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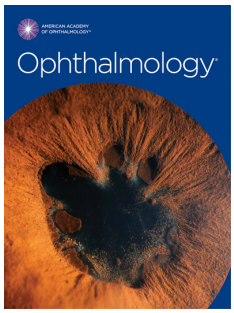

Three-year findings of the HORIZON trial: a Schlemm canal microstent for pressure reduction in primary open angle glaucoma and cataract

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TITLE

Three-year findings of the HORIZON trial: a Schlemm canal microstent for pressure reduction in primary open angle glaucoma and cataract

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ABSTRACT

Objective: To report 3-year outcomes of the HORIZON study comparing cataract surgery with Hydrus Microstent versus cataract surgery alone.

Design: Multicenter randomized clinical trial.

Participants: Five hundred fifty-six eyes from 556 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: Following phacoemulsification, eyes were randomized 2:1 to receive a Hydrus® Microstent (Ivantis, Inc.) or no stent. Follow-up included comprehensive eye examinations through 3 years postoperatively.

Main outcome measures: Outcome measures included IOP, medical therapy, reoperation rates, visual acuity, adverse events, and changes in corneal endothelial cell counts.

***Results*:** 369 eyes were randomized to microstent treatment (HMS) and 187 to cataract surgery only (CS). Preoperative IOP, medication usage, washed out DIOP, and glaucoma severity did not differ between the two treatment groups. At 3 years, IOP was 16.7 ± 3.1 in the HMS group and 17.0 ± 3.4 in the CS group (p=0.85). The number of glaucoma medications was 0.4 ± 0.8 in the HMS group and 0.8 ± 1.0 in the CS group (p<0.001), and 73% of eyes in the HMS group were medication free compared to 48% in the CS group (p<0.001). The HMS group had a higher proportion of eyes with IOP ≤18 mmHg without medications compared to CS (56.2% vs. 34.6%, p<0.001) as well as IOP reduction of at least 20, 30 or 40 percent compared to CS alone. The cumulative probability of incisional glaucoma surgery was lower in the HMS group (0.6% vs. 3.9%, hazard ratio = 0.156, 95% CI 0.031 to 0.773, p=0.020). There was no difference in

postoperative corneal endothelial cell loss between groups. There were no procedure or device related serious adverse events resulting in vision loss in either group.

Conclusions: Combined cataract surgery and microstent placement for mild to moderate POAG is safe, more effective in lowering IOP with fewer medications, and less likely to result in further incisional glaucoma filtrations surgery than cataract surgery alone at 3 years.

INTRODUCTION

Age-related cataract and glaucoma are the two most commonly diagnosed ocular disorders in the United States.[1] At least 4 different prospective, multicenter randomized clinical studies have demonstrated that minimally invasive glaucoma surgery (MIGS) implants placed in Schlemm's canal in conjunction with cataract surgery lowers IOP and hypotensive medication use compared to cataract surgery alone for 2 years.[2,3,4,5] It is also noteworthy that implantation of these devices have safety profiles similar to cataract surgery alone, thereby presenting an opportunity to surgically treat glaucoma without the common postoperative complications associated with bleb forming filtration procedures.[6] While there are several alternative MIGS techniques not involving surgical implants that can be combined with cataract surgery, none of these have been evaluated in large scale, prospective multicenter randomized trials.[7,8,9]

Previously reported randomized data for the Hydrus microstent showed that the device significantly reduced IOP and medication use in primary open angle glaucoma, and that the primary effectiveness margin improved compared to control from year 1 to year 2.[3] The clinical findings were consistent with previous laboratory studies which demonstrated that the Hydrus device increases outflow facility.[10] The durability of the treatment effect beyond 2 years with other Schlemm's canal implants has not been previously established in prospective multicenter randomized trials. Reduced effectiveness from year 1 to year 2 was reported for the iStent in a randomized study.[11] In contrast to Schlemm's canal implants, long term follow-up for a supraciliary MIGS microstent showed that it was associated with significant late corneal endothelial cell loss compared to cataract surgery alone,[12] resulting in market withdrawal. Therefore, prior

experience with MIGS devices shows that long term follow-up is essential for a full assessment of device performance and safety. Accordingly, the objective of this report is to assess 36-month safety and effectiveness outcomes from the HORIZON study.

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 local 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,[13] best-corrected visual acuity (BCVA) 20/40 or worse with or without brightness acuity testing (BAT), 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, with an increase of at least 3 mmHg compared to the medicated IOP value recorded at the screening visit.

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 follow-up visits were scheduled at 1 day, 7±2 days, 30±7 days, 90±14 days, 180±21 days, 365 -28/+42 days, 545±28 days, 738 -28/+42 days, and 1095 -28/+42 days. Follow-up procedures included slit lamp examination with gonioscopy, fundus examination, BCVA and IOP assessments with Goldmann Applanation Tonometry. While medication wash out followed by diurnal IOP assessment was performed after the 12 and 24 month visits, the 36 month visit did not for reasons related to cost and time burden on patient and investigational site staff. Perimetry testing was repeated at 6, 12,

18, 24, and 36 months postoperatively. Specular microscopy was used to determine endothelial cell density preoperatively and at 3, 6, 12, 18, 24 and 36 months postoperatively. Specular microscopy images were analyzed at an independent core laboratory.

