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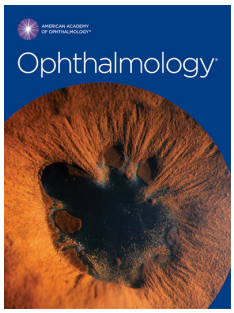

Long term outcomes from the HORIZON randomized trial for a Schlemm's canal microstent in combination cataract and glaucoma surgery

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TITLE

Long term outcomes from the HORIZON randomized trial for a Schlemm's canal microstent in combination cataract and glaucoma surgery

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THIS ARTICLE CONTAINS ADDITIONAL ONLINE-ONLY MATERIAL. The following should appear online-only: Table S1 and Table

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ABSTRACT

Objective: 5-year results of the HORIZON trial comparing cataract surgery combined with an intracanalicular microstent to cataract surgery alone.

Design: Prospective, multicenter, controlled randomized clinical trial.

Participants: Patients with cataract and POAG treated with ≥ 1 glaucoma medication, washed out diurnal intraocular pressure (DIOP) 22-34 mmHg and no prior incisional glaucoma surgery.

Methods: Eyes were randomized 2:1 to receive a Hydrus® Microstent (Ivantis, Inc.) or no stent after successful cataract surgery. Follow-up was conducted through 5 years postoperatively.

Main outcome measures: IOP, glaucoma medication usage, repeat glaucoma surgery, visual acuity, visual field, procedure related adverse events, and corneal endothelial cell counts.

Results**:** 369 eyes were randomized to microstent treatment (HMS) and 187 to cataract surgery only (CS). Study groups were well matched for preoperative IOP, medication usage, washed out DIOP, and glaucoma severity. Five year follow up was completed in 80% of patients. At 5 years, the HMS group had a higher proportion of eyes with IOP ≤18 mmHg without medications compared to CS (49.5% vs. 34.8%, p=0.003) as well as a greater likelihood of IOP reduction of ≥ 20% without medications compared to CS alone (54.2% vs. 32.8%, p<0.001). The number of glaucoma medications was 0.5 ± 0.9 in the HMS group and 0.9 ± 0.9 in the CS group (p<0.001), and 66% of eyes in the HMS group were medication free compared to 46% in the CS group (p<0.001). The cumulative risk of incisional glaucoma surgery was lower in the HMS group (2.4% vs. 6.2%, log-

rank p=0.027). There was no clinical or statistically significant difference in the rate of endothelial cell loss from 3 months to 60 months between the HMS and CS groups (p=0.261).

Visual acuity did not differ between groups, and there was no difference in long term postoperative adverse events.

Conclusions: The addition of a Schlemm's canal microstent in conjunction with cataract surgery was safe, resulted in lowered IOP and medication use, and reduced the need for postoperative incisional glaucoma filtration surgery compared to cataract surgery alone after 5 years. Long term presence of the implant did not adversely affect the corneal endothelium.

INTRODUCTION

The number of people affected by blindness due to age-related cataract and glaucoma remains a major worldwide health problem.[1] Combined glaucoma and cataract surgery has become increasingly common in North America with the introduction of minimally invasive glaucoma surgery (MIGS) devices and techniques. While several angle surgery devices and techniques have been described,[2] only Schlemm's canal stents have demonstrated safety and effectiveness in large scale, prospective, multicenter randomized trials.[3,4] As a result, glaucoma surgery is being performed in patients with early and moderate stage glaucomatous disease who are not suitable candidates for higher risk filtration procedures. The near-term impact of these devices has been to reduce medication burden.[5]

Two previously reported randomized studies for the Hydrus Microstent (Ivantis Inc, Irvine, CA) showed that implantation of the device significantly reduced IOP and medication use in pateints with primary open angle glaucoma over the short and medium term, and that the effectiveness margin improved compared to control from year 1 to year 2.[3,6] These clinical findings were consistent with laboratory studies which demonstrated that implantation of the Hydrus device increases outflow facility.[7]

In procedures where intervention is performed at an early disease stage, safety outcomes are especially important. The HORIZON trial followed the randomized cohorts for 5 years in order to assess long term outcomes. Three year follow up from this study showed that eyes treated with Hydrus implantation were liess likely to require subsequent incisional glaucoma surgery compared to eyes randomized to cataract surgery alone.[8] The

objective of this report is to provide 5-year safety and effectiveness results, including impact on the corneal endothelial cell layer.

METHODS

Study Design and Inclusion Criteria

The HORIZON study was a prospective, multicenter, single masked, randomized, controlled clinical trial. The study was conducted at 38 investigational centers worldwide (26 sites in the US and 12 international). The study protocol was approved by the by the governing Institutional Review Board or Ethics Committee at all participating centers and by national regulatory agencies where applicable. The study was conducted according to the principles described in the Declaration of Helsinki and complied with Health Insurance Portability and Accountability Act and local patient privacy protection regulations. All study subjects provided written informed consent prior to initiating study procedures and including follow-up for 5 years postoperative. The study is registered in the National Library of Medicine database (http://www.clinicaltrials.gov identifier NCT01539239).

