ≥ 2.5 dB | 73 (18.5) | 27 (20.6) | 0.580 |
| Loss of ≥ 2 lines of BCVA | 56 (14.2) | 23 (17.6) | 0.369 |
| Bleb leak | 36 (9.1) | 19 (14.5) | 0.113 |
| Corneal edema | 35 (8.9) | 8 (6.1) | 0.277 |
| Shallow anterior chamber | 27 (6.8) | 11 (8.4) | 0.568 |
| Diplopia | 26 (6.6) | 7 (5.3) | 0.595 |
| Choroidal effusion/detachment | 19 (4.8) | 10 (7.6) | 0.270 |
| Cataract progression | 56 (14.2) | 28 (21.4) | 0.071 |
| Ptosis | 33 (8.4) | 7 (5.3) | 0.211 |
| Pain | 26 (6.6) | 13 (9.9) | 0.248 |
| Encapsulated bleb | 23 (5.8) | 3 (2.3) | 0.045 |

BCVA = best-corrected visual acuity; dB = decibels; IOP = intraocular pressure; MD = mean deviation; VF = visual field.

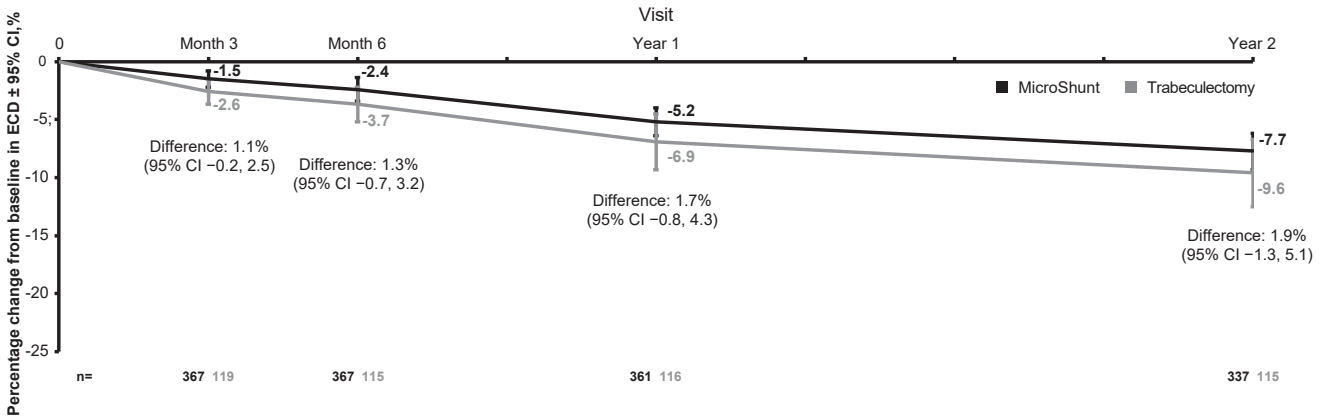


**Figure 7.** Percentage change in endothelial cell density. Data presented for the safety population. CI = confidence interval; ECD = endothelial cell density; SD = standard deviation.

manipulate bleb formation. Antifibrosis therapy with MMC or 5-fluorouracil is often used both intraoperatively and postoperatively to minimize scarring. The specific antimetabolite used, as well as its dose and method of delivery, is standardized within studies but differs between studies.[17-22] In the current pivotal trial, 0.2 mg/ml of MMC was applied to the scleral bed for 2 minutes, according to a protocol finalized in 2017. Subsequently, the results of Schlenker et al[25] have suggested that for MicroShunt implantation, an MMC concentration of 0.2 mg/ml is associated with a higher risk of surgical failure compared with a concentration of 0.4 to 0.5 mg/ml (hazard ratio, 2.51; 95% CI, 1.01−6.23). Likewise, a 2-year, nonrandomized, multicenter study of the MicroShunt device showed that 90.3% of patients treated with MMC 0.4 mg/ml were medication-free, compared with 51.9% of patients treated with MMC 0.2 mg/ml.[20] It is possible that outcomes in the MicroShunt arm of the current study would have been improved had a higher dose of MMC been used, especially in patients at higher risk of failure due to scarring. It is interesting that the rate of surgical success with the MicroShunt was substantially different between the United States (47.5%) and Europe (69%), whereas the surgical technique and MMC concentration and delivery were the same. The significantly higher percentage of Black patients in the US cohort may have contributed to this difference, because Black race is known to be a risk factor for worse outcomes after glaucoma surgery.[26,27]