Postoperative Care

Postoperatively, a topical antibiotic was administered for 7 days and a tapering dose of a topical corticosteroid for up to 4 weeks. Topical hypotensive medications were reintroduced or discontinued at the discretion of the examining investigator at any time after the procedure. In the event that medications did not result in sufficiently controlled IOP, SLT or incisional glaucoma surgery was performed, also at the investigator's discretion. Wash out of medications and IOP assessment were conducted only at 12 and 24 months postoperatively.

Outcome Measures

Outcome measures included IOP, the need for glaucoma medical therapy, repeat glaucoma surgery rates, visual acuity, procedure-related adverse events, and corneal endothelial cell counts. A repeat glaucoma surgery was defined as any IOP-lowering procedure requiring a trip to the operating room, such as trabeculectomy or tube shunt implantation, or a cyclodestructive procedure, whether performed in the operating room or clinic. Since the 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 (IA, TWS, GG, NR, DR) masked to treatment group reviewed each case for surgical necessity. Non-incisional procedures such as SLT were not considered repeat glaucoma surgery. Safety

assessments included visual acuity, slit lamp and fundus examinations, pachymetry measurements, automated visual field measurement (Humphrey 24-2 SITA standard), and specular microscopy. An adverse event was defined as any surgical complication or untoward finding relating to the patient's vision or ocular health, regardless of whether 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.

Statistical Analysis

The study was powered to detect adverse events occurring at a frequency of 1% in the HMS group with a probability of ≥ 95%. A minimum of 300 subjects in the treatment group were therefore required based on this power calculation. Allowing for loss to follow-up and 2:1 randomization, a sample size of 556 was selected. Mean and standard deviation measurements are presented as continuous variables. Between and within group differences were tested with the use of two sample t-tests. For categorical variables, counts and percentages were presented according to treatment group; values were compared with the use of the Fisher's exact test for binary variables. Treatment comparisons of cumulative rate of failure and reoperation for glaucoma were assessed with the Kaplan-Meier survival analysis log-rank test. A p-value of 0.05 was considered statistically significant in the analysis.

RESULTS

A total of 556 eyes were randomized to either HMS (N=369) or CS (N=187). Baseline subject demographics and preoperative characteristics were described previously and are available in **Table S1** (www.aaojournal.org). There were no significant differences between the two groups with regard to demographic or preoperative ocular

characteristics. Preoperatively, mean IOP was 17.9 ± 3.1 in the HMS group and 18.1 ± 3.1 mmHg in the CS group. 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 wash out procedure resulted in a mean baseline unmedicated DIOP of 25.5± 3.0 mmHg in the HMS group and 25.4 ± 2.9 mmHg in the CS group. The implant was successfully placed in 97.0% of subjects randomized to the HMS group.Three-year follow-up was completed in 332/369 (90.0%) subjects in the HMS group and 153/187 (81.8%) subjects in the CS group.

All patients who completed the 3-year postoperative examination or who had secondary incisional glaucoma surgery within the follow-up period were included in this analysis. While patients who had secondary surgical procedures were counted as failures against success critera, these patients were not included in the calculation of mean IOP or medications. As shown in **Figures 1 and 2**, IOP was stable throughout follow-up and equal between study groups after 3 months, but there was a consistent reduction in medication count in the HMS group. After 3 years, mean ± standard deviation IOP was 16.7 ± 3.1 in the HMS group and 17.0 ± 3.4 in the CS group (p=.85). The number of glaucoma medications was 0.4 ± 0.8 in the HMS group and 0.8 ± 1.0 in the CS group (difference = 0.4, p<0.001). The mean medication count increased by 0.1 in both goups from 12 months to 36 months, so the between group difference in medication usage remained stable over the time period from 12-36 months.

Consistent with earlier timepoints (**Table S2**, www.aaojournal.org), significantly more eyes in the HMS group remained medication free at 3 years compared to the CS group (73% vs. 48%, difference = 25%, p<0.001). The mean 3-year IOP of the unmedicated

eyes was 16.4±3.2 and 17.1±3.1 in the HMS and CS groups respectively, a finding consistent with earlier visits. The mean IOP in unmedicated eyes was slightly lower than the overall average IOP. These findings suggest there was no bias toward leaving HMS group eyes unmedicated at a higher IOP, even though the investigator was not masked to treatment group..

Medication free rates stratified by baseline medication count at 2 and 3 years are shown in **Table 1**. Eyes on 1 or 2 medications preoperatively were more likely to be medication free postoperatively compared to eyes on 3 or 4 medications. As shown in **Table 2**, significantly more eyes maintained an IOP of ≤18mmHg without medications (56.2% vs. 34.6%, $p<0.001$) and the fraction of eyes with medication-free reductions in IOP of 20%, 30% and 40% vs. washed out baseline was consistently greater in the HMS versus the CS group.