Study oversight, randomization, wash out, and surgical procedures have been described previously.[3] Briefly, patients with age-related cataract and a diagnosis of mild to moderate POAG receiving 1–4 topical hypotensive medications were prospectively enrolled into the study. Eligible patients had ophthalmoscopically detectable glaucomatous optic neuropathy, mild to moderate visual field (VF) loss as defined by Hodapp-Anderson-Parrish criteria,[9] best-corrected visual acuity (BCVA) 20/40 or worse with or without brightness acuity testing, Schaffer grade III-IV angle width in all four quadrants, and a medicated IOP of 31 mmHg or less. After wash out of all hypotensive

medications, continuation to randomization required a mean diurnal IOP (defined as the average of 3 Goldman tonometry measurements taken at 8 am, 12 pm and 4 pm) between 22 and 34 mmHg.

Patients with angle closure glaucoma, any secondary glaucoma, a visual field mean deviation worse than -12 dB, exudative age-related macular degeneration (AMD), proliferative diabetic retinopathy, or significant risk of glaucomatous progression due to wash out of IOP-lowering medications were excluded. Anatomical exclusion criteria were narrow anterior chamber angle (Shaffer grade I-II) or other angle abnormality visible upon gonioscopy, central corneal thickness of < 480 or >620 microns, or clinically significant corneal dystrophy. Patients with prior corneal surgery, cycloablation, or any incisional glaucoma procedure such as trabeculectomy, tube shunt implantation, deep sclerectomy or canaloplasty were also excluded. Prior selective laser trabeculoplasty (SLT) was allowed, but patients who had undergone prior argon laser trabeculoplasty were excluded.

Postoperative study visits were scheduled at 1, 7, and 30 days, then at 3, 6, 12, 18, 24, 36, 48 and 60 months. Follow-up procedures included slit lamp examination with gonioscopy, fundus examination, BCVA and IOP assessments with Goldmann Applanation Tonometry. Medications were allowed throughout the study as needed to reach IOP targets. A medication washout was carried out at months 12 and 24 to permit assessment of full unmedicated diurnal IOP. For reasons related to cost and time burden on the patient and investigational site staff, washed out IOP assessment not repeated after 24 months.

Perimetry testing and specular microscopy were repeated at each annual visit from 2 to 5 years.

Mean central corneal endothelial cell density (ECD) was determined by analyzing specular microscopic images (CellChek®, Konan Medical, Inc, Hyogo, Japan) obtained at baseline and then repeated at least annually through 5 years. Triplicate images of the central endothelium were obtained for each eye at each timepoint. Images were analyzed at an independent reading center masked to the treatment assignment of the study eye (Cornea Image Analysis Reading Center, University Hospitals Eye Institute, Cleveland OH). Cell counts were determined by 2 certified readers masked to the study group using the Konan Center method; ≥5% differences were resolved by adjudication with a third reader. The effects of MIGS devices on the corneal endothelium has become an important metric requiring careful monitoring and reporting. Accordingly, it is important to emphasize that while other components of the Horizon Trial were single-masked, readers were masked to the study group for all specular microscopy images.

Outcome Measures

Long term Outcome measures included surgical success rate (20% reduction in IOP without medications or IOP ≤18 mmHg), mean IOP, need for glaucoma medical therapy, repeat glaucoma surgery, loss of visual acuity, visual field progression, procedure-related adverse events, and corneal endothelial cell counts. An adverse event was defined as any surgical complication or untoward finding relating to the patient's vision or ocular health, regardless of whether or not it was related or not to the device or the procedure. Loss of ≥2 lines of BCVA or ≥2.5dB of visual field were defined as adverse events. Endothelial

cell density findings were expressed as means, % change from previous timepoints, and frequency of 30% loss from baseline at respective follow up time points.

A repeat glaucoma surgery was defined as a major surgical intervention for IOP-lowering, such trabeculectomy (or gel stent), glaucoma drainage device implant, or transscleral cyclophotocoagulation**.** Since investigators were not masked to treatment assignment, there was a potential for bias in the decision to perform subsequent surgery. Therefore, an adjudication committee composed of 5 independent glaucoma specialists masked to treatment group reviewed each case for surgical necessity (supplemental material www.aaojournal.org). Other IOP-lowering procedures (such as SLT, ECP, needling, membranectomy/laser goniotomy) were not considered major glaucoma surgery.

Statistical Analysis

Continuous variables are analyzed using means and standard deviations. Between and within group differences were tested with the use of two sample t-tests. For categorical variables, counts and percentages are presented according to treatment group; values were compared with the use of Fisher's exact test for binary variables. Hazard ratios were calculated using the Cox proportional hazards model. Comparisons of cumulative rate of failure and reoperation for glaucoma were assessed with Kaplan-Meier survival analysis. Long term endothelial cell count changes were assessed using linear regression analysis. A p-value of 0.05 was considered statistically significant in the analysis.

RESULTS

A total of 556 eyes were randomized to either HMS with CS (N=369) or CS alone (N=187). Baseline subject demographics and preoperative characteristics were described

previously and are also provided in the online supplement (Table S1 www.aaojournal.org). There were no significant differences between the two groups with regard to these baseline variables.

Preoperatively, mean ± standard deviation IOP was 17.9 ± 3.1 in the HMS group and 18.1 ± 3.1 mmHg in the CS group (p=0.55). Approximately half of all subjects were taking one topical medication with the other half taking two or more medications at the time of initial screening (average 1.7 ± 0.9 in both groups). The post wash out mean baseline unmedicated DIOP was 25.5± 3.0 mmHg in the HMS group and 25.4 ± 2.9 mmHg in the CS group (p=0.89).

