Five-Year Visual Field Outcomes of the HORIZON Trial

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• PURPOSE: To compare visual field (VF) progression between glaucoma patients receiving cataract surgery alone (CS) or with a Hydrus microstent (CS-HMS).
• DESIGN: Post hoc analysis of VF data from the HORIZON multicenter randomized controlled trial.
• METHODS: A total of 556 patients with glaucoma and cataract were randomized 2:1 to either CS-HMS (369) or CS (187) and followed up for 5 years. VF was performed at 6 months and then every year after surgery. We analyzed data for all participants with at least 3 reliable VFs (false positives < 15%). Average between-group difference in rate of progression (RoP) was tested using a Bayesian mixed model and a 2-sided Bayesian *P* value <.05 (main outcome). A multivariable model measured the effect of intraocular pressure (IOP). A survival analysis compared the probability of global VF sensitivity dropping by predefined cutoffs (2.5, 3.5, 4.5, and 5.5 dB) from baseline.
• RESULTS: Data from 352 eyes in the CS-HMS arm and 165 in the CS arm were analyzed (2966 VFs). The mean RoP was –0.26 dB/y (95% credible interval –0.36, –0.16) for CS-HMS and –0.49 dB/y (95% credible interval –0.63, –0.34) for CS. This difference was significant ($P = .0138$). The difference in IOP only explained 17% of the effect ($P < .0001$). Five-year survival analysis showed an increased probability of VF worsening by 5.5 dB ($P = .0170$), indicating a greater proportion of fast progressors in the CS arm.
• CONCLUSIONS: CS-HMS has a significant effect on VF preservation in glaucoma patients compared with CS alone, reducing the proportion of fast progressors. (Am J Ophthalmol 2023;251: 143–155.

Lowering the intraocular pressure (IOP) by means of surgery or medications currently is the only evidence-based treatment for glaucoma.[1-3] Incisional surgery, such as trabeculectomy, is by far the most effective way of achieving low IOP.[4] However, patients are often managed medically, mostly with eye drops, for extended periods of time as surgery carries the risk of sight-threatening complications.[5,6] Alternatives to eyedrops have been proposed, such as selective laser trabeculoplasty,[7,8] which has proven able to control IOP and to be more effective than drops in slowing down progression of visual field (VF) damage.[9] Cataract surgery (CS) alone is also associated with some IOP-lowering effect[10-13] and is often required in an aging population such as those with primary open angle glaucoma (POAG).[14]

Minimally invasive glaucoma surgery (MIGS) devices that can be implanted into the Schlemm's canal in conjunction with CS, such as the Hydrus microstent (HMS; Alcon), have been tested in prospective multicenter randomized clinical trials, demonstrating significantly greater reduction in medication use and IOP compared to CS alone, with similar safety,[10,12,15,16] providing cataract patients with an opportunity for combined surgical treatment of glaucoma without the risks of filtration surgery.[17] Recent results from the HORIZON trial, a prospective randomized multicenter study, confirmed long-term effectiveness in controlling IOP and safety of the HMS at 36[11] and 60 months.[18] This contrasts with other MIGS devices for which long-term data were either not available, showed shorter duration of efficacy,[19] or exhibited serious long-term side effects, such as corneal endothelial cell loss.[20]

A fundamental and unanswered question concerning all MIGS devices is whether they have any measurable ability to help POAG patients retain their vision. VF damage measured by Standard Automated Perimetry (SAP) is the standard of clinical care and the most important functional outcome of all major glaucoma trials.[2,3,21-26] The extent of VF damage measured with SAP also correlates with vision-related quality of life and important functional measures relevant to patients.[27-30] We performed a detailed analysis

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of 5-year VF data collected during the HORIZON trial to determine whether CS combined with HMS implant (CS-HMS) reduced the rate of VF worsening compared with CS alone in POAG patients.

METHODS

• **PARTICIPANTS:** The current study evaluated data from HORIZON, a prospective, multicenter, single-masked, randomized, controlled clinical trial comparing CS and CS-HMS,[11,16,18] involving 38 centers (26 in the United States and 12 international) with up to 5 years of follow-up. The protocol was approved at all centers by local governing institutional review boards, ethics committees, and national regulatory agencies where needed and conducted according to the principles in the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act and local patient privacy protection regulations. All study participants provided written informed consent before any procedure. The trial is registered in the National Library of Medicine database (clinicaltrials.gov identifier, NCT01539239).

Details of recruitment and postoperative protocols were previously described in detail.[11,16,18] Briefly, patients with age-related cataract and a diagnosis of mild to moderate POAG using 1 to 4 topical hypotensive medications were prospectively enrolled. Inclusion criteria were ophthalmoscopically detectable glaucomatous optic neuropathy, mild to moderate VF loss according to Hodapp-Anderson-Parrish criteria,[31] best-corrected visual acuity of 20/40 or worse, open iridocorneal angle, and a medicated IOP of 31 mm Hg or less. After washout of all hypotensive medications, only patients with a mean diurnal IOP (defined as the average of 3 Goldman tonometry measurements obtained at 8 AM, 12 PM, and 4 PM) between 22 and 34 mm Hg (inclusive), with an increase of at least 3 mm Hg compared with the medicated IOP value, were included.

Patients were excluded if they had angle-closure or any secondary glaucoma (including pseudoexfoliative and pigment dispersion), exudative age-related macular degeneration, proliferative diabetic retinopathy, or significant risk of glaucomatous progression resulting from washout of IOP-lowering medications as judged by the local investigator. Other exclusion criteria were narrow iridocorneal angle (Shaffer grade I or II) or any angle abnormality on gonioscopy, central corneal thickness <480 or >620 mm, clinically significant corneal dystrophy, prior corneal surgery, cycloablation, and any incisional glaucoma procedure such as trabeculectomy, tube shunt implantation, deep sclerectomy, or canaloplasty. Patients who underwent prior selective laser trabeculoplasty, but not argon laser trabeculoplasty, were eligible.

A total of 556 participants (1 eye per participant) were randomized 2:1 in the operating room to receive either CS-HMS (n = 369) or CS alone (n = 187). Patients were followed for 5 years after surgery. Follow-up visits included slit-lamp examination with gonioscopy, fundus examination, best-corrected visual acuity, and IOP measurements (with Goldmann applanation tonometry). Diurnal washout IOP (8 AM, 12 PM, and 4 PM) was also measured at 12 and 24 months after surgery, but not used in our analyses.