Secondary IOP Lowering Procedures

After 3 years of follow-up, there were 2 incisional glaucoma surgeries in the HMS group (0.6%) and 6 in the CS group (3.9%) at 3 years. The 8 surgeries consisted of 4 tube shunt implants and 4 trabeculectomies, and all were found to be warranted due to worsening glaucoma by the adjudication committee. The preoperative mean deviation in the eyes undergoing repeat surgery was -4.1 dB compared to the study mean of -3.6 dB, and 6 of 8 surgeries were performed in eyes with mild preoperative glaucoma per Hodapp-Anderson-Parrish criteria.

As shown in **Figure 3,** Kaplan-Meier time to event analysis showed a significant increase in the risk of incisional surgery between groups at three years ($p=0.0086$, log rank test).

The cumulative probability of incisional glaucoma surgery was 0.6% in the HMS group and 3.9% in the CS group (hazard ratio = 0.156, 95% CI 0.031 to 0.773, p=0.020).

Safety

Vision and ocular health were assessed at each visit. By the first postoperative week, ≥94% of eyes had best corrected visual acuity of 20/40 or better in both study groups, and at 36 months this percentage increased to 97%. As shown in **Table 3**, there were very few new adverse findings between 2 and 3 years. The only change in event rate of more than 1% was for visual field loss of ≥2.5 dB in both HMS and CS groups and an increase in the number of SLT procedures in the CS group. There were no new reports of inflammation or corneal edema after the 3-month visit. The only findings unique to the HMS group were focal adhesions consisting of PAS or iris tissue near the device inlet. Gonioscopically observed PAS were present in 7.6% of HMS eyes at 3 years, of which 4.3% visually obscured the inlet of the microstent. The observed rates for these events increased less than 1% between 2- and 3-year follow-up, and there were no adverse clinical sequelae, specifically IOP elevations, associated with these findings.

ECD Findings

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 3, 6, 12, 18, 24 and 36 months. Triplicate images of the central endothelium were obtained for each eye at each timepoint. Images were analyzed at an independent reading center (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.

Mean central ECD at baseline was 2417 ± 390 in the HMS group and 2426 ± 371 in the CS group. There was a reduction of 339 cells/mm^2 (13%) in the HMS group and 264 cells/mm^2 (11%) in the CS group observed at the first postoperative ECD assessment at 3 months; both of these values represented significant reductions in mean ECD compared to preoperative counts. The between group difference in mean central cell loss was not significant at this time point (difference = 75 cells, p=ns). At 3 years, cumulative cell loss increased by 2% in the HMS group to 15% (95% CI 13% to 16%) and remained at 11% in the CS group (95% CI 9% to 13%, difference = 4%, p=ns). Three-year mean central cell count was 2056 ± 483 in the HMS group vs. 2167 ± 440 in the CS group (difference = 111 cells, p= ns). There was no significant difference in between group cell loss from 2 to 3 years follow-up.

After the initial ECD reduction related to the surgical procedure, sequential visit-to-visit changes in endothelial cell counts were consistent between the study groups, as shown in **Figure 4**. Between 3 months and 12 months, mean central cell count increased in both HMS and CS groups (+9 and +13 cells/mm^2, respectively). Thereafter, the change in ECD counts (HMS – CS) from 12 months to 24 months and from 24 months to 36

months was -44 and +12 cells/mm^2. None of the visit to visit changes in endothelial cell counts were significant.

A loss of ≥30% in ECD is considered a threshold for significant change.[14] 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=0.014). Over the course of follow-up, the between group differences decreased as shown in **Figure 5**. At 36 months, the proportion of eyes with ≥30% endothelial cell loss dropped to 14.2% in the HMS group and increased to 10.0% in the CS group (difference = 4.2%, p=0.239). After the initial loss in cell count related to the surgery, there was no difference in the year to year change in the proportion of eyes with 30% endothelial cell between groups.

DISCUSSION

This prospective, multicenter, randomized, trial demonstrates that Hydrus Microstent implantation combined with cataract surgery provides sustained reduction in the number of medications required to maintain a stable IOP compared to cataract surgery alone for 3 years postoperative. In addition, 73% of HMS eyes required no medication compared to 48% in the CS group, and the device implantation was associated with a greater proportion of eyes with IOP ≤18 mmHg or with IOP reductions of 20%, 30% or 40% compared to baseline. While there were significant differences in the number of medications, mean IOP for medicated and unmedicated eyes was not significantly different in either group.

