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# FROM CLINICAL TRIAL TO REAL-WORLD PRACTICE

An expert panel review of 2- and 5-year outcomes from the HORIZON Trial.

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## INTRODUCTION

*Taken together, the data from the HORIZON trial, in which the **Hydrus® Microstent (Alcon) + cataract surgery (CS)** was compared to **CS alone**, offer an example of the impact we can have on patients' daily lives. Because of the safety profile of this microstent, we can feel confident in surgically intervening earlier in the disease continuum. As a result, we can accomplish long-term control of IOP, the only known modifiable risk-factor for glaucomatous progression, and we are doing so in a way that addresses the significant medication compliance issues our patients face.*

*Regardless of how impressive the data may seem, however, it is fair to ask, "to what extent should these clinical trial data guide clinical practice when treating mild-to-moderate primary open-angle glaucoma?" We can question, for example, whether the outcomes from HORIZON are because of the study's demographics, or whether they are representative of what is observed in real-world practice. As clinicians, we also want to be assured that the outcomes are, indeed, clinically meaningful.*

*To answer these questions, I recently met with two of my colleagues, Brian Flowers, MD, and Pradeep Ramulu, MD, PhD, to discuss the findings from the HORIZON trial and how we use these data in our own clinical practices. A summary of our discussion is presented in the following pages.*

*In short, we concluded that, rather than a single data point, it was the total evidence from HORIZON that suggests that **Hydrus® + CS** is a rational option for addressing primary open-angle glaucoma, regardless of the stage of the disease. Furthermore, the rigor of the trial gives us confidence as we counsel patients in our clinics about their options to manage their glaucoma.*

**– I. Paul Singh, MD**

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# Early Intervention in Primary Open-Angle Glaucoma and the Implications for Long-Term Outcomes

The evolution of the MIGS class allows surgeons greater ability to individualize treatment choices for patients.

BY I. PAUL SINGH, MD; BRIAN FLOWERS, MD; AND PRADEEP RAMULU, MD, PHD

In glaucoma management, one of our goals is to individualize the approach to treatment while considering the impact on patients' quality of life. Yet, in everyday practice, ophthalmologists have historically lacked options with which to achieve that goal. Each of us learned in training, for instance, that patients with primary open-angle glaucoma (POAG) should be started on drops, with more drops added as necessary, before moving to laser if necessary, and finally to incisional surgeries if all else failed. It is important to understand the rationale for this way of treating POAG: prior to the introduction of minimally invasive glaucoma surgery (MIGS), drop therapy was considered sufficient for controlling intraocular pressure (IOP), even if its use was associated with side effects and compliance issues. Furthermore, the only surgical options at our disposal at that time, namely trabeculectomy and glaucoma drainage devices, carried with them appreciable risks of complications and failure.[1,2] In short, procedural interventions were considered second- and third-line choices because their use precluded future options.

The introduction of the MIGS class altered the approach to management of POAG (see *The Definition of MIGS*).[3] The favorable safety profile of MIGS relative to traditional incisional surgeries may be a reason that ophthalmic surgeons have increasingly employed MIGS at earlier stages of the disease.[4] Indeed, the broad array of MIGS devices and surgeries now available for clinical use has fostered a proactive versus reactive approach to treatment that has come to be known as *interventional glaucoma*.[5] The stated goals of this approach are to reduce and steadily maintain IOP targets, delay or avoid higher-risk surgery, and decrease reliance on patient adherence and compliance, while secondarily resetting the burden on patients by decreasing medication load.[5]

## THE DEFINITION OF MIGS[3]

1. Use of an *ab interno* approach
2. Minimal trauma to the target tissue with negligible disruption of normal anatomy and physiology
3. At least modest efficacy
4. High safety profile
5. Rapid patient recovery with minimal impact on their quality of life

It is our belief that the array of procedures, devices, and surgeries in the glaucoma treatment armamentarium collectively improve the ability to individualize treatment for each patient while considering the impact on their quality of life. Furthermore, because of the many benefits associated with MIGS, including the prospect of reducing or eliminating medication burden, we should not be constrained by traditional definitions of a successful outcome. Instead, because of the greater ability to personalize care, we can have meaningful conversations with patients regarding their options and consider the risk-benefit profile on an individual basis.