Goldmann applanation tonometry was performed during clinic office hours: we refer to these IOP measures as "daytime" IOP because this better reflects the times at which these measurements were sampled. Topical hypotensive medications were managed after surgery according to clinical practice and at the discretion of the examining investigator. Investigators could decide to perform selective laser trabeculoplasty or incisional surgery if medications were deemed insufficient to control the disease.

• **VF ASSESSMENT:** VF examinations were performed at preoperative baseline and 6, 12, 24, 36, 48, and 60 months after surgery using a Humphrey field analyzer (Zeiss Meditec), 24-2 pattern, SITA-Standard strategy. Additional VF tests were performed if worsening in mean deviation of 2.5 dB or more from the preoperative baseline was observed, as this was defined in the protocol as an adverse event[11,18] and required confirmation with 2 additional reliable VFs.

For this analysis, anonymized printouts of the VF tests were provided by the individual centers as scanned copies. A bespoke optical character recognition algorithm extracted pointwise sensitivity values from the printouts. The output of the algorithm was evaluated by 2 independent graders (G.M. and G.O.), who visually inspected all values for correctness. The rate of false-positive errors was also recorded by the graders. This was the only metric used to establish the reliability of the VF test, because fixation losses and false-negative errors have been shown to be poor indicators of reliability.[32] The exact date of the test was also extracted and used to precisely calculate the time from surgery. Both graders were masked to treatment allocation. For all the analyses, VF data from left eyes were converted to a right eye spatial orientation.

• **STATISTICAL ANALYSIS:**

Data selection

A total of 3701 VFs from 554 patients (99.6%) were available for analysis. Of these, 121 VFs were excluded because of poor reliability (false-positive error rate > 15%). To eliminate the confounding effect of cataract, all preoperative baseline tests were not included in the analysis (561 reliable VFs). We justify this decision with a supplementary analysis, showing a mean improvement of 0.99 dB (95% CI 0.93, 1.04) in sensitivity after surgery. There was also considerable variability in this effect, as shown in detail in the Supplementary Material. For 5 subjects, no reliable VFs were available postsurgery.

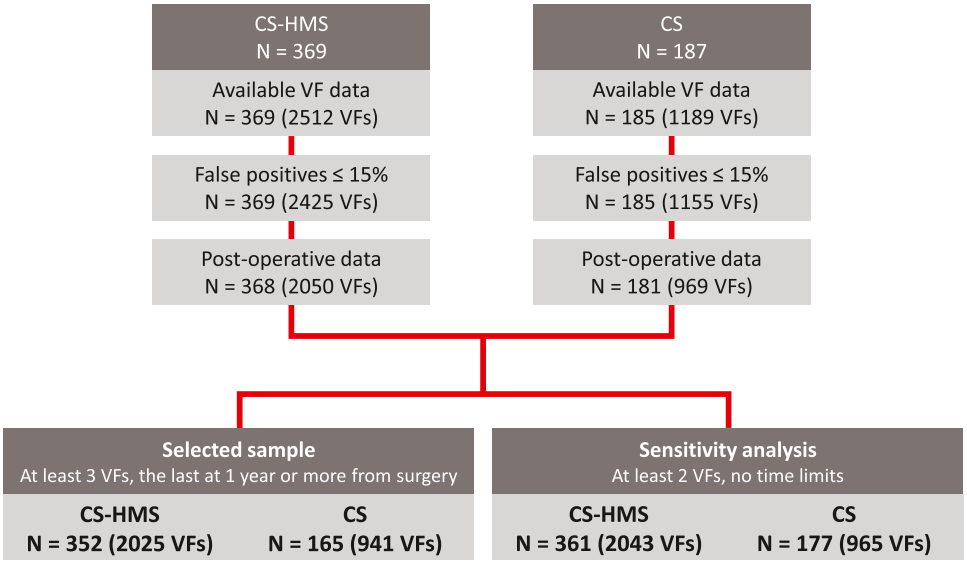

FIGURE 1. Flowchart of the selection steps for the data sets used for analysis. N indicates the number of participants. The boxes report the criterion for inclusion of the tests at each step. CS = cataract surgery, HMS = Hydrus microstent, VF = visual field.

The analysis was performed on all VFs from patients with at least 3 postoperative tests, the last performed at least 1 year after surgery, so that progression could be reliably estimated for the subjects analyzed. A sensitivity analysis was also performed for the primary outcome including all VFs from patients with at least 2 postoperative tests, regardless of the time span, to confirm the results with the least restrictive criteria possible, minimizing any selection bias. All selection steps are reported in the flowchart in Figure 1.

Primary outcome

The primary outcome measure was the difference in the rate of progression (RoP) of VF damage between the 2 groups (CS-HMS and CS alone), measured using a linear mixed effect model (LMM), a well-established technique for VF analysis.[9,30,33-44] LMMs for pointwise data were used in the VF analysis of the Laser in Glaucoma and Ocular Hypertension Trial (LiGHT),[9] and the specific methodology used in this work has been recently employed for the analysis of the VF outcomes in Treatment of Advanced Glaucoma Study (TAGS).[45] The response variable was the pointwise sensitivity over time (ie, at each tested location of the VF for each subject). Time from surgery (in years) and the allocation arm (coded as a binary discrete factor) were used as fixed effects. The interaction between these fixed effects modeled the difference in RoP between the 2 arms (primary outcome of interest).

Observations were then grouped by location, VF cluster, and eye in a hierarchical nested fashion (random effects). Clusters were defined according to Garway-Heath and associates,[46] based on the trajectory of nerve fiber bundles. Random intercepts and random slopes were used at the eye, cluster, and location level to allow different RoPs for individual locations and clusters within each eye. LMMs also adjust population estimates to be more influenced by patients with longer, and more informative, VF series, while still extracting useful information from eyes with fewer VFs.

We accounted for the measurement floor at 0 dB by censoring the sensitivity values indicating that no response was recorded (<0 dB on the VF printout), to avoid bias from the measurement floor.[42] In this case, censoring indicates that the model would account for the fact that some sensitivities were not recorded and that their true value was below the 0-dB measurement floor.

