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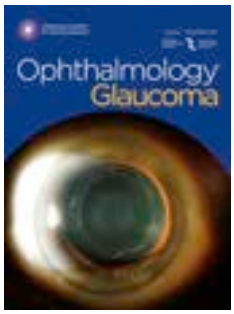

Intermediate Outcomes of the Novel 63µm Gelatin Microstent versus the Conventional 45µm Gelatin Microstent

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Intermediate Outcomes of the Novel 63µm Gelatin Microstent versus the Conventional 45µm Gelatin Microstent

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Running Head:
Xen63 vs. Xen45 Intermediate Outcomes

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Keywords: glaucoma surgery, subconjunctival filtering, gelatin microstent

Abstract

Purpose: To determine intermediate IOP-lowering and adverse event profile of the 63 µm gelatin microstent (Xen63) with mitomycin C (MMC) compared to the 45 µm gelatin microstent (Xen45) with MMC.

Design: Single centre, consecutive**,** retrospective cohort study

Participants: Eighty-four glaucomatous eyes (42 Xen63 and 42 Xen45) with or without previous subconjunctival glaucoma surgery.

Methods: Consecutive eyes that underwent Xen63 implantation with MMC from February 2020 to June 2021 were compared with eyes who underwent Xen45 implantation with MMC. Standalone and combined cases with phacoemulsification were included.

Main Outcome Measures: Primary outcome was the hazard ratio (HR) of failure of Xen45 vs. Xen63 eyes at 12-months, with failure defined as 2 consecutive intraocular pressures (IOP), (1)>17 mmHg, (2)<6 mmHg with 2 lines of vision loss, or (3)<20% reduction from baseline IOP, without (complete) or with (qualified) glaucoma medications. Secondary outcomes included IOP thresholds of 14 mmHg and 21 mmHg, postoperative IOP, medications, adverse events, interventions, and reoperations.

Results: The complete success rate was higher in the Xen63 group (59.5% vs. 28.6%, p=0.009) at the primary IOP threshold of 6 to 17 mmHg but did not differ significantly for qualified success (66.7% vs. 45.2%, p=0.08). The crude HR of failure of Xen45 relative to Xen63 was 2.28 (95% confidence interval [C1], 1.21–4.32) and the adjusted HR was 7.90 (95%

CI, 2.12–29.43). Xen63 eyes had significantly lower mean IOP (12.7 ±4.8 vs. 15.5 ±5.1mmHg, p=0.001) and fewer medication classes (0.6 ±1.1 vs. 1.7 ±1.6 meds, p=0.0005), with the degree of reduction in IOP and medication count being significantly greater in Xen63 eyes. There were 28 and 21 distinct interventions in Xen63 and Xen45 eyes respectively, with 11.9% of eyes undergoing needling in each group. There were 34 and 19 distinct adverse events, in Xen63 and Xen45 eyes respectively, most of which were early and transient. Nine Xen63 eyes (21.4%) and 6 Xen45 eyes (14.3%) underwent reoperation.

Conclusions: Xen63 resulted in higher surgical success rates and fewer medications compared with Xen45. This was tempered by more postoperative interventions and adverse events, although most were transient.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide and its prevalence continues to increase.[1] Uncontrolled glaucoma poses a significant socioeconomic burden, as it often results in visual impairment from progressive visual field loss.[1,2] As such, appropriate diagnosis and management of this disease remains a priority.

The effectiveness of first-line treatments like topical drops is restricted by associated side-effects, cost, and compliance.[3,4] Some patients are not able to achieve intraocular pressure (IOP) control despite being on maximal medical therapy, thus requiring surgical intervention. In recent years, microinvasive approaches to glaucoma surgery has shifted the paradigm of glaucoma treatment, offering an alternative to decreasing IOP and reducing drop burden through a potentially safer and less invasive surgical approach than traditional glaucoma filtration surgery (trabeculectomy and tube shunt).[5–7] MIGS (microinvasive glaucoma surgery) have been described to access physiologic outflow thru conventional and non-conventional pathways, while MIBS (microinvasive bleb surgery) are more controlled ways to create bleb filtering procedures. Although the traditional surgical options have the most significant IOP-lowering potential, these approaches can have unpredictable outcomes, prolonged recovery, and relatively high incidence of both early and late complications.[8] Studies have demonstrated that MIGS and MIBS devices can reduce IOP with a high safety profile and rapid recovery.[9–11]