## ADDRESSING MULTIPLE PARTS OF THE AQUEOUS DRAINAGE PATHWAY

One of the difficulties of treating glaucoma in real-world practice is that we do not know where in the aqueous drainage system the blockage is occurring.

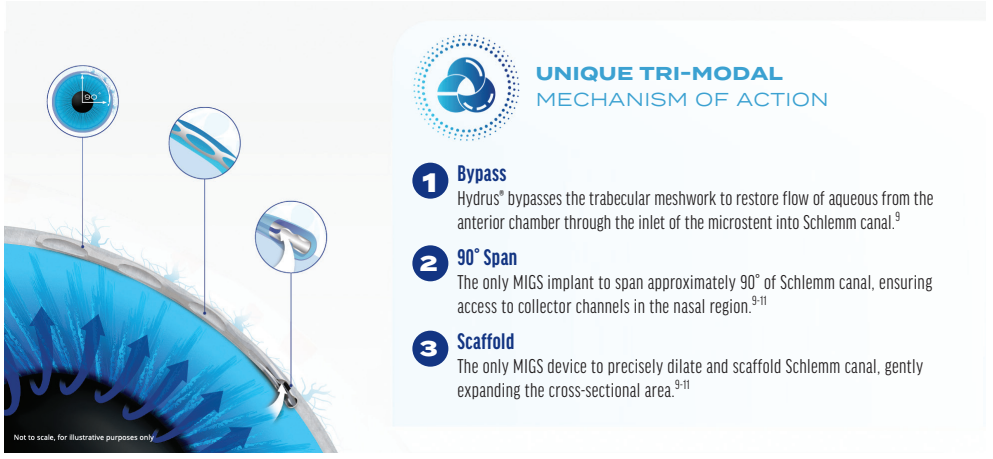


Figure 1. Mechanisms of action for Hydrus® Microstent.

We can be partially guided in this regard by the published literature. We know, for instance, that while the trabecular meshwork (TM) is a source of resistance in POAG, the juxtacanalicular region and the Schlemm canal (SC) are also important areas of blockages.[6] Furthermore, the collector channels direct flow to the distal drainage system, and ultimately to the episcleral venous system,[7] but blockages/herniations or collapse of the SC may block the ostia of the collector channels in eyes with POAG.[8] Collectively, this information suggests that one or more of the anatomic structures of the complex aqueous drainage pathway may cause interruptions in flow dynamics. And so, MIGS options that address multiple potential sources of resistance may offer an advantage.

It is notable, then, that the Hydrus® Microstent (Alcon) is associated with a trimodal mechanism of action: it (1) directs aqueous to bypass the TM through the inlet of the device to allow fluid to pass from the anterior chamber into the SC[9]; (2) it scaffolds the SC to provide permanent patency in the canal to prevent SC collapse[9-11]; and (3) it maintains patency across a 90° span of the canal,[9-11] providing access to multiple collector channels over time with no need to specifically target them for intervention (Figure 1). Made of nitinol, a commonly used material proven to be biocompatible, the Hydrus® Microstent is designed with a slight contour that matches the natural curvature of the SC with three open windows along its 8-mm length that face the anterior chamber, thereby facilitating access to the collector channels.[12] Thus, successful implantation of a Hydrus® Microstent mechanically opens and maintains the patency of 90° of SC, which restores aqueous flow. By contrast, bypassing the canal with a focal stent may be insufficient to counteract a collapse of the SC.[13]

This trimodal mechanism of action and other considerations appear to have contributed to superior outcomes when **Hydrus® + cataract surgery (CS)** was compared to **CS alone** in the HORIZON pivotal trial.[11,14,15] The important data from this study are reviewed elsewhere in this monograph (see *Highlighting Key Data from HORIZON After 2 and 5 Years of Follow-up* on page 6). Briefly, Hydrus® Microstent received regulatory approval on the basis of findings from the first 2 years of the study, which demonstrated a high percentage of patients with at least 20% reduction in mean washed-out diurnal IOP from baseline (77.3% **Hydrus® + CS** vs 57.8% **CS alone**).[11] The study was then continued out to 5 years of follow-up to monitor safety and efficacy outcomes; however, medication washout was not continued beyond 24 months. Data from years 3 to 5 demonstrated continued durability in the IOP response, while also providing insights into the impact that MIGS can have on the clinical course relative to **CS alone**. For example, the data at both 2 and 5 years of follow-up demonstrated a higher percentage of patients on zero medications, a significant reduction in the need for invasive