Five-year follow-up was completed in 308/369 (83.4%) subjects in the HMS group and 134/187 (71.7%) subjects in the CS group (details of follow up from 1 to 5 years can be found in online supplement Table S2 www.aaojournal.org). All patients who completed the 5-year postoperative examination or who had secondary glaucoma surgery within the follow-up period were included in this analysis. As patients who had secondary procedures were counted as failures employing dichotomous success criteria, IOP and medication counts for these patients were not included in the calculation of overall mean IOP and medications usage after the secondary procedure.

Throughout the follow-up period, mean IOP was similar and stable between the groups (Figure 1). At 5 years, the mean ± standard deviation IOP was 16.8 ± 3.1 in the HMS group and 17.2 ± 3.2 in the CS group (p=0.24). There was a consistent difference in medication count in favour of the HMS group over the time period, with mean medications at 0.5 ± 0.9 in the HMS group and 0.9 ± 0.9 in the CS group (difference = 0.4 medications, p<0.001). From 1 year to 5 year follow up, the mean medication count

increased by 0.2 in both groups, resulting in no change in the between-group margin over the course of the study.

Significantly more eyes in the HMS group remained medication free at 5 years compared to the CS group (66% vs. 46%, difference = 20%, p<0.001). Eyes on 1 or 2 medications preoperatively were more frequently medication free postoperatively compared to eyes on 3 or 4 medications, as shown in Table 1. Eyes in the HMS group, whether on 1, 2, or 3 or 4 medications, were significantly medication free more often compared to CS alone.

Due to the greater reduction in the need for medications, the HMS group demonstrated significantly higher rates of procedure success relative to the CS group. As shown in Table 2, among eyes that remained medication free, there was a greater mean IOP reduction compared to preoperative washed out diurnal IOP (-8.3 ±3.8 vs. -6.5 ± 4.0, p<0.001), and significantly more eyes in the HMS group maintained an IOP of ≤18 mmHg (49.5% vs. 33.8%, p=0.003). Additionally, the fraction of eyes with medication-free reductions in IOP of 20%, 30% and 40% vs. preoperative levels was consistently greater in the HMS compared to the CS group.

Secondary IOP Lowering Procedures

A summary of IOP lowering procedures are provided in Table 3. There were 22 events in 18 eyes (4.9%) in the HMS group and 30 events in 14 eyes (7.5%) in the CS group. As shown in Table 3, through 5 years, 8 eyes in the HMS group and 10 in the CS group required major glaucoma surgery, a significant reduction in the event rate (hazard ratio = 0.365, 95% CI 0.144 to 0.926, p=0.034). All glaucoma surgeries were adjudicated as clinically warranted due to worsening glaucoma by the Clinical Events Committee. As shown in Figure 2**,** Kaplan-Meier survival analysis showed a significant increase in the

risk of major incisional surgery between groups at five years (6.2% vs. 2.4%, p=0.027, log rank test). Among other IOP-lowering procedures, SLT was the most common procedure in both study groups and twice as frequent in the CS group *(1.6% vs. 3.7% p = 0.12)*. Procedures secondary to trabeculectomy or tube shunts such as bleb needling, revisions, or paracenteses were also less frequent in the HMS group.

Safety

Vision and ocular health were assessed at each visit. As shown in Table 4, there were very few new adverse findings in the late follow up period.. After 5 years, cumulative BCVA loss of ≥ 2 lines was 1.9% in the HMS group and 2.1% in the CS group. A loss of ≥2.5 dB in VF mean deviation was defined as an adverse finding in the protocol. This condition was met in 8.4% of HMS eyes and 9.6% of CS eyes. There were no late observations of inflammation or corneal edema or need for device removal. The only long-term finding uniquely related to the device were focal PAS or tissue adhesions near the trabecular entry point. The percentage of patients with PAS in the CS group was 3.7% and 14.6% in the HMS group (p=0.0001). There were no differences in IOP control between those with and without PAS (16.9± 3.3 vs. 16.6± 3.5, p=0.49). A patient questionnaire was conducted at 2 years and found no differences in ocular discomfort or pain between study groups. This assessment was not repeated at the 5- year mark; however, no adverse events related to pain or other discomfort were reported.

ECD Findings

Mean central ECD findings are presented in Figure 3. Mean central ECD (± SD, cells/mm^2) at baseline was 2417 ± 390 in the HMS group and 2426 ± 371 in the CS group (p=0.81). At the first postoperative evaluation (3 months), the mean endothelial cell counts were 2086 ± 519 (95% CI 2032 to 2140) in the HS group and 2162 ± 444 (95% CI 2097 to 2227) in the CS group (p=0.09), representing endothelial cell loss (ECL) of 13% and 11% in the respective groups compared to preoperative measurements. The between group difference was not statistically significant (p=0.08, t-test). There was a modest but significant decline in ECD in both groups from 3 monhts to 5 years. The last observed mean counts were 1967 ± 522 (p=<0.01 vs. 3M) and 2117 ± 442 cells/mm^2 (p<0.01 vs. 3M) in the HMS and CS groups, respectively.