The most common reason for surgical failure through 2 years of follow-up in trabeculectomy-treated eyes was persistent hypotony (15.2% vs. 3.8% in MicroShunt-treated eyes), defined as IOP < 6 mmHg at 2 consecutive visits after 3 months. In contrast, the most common cause of surgical failure in MicroShunt-treated eyes was an IOP reduction of less than 20% from baseline (29.4% vs. 9.1% in

Table 6. Postoperative Interventions, Including Qualifying Operations through 2 Years, in the MicroShunt and Trabeculectomy Groups

| | MicroShunt Group (n = 395), n (%) | Trabeculectomy Group (n = 132), n (%) | *P* Value |
|---|---|---|---|
| Any postoperative intervention | 219 (55.4) | 93 (70.5) | <0.001 |
| Qualifying reoperation in the study eye* | 74 (18.7) | 14 (10.6) | 0.014 |
| Bleb revision | 40 (10.1) | 10 (7.6) | 0.3551 |
| Placement of drainage device | 19 (4.8) | 4 (3.0) | |
| Removal of implant | 19 (4.8) | 0 (0.0) | |
| Trabeculectomy | 9 (2.3) | 1 (0.8) | |
| Repositioning of the MicroShunt | 8 (2.0) | 0 (0.0) | |
| Resuturing of the sclera flap | 6 (1.5) | 4 (3.0) | |
| Iridotomy/iridectomy | 3 (0.8) | 0 (0.0) | |
| Needling of bleb with or without injected antifibrotic | 98 (24.8) | 12 (9.1) | <0.001 |
| Laser suture lysis before secondary trabeculectomy | 0 (0.0) | 69 (52.3) | <0.001 |
| Introduction of glaucoma medication | 201 (50.9) | 52 (39.4) | 0.020 |
| Other† | 18 (4.6) | 2 (1.5) | 0.042 |

*P* values based on 2-sample proportion test (Wald type).
*Qualifying reoperations include trabeculectomy, placement of a drainage device, bleb revision (other than needling), explantation or repositioning of the MicroShunt, iridectomy, or resuturing of the scleral flap. *P* values are not calculated for all reoperation subcategories due to the low number of events.
†Including laser removal of blockage, laser suture lysis after any secondary trabeculectomy, glaucoma laser procedure, or use of viscoelastic to limit aqueous flow.

trabeculectomy-treated eyes). These data provide evidence of the relative protection against hypotony afforded by the inherent resistance to fluid flow of the MicroShunt device. Conversely, limitations imposed by this inherent resistance may predispose to episcleral fibrosis and IOP elevation, particularly in patients at higher risk for postoperative scarring. Postoperative needling at the slit lamp was performed in 98 patients (24.8%) in the MicroShunt group and 12 patients (9.1%) in the trabeculectomy group ($P < 0.001$). When performing needle revision, surgeons were allowed to apply additional MMC at their desired dose. Of patients who underwent needling without prior glaucoma reoperation, 25.3% (24/95) of patients in the MicroShunt arm and 54.5% (6/11) of patients in the trabeculectomy arm went on to achieve surgical success. Likewise, open bleb revision in the operating room allowed for surgeons to place additional MMC at the time of the procedure. Forty patients (10.1%) underwent open revision in the operating room in the MicroShunt group, and 10 patients (7.6%) required revision in the trabeculectomy arm. Among patients who underwent bleb revision without prior reoperation, 33.3% (13/39) in the MicroShunt group and 0% (0/10) in the trabeculectomy group ($P = 0.045$) went on to need traditional glaucoma surgery, including placement of a glaucoma drainage device or trabeculectomy by the end of year 2.