## IN THEIR OWN WORDS

**How Can the Evidence From HORIZON Inform Decision-Making?**

**Pradeep Ramulu, MD, PhD:** Every eye that has moderate or advanced glaucoma once had mild disease. That fact should guide our thinking about how we treat patients with mild primary-open angle glaucoma (POAG)—we just do not know which patients will progress and which won't. Based on the HORIZON trial, we have evidence that intervening early has a meaningful impact on the long-term outcome: more eyes achieved medication-free status and fewer eyes required a secondary surgical intervention. Based on that, one could argue that you have an obligation to discuss minimally invasive glaucoma surgery (MIGS) options with patients who take medications for POAG and have a visually significant cataract if they are eligible for the surgery. If you don't, there's a chance that patient will hear about it from a friend or family member, and you suddenly have a dissatisfied patient.

**I. Paul Singh, MD:** The HORIZON trial showed that **Hydrus® + cataract surgery** is an effective IOP-lowering procedure that has a good chance of lowering patients' reliance on medications. These data give me confidence in using the device in appropriately selected patients regardless of glaucoma stage. In my thinking, the reduced requirement for secondary interventions in the **Hydrus® Microstent + cataract surgery** group compared to the **cataract-surgery-alone** group suggests that treating the anatomy underlying the glaucomatous pathology had a meaningful effect on long-term outcomes. If you believe that to be the case, why not present it as an option for patients with POAG, regardless of whether it is mild or moderate?

**Brian Flowers, MD:** When we sit with our patients, the options are often presented in a binary fashion. What we have learned from HORIZON and other studies forces us to rethink whether this is the case. There is mounting evidence that MIGS offers not only pressure control, but also less medication burden long-term with procedural interventions. It is difficult to know if this is based strictly on compliance or some other factors. Nevertheless, it's becoming difficult to ignore at this point.

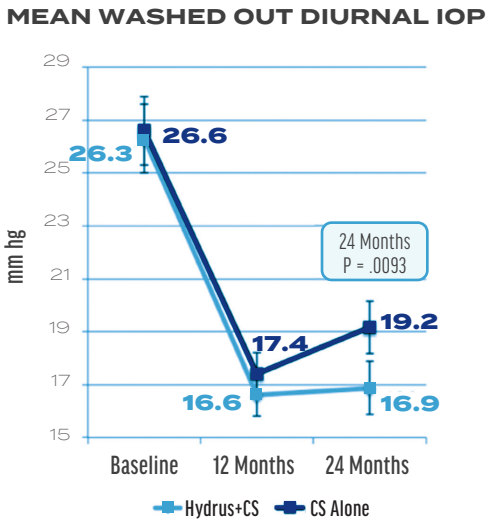


Figure 2. Graph showing the IOP response to **Hydrus® + cataract surgery (CS)** and **CS alone** in the Hydrus II study. The rebound of IOP in year 2 in the CS group suggested greater durability with the Hydrus® Microstent.[12]

secondary surgical intervention, and a greater-magnitude reduction in IOP in the **Hydrus® + CS group** compared to **CS alone**.[11,15]

## CONFIDENCE IN THE DATA

From our perspective, there are several reasons why the HORIZON data should help to shape clinical decision-making (see *In Their Own Words*). For instance, there is accumulating evidence to support the idea that MIGS devices have an additive, clinically meaningful effect on IOP lowering compared to **CS alone**. Although it is well known that **CS alone** lowers IOP,[16] data from major clinical trials suggest that MIGS devices deliver consistently better IOP-lowering efficacy. In the COMPASS, HYDRUS II, and HORIZON trials, a MIGS device plus CS was compared to **CS alone**. Across the three studies, the IOP-lowering efficacy of **CS alone** was similar. However, in each trial, MIGS plus CS conferred a consistently greater reduction in IOP.[11,12,17] Furthermore, in the HYDRUS II Study, mean diurnal washed-out IOP in the **Hydrus® + CS** group was slightly lower when compared to the **CS alone** group at 12 months, and then the IOP rebounded at 24 months in the **CS alone** group, suggesting greater durability with MIGS devices (Figure 2).[12]