These models are complex to estimate with traditional methods, especially when accounting for censoring. Therefore, we used R (R Foundation for Statistical Computing) and JAGS (Just Another Gibbs Sampler[47]) to estimate the model parameters through Bayesian computation to overcome these technical challenges. Bayesian computation of similar LMMs also has been extensively validated by our and other groups on large VF data sets of glaucoma patients.[34,35,42] Details of the computation are provided as Supplementary Material.

Bayesian methods do not produce frequentist *P* values. However, a conceptually identical metric can be derived from the Bayesian *P*-direction,[48] which has been shown to have a strong 1:1 correlation with the *P* value.[48] This index will be denoted as P_d, whereas *P* will refer to the usual *P* value. This was preferred to other Bayesian indices of statistical significance because the objective of our analysis was to use Bayesian computation as a tool to provide a more accurate implementation of frequentist LMMs, while maintaining the same interpretation of the results.

For the sensitivity analysis, the inclusion of participants with fewer than 3 VF tests to estimate global differences in

TABLE 1. Baseline and Descriptive Statistics of the Selected Sample

	Selected Sample			Sensitivity Analysis		
	CS-HMS (n = 352)	CS (n = 165)	*P*	CS-HMS (n = 361)	CS (n = 177)	*P*
Age (y)	70 (70, 80)	70 (70, 80)	.665	70 (70, 80)	70 (70, 80)	.790
Sex (female/male), n	195/157	96/69	.617	202/159	103/74	.690
Race, n			.686			.424
Asian	21	8		21	9	
Black or AA	39	14		43	14	
Other	11	7		11	8	
White	281	136		286	146	
Corneal thickness (μm)	550 (530, 570)	550 (530, 580)	.465	550 (530, 570)	550 (520, 570)	.620
Baseline MD (dB)	–3.22 (–5.21, –1.71)	–2.82 (–5.16, –1.40)	.639	–3.21 (–5.21, –1.70)	–2.95 (–5.16, –1.41)	.846
Screening IOP (mm Hg)	18 (16, 20)	18 (16, 20)	.691	18 (16, 20)	18 (16, 20)	.591
Baseline IOP (mm Hg)	25 (23, 27)	25 (23, 27)	.551	25 (23, 27)	25 (23, 27)	.816
No. of medications at baseline	1 (1, 2)	1 (1, 2)	.699	1 (1, 2)	1 (1, 2)	.955
No. of postoperative VFs	6 (5, 6)	6 (5, 6)	.872	6 (5, 6)	6 (5, 6)	.295
Follow-up time (y)	4.9 (4.8, 5.0)	4.9 (4.8, 5.0)	.176	4.9 (4.8, 5.0)	4.8 (4.0, 5.0)	**.030**

AA = African American, CS = cataract surgery, HMS = Hydrus microstent, IOP = intraocular pressure, MD = mean deviation, VF = visual field.

The same statistics are also reported for the sample used for the sensitivity analysis. All continuous variables are reported as median (interquartile range). The number of postoperative VFs and the follow-up time are calculated per patient. All *P* values for continuous variables are from a 2-sample *t* test, except for the number of medications where a Mann-Whitney test was used. Differences in discrete variables were instead tested with a χ^2 test. Screening IOP was on medications. Baseline IOP was after washout.

RoP was made possible by the hierarchical nature of the model and the use of random effects. For further confirmation, the analysis was repeated with a maximum likelihood approach using a simplified LMM (without accounting for VF clusters or censoring) with the *lme4* package for R, which produces traditional *P* values for the estimates[49] (Supplementary Material), as for the analysis performed in LiGHT.[9] All *P* values were 2-sided, because we could not exclude a priori that patients undergoing CS-HMS would have worse progression of VF damage.

The main analysis and data extraction was performed by G.M. and G.O. masked to arm allocation. To achieve masking, participants assigned to CS-HMS were split into 2 similar size groups, so that they could not be distinguished from the CS group by the group size. The analysis was repeated 3 times, each time setting a single different masked group as the CS arm and the other 2 as the CS-HMS arm. The results of the analysis were then locked before unmasking, and those obtained with the correct allocation were retained.

Secondary outcomes

Localized progression. Population-based differences in baseline damage and RoP for different parts of the VF were examined by modifying the model used for the main analysis to include Garway-Heath clusters[46] as fixed effects, including interactions with the treatment arm (details in Supplementary Material). In short, such a variation on the LMM provides estimates that can be interpreted exactly as the results from the primary outcome analysis, but for each VF cluster, while simultaneously accounting for correlations among observations from the same eyes.

Finally, because LMMs model pointwise data, cluster and pointwise slopes can be extracted from the random effect estimates. We used these slopes to perform clusterwise and pointwise analyses, testing differences between the 2 arms in the RoP of the fastest-progressing cluster and the fastest-progressing location for each eye using a *t*-type statistic from a simple nonhierarchical linear model. For this analysis, RoP values were calculated by fitting individual models to each eye regardless of their allocation.[42]

Time to progression. To evaluate the impact of VF damage progression on individual eyes, as opposed to the population effect measured with the primary outcome, we performed a survival analysis where the event was the global progression of the VF damage beyond a predefined threshold from the estimated sensitivity on the day of surgery. The thresholds used for this analysis were 2.5 dB (defined as adverse event in the trial) and three 1-dB steps from this threshold (3.5, 4.5, and 5.5 dB).

However, a robust and precise estimate of the event is difficult to obtain from the raw data, owing to their relatively sparse frequency over time and perimetric test-retest variability.[50] Instead, we first calculated the global RoP using a separate hierarchical model for each eye,[42] independently of their arm allocation. The time of the event was then simply calculated by dividing the chosen threshold for the event by the global RoP. For example, the time taken for

TABLE 2. Results for the Primary Outcome Analysis.

	CS-HMS	CS	Difference	P_d
Primary outcome				
Baseline (dB)	26.73 (26.43, 27.03)	26.74 (26.30, 27.18)	0.01 (–0.52, 0.54)	.9618
RoP (dB/y)	–0.26 (–0.36, –0.16)	–0.49 (–0.63, –0.34)	–0.23 (–0.40, –0.05)	**.0138**
Sensitivity analysis				
Baseline (dB)	26.74 (26.45, 27.03)	26.79 (26.37, 27.22)	0.05 (–0.47, 0.56)	.8586
RoP (dB/y)	–0.29 (–0.40, –0.18)	–0.51 (–0.67, –0.35)	–0.22 (–0.41, –0.02)	**.0284**

CS = cataract surgery, HMS = Hydrus microstent, RoP = rate of progression.