The 2-year findings from the HORIZON study showed that HMS group was associated with greater IOP reduction after medication wash out compared to CS alone after medication wash out, as measured by a variety of metrics, including frequency of ≥20%

IOP reduction and mean change in IOP. These results confirm the findings from an earlier randomized study[4] and are supported by a recent meta-analysis of the published literature for the Hydrus Microstent.[15] Although the 3-year findings do not include medication wash out, the IOP and medication usage findings are consistent with the 1 and 2 year results where a significant IOP reduction in the HMS group was confirmed after medication wash out. The study design allowed investigators to add medication as needed to control IOP. Since that average IOP was similar in both treatment groups for both medicated and unmedicated eyes through the follow-up period, we do not see any indication that HMS eyes had medications withheld. Indeed, the mean IOP of unmedicated eyes was consistently lower in HMS eyes vs. CS eyes throughout the course of follow up (see supplement Table S2, www.aaojournal.org).

We found eyes on 1 preoperative medication were more likely to remain medication free at 3-years compared to eyes on ≥ 2 drops. There are many possible factors that could contribute to this finding. The most likely factor is IOP. A higher medication count correlates to a higher preoperative IOP. A recently published meta analysis of IOP changes after wash out in 1400 eyes with mild to moderate POAG from the HORIZON and COMPASS studies showed that the IOP increase after wash out is proportional to the number of medications.[16] Throughout follow up, there was a slight increase in visual field loss between medicated and unmedicated eyes, but the difference was small, within 1 dB or less. Further, significant VF loss, defined as a loss of VF MD ≥2.5 dB, was 6.2% and 8.6% in the HMS and CS group. These results suggest there may be a modest influence of VF on medication decisions. Finally, it is possible that more severe disease correlates to a damaged outflow system, making these eyes more difficult to treat with

angle surgery. However, covariate analysis showed that mean deviation was not a predictor of 2 year washed out IOP reduction in the HORIZON study.[17] This finding may be related to constraints on allowable severity imposed by study entry criteria.

Medication usage is an important consideration in assessing outcomes for MIGS devices in combination with cataract surgery. This reflects the mild to moderate disease severity status of the population, and also that that the majority of the study population had a mid-teens IOP prior to the procedure, and would not otherwise be candidates for glaucoma surgery if not for the presence of an operable cataract. These findings are consistent with a previously published survey of Center for Medicare and Medicaid Services data for MIGS procedures showing that the primary impact of MIGS procedures has been to reduce the number of medications required to maintain IOP in the mid-teens.[18]

A notable finding in this study is the lower risk of glaucoma reoperations in the HMS group at 3 years. Although the incidence of such surgery is small, it cannot be discounted considering that filtering surgery is a major escalation in therapy with known serious risks, potential persistent ocular surface discomfort, refractive and anatomical alterations, and life-altering behavioral modifications.[19,20,21] Considering the morbidity of incisional bleb filtering surgery, both in the early and late postoperative period, any difference in these rates is likely to have a significant impact on the quality of life and long-term consequences faced by the patients, including the risk of bleb-related endophthalmitis and loss of visual acuity.

The study population in HORIZON had mild to moderate severity glaucoma, and the groups were well-balanced for significant risk factors (age, race, severity) at baseline. While postoperative wash outs were limited to 12 and 24 months, subsequent follow-up

visits included continuation and adjustment of required topical medical therapy to control IOP. The similarity in IOP values over the course of 3 years follow-up suggests that treatment targets were similar between groups and were generally maintained by titrating medication usage.

There was nothing remarkable about the visual field characteristics for the patients that required glaucoma surgery. There was no preoperative difference between the overall study visual field mean deviation and the visual field mean deviation for eyes that required repeat glaucoma surgery during follow-up. Indeed, 75% of eyes undergoing incisional glaucoma surgery had mild disease severity per study defined criteria prior to randomization. These findings are very similar to the difference in glaucoma surgery rates between SLT and medication groups over the same timeframe in the LiGHT study.[22] To address the potential for bias, incisional surgery events were adjudicated for clinical necessity by an independent committee masked to the treatment group. There was complete consensus among 5 glaucoma surgeons that each of the procedures were justified based on clinical presentation at the time of the surgery.

The difference in rate of secondary glaucoma surgery may be related to the number of eyes that achieved drop-free IOP control in the HMS group. Persistence and adherence with medication use are well known limitations of topical medication regimens,[23] and poor adherence has been associated with increased visual field defect severity.[24] A recent analysis of visual field data from the LiGHT trial showed greater visual field preservation in the SLT group after 3 years, probably due to greater drop-free IOP control.[25] Another possible explanation for the lower surgery rate in the HMS group may be less circadian fluctuation associated with surgical vs. medical control of IOP. A recent study showed

that surgical IOP control (either trabeculectomy or Hydrus) resulted in significantly less circadian fluctuation than medication alone in a contact lens stress model.[26] While the 3-year rate of loss in visual field mean deviation ≥2.5 dB did not reach the threshold for statistical significance, the observed rates of visual field progression and postoperative IOP elevations were lower in the HMS group.

Overall BCVA and ocular health findings did not differ between the two groups. Visual recovery was rapid and 97% of eyes BCVA measured 20/40 over the course of follow-up. The most frequent 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. Obstructive vs. non-obstructive status was determined by the ability to visualize the device inlet. Presence of PAS was not associated with loss of device function or other adverse events.