The rate of change in endothelial cell density is a better indicator of corneal stability than the cell density value alone. (add citation: Lass J, Sugar A, Benetz BA, et al. Endothelial cell density to predict endothelial graft failure after penetrating keratoplasty. *Arch Ophthalmol* 2010;128(1):63-69.) As shown in Figure 4, year to year endothelial cell loss (ECL) ranged from 0% to 2% in the HMS group and 0% to 1% in the CS group (note: the change indicated in year 1 is from the 3 month postoperative visit). The rate of yearly change was evaluated using linear regression, and there was no clinical or statistically significant difference in the rate of ECL from 3 months to 60 months between the HMS and CS groups (p=0.261). Additionally, there was no shift towards increased ECL in years 4 or 5 compared to prior years.

A loss of ≥30% in ECD is considered a threshold for significant change.[10] At 3 months, ≥30% loss was observed in 17.3% of eyes in the HMS group and 9.4% of CS eyes, a

between group difference of 7.9% (p=0.01). Over the 5 year follow up period, the proportion of eyes with 30% ECL increased to 20.8% (p=0.27 vs 3M) in the HMS group and 10.6% (p=0.85 vs. 3M) in the CS group. A logistic regression analysis showed that there was no difference in the rate of change in ≥30% ECL between the groups in the postoperative period from 3M to 5 years (p=0.82). None of the eyes with ≥30% ECL in either group had associated corneal edema, decompensation or other clinical sequelae.

DISCUSSION

This study is the longest continuous follow-up of a pivotal MIGS randomized clinical trial; 442/556 (80%) of eyes completed 5 year follow up. The data demonstrate that the implantation of the Hydrus Microstent in conjunction with cataract surgery is associated with a sustained, clinically significant reduction in the number of medications required to maintain a therapeutic IOP compared to cataract surgery alone over 5 years postoperatively. There was no statistically significant difference in medicated IOP between the two groups at 5 years. This was expected, as clinicians were allowed to add medications to reach target IOP as necessary. However, medication elimination was maintained at significantly higher rates at 5 years in the HMS group compared to the CS group. There was a greater proportion of eyes without medications and IOP ≤18, as well as with IOP reductions of 20%, 30% or 40% in the HMS group compared to CS alone. A lower proportion of patients who received the Hydrus microshunt needed to undergo further glaucoma surgery due to glaucomatous disease progression or poor IOP control versus cataract surgery alone. For these reasons, Hydrus combined with cataract surgery has been shown to be both cost-effective and to maintain a favorable QALY compared to cataract surgery alone.[11]

The 2-year findings from the HORIZON study showed that Hydrus Microstent implantation combined with cataract surgery provided a statistically and clinically significant reduction in unmedicated diurnal IOP compared with cataract CS alone. Although the 5-year results do not include medication wash out, the IOP and medication usage are consistent with the 1 and 2 year findings. The mean IOP of unmedicated eyes was consistent lower in the HMS vs CS eyes, and mean change in IOP from baseline remained greater, suggesting that investigators treated the study groups similarly in terms of adding medications.

Medication usage is an area that is often underestimated when it comes to impact on patient quality of life and is a critical consideration in assessing outcomes for MIGS devices in combination with cataract surgery. Adherence has been shown to drop for multiple medication regimens.[8] Reduction in the number of glaucoma medications lessens the burden of medication related adverse effects and may promote better adherence, which in turn may reduce the risk of disease progression and need for further surgery. Consistent with the 2- and 3-year findings, the drop free rate was proportional to the starting medication count, especially for the HMS group. Eyes requiring only a single medication for pressure control pre-operatively reached a higher rate of drop-free IOP control compared to eyes on multiple drops. Even among eyes on maximal preoperative medical therapy (3 or 4 classes of medicaitons), 59% were on fewer medications at 5 years, and 48% were completely medication free in the HMS group.

A finding of particular interest in this study is that among a cohort of predominantly mild glaucoma patients controlled on 1 or 2 topical medcations, a significant proportion needed invasive glaucoma surgery over 5 years, particularly in the CS group. Filtering

surgery is a major escalation in therapy associated with significant side effects, refractive and anatomical alterations, and resultant life-altering behavioral modifications.[9,10,11] Kaplan Meier time-to-event analysis demonstrates that the risk of surgery was reduced by more than half in HMS group over the course of follow-up. Combined with reduced dependency on topical medications and lack of significant long-term complications, HMS treatment has a durable, significant impact on the quality of life and long-term consequences faced by early-stage glaucoma patients.

There are a number of possible explanations for the difference in secondary surgical intervention rates between the study groups. Poor long term adherence to treatment regimens is commonly observed in glaucoma patients[12] and may be associated with subsequent visual loss and irreversible optic nerve damage. The lower average medication use as well as the higher frequency of eyes that achieved drop-free IOP control in the HMS group will likely translate into improved patient well being both with regard to slowing disease grogression and improved patient quality of life.[13] A similar finding was observed in a study comparing the use of first line SLT versus medical therapy for early stage glaucoma.[14] An analysis of visual field data from this study showed greater VF progression in patients treated first with medical therapy compared to those treated first with SLT.[15] This finding could be related to the advantage of more frequent drop-free IOP control in the SLT group.