All estimates are reported as mean (95% credible intervals). Baseline indicates the estimated sensitivity at the day of surgery (intercept of the model).

an eye progressing by 1 dB/y to drop 2.5 dB below the baseline would be 2.5 years. Therefore, eyes losing 5.5 dB over 5 years would be fast progressors (RoP ≤–1.1 dB/y). This provided us with a continuous estimate of the time of the event that was less affected by perimetric noise and large time gaps between tests.

Note that this approach calculates the change in VF sensitivity from the estimated sensitivity at the day of surgery, that is, from the intercept of the LMM. This avoids the confounding effect of cataract that would come from using the preoperative baseline data. To avoid extrapolations beyond the data, all eyes that were estimated to reach the event beyond their actual observation period were censored at the time of their last follow-up. This included positive slopes, for which no event could be observed within the observation time.

The main survival analysis was performed with a Cox model using the *survival* package for R.[51] This analysis was exploratory and mainly meant to provide a description of the distribution of the RoPs. Therefore, the findings were not corrected for multiple comparisons, following recommendations in the literature.[52] Additional testing was performed using a methodology that does not assume proportional hazards using the package *survELtest* for R.[53,54] This package implements 2 test statistics based on pointwise comparison of the empirical likelihood (EL) ratio between the survival curves: the integrated EL (intEL), to detect global differences, and the maximally selected EL (supEL), to detect localized differences.

Effect explained by daytime IOP. We studied the relationship between the RoP and the average IOP over the course of the trial in the 2 arms. Postoperatively, IOP was measured more frequently at the beginning and less often toward the end. Therefore, a simple average would be biased toward IOP measurements during the early postoperative period (likely lower). Instead, we calculated a time-weighted average IOP by linearly interpolating between the recorded IOP values of each eye and by densely resampling the interpolated curve at 1-day intervals. The average of these interpolated values was then taken and used as the average IOP, as determined by medicated daytime measurements.

For this analysis, the LMM used for the main outcome was modified to include the time-weighted average IOP as a predictor. The interaction with time from surgery was used to model the effect of IOP control on progression rate. The details of the model, including the formula for the fixed effects, and an example of average IOP control calculations are reported as Supplementary Material.

RESULTS

• **SAMPLE DESCRIPTION:** Descriptive statistics of the final sample analyzed are reported in Table 1. Additional descriptive statistics for continuous values are reported as Supplementary Material. Despite being a post hoc analysis of a randomized trial, there were no significant differences in the baseline characteristics of the 2 arms. For the main analysis, the mean (SD) number of VFs in the follow-up was 5.7 (1.3), with a median (interquartile range) of 6 (3-14) tests.

• **PRIMARY OUTCOME:** There was no significant difference in the estimated baseline VF sensitivity (global intercepts of the model for the 2 groups, ie, the estimated sensitivity at the day of surgery). The progression of VF damage was significantly faster in the CS group compared with CS-HMS (global slopes of the model for the 2 groups). Results are reported in Table 2 and shown in Figure 2. The results were confirmed in the sensitivity analysis, which included any patient with at least 2 reliable postoperative VF tests (Table 2). Similar results were obtained with the LMM calculated with the *lme4* package (Supplementary Material).

• **SECONDARY OUTCOMES:**

Localized progression

The regional analysis of the VF showed similar results to the primary outcome analysis (Table 3). A significant difference in the RoP of VF damage between the 2 arms

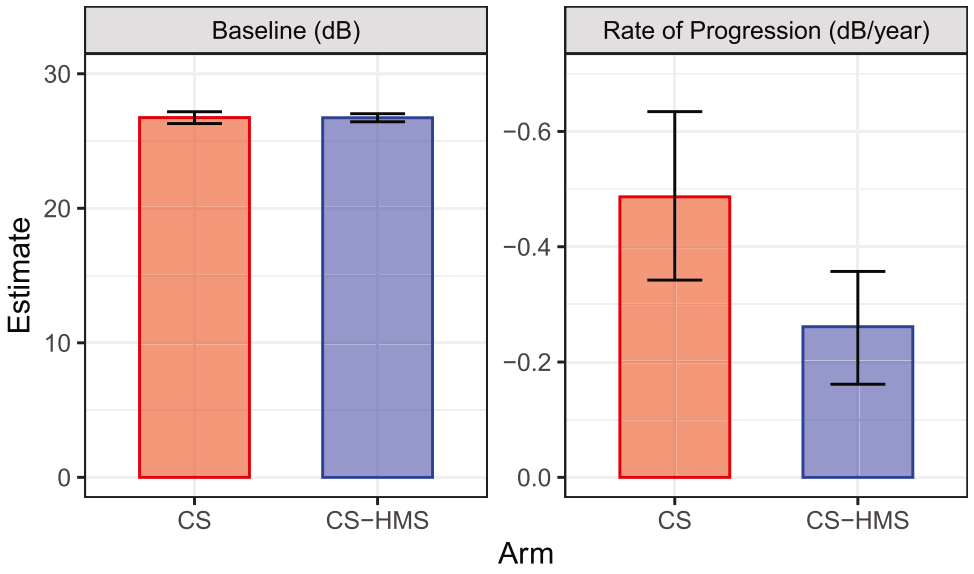

FIGURE 2. The bar plots represent the estimates for the baseline sensitivity and the RoP for the 2 arms using the main and supporting selections. The error bars represent the 95% credible intervals from the hierarchical LMM. CS = cataract surgery, HMS = Hydrus microstent, LMM = linear mixed model, RoP = rate of progression. See Table 2 for numerical values.