The long-term impact of cataract surgery on corneal endothelial cell counts in glaucoma patients compared to normal eyes is not well understood. We found an 11% reduction in mean cell count in the CS group. This is consistent with previous studies of effect of phacoemulsification on endothelial cells.[27, 28] The initial postoperative findings in this study suggests that the addition of the microstent induced an incremental non-significant loss in mean central cell count of 2% (approximately 75 cells/μm^2). This finding may be related to the additional surgical manipulation with insertion and removal of additional cohesive viscoelastic when placing the device. However, after the initial postoperative measurement, there were no differences in the rate of subsequent endothelial cell loss from 3 months to 3 years, suggesting that the presence of the device itself does not adversely threaten corneal health compared to cataract surgery alone. While significant

differences in endothelial cell loss were found with a supraciliary microsent,[29] the differences were first detected after 4 years of follow up. While it is possible that ECD differences may have been apparent at 3 years, follow up at 3 years was available in a very small number of eyes compared to 4 and 5 years. Annual specular microscopy will be performed in the HORIZON study out to 5 years to monitor changes in ECD.

The 3-year HORIZON study findings suggest the following: (1) combining Hydrus with phacoemulsification reduces medication use and improves the likelihood of remaining drop-free; (2) the IOP lowering effect and reduced medication burden following Hydrus plus phacoemulsification is durable; (3) combining Hydrus Microstent with cataract surgery reduces the risk of additional incisional glaucoma surgery compared to cataract surgery alone; and (4) there were no significant differences in safety outcomes between the groups, including the long-term rate of endothelial cell loss.

Study Limitations

Despite multiple measures to minimize bias, it was not possible to mask the surgeon as to treatment group during postoperative examinations, although the study group for specular microscopy scans were masked to the reading center. The majority of surgeons had limited prior experience with the implantation technique. The study excluded patients with secondary open angle glaucoma 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. Medication wash out was not repeated after 2 years, and so IOP reduction attributable to the device alone at 3 years is indirect. The rate of re-intervention was not a prespecified endpoint, and will require further follow-up to confirm the 3-year

findings. Despite the limitations, we believe the study is sufficiently powered to demonstrate a significant difference in long term IOP and medication reduction and need for IOP-lowering procedures with Hydrus Microstent implantation versus cataract surgery alone.

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Figure 1: Mean IOP (washout IOP shown at day 0). Error bars are 95% confidence intervals. Wash out value shown for Day 0 (operative day).

Figure 2: Mean Medication Count. Error bars are 95% confidence intervals.

Figure 3: 3-year Kaplan-Meier cumulative probability of repeat glaucoma surgery

Figure 4: Change in Endothelial Cell Density from prior visit. Specular microscopy images taken preoperatively and postoperatively at 3, 6, 12, 18, 24, and 36 months. Error bars are 95% confidence intervals.

Figure 5: Change in rate of 30% endothelial cell loss from prior visit. Specular microscopy images taken preoperatively and postoperatively at 3, 6, 12, 18, 24, and 36 months.

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

Preoperative Count	2 years		3 years	
	HMS	CS	HMS	CS
1	88%	48%	79%	48%
2	79%	61%	74%	56%
3 or 4	51%	30%	51%	33%
Mean	78%	48%	72%	46%
IOP – mmHg*	16.6±3.2	17.4±2.8	16.4±3.2	17.1±3.1

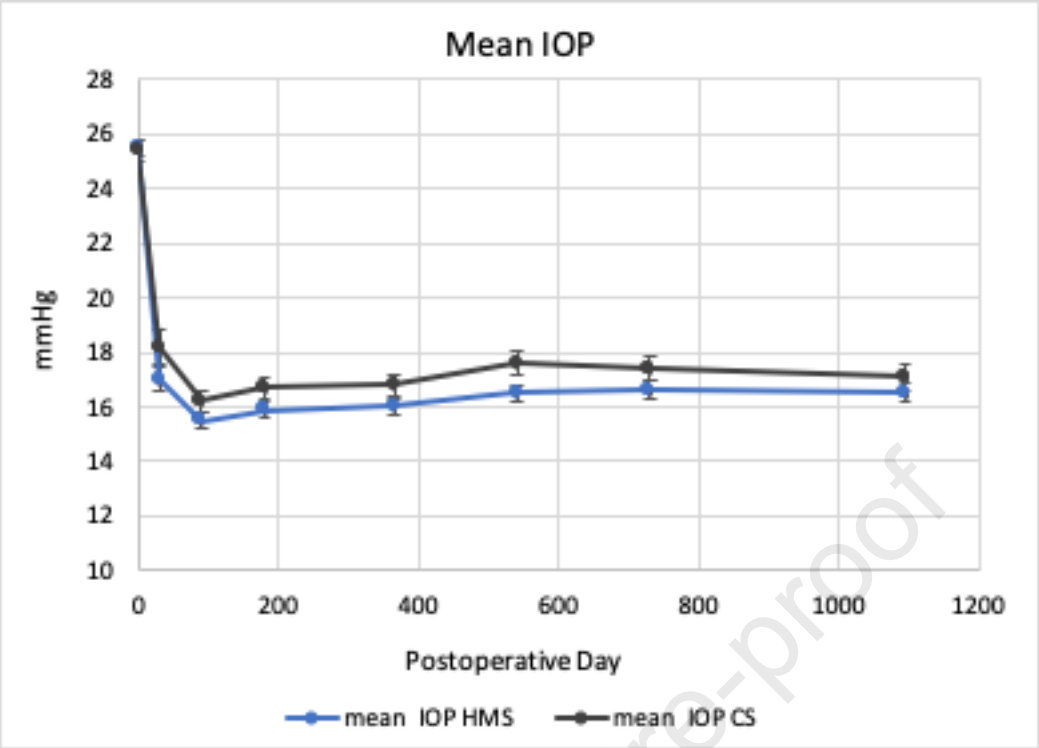
***Mean IOP of <u>unmedicated</u> eyes**