Reduced diurnal IOP fluctuation in surgical vs. medical controlled IOP may be another possible explanation for the lower secondary glaucoma surgery rates in the HMS group. Additionally, a 24 hour assessment of the circadian rhythm of intraocular pressure (IOP) using a contact lens sensor in patients with open-angle glaucoma showed that the signal

fluctuation range was significantly smaller in patients treated surgically (Ex-PRESS or Hydrus) compared to the medically treated group.[16]

Overall BCVA and ocular health findings did not differ between the two groups. Visual recovery was rapid and loss of ≥2 lines of vision was observed in only 2% of eyes in both groups after 5 years of follow up. The only adverse finding unique to Hydrus Microstent group was the formation of PAS or adhesions near the device. It is important to note that the presence of PAS was determined by gonioscopy and not related to IOP. Potentially obstructive vs. non-obstructive status was determined by whether or not the device inlet could be visualized. Presence of PAS was not associated with loss of device function as determined by IOP or other adverse events.

We observed an endothelial cell loss (ECL) of 13% and 11% in the HMS and CS groups, respectively, at the first postoperative assessment performed at 3 months. Postoperative ECL of this magnitude is consistent with previous studies on the effect of phacoemulsification in either normal or glaucomatous eyes.[17, 18] Although the between group difference was not significant, the slightly higher ECL observed in the Hydrus group may be related to additional surgical manipulation required to place the device or early surgical experience with the device. A gradual decline in cell counts was noted for both groups in the postoperative the follow up period, and the rate of endothelial cell loss from 3 months to 5 years was similar in both treatment groups. While the proportion of eyes with 30% ECL was higher in the HMS group by 8.1% at 3 months, there was no significant increase in the rate of ECL in the HMS group compared to CS over the 5 year follow up period. In a previous study, a supraciliary microstent was associated with a significant and progressive decline in mean endothelial cell count and frequency of eyes

with ≥30% cell loss at 4 and 5 year follow up. [19] We found no similar pattern of late acceleration of ECL with the Hydrus microstent implantation.

The 5-year HORIZON study findings suggest the following: (1) combining Hydrus with phacoemulsification reduces medication dependence and improved the likelihood of remaining drop-free regardless of preoperative medication count; (2) the percentage of eyes that were medication free was durable; (3) combining Hydrus Microstent with cataract surgery reduced the need for further incisional glaucoma surgery compared to cataract surgery alone; and (4) there were no clinically significant differences in safety outcomes between the HMS and CS groups, including the long-term rate of endothelial cell loss. By reducing dependency on topical medicatons and reducing the risk of further glaucoma surgery without introducing significant complications, HMS treatement has a durable and significant impact on the quality of life and long-term consequences faced by early stage glaucoma patients.

Study Limitations

Despite multiple measures to minimize bias, it was not possible to mask the surgeon as to treatment group during postoperative examinations. It is noteworthy that those interpreting specular microscopy scans at the reading center were masked to the study group. The majority of surgeons had limited prior experience with the hydrus microstent implantation technique. The study excluded patients with secondary open angle glaucomas and thus the results may not be generalizable to these populations. Inclusion was limited to POAG eyes with age related cataract as the only comorbidity, and the procedure was assessed in combination with phacoemulsification. The medication wash-

out requirement enabled a direct assessment of the device alone on IOP not confounded by medication use, but at the same time limited the population to mild and moderate severity patients who could tolerate the wash out procedure safely. Additionally, medication wash out was not repeated after 2 years, thus the possibility of medication introduction bias must be considered for later IOP assessments. Despite these limitations, we believe the study is sufficiently powered to demonstrate a significantly reduced need for medication to achieve IOP control and reduced need for incisional IOP-lowering procedures in patients treated with combined Hydrus Microstent implantation and cataract surgery versus cataract surgery alone.

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Figure Legends

Figure 1: Mean IOP at each visit throughout the study. Patients with any secondary IOP lowering procedure are excluded. Error bars are standard deviation.

Figure 2: Cumulative Risk of a major surgical intervention for glaucoma (bleb forming procedures or transscleral cyclophotocoagulation).

Figure 3: Mean central endothelial cell density. Error bars are standard deviation.

Figure 4: Mean endothelial cell loss from the prior visit. The 3-month value indicates the ECL compared to the preoperative value. The 12-month value indicates the ECL from the 3 month value. N represents the patients at the time point who completed the microscopy exam. Error bars are 95% confidence intervals for the mean.

Table 1: Medication-Free Rates stratified by preoperative medication count

Preoperative Count	2 years		3 years		4 years		5 years	
	HMS	CS	HMS	CS	HMS	CS	HMS	CS
N	357	170	332	153	319	144	308	134
1	88%	48%	79%	48%	71.0%	42.3%	72.7%	47.9%
2	79%	61%	74%	56%	71.3%	44.7%	65.4%	52.3%
3 or 4	51%	30%	51%	33%	36.5%	27.6%	46.8%	33.3%
Overall Med Free	78%	48%	72%	46%	64%	40%	66%	46%
P-°	<.0001		<.0001		<.0001		.0002	
IOP (mmHg), mean ± SD *	16.6 ± 3.2	17.4±2.8	16.4±3.2	17.1±3.1	16.7±3.1	17.3±3.2	16.6±3.2	17.6±3.6

*Mean IOP of unmedicated eyes with no repeat interventions

°p-value for overall med-free rate between groups

Table 3: Post Operative IOP Lowering Procedures (N=369 HMS, N=187 CS)