Another reason we can feel confident in the HORIZON data is the study's design and methodology. Conceived as a 5-year prospective study, the first 2 years of the study comprised the pivotal phase, and then patients were followed for an additional 3 years to further assess safety and efficacy. The length of prospective follow-up in HORIZON is unprecedented in terms of MIGS studies, as is its patient retention rate: the study was able to retain 80% of patients (n = 442/556) originally randomized to receive a Hydrus® Microstent through 5 years.[15] Furthermore, compared to other pivotal studies which only enrolled patients from the United States, HORIZON enrolled patients from nine countries on three continents. Taken together, these facts make it more straightforward to apply the data in real-world settings as we counsel patients on their options for managing POAG.

## CONCLUSION

The HORIZON Trial met its primary endpoint at 2 years in demonstrating a higher percentage of patients with a reduction of at least 20% in mean washed-out diurnal IOP from baseline after receiving **Hydrus® + CS** compared to **CS alone**.[11] Longer-term follow-up helped to confirm the safety and efficacy of the device.[14,15] These data alone are impressive in showing the benefits of a MIGS device in delivering long-term outcomes. Yet, a deeper look at the findings from HORIZON suggests that adopting a proactive mindset by intervening earlier in the disease course with **Hydrus® + CS** has many benefits: at both 2 and 5 years of follow-up, patients in the **Hydrus® + CS** arm of the HORIZON Trial were more likely to be on zero medications and were less likely to require more invasive surgical intervention.[11,14,15] Furthermore, it is worth noting that Hydrus® is consistently recognized for the highest data quality among all MIGS.*[18-20]

Based on these learnings, we can have confidence in counseling patients regarding how the Hydrus® Microstent could decrease their medication burden. It is, indeed, the total evidence from HORIZON that supports the idea that MIGS can have a meaningful impact on patients' quality of life. These learnings can guide clinical decision-making with respect to the treatment algorithm for the patient with POAG. ■

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*AAO: Hydrus® received a data rating of "moderate quality, strong recommendation," the highest rating among all MIGS; Cochrane: Hydrus received the "moderate certainty" grade of evidence in an independent systematic review in 2020; EGS: Hydrus® received a data rating of "moderate," the highest rating among all MIGS.

Refer to page 8 for Important Product Information. 

# Highlighting Key Data from HORIZON After 2 and 5 Years of Follow-up

**BY I. PAUL SINGH, MD; BRIAN FLOWERS, MD; AND PRADEEP RAMULU, MD, PHD**

The HORIZON trial, a phase 3 clinical trial that compared **Hydrus® Microstent (Alcon) + cataract surgery (CS)** to **CS alone**, was the largest minimally invasive glaucoma surgery (MIGS) pivotal trial conducted to date, with 38 sites in nine countries.[1-3] Approximately 40% of the Hydrus® patient population came from outside the United States. For the study, patients with mild-to-moderate primary open-angle glaucoma (POAG) on one to four medications underwent CS and then were randomized 2:1 to Hydrus® Microstent placement (n = 369) or **CS alone** (n = 187).[1] The primary endpoint of the study was the percentage of patients with a 20% or greater reduction in washed-out diurnal intraocular pressure (DIOP) after 2 years of follow-up. The main secondary endpoint was the change in washed-out DIOP at 2 years.[1] In the second phase of the study, patients were continuously followed for an additional 3 years to monitor safety outcomes and to assess predefined efficacy endpoints.[2,3] Notably, approximately 80% of patients (n = 442/556) originally enrolled to receive Hydrus® Microstent were followed to the 5-year study endpoint.[3]

## THE PIVOTAL PHASE: YEAR 2 DATA

The study met its primary endpoint at 2 years (Figure 1).[1] The mean reduction in mean washed-out DIOP at 2 years was -7.6 ±4.1 mm Hg and -5.3 ±3.9 mm Hg in the **Hydrus® + CS** group and **CS alone** group, respectively (difference = -2.3 mm Hg; *P* <.001). The mean number of medications was reduced from 1.7 ±0.9 to 0.3 ±0.8 in the **Hydrus® + CS** group and from 1.7 ±0.9 to 0.7 ±0.9 in the **CS alone** group (difference = -0.4 medications; *P* <.001).[1]