The Xen microstent (Allergan, CA, USA) is a biocompatible 6 mm MIBS device that promotes aqueous humor drainage to the subconjunctival space.[12] The creation of a filtering bleb, through a controlled lumen size and length, bypasses the natural outflow pathway of aqueous humor, thereby lowering IOP.[12–14] At time time of development, three different models, with different lumen sizes were created: 45 µm (Xen45), 63 µm (Xen63), 140 µm (Xen140).[15,16] However,

initially, only Xen45 was made commercially available.[15,16] Xen45 has previously been shown to produce effective IOP lowering with a good safety profile.[11,17–28] Its main benefits are the controlled lumen size to avoid hypotony and the creation of a bleb without dissection, hence reducing conjunctiva disruption and surgical invasiveness.[9,12]

Given its novelty, the experience with Xen63 has been limited. This study aimed to determine the intermediate IOP-lowering and adverse event profile after 63 µm gelatin microstent implantation with mitomycin C (MMC) compared to the 45 µm microstent with MMC. This study is amongst the first compare the impact of the Xen63 device on IOP and glaucoma medication use versus the Xen45 device.

Methods

This is an investigator initiated, single centre, retrospective cohort study of consecutive patients who underwent Xen63 implantation with MMC either standalone or combined with phacoemulsification from February 2020 to June 2021, by 3 surgeons and clinical fellows in an academic ophthalmology center in the Greater Toronto Area, Canada. The results were compared with a matched cohort of patients who underwent Xen45 implantation, with MMC. This study reports 1-year outcomes or longer when available. The protocol adhered to the tenets of the Declaration of Helsinki and institutional review board approval was obtained from Trillium Health Partners. Cases were identified by chart review. Preoperative baseline characteristics, including demographics (age, sex, eye, ethnicity, diabetes status) and ocular characteristics (best-corrected visual acuity [BCVA]; IOP when the decision for surgery was made [decision IOP]; glaucoma medications; glaucoma diagnosis; glaucoma severity; cup-to-disc ratio; visual field mean deviation; prior glaucoma interventions; and lens status), as well as follow-up data were collected through chart review.

Inclusion and Exclusion Criteria

Patients between 30 and 90 years of age with a diagnosis of primary open-angle, pseudoexfoliation, pigment dispersion, normal-tension, angle recession, combined mechanism, history of angle-closure, or juvenile glaucoma and undergo Xen63 or Xen45 implantation were included. Standalone Xen procedures, procedures combined with phacoemulsification, and those in patients with prior surgical interventions were included. All eligible patients had above target IOP, despite medical therapy.

Eyes that had atypical forms of glaucoma (neovascular glaucoma, uveitic glaucoma, iridocorneal endothelial syndrome, and Axenfeld-Rieger syndrome), had undergone previous corneal graft or retinal surgery, or had a follow-up duration less than 1 month were excluded.

Gelatin Microstent Procedures

The surgical approach was decided by the treating surgeon. In the closed conjunctival ab interno approach, the injector was placed in the main incision, and the needle was directed toward the superonasal quadrant, across the anterior chamber, remaining just anterior to the trabecular meshwork. A mirrored gonioscope was used to confirm proper placement. With another instrument providing countertraction, a needle was used to tunnel through scleral, coming out subconjunctival 2.5 mm from the limbus. Once the injector was withdrawn, proper subconjunctival and anterior chamber placement of the device was confirmed again under gonioscopic visualization. Primary needling with a 30G needle was performed around the implant to ensure it was free of Tenon's capsule, after which an an intra-Tenon dose of 0.1mL MMC 0.2 mg/mL or 0.4 mg/mL was injected and massaged over the area. Viscoelastic was then removed from the anterior chamber manually with balanced saline solution (BSS), and the presence of a bleb was confirmed. A suture was variably placed at the side port incision.

In the open surgical approach, a traction suture was placed, and the eye was brought to an inferior position. A superior fornix based conjunctival flap was created by making a 6 mm peritomy, then bluntly dissecting Tenon's from sclera. Light cautery was applied. MMC on three merocele sponges, with concentrations from 0.2 mg/mL to 0.5 mg/mL, were placed under conjunctiva for a total of 2 minutes. After the sponges were removed, sub-Tenon's spaces was irrigated with BSS. The implant was then injected with an ab-interno technique as described above. BSS was put into the anterior chamber. Once adequate flow through the implant was

confirmed, Tenon's and conjunctiva were closed in two separate layers using 9-0 Vicryl sutures. The presence of a bleb with a watertight seal was confirmed at the end of each case. If combination cataract surgery was performed, it was completed prior to gel microstent implantation.