	1 Year		2 Years		3 Years		4 Years		5 Years		Cumulative	
	HMS	CS	HMS	CS	HMS	CS	HMS	CS	HMS	CS	HMS	CS
Patients with a major surgical intervention* n (%)	**0 (0)**	**1 (0.5)**	**1 (0.3)**	**3 (1.6)**	**1 (0.3)**	**1 (0.5)**	**4 (1.1))**	**4 (2.1)**	**3 (0.8)**	**1 (0.5)**	**8 (2.1)**	**10 (5.3)**
Number of events												
Trabeculectomy		1	1	1		1	2	3	3		6	6
Tube Shunt		1		2	1						1	3
Gel Stent							1	1			1	1
Other procedures		1								1	0	2
TSCPC			1								1	0
Patients with other IOP lowering procedures* n (%)	**3 (0.8)**	**2 (1.1)**	**1 (0.3)**	**1 (1.1)**	**3 (0.8)**	**3 (1.6)**	**4 (1.2)**	**1 (0.5)**	**1 (0.3)**	**1 (0.5)**	**12 (3.3)**	**8 (5.3)**
Number of Events												
SLT				2	2	3	3	2	1		6	7
ECP							1				1	0
Membranectomy/ laser goniotomy	3		1		1					3	5	3
Needling/ Bleb Revisions						1		1		1	0	3
Paracentesis > 7 days postop	1	5									1	5

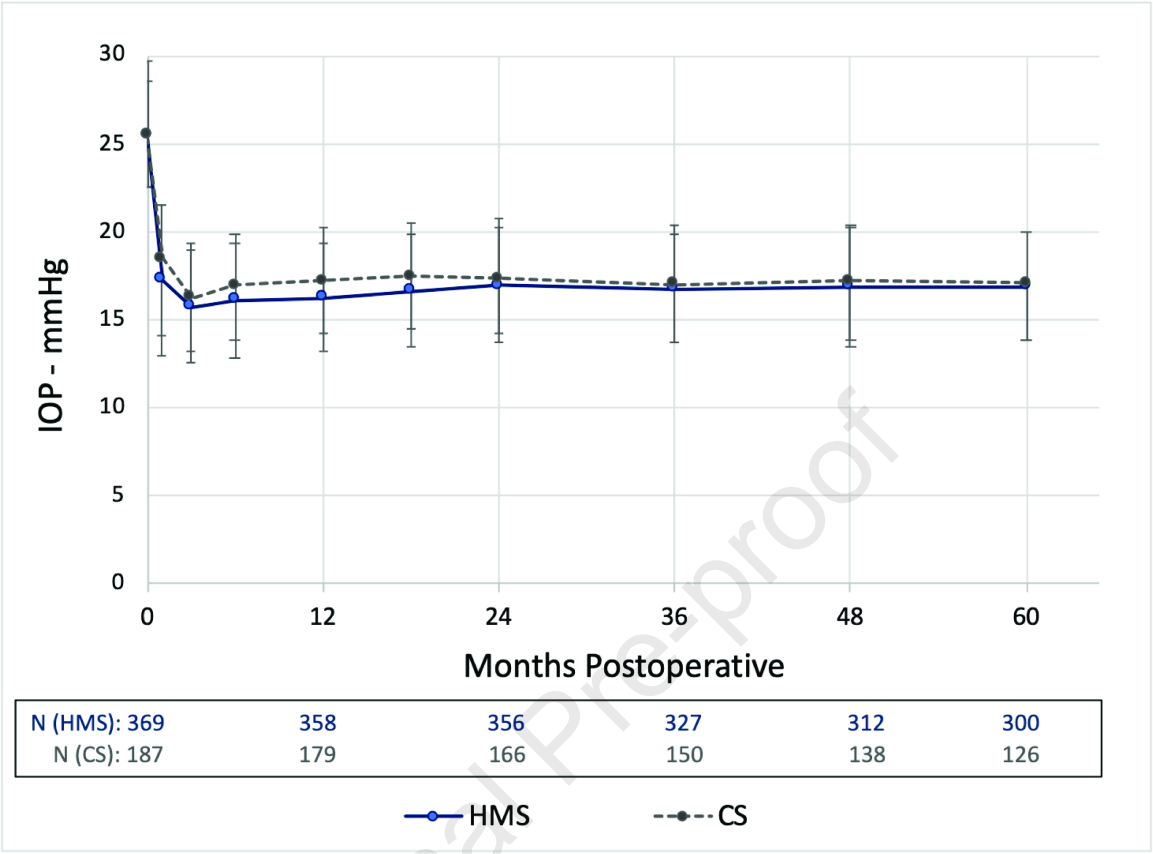
*Patients with at least 1 event. A single patient may have more than one event
TSCPC: transscleral cyclophotocoagulation; SLT: selective laser trabeculoplasty; ECP: endoscopic cyclodestructive procedure;
Other surgical interventions: deep sclerectomy, Express shunt removal
Patients may have multiple events.