TABLE 3. Comparison of RoPs by Cluster

	CS-HMS	CS	Difference	P_d
Cluster 1 (peripheral superior)				
Baseline (dB)	23.86 (23.42, 24.29)	24.06 (23.44, 24.68)	0.20 (–0.58, 0.94)	.602
RoP (dB/y)	–0.27 (–0.40, –0.15)	–0.58 (–0.77, –0.40)	–0.31 (–0.54, –0.08)	**.006**
Cluster 2 (paracentral superior)				
Baseline (dB)	26.26 (25.86, 26.66)	26.33 (25.75, 26.92)	0.07 (–0.63, 0.77)	.839
RoP (dB/y)	–0.28 (–0.39, –0.16)	–0.57 (–0.75, –0.40)	–0.30 (–0.51, –0.09)	**.004**
Cluster 3 (macular)				
Baseline (dB)	29.78 (29.50, 30.05)	29.84 (29.44, 30.25)	0.06 (–0.43, 0.55)	.794
RoP (dB/y)	–0.25 (–0.34, –0.17)	–0.38 (–0.51, –0.25)	–0.13 (–0.29, 0.03)	.099
Cluster 4 (paracentral inferior)				
Baseline (dB)	28.15 (27.80, 28.50)	28.01 (27.48, 28.54)	–0.14 (–0.77, 0.48)	.675
RoP (dB/y)	–0.31 (–0.41, –0.20)	–0.44 (–0.59, –0.28)	–0.13 (–0.32, 0.06)	.171
Cluster 5 (peripheral inferior)				
Baseline (dB)	25.98 (25.62, 26.33)	25.88 (25.34, 26.41)	–0.10 (–0.73, 0.53)	.753
RoP (dB/y)	–0.28 (–0.38, –0.16)	–0.48 (–0.64, –0.32)	–0.20 (–0.40, –0.01)	**.041**
Cluster 6 (temporal)				
Baseline (dB)	26.47 (26.10, 26.83)	26.50 (25.94, 27.04)	0.02 (–0.64, 0.67)	.927
RoP (dB/y)	–0.19 (–0.31, –0.07)	–0.49 (–0.67, –0.30)	–0.30 (–0.52, –0.08)	**.007**

CS = cataract surgery, HMS = Hydrus microstent, RoP = rate of progression.

All estimates are reported as mean (95% credible interval). Baseline indicates the estimated sensitivity at the day of surgery (intercept of the model). Clusters according to Garway-Heath and associates[33] (see also Figure 3).

was found for all clusters except cluster 3 (macular) and 4 (inferior paracentral). For these clusters, the direction of the difference was in agreement with the global trend, but smaller in magnitude. Results by cluster are also presented in Figure 3.

Clusterwise and pointwise analyses, estimated via random effects, also showed significant differences. The mean RoPs for the fastest location and cluster were significantly faster for the CS arm (fastest location: –2.48 dB/y, 95% CI –2.95, –2.00; fastest cluster: –1.37 dB/y, 95% CI –1.77, –0.98) compared to the CS-HMS arm (fastest location: –1.55 dB/y, 95% CI –1.88, –1.23; fastest cluster: –0.79 dB/y, 95% CI –1.06, –0.52). These results are reported in Figure 4.

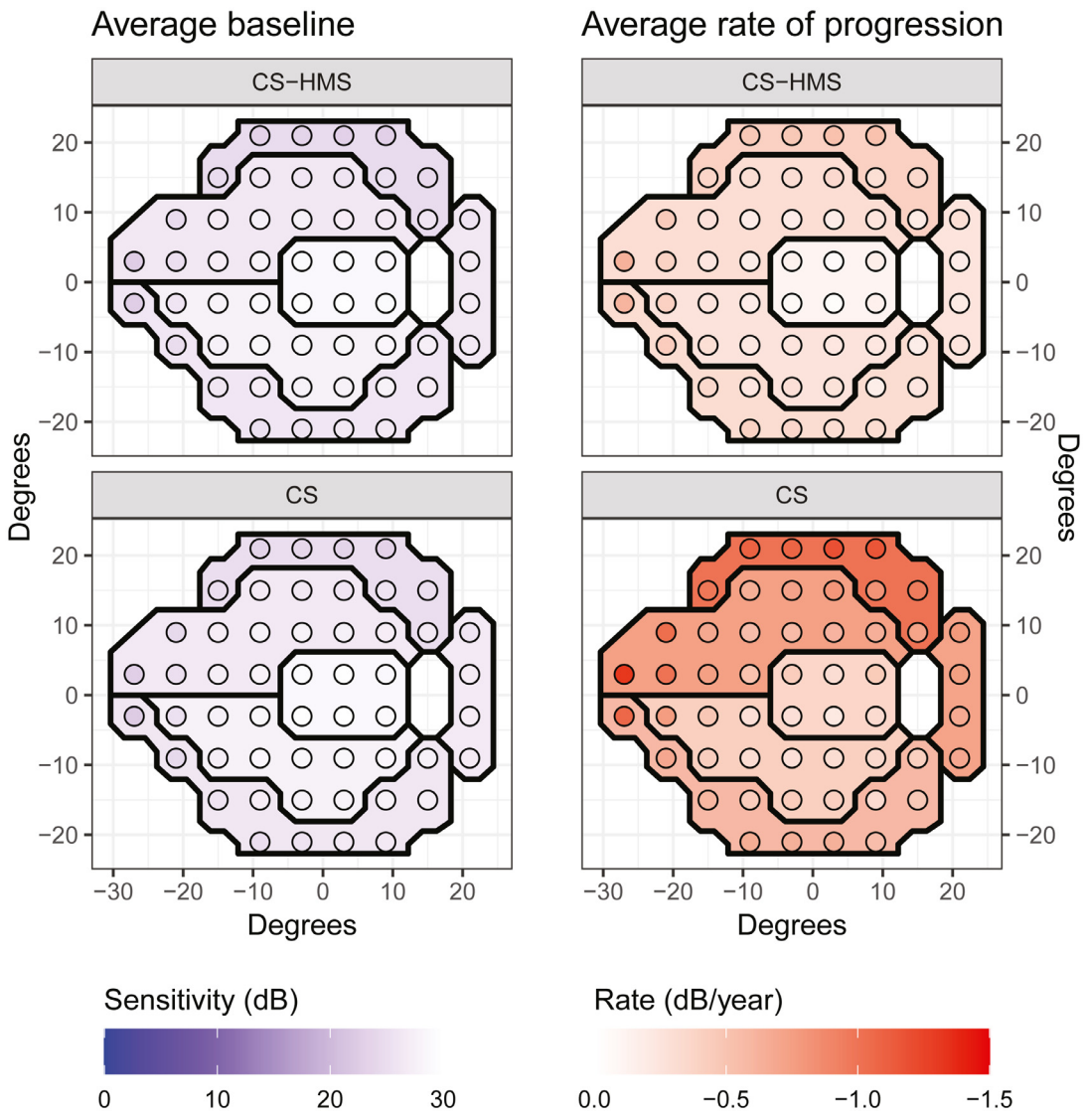

FIGURE 3. Average baseline sensitivity and rate of progression per location and cluster of the 24-2 grid, calculated as the average of the estimates from the models fitted on individual eyes. CS = cataract surgery, HMS = Hydrus microstent. Clusters according to Garway-Heath and associates.[33]