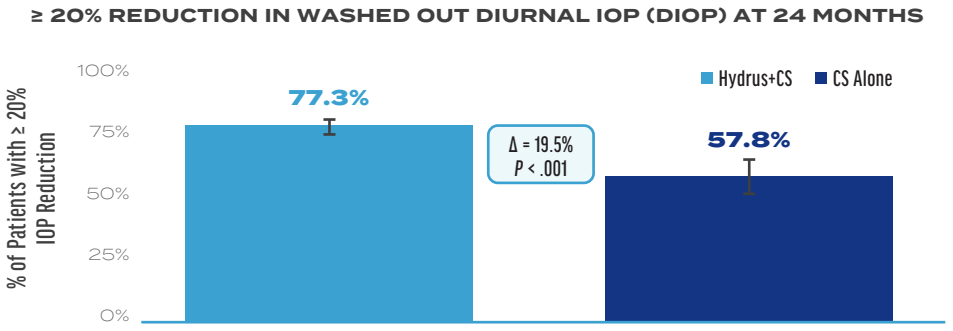



Figure 1. A greater percentage of patients achieved ≥ 20% reduction in washed-out diurnal IOP at 24 months in the **Hydrus® Microstent + cataract surgery (CS)** group compared to **CS alone**, which was the primary endpoint in the HORIZON trial.[1]

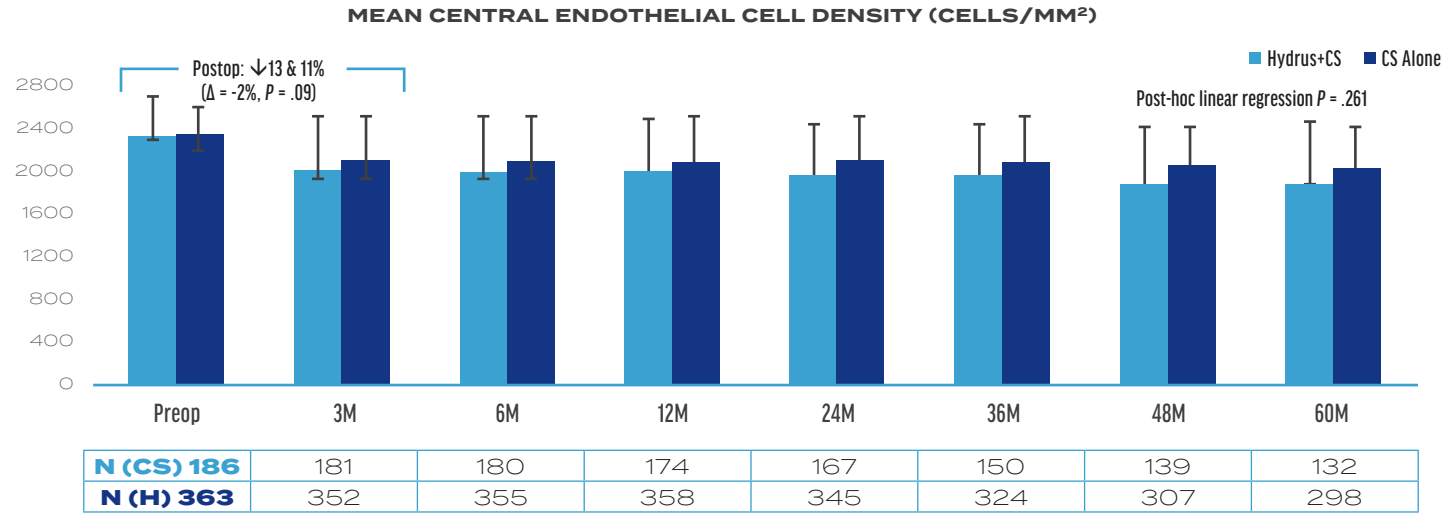
As for safety, there was a low percentage of adverse events overall. Postoperative cell and flare were more common in the **Hydrus® + CS** group in the first week, but all cases resolved within the first month.[1] The most common adverse event reported in the **Hydrus® + CS** group was peripheral anterior synechiae (PAS) or iris tissue near the inlet; these were considered obstructive in 14 of 369 (3.8%) affected eyes and nonobstructive in 55 of 369 (14.9%) eyes. The investigators noted that observation of PAS or adhesion did not affect the outcome.[1]