Postoperative Management

All patients were instructed to stop all glaucoma medications on the day of the surgery. Immediately after completion of the surgery, patients received Maxitrol (neomycin, polymyxin b and dexamethasone ophthalmic) ointment. The postoperative topical regimen included 1 week of topical antibiotic, 4 weeks of nonsteroidal anti-inflammatory drugs, and topical steroid every 2 hours for the first week, followed by a taper over 8-10 weeks. Follow-up started on postoperative day 1, and patients were seen thereafter as per the treating surgeon's discretion. All visits included a full anterior segment and bleb examination. If wound dehiscence, frank hypotony, or clinical signs of hypotony was noted, Seidel sign was assessed using a fluorescein strip and choroidal detachments were checked for by dilated examination. Throughout the course of follow-up, the need for glaucoma medications, interventions (e.g., needling, anterior chamber paracentesis, digital ocular compression), and reoperation was determined at the clinical judgement of the treating surgeon.

Needling was performed at the slit lamp using a 27G needle or 30G needle. Twenty minutes before needling, 0.1 mL of MMC 0.5mg/mL was injected. Post-needling topical regimen included 1 week of topical antibiotics and 1 week of steroid drops administered every 2 hours, which was then slowly tapered.

Outcome Measures

The primary outcome was the hazard ratio (HR) of failure of Xen45 relative to Xen63 at 12 months, with failure defined as: (1) IOP readings of less than 6 mmHg with more than 2 lines of vision loss from baseline (clinical hypotony) on two consecutive visits, (2) IOP readings of more than 17 mmHg without glaucoma medications (complete success), at least 1 month after surgery despite in-clinic interventions (including needling) (3) IOP reduction of less 20% from the decision IOP on two consecutive visits, (4) undergoing reoperation for glaucoma, or (5) no light perception (NLP) vision. Out-of-range IOP readings or medication use within the first postoperative month did not result in failure. Reoperation or loss of light perception vision were considered immediate failures. Cyclophotocoagulation, any glaucoma or conjunctival incisional surgery, and in-operating room revision of previous surgery were considered reoperations. These success and failure criteria have been previously described and are in line with World Glaucoma Association Guidelines on Design and Reporting of Glaucoma Surgical Trials.

Secondary efficacy outcomes included success and failure criteria allowing for topical glaucoma medications or laser trabeculoplasty (qualified success), modified IOP thresholds of 6 to 14 mmHg and 6 to 21 mmHg for complete and qualified success criteria with a 20% IOP reduction from baseline, and postoperative IOP, medication use, and BCVA in logarithm of the minimum angle of resolution (logMAR) units. We also investigated potential risk factors for failure, including sex, age, ethnicity, diabetes status, history of trabeculoplasty, history of laser peripheral irodotomy (LPI), glaucoma severity, decision IOP, preoperative vision, combination with phacoemulsification, and open conjunctival approach.

Safety outcomes were early and late adverse events (including leak or dehiscence, hyphema, vitreous hemorrhage, choroidal detachments, macular folds, prolonged inflammation, corneal decompensation, macular edema, diplopia, iris incarceration, or blocked or exposed microstent),

more serious adverse events (including angle closure, retinal detachment, suprachoroidal hemorrhage, malignant glaucoma, blebitis, endophthalmitis, or NLP vision), postoperative interventions (such as needling, AC reformation or AC paracentesis), and reoperations for glaucoma.

Statistical Analysis

Descriptive statistics were performed for baseline characteristics and follow-up measurements. Categorical variables were reported as counts and percentages and Fisher exact tests were used to compare treatment groups. Depending on normality, continuous variables were presented as means (standard deviation, SD) or medians (interquartile quartile range, IQR) and compared with either two-sided Student t-tests or Wilcoxon tests. LogMAR equivalents were determined from Snellen visual acuity measurements.

For each IOP threshold, survival analysis for complete and qualified success was calculated and displayed with Kaplan-Meier curves, which ensured loss to follow-up was accounted for. Log-rank tests were performed to compare survival between the two treatment groups. Cox proportional-hazards models were used to evaluate risk for failure of Xen45 relative to Xen63, on a univariate (crude) and multivariable (adjusted) basis: sex, age, ethnicity, diabetes status, history of trabeculoplasty, history of LPI, history of prior subconjunctival surgery, disease severity, elevated decision IOP, poor preoperative vision, combination with phacoemulsification, and open conjunctival approach. To approximate date with equivalent failure intervals, the Efron method was employed. Statistical significance was set at a 2-sided P value of 0.05 or less. All statistical analyses were carried out using SAS Studio software (SAS Institute Inc, Cary, North Carolina, USA) and graphs were created using either SAS Studio or Prism9 (Version 9.4.1, GraphPad Software, LLC).