Time to progression

Curves for the survival analysis for the 2 arms are reported in Figure 5. Overall, patients in the CS arm took a shorter time to reach the progression event with all predefined thresholds, but this difference was significant only at 5.5 dB ($P = .017$) with the Cox model, indicating that the CS arm had a larger proportion of fast progressors but similar proportions of slow and moderate progressors. More significant differences were found when proportional hazards were not assumed (intEL test) and all cutoffs showed at least a significant localized difference (supEL test).

Effect explained by daytime IOP

The time-weighted average daytime IOP, as estimated from clinic measurements, was compared using a simple linear model. The estimates were 16.62 mm Hg (95% CI 16.37, 16.87) for the CS-HMS arm and 17.22 mm Hg (95% CI 16.85, 17.58) for the CS arm. The estimated difference was small (0.59 mm Hg, 95% CI 0.16, 1.03) but significant ($P = .008$). The multivariate LMM showed a significant effect of time-weighted average IOP onto the RoP (–0.06 dB/y/mm Hg, 95% CI –0.10, –0.03, $P_d < .0001$). However, when multiplied by the small average IOP difference, this effect, although significant, would explain only a small proportion (17%) of the observed difference in RoP between the 2 arms (–0.04 dB/y, 95% CI –0.06, –0.02; $P < .0001$). Indeed, there was a larger and significant residual difference in RoP that was unexplained by the difference in daytime average IOP control (–0.19 dB/y, 95% CI –0.37, –0.02, $P = .0328$; 83% of the total difference).

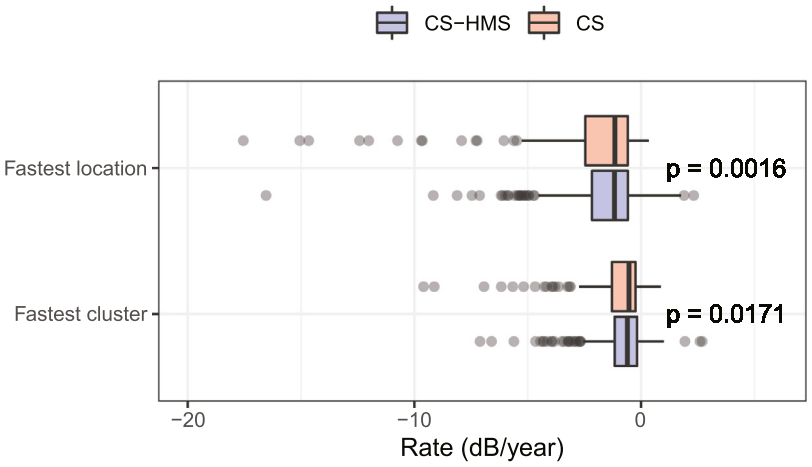

FIGURE 4. The box-plots represent the distribution of the rate of progression of the fastest progressing clusters and location. The boxes enclose the interquartile range; the vertical midline indicates the median. The whiskers indicate the 95% quantiles.

DISCUSSION

We provide the first analysis of the effect of a canal-based MIGS device on VF damage progression in glaucoma patients monitored for up to 5 years within the HORIZON study, a prospective, randomized multicenter trial. We present multiple lines of evidence to show that CS-HMS preserved VF by reducing the rate of progression compared with CS alone. Most MIGS studies have reported and compared their efficacy for reducing mean IOP and number of IOP medications. However, preventing visual loss is the true goal of glaucoma treatment. Because individual IOP measurements are samples of what the actual IOP effectively is, this parameter may not always correlate with visual preservation.

Our primary outcome measure was a direct comparison of the RoP of VF damage between the 2 arms of the trial. We used a hierarchical LMM model, able to maximally exploit the detailed pointwise information contained within individual VF tests, to accurately estimate the mean global RoP for the 2 treatment arms. Our approach also addressed specific issues arising in VF data from glaucoma patients, such as censoring at the measurement floor and the peculiar spatial patterns of damage.[42] LMMs, with different levels of complexity, have been successfully used to detect and quantify progression in glaucoma patients.[33-35,43,44]

Recent simulation studies have shown that trend analyses performed with hierarchical LMMs are more powerful than event-based methods in detecting significant treatment effects, justifying our choice.[33] The same methodology has been employed to test the differences in VF damage progression in TAGS.[45] Moreover, methods that provide estimates of the RoP allow better understanding of long-term implications of glaucoma treatments. For example, an RoP of –0.5 dB/y is commonly reported for glaucoma cohorts under standard clinical care,[43,55,56] which is in excellent agreement with our estimates for the CS arm (Table 2).

It has been postulated that as little as 10% reduction in the RoP might prevent blindness in thousands of eyes if broadly applied.[55] The effect observed in the CS-HMS arm was far greater (47% and 43% RoP reduction with the main and sensitivity analysis, respectively, calculated from the RoP in Table 2 as Difference/CS) with important potential implications for preventing blindness and reduced quality of life from glaucoma.[30,57,58] Prior evidence suggests that disability increases with the severity of VF damage across the full range of VF sensitivity for a variety of daily activities including driving,[59] reading,[59,60] physical activity,[61] the ability of patients to leave their home,[61] and increase the rate of hazardous falls.[62,63]

Although the immediate impact of small amounts of VF loss may not be catastrophic to patients, especially those with greater functional reserve, they are not insignificant. For example, even a 1-dB VF loss corresponds, on average, to a 22% increased chance of driving cessation[59] and a 21% increased chance of patients not leaving their homes.[61] Furthermore, studies have shown that even in mild VF loss, contrast sensitivity can be reduced with early symptoms reported by patients.[64]

Contrast sensitivity may be affected before white-on-white perimetric loss[65] and worsens as VF loss progresses from mild to moderate to severe.[64,66] Considering that contrast sensitivity loss may occur earlier than peripheral vision loss and its impact on patient-related outcomes and quality of life,[57] protection even in mild-moderate disease, as in this study, is likely to provide a tangible benefit in patient symptomatology and function.