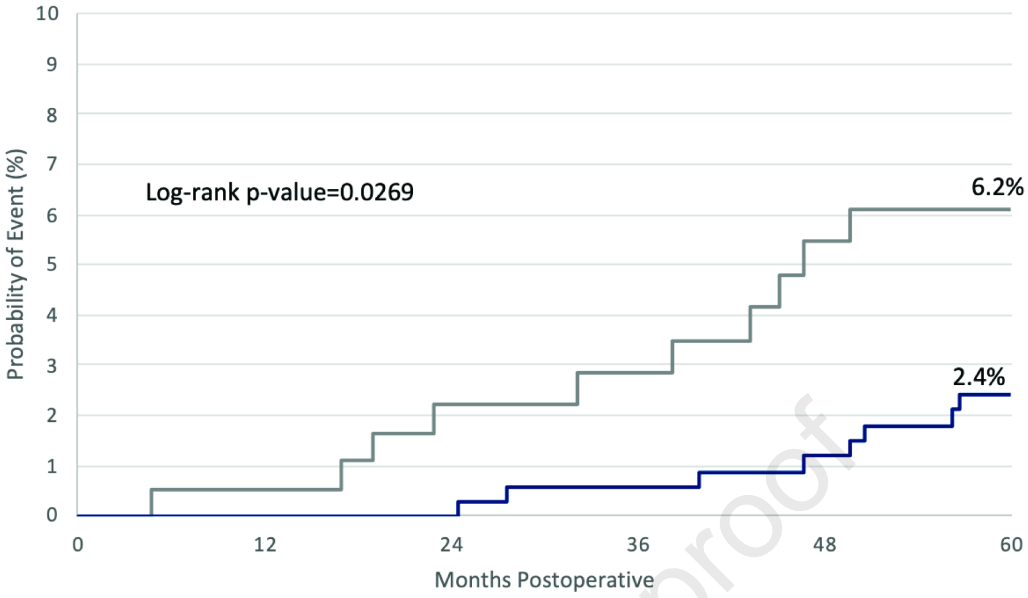
Table 4: Adverse Events. Most frequent adverse events at 3 years.

	Cumulative Events 2 Years		Cumulative Events 3 Years		Cumulative Events 4 Years		Cumulative Events 5 Years		
	HMS	CS	HMS	CS	HMS	CS	HMS, % (95% CI)	CS, % (95% CI)	P-value
BCVA loss of ≥ 2 ETDRS lines ≥ 3 months	1.4%	1.6%	1.6%	2.1%	1.9%	2.1%	1.9% (0.8%, 3.9%)	2.1% (0.6%, 5.4%)	1.0
Worsening in visual field MD ≥2.5 dB	4.3%	5.3%	6.2%	8.6%	7.3%	9.1%	8.4% (5.8%, 11.7%)	9.6% (5.8%, 14.8%)	0.63
Inflammation requiring additional steroids > 1 month	5.9%	3.7%	5.9%	3.7%	5.9%	3.7%	5.9% (3.8%, 8.9%)	3.7% (1.5%, 7.6%)	0.27
Peripheral anterior synechiae	10.6%	2.1%	12.4%	3.2%	13.5%	3.2%	14.6% (11.2%, 18.7%)	3.7% (1.5%, 7.6%)	0.0001
Device Related Events									
Postoperative malposition	1.4%	-	1.4%	-	1.4%	-	1.4% (0.4%, 3.1%)	-	
Peripheral anterior synechiae with device obstruction	3.5%	-	4.3%	-	5.1%	-	5.4% (3.3%, 8.3%)	-	
Device obstruction, partial or complete	7.3%	-	7.6%	-	8.4%	-	8.4% (5.8%, 11.7%)	-	
Device removal	0	-	0	-	0	-	0	-	

Table 2: 5-Year Effectiveness Outcomes.

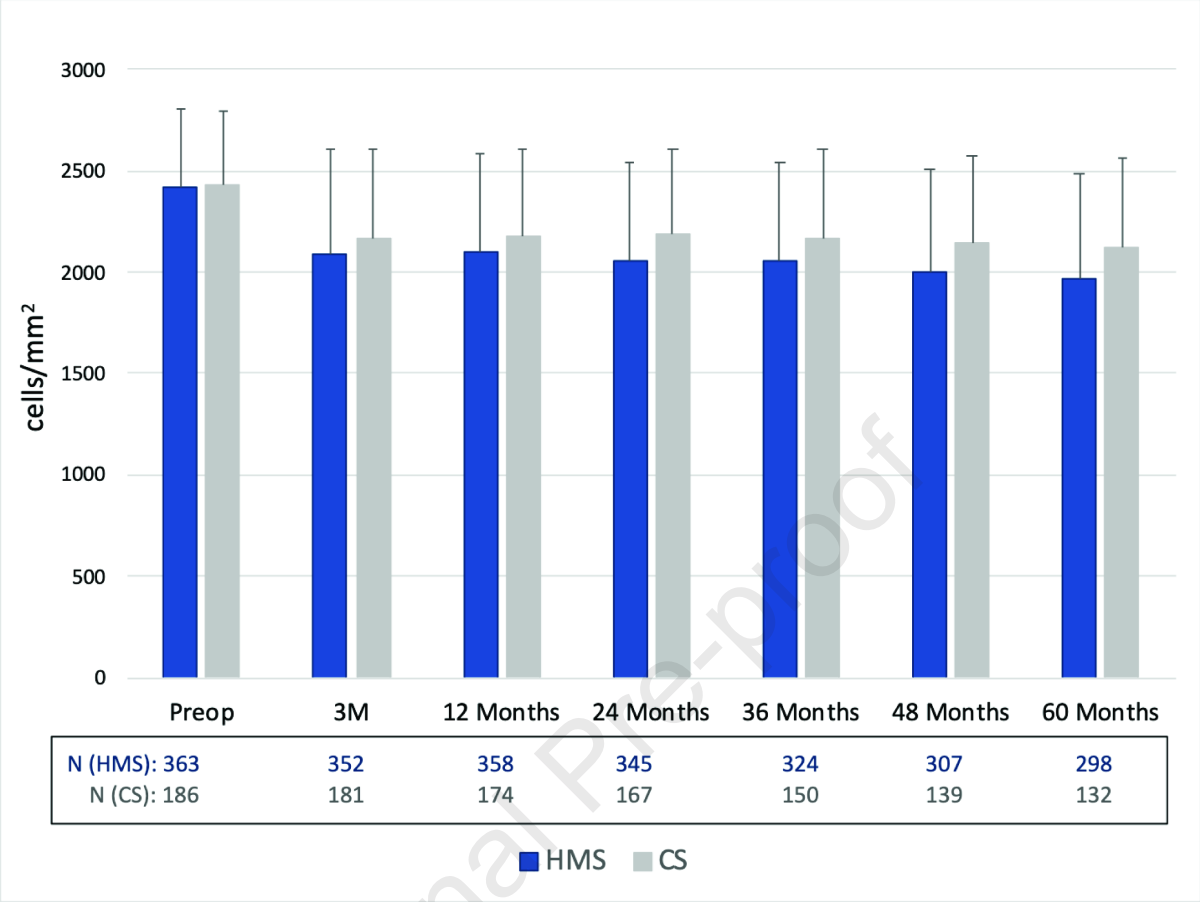
	HMS	CS	*P*-value
N	308	134	-
Medication Free Eyes, %	66%	46%	<0.001
ΔIOP vs. preop (mmHg), mean ± SD	-8.3 ±3.8	-6.5 ± 4.0	<0.001
Medication Free and:			
≤18 mmHg, %	49.5%	33.8%	0.003
≥20% IOP Reduction, %	54.2%	32.8%	<0.001
≥30% IOP Reduction, %	39.6%	17.2%	<0.001
≥40% IOP Reduction, %	17.5%	9.0%	0.020