Results

Study Populations and Baseline Characteristics

The study population included 42 eyes from 41 patients implanted with Xen63 between February 2020 to June 2021 and 42 eyes from 41 patients implanted with Xen45 between July 2017 to September 2021, resulting in a total of 84 eyes. The 12-month IOP assessment was completed in 41 of 42 (97.6%) Xen63 eyes and 37 of 42 (88.1%) Xen45 eyes. More than half of all surgeries were done by one surgeon (58.2%).

Overall, the demographic and key ocular baseline characteristics were similar between the treatment groups, which no statistically significant differences detected for any characteristic. Baseline characteristics are presented in **Table 1**.

Complete and Qualified Surgical Success

The unadjusted Kaplan-Meier survival curves for the IOP thresholds of 6 to 14 mmHg, 6 to 17 mmHg, and 6 to 21 mmHg for complete and qualified success are presented in **Figures 1A-C** and **1D-F**, respectively. The 12-month cumulative event-free survival rate for primary IOP threshold of 6 and 17 mmHg with no medications was 28.6% in the Xen45 group and 59.5% in the Xen63 group ($p = 0.009$, log-rank test). For qualified success criteria, which allows for the addition of glaucoma medications, surgical success improved to 45.2% and 66.8% ($p = 0.08$, log-rank test), in Xen45 and Xen63 eyes respectively (reasons for treatment failure at the primary outcome for complete and qualified success showed in **Table S2**). The crude HRs of failure of the Xen45 group relative to the Xen63 group, at all IOP thresholds (6 to 14, 17, and 21 mmHg), were examined (**Table 3**). The Xen45 group showed a statistically higher risk of

surgical failure compared with the Xen63 group for complete success at all IOP thresholds, with the highest hazard at IOP of 6 to 14 mmHg (HR, 2.44, [95% CI, 1.32–4.51]; p = 0.0033) compared to the other complete success criteria, IOP of 6 to 17 mmHg (HR, 2.28 [95% CI, 1.21–4.32]; p = 0.0087) and 6 to 21 mmHg (HR, 2.28 [95% CI 1.21–4.30]; p = 0.0089). Similar effect was seen for qualified success criteria at IOP of 6 to 14 mmHg (HR, 2.32 [95% CI, 1.20–4.50; p = 0.0111), but this effect did not reach statistical significance at the IOP thresholds of 6 to 17 mmHg (HR, 1.86 [95% CI, 0.91–3.78; p = 0.0841), and 6 to 21 mmHg (HR, 1.75, [95% CI, 0.85–3.58]; p = 0.1238).

For the regression anlaysis identifying risk factors for failure, we used the strictest success criteria (IOP threshold 6 to 14 mmHg with ≥ 20% IOP reduction from baseline) for the greatest statistical power. In the adjusted analysis, the Xen45 group showed a statistically higher risk of surgical failure compared to the Xen63 group, at all IOP thresholds, for both complete and qualified success. All adjusted hazard ratios were of greater mangnitude than crude hazard ratios, with the highest hazard seen for complete success at IOP 6 to 14 mmHg (HR, 8.81, [95% CI, 2.51–30.96]). There were no other significant risk factors for failure identified on a univariable or multivariable basis (**Figure S2**).

Intraocular Pressure and Medication Use

Mean IOP and medication use up to 1 year are shown in **Figure 3A-B** and **Figure 4**. IOP significantly decreased throughout the follow-up period in both Xen45 and Xen63 eyes, although the IOP was significantly lower in Xen63 eyes compared to Xen45 eyes at all follow-up time points except postoperative month 9 where there was no significant difference (**Figure 4**). At the 1-year follow-up, the mean IOP was 15.5 mmHg (standard deviation [SD], 5.1) for the Xen45 group and 12.7 mmHg for the Xen63 group (SD 4.8) (p = 0.001). Similarly, medication use was

significantly lower in the Xen63 group at postoperative month 3, 6, and 12, although this difference did not reach statistical significance at postoperative month 9. Mean medication count at 1-year follow-up was 1.7 (SD 1.6) for Xen45 eyes and 0.6 (SD 1.1) for Xen63 eyes (p = 0.0005).

The results of the analysis for change in IOP and medications from preoperative to 12 months are shown in **Figure 5A-B**. Compared to baseline, both groups significantly reduced IOP and medication use at 12 months; however, the reduction in the Xen63 group was significantly greater for both IOP (difference in change = - 4.8 mmHg; p = 0.02) and medication count (difference in change = -1.5 medications; p = 0.0001). At 12 months 34.1% of Xen45 patients and 73.2% of Xen63 eyes were medication free (P = 0.001) (**Figure 6**).