Importantly, patients in both arms were treated according to standard clinical practice, with treatment escalated as necessary, making these results translatable to the clinic.

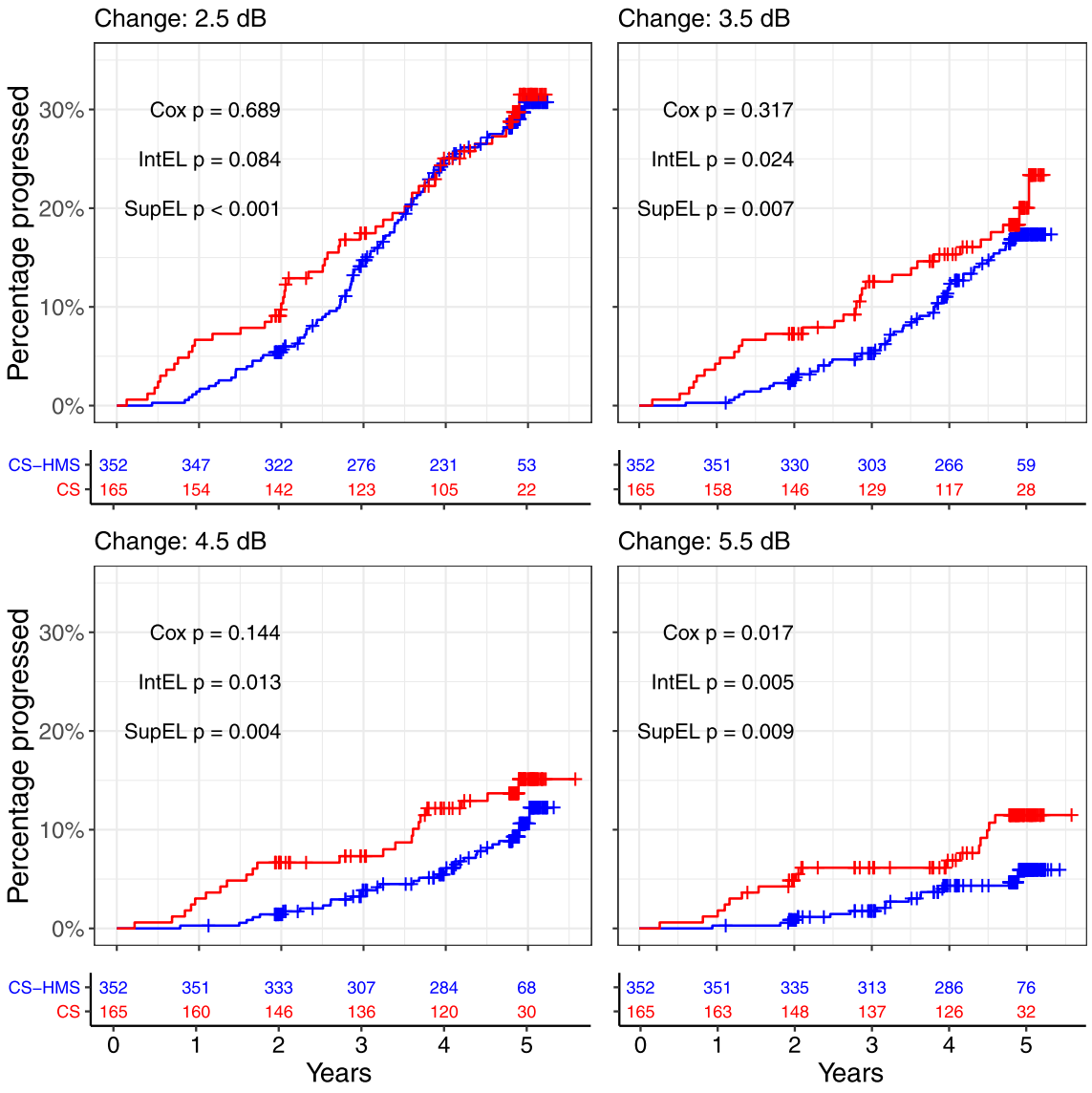

FIGURE 5. Survival curves for the time to detect change in the 2 arms at defined thresholds. Cataract surgery alone in red, and cataract surgery and Hydrus-Microshunt in blue. The small crosses indicate censored data. The tables at the bottom of each graph report the number of subjects at risk.

One important aspect is that the average RoP in our analyses refers to VF sensitivity. This differs from calculations based on mean deviation because it includes the effect of normal aging and does not attribute more weights to the central locations.[67]

However, the reported effect of aging is small in magnitude (–0.06 dB/y in Spry and associates[68]) and would apply homogeneously to the 2 arms, not affecting the validity of our comparison. Moreover, despite attributing more weight to central locations, mean deviation has a strong 1:1 relationship with mean sensitivity (correlation coefficient: 0.98 in our data); this would make our findings largely comparable with previous literature.

However, VF damage progression might not be entirely captured by the average RoP. For example, in the LiGHT trial, most of the difference in progression between the 2 arms was observed in the extreme negative tail of the distribution of pointwise progression slopes, with no difference in the average RoP.[9,69] We performed a similar analysis by comparing the RoP of the fastest-progressing cluster and location per eye between the CS and CS-HMS. These results confirmed the main analysis, showing a significant difference for both clusters (42% reduction in the fastest RoP) and locations (37% reduction).

Interestingly, with our Cox survival analysis, we showed a significant difference only when changes greater than

5.5 dB from the day of surgery were considered, despite a consistent trend for all cutoffs. This result indicates that our observed difference in the mean RoP is, at least in part, influenced by a subgroup of fast-progressing eyes. Additional statistical tests that do not assume proportional hazards identified more significant differences. Interestingly, all cutoffs showed a significant localized difference with the supEL statistics.