## EXTENDED FOLLOW-UP: YEAR 5 DATA

The percent of subjects with reported serious adverse events was 3.5% in the **Hydrus® + CS** group (n = 13/369) and 4.3% in the **CS alone** group (n = 8/187).[3] There was no difference from year 2 to 5 in secondary safety outcomes, except for the rate of PAS, which was significantly higher at 5 years in the **Hydrus® + CS** group (14.6%) compared to **CS alone** (3.7%; *P* = .0001). However, the majority of eyes with PAS in the Hydrus® Microstent group (8.7%) were not device obstructing, and there was no difference in IOP between patients with (16.9 ±3.3 mm Hg) and without PAS (16.6 ±3.5 mm Hg; *P* = .49). In the majority of eyes with PAS (30/42; 71.4%), PAS were focal or less than 1 clock hour in size. There was no impact on IOP or visual acuity due to PAS, and there were no sequelae observed in eyes with device obstruction.[3]

The investigators observed a 2% between-group difference in mean central endothelial cell density (ECD) at 3 months postoperatively (11% rate of endothelial cell loss [ECL] **CS alone** vs 13% ECL **Hydrus® + CS**; *P* = .08). The difference may be attributable to the additional manipulation required when inserting the Hydrus® Microstent. The between-group difference increased to 6% over 5 years (13% ECL **CS alone** vs 19% ECL **Hydrus® + CS**), but the difference was not statistically significant (Figure 2).[3]

In addition to ECD values alone, the rate of change of ECD was also looked at. In the study, the year-to-year ECL ranged from zero to 2% in the **Hydrus® + CS** group and zero to 1% in the **CS alone** group. There was no statistically significant difference in the rate of ECL from 3 months to 5 years in either group, and there was no shift toward increased ECL in years 4 or 5 compared to prior years.

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|---|---|---|---|---|---|---|---|
| **N (CS) 186** | 181 | 180 | 174 | 167 | 150 | 139 | 132 |
| **N (H) 363** | 352 | 355 | 358 | 345 | 324 | 307 | 298 |

Figure 2. Mean central endothelial cell density in the **Hydrus® + cataract surgery (CS)** and **CS alone** groups at 5 years in the HORIZON trial.[3]

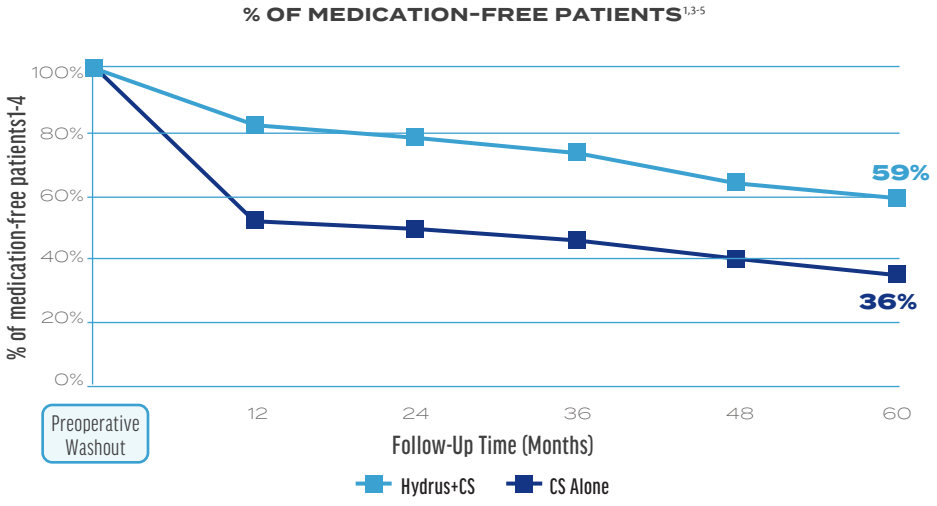


Figure 3. A higher percentage of patients in the **Hydrus® Microstent + cataract surgery (CS)** group achieved medication-free status at 5 years compared to the **CS alone** group.