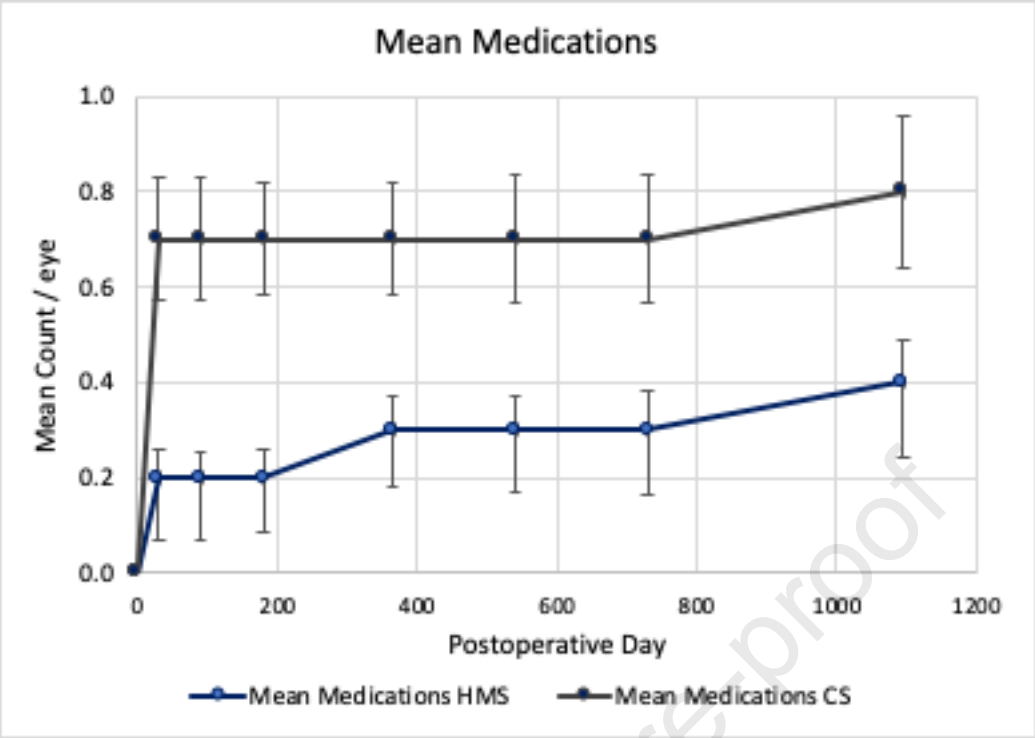
Table 2: 3-Year Medication-free IOP Reduction