This further supports the presence of a significantly higher proportion of fast progressors in the CS group, because localized differences earlier in the curves for smaller cutoffs, such as 2.5 dB, would be created by fast-progressing eyes reaching that cutoff more quickly (Figure 5). This is clinically meaningful, as it indicates that the implant is able to reduce the risk of extremely fast VF progression, potentially sparing blindness. It is also consistent with the results of the LiGHT trial in which the medication-dependent arm showed higher rates of fast to moderate VF progression in the presence of equal office IOP measurements.[9]

Different results were obtained with the same analysis performed in TAGS, where most of the difference was found for the slow- and intermediate-progression cutoffs.[45] It should be noted that rather than serving as a traditional survival analysis, our time-to-event methodology was mainly aimed at characterizing differences in the proportion of RoP slopes faster than specific cutoffs. A more conventional description of the distribution of the slopes is reported as Supplementary Material. More sophisticated VF denoising techniques that do not assume a linear decay of sensitivity might also be employed in the future.

Although not all patients are fast progressors, these patients are the most vulnerable to serious vision loss. Yet it is difficult to predict those who will deteriorate rapidly and, thus, when treating glaucoma, we usually treat all to protect those who may progress fast. Based on our findings, combining HMS with CS resulted in an absolute risk reduction of fast progression of 5.5% (95% CI 1.5%, 9.6%), even when both groups had equal access to medical IOP lowering. This corresponds to a number needed to treat of 18 (95% CI 10, 67).

Interestingly, the observed reduction in VF deterioration was achieved in the CS-HMS arm despite similar daytime IOP measurements and thresholds for postoperative reintroduction of medications during follow-up in both arms. Moreover, this reduction in VF deterioration was achieved in the CS-HMS arm despite a lower number of postoperative medications, suggesting that VF protection did not arise from more intensive pharmacologic treatment of one arm.[11,18]

As in the case of LiGHT,[9] this might be explained by a better and more consistent IOP control achieved with the Hydrus implant, whose outflow effect is not affected by medication compliance or gaps in dosing, such as during sleep. This is supported by our secondary analysis on the effect of daytime IOP: the IOP measured during daytime clinic hours was very similar between the 2 arms,[11,18] albeit requiring significantly more medications in the CS arm.

In fact, the very small difference in average daytime IOP control does not fully explain the difference in RoP between the 2 arms. Poor or inconsistent medication compliance or worse IOP control outside our daytime measurement windows in the clinic may be responsible for the difference between the 2 groups,[70] but would not be captured by our study design. Further research would be needed to confirm this hypothesis, for example, by collecting 24-hour IOP profiles and monitoring VF progression over many years.

There is evidence that the Hydrus implant might reduce circadian fluctuations in aqueous dynamics,[71] supporting this as a plausible mechanism for the observed effect. Poorer disease control in the CS arm is also strongly supported by the higher incidence of subsequent incisional glaucoma surgery, significantly higher at 3[11] and at 5 years.[18] Another potential reason for the small effect of IOP is the use of the average value over the time of follow-up for our analysis. This was meant to capture the effect of the average IOP control on the RoP.

A more accurate model could be devised by treating the IOP as a time-varying covariate. However, such a model would require much more frequent IOP measurements and knowledge of the temporal relationship between changes in IOP and changes in VF progression. This will be the objective of future work. Additional investigation will also be required to elucidate the role of other baseline characteristics, such as race, sex, age, axial length, and number of medications and damage at baseline. However, because of randomization (see Table 1), these factors are unlikely to have had a meaningful effect on the comparisons between the 2 arms presented in this work.

The spatial distribution and level of damage at baseline was very similar between the 2 arms. In the analysis by cluster, the fastest RoP was observed in the superior VF, which also showed the largest differences between the 2 arms. This is in agreement with previous observations that the superior VF is the most vulnerable to glaucoma damage.[72-74] No difference in RoP between the 2 arms were observed in the macular and inferior paracentral clusters, largely composed of locations close to central fixation in the 24-2 grid. However, despite not reaching significance and being smaller in magnitude, the direction of the difference between the 2 arms in these clusters was in agreement with the global trend (slower RoP for the CS-HMS arm).

The RoP was also generally slower compared to the other clusters. The central and paracentral VF is known to be mostly spared until later in the history of the disease when tested with the conventional 24-2 grid. This is often explained by the larger number of retinal ganglion cells in the central retina,[75] which might mask progression until a significant proportion of cells is lost. In fact, when investigated with a Goldmann III stimulus, such as in standard perimetry, spatial summation might make the relationship

between VF loss and ganglion cell loss shallower near the macula than in the periphery.[76-78]

This might explain the slower RoP and the smaller differences observed for the central clusters in our results. Therefore, rather than an actual regional effect, such variations might be the artifactual product of how visual function is measured in standard perimetry. This aspect could be further investigated with tests using bespoke stimuli and denser macular grids.[69]

This analysis has limitations. It was not possible to mask the investigating clinician or the patient to the type of treatment administered. However, although this could have biased Goldmann applanation tonometry measurements, it is unlikely to have significantly affected the execution of the VF test. Moreover, we took special care to minimize bias for the primary outcome analysis by masking the investigators performing the data extraction and analysis to the treatment allocation of the participants.

Another important aspect to consider is that such a detailed evaluation of VF progression was not part of the preplanned analysis for the trial, and therefore pointwise VF data were not systematically stored by the centers. However, we were able to retrieve usable data for the vast majority of the participants.

For the main analysis, the attrition rate was <10% (see flowchart in Figure 1), which is often considered an acceptable threshold in planned trial analyses. A larger proportion of patients was lost for the CS arm (12%) compared to the CS-HMS arm (4%), but we accounted for this by confirming our results with our sensitivity analysis, bringing the attrition rate below 10% for both arms (5% and 2%, respectively).

Additionally, although a time span of 5 years was sufficient to detect differences between the 2 arms, glaucoma is a lifetime disease and it is difficult to predict very long term effects without prolonged follow-up periods.

Finally, the population of this trial is composed of people with early or moderate disease undergoing cataract surgery, and these results might not generalize to people with advanced glaucoma, patients with secondary POAG, or standalone HMS. Nevertheless, people with early damage at presentation make up a large proportion of the population in glaucoma clinics.[79] These results are therefore likely to be relevant for a considerable number of patients.

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