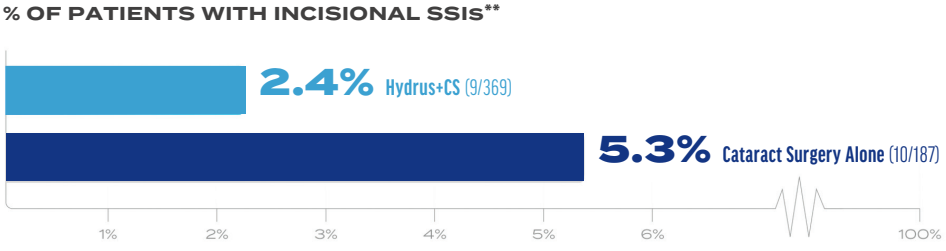


Figure 4. **Hydrus® Microstent + cataract surgery (CS)** delivered a 50% reduction in incisional secondary surgical interventions (SSIs) compared to **CS alone**.[3] **Secondary Surgical Intervention (SSI) include trabeculectomy, tube shunt, gel stent, ECP/TSCP, non-penetrating; (9/369 Hydrus and 10/187 CS).

Of note, at the 5-year follow-up, the proportion of eyes with ≥ 30% ECL increased from 17.3% at 3 months to 20.8% (*P* = .27) in the **Hydrus® + CS** group and from 9.4% at 3 months to 10.6% (*P* = .85) in the **CS alone** group. Logistic regression showed no difference in the rate of change of ≥ 30% ECL between the **Hydrus + CS** group compared to the **CS alone** group from 3 months to 5 years (*P* = .82). Furthermore, no eyes with ≥ 30% ECL in the **Hydrus® + CS** or **CS alone** groups had associated clinical sequelae.[3]

As for secondary effectiveness outcomes, a higher percentage of patients achieved medication-free status with **Hydrus® + CS** versus **CS alone** (Figure 3),[3] and **Hydrus® + CS** was associated with a reduction in the rate of secondary incisional surgery (Figure 4).[3] ■

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# Bringing it All Together

**BY I. PAUL SINGH, MD; BRIAN FLOWERS, MD; AND PRADEEP RAMULU, MD, PHD**

When each of us discusses treatment options with patients with primary open-angle glaucoma (POAG) in the clinic, we are focused on determining what course of action would be best for the individual in front of us, now and in the future. The data from clinical trials may or may not be part of that conversation, but they nevertheless guide the treatment options we consider. Thus, the robustness and believability of data from a clinical trial, and to what extent a study demonstrates clinically meaningful outcomes, are important for informing the individualized risk-benefit analysis we perform for each patient. What impact the treatment may have on the patient's quality of life is also an important consideration.

As we consider the 2- and 5-year outcomes from the HORIZON trial, we can draw some conclusions as to how they impact clinical decision-making. For example, the totality of this evidence changes the definition of success with a patient. As noted in the study, **Hydrus® Microstent (Alcon) + cataract surgery (CS)** resulted in a greater magnitude reduction in IOP and higher success rates compared to **CS alone**. Of particular interest to us is that a greater percentage of patients randomized to receive the Hydrus® Microstent achieved medication-free status, and a lower percentage required secondary surgical interventions. These data points highlight that the Hydrus® Microstent has a durable and significant impact on patients' quality of life.[1]

In the HORIZON study, the data show that **Hydrus® + CS** provided durable postoperative pressure in the mid-teens.

Fundamentally, the array of interventions that meet the definition of minimally invasive glaucoma surgery (MIGS) has altered our approach to managing POAG. Data such as those from the HORIZON trial help to confirm that it is safe and efficacious to intervene earlier in the disease course. Based on what we have learned from well-run and robust clinical trials such as HORIZON, we now know we do not have to wait and watch uncontrolled IOP, because the safety profile of MIGS, such as the Hydrus® Microstent, is favorable enough to consider surgery even with controlled IOP. ■

Every eye that has moderate or advanced glaucoma once had mild disease.

1. Ahmed IIK, De Francesco T, Rhee D, et al; HORIZON Investigators. Long-term outcomes from the HORIZON Randomized Trial for a schlemm's canal microstent in combination cataract and glaucoma surgery. *Ophthalmology*. 2022;129(7):742-751.

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