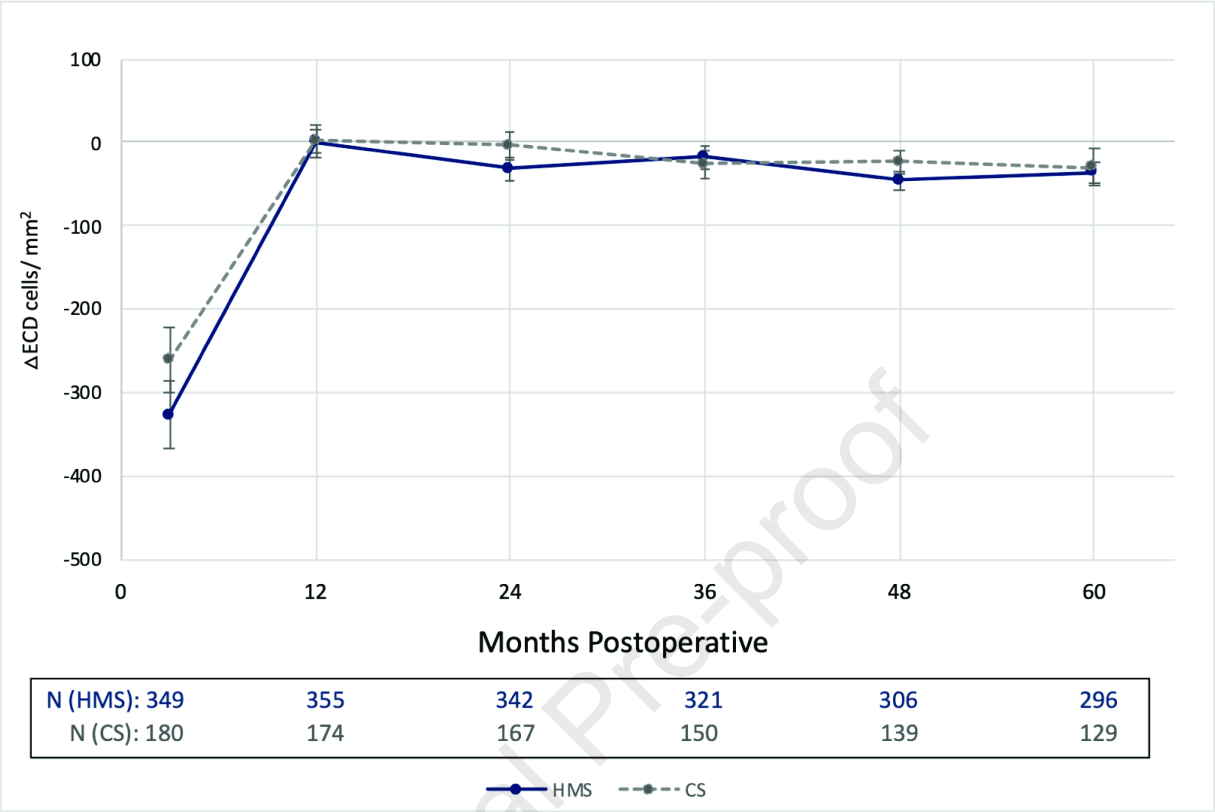




Number at Risk						
CS	187	182	168	154	142	59
HMS	369	366	360	338	322	148

CS HMS





Combining a Schlemm's canal microstent with phacoemulsification is safe and provides a durable effect on IOP lowering and reducing medication burden, and reduced the need for further incisional glaucoma surgery compared to cataract surgery alone.