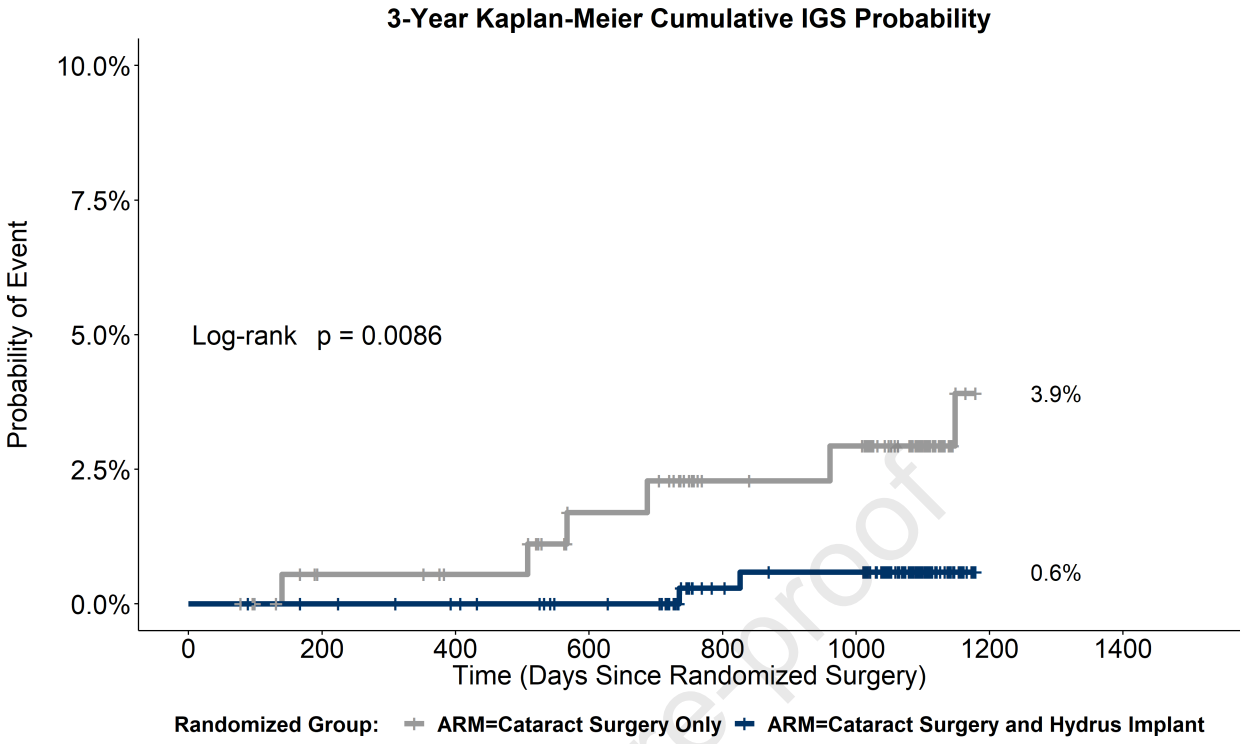
Medication Free Eyes	HMS	CS	p-value
Preoperative mean ± SD	25.5±3.0	25.4±2.9	0.95
3 Year Follow-up			
≤18 mmHg	56.2%	34.6%	<0.001
≥20% IOP Reduction	62.0%	41.1%	<0.001
≥30% IOP Reduction	40.9%	21.5%	0.003
≥40% IOP Reduction	22.6%	8.4%	<0.001

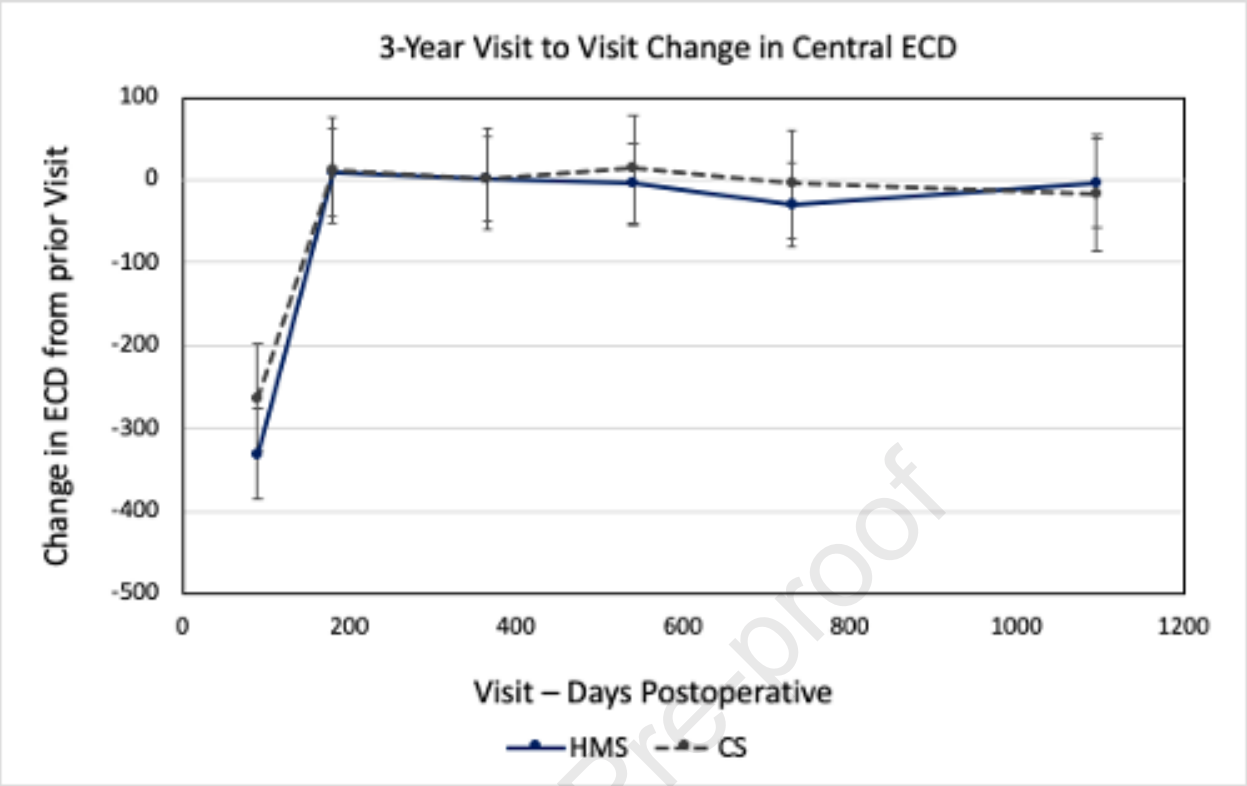
Table 3: Adverse Events. Most frequent adverse events at 3 years.