When selecting therapy, the risks of each treatment should be weighed against patient-specific treatment goals. A procedure that carries a higher risk of serious complications such as hypotony may be preferred for patients with more advanced, sight-threatening glaucoma or for those at higher risk of surgical failure due to postoperative scarring if this procedure is more likely to result in lower interventional IOP. Conversely, a safer procedure may be better for patients with more modest pressure goals and those at lower risk for filtration failure. The nature and rates of adverse events at 2 years were similar in the 2 groups, except for hypotony, which was more common in eyes undergoing trabeculectomy compared with MicroShunt implantation (51.1% vs. 30.9%, $P < 0.001$). Adverse events, such as a shallow anterior chamber and choroidal effusions, were transient and generally resolved with conservative management. Only 1 eye in the trabeculectomy group required drainage of choroidal effusions. At year 2, cataract progression was observed in 14.2% of eyes in the MicroShunt group and 21.4% of eyes in the trabeculectomy group ($P = 0.071$). No serious bleb-related complications, such as blebitis or bleb-related endophthalmitis, were observed in either group.

The skill and experience of the surgeon have a significant effect on the outcome obtained with any surgical procedure. This is particularly true for a procedure such as trabeculectomy that requires a delicate series of operative and postoperative manipulations and adjustments to achieve a positive result. Although trabeculectomy is still regarded as standard first-line treatment for patients requiring glaucoma surgery, the number of trabeculectomies performed each year continues to decrease while the number of micro-invasive glaucoma surgeries increases.[28] Risks of the procedure as well as intraoperative and postoperative challenges are typically cited as the main reasons surgeons are moving away from trabeculectomy. The trabeculectomy arm of the present study demonstrated exceptional outcomes with respect to IOP reduction: The mean IOP at 2 years was 10.7 mmHg, using an average of 0.4 medications. Additionally, few serious complications were observed. All surgeons who participated in this trial had extensive experience with trabeculectomy. The benefits of MicroShunt procedures may include a reduction in the number, variability, and complexity of surgical manipulations, as well as a reduced need for postoperative adjustments. It is possible that surgeons with less experience performing and managing trabeculectomy would experience outcomes that are not as favorable as those obtained in this study and closer to those achieved with the MicroShunt. The relative performance of MicroShunt might be better in surgeons with limited trabeculectomy experience, but this needs to be confirmed with future studies.

### Study Limitations

This study had several limitations. Although subjects were masked to treatment assignment, masking of surgeons was not feasible. Baseline IOP was < 18 mmHg in 31% of eyes (no washout before surgery), which may have led to the relatively high rates of failure in both groups. Therefore, the chosen primary outcome measure may not have been an ideal measure for determining surgical success. This is supported by the finding that the percentage of patients in each group who were medication-free was higher than the percentage who achieved overall surgical success. An additional study limitation may have been the use of MMC-soaked sponges at a fixed concentration for a fixed period of time. Future studies comparing the MicroShunt and trabeculectomy that use varying concentrations of MMC and different delivery methods (e.g., via injection) may yield different results.

## Conclusions

This prospective, randomized, single-masked trial showed that both trabeculectomy and MicroShunt implantation resulted in significant and sustained IOP reduction at year 2, with trabeculectomy continuing to result in greater surgical success based on the primary end point.

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Abbreviations and Acronyms:
**BCVA** = best-corrected visual acuity; **CI** = confidence interval; **IOP** = intraocular pressure; **MIGS** = micro-invasive glaucoma surgery; **MMC** = mitomycin C; **POAG** = primary open-angle glaucoma.

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