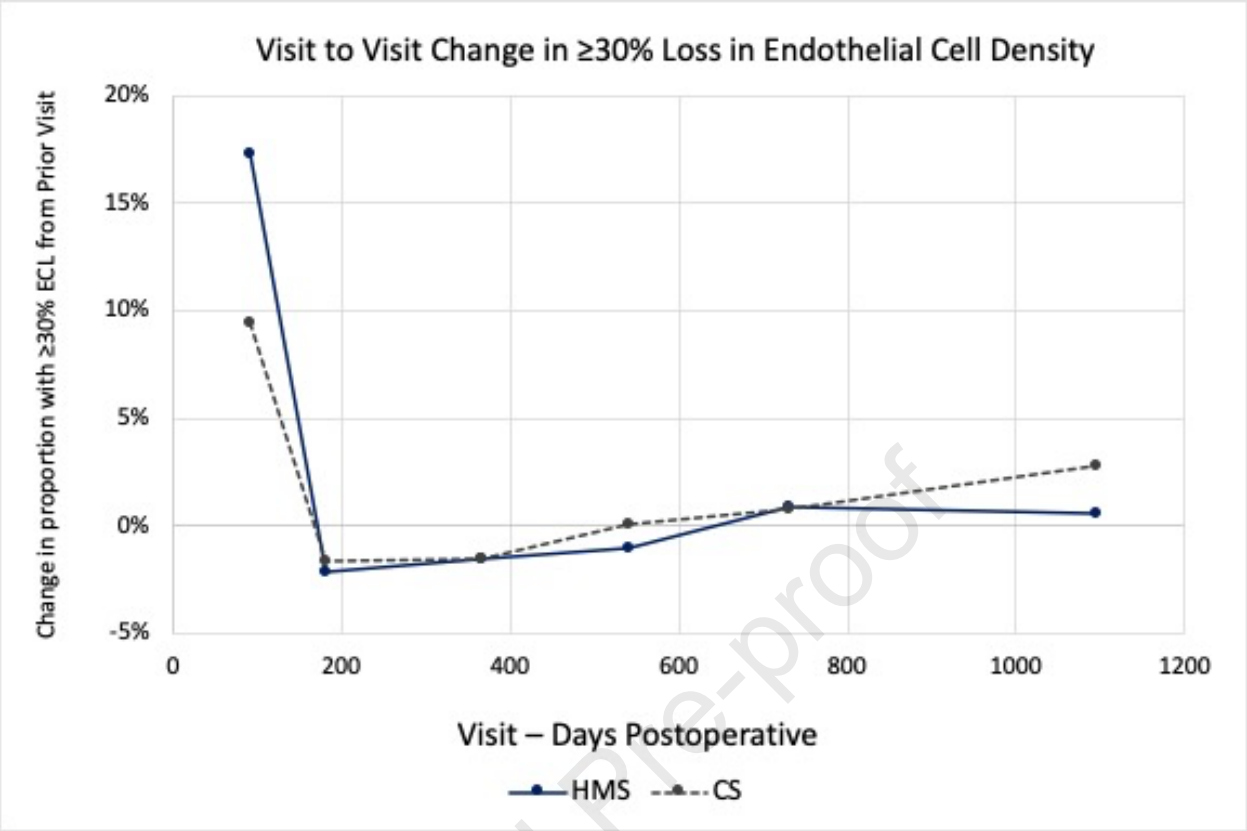
	Cumulative Events 2 Years			Cumulative Events 3 Years		
	HMS	**CS**	**Difference**	**HMS**	**CS**	**Difference**
BCVA loss of ≥ 2 ETDRS lines ≥ 3 months	1.4%	1.6%	-0.2%	1.6%	2.1%	-0.5%
Worsening in visual field MD ≥2.5 dB	4.3%	5.3%	-1.0%	6.2%	8.6%	-2.3%
Postoperative malposition	1.4%	0.0%	1.4%	1.4%	0.0%	1.4%
Peripheral anterior synechiae with device obstruction	3.5%	0.0%	3.5%	4.3%	0.0%	4.3%
Peripheral anterior synechiae - non obstructive	7.3%	2.1%	7.3%	8.1%	2.7%	8.1%
Device obstruction, partial or complete	7.3%	0.0%	7.3%	7.6%	0.0%	7.6%
SLT/Trabeculoplasty	0	0.5%	-0.5%	0.8%	2.7%	1.9%











3-year follow-up of a prospective, randomized trial evaluating the safety and effectiveness of the Hydrus Microstent combined with phacoemulsification for treatment of open angle glaucoma shows reduced IOP and medication use compared to phacoemulsification alone.