There were no significant changes in BCVA from baseline in either treatment group, as shown in **Figure S7**.

Postoperative Adverse Events and Interventions

Table 4 shows early and late adverse events over a 12-month period. Overall, most adverse events occurred in the early postoperative period. There were more early adverse events in Xen63 eyes compared to Xen45 eyes (n=30 vs. n=15), but the same rate of late adverse events between the two groups (n=4 vs. n=4).

Choroidal detachments and effusions occurred in the early postoperative period and occurred at a greater rate in the Xen63 group compared to the Xen45 group (n = 10, 23.8% vs. n = 2, 4.8%). Of the 10 Xen63 eyes that had choroidals, 9 had documented IOP less than 6 mmHg. Nine patients had choroidal resolution with conservative management. One patient required AC

reformation with air fill (despite deep AC) on three separate visits for worsening choroidals and persistent hypotony. This patient eventually required a bleb revision to reduce the size of an overfiltering bleb (bleb compression surgery). There was resolution of the 2 choroidals in the Xen45 eyes with conservative management. All choroidal detachments resolved within 6 months.

All cases of hyphema were less than 2 mm in size. All, but one case, resolved with observation alone. One Xen63 eye with an expanding hyphema (from 1 mm to 1.5 mm) resolved after an AC reformation with air fill to stop active bleeding.

There was 1 case of vitreous hemorrhage (VH) in a Xen63 eye and 2 cases of VH in the Xen45 treatment group, all of which occurred in diabetic patients. One diabetic patient in each treatment group had macular edema, which required treatment with ketorolac and topical steroids.

Bleb related adverse events also occurred infrequently in both groups. There was one case of persistent, postoperative binocular vertical diplopia secondary to hyperopia in a Xen63 eye, which was well controlled with prisms. One eye in each group had a positive seidel sign that required management with bandage contact lenses.

Serious adverse events included corneal decompensation and malignant glaucoma (MG). There were no cases of angle closure, retinal detachment, suprachoroidal hemorrhage, blebitis, endophthalmitis, or loss of light perception. There was one case of corneal decompensation, occurring just past postoperative month 3, in a Xen45 eye with a history of underlying corneal endothelial dysfunction. The patient was initially managed with increased topical steroids, but eventually required Descemet's stripping endothelial keratoplasty. One case of MG occured in

each treatment group. In the Xen63 group, the patient presented with iridocorneal touch, shallow AC, and hyphema and was suspected to have MG. This patient saw improvement after AC reformation with OVD and YAG laser and needling iridozonulovitrectomy (IZH). In the Xen45 group, the patient presenting with MG was treated with YAG laser IZH and atropine, after which the AC deepened. Other cases of shallow AC occurred outside the picture of MG and resolved with observation.

There were 21 distinct interventions in a total of 17 eyes and 28 distinct interventions in a total of 17 eyes in the Xen45 and Xen63 groups respectively (**Table 5**). The most common interventions were 5-FU injection and needling, which occurred at the same rate in both treatment groups (14.3% and 11.9% respectively). Both treatment groups had one IZH. Otherwise, MMC injection, device repositioning, and SLT only occurred in Xen45 eyes, at rate under 3%. All other interventions occurred at a greater rate in Xen63 eyes (AC reformations, AC taps, laser to ostomy, slit lamp goniosynechialysis (GSL), iris sweep, conjunctival suturing), with the rate of slit lamp GSL, iris sweep, and conjunctival suturing being under 3% overall. AC taps were done either very early in the post-operative period likely due to OVD left in the AC or to temporize IOP before going on to re-operation.

Reoperations

Six eyes in the Xen45 group and 9 eyes in the Xen63 group underwent reoperation (**Table 6**). The most common operations were tube shunt surgeries (Baerveldt tube shunt and Ahmed valve), followed by Xen revision, in which surrounding scar tissue was removed and the device was exchanged, if necessary.

Discussion

This is single centre, consecutive**,** retrospective cohort study provides the largest dataset of relative IOP-lowering and adverse event profile of the novel Xen63 microstent to the conventional Xen45 microstent. The results showed, at postoperative year 1, there is a benefit in reducing IOP and medication burden and improving surgical success in glaucoma patients, in favor of Xen63 over Xen45. Glaucoma treatment with Xen63 reduced IOP to a greater extent than Xen45 (difference in change = - 4.8 mmHg; p = 0.02). There was a greater degree of reduction in medication count (difference = -1.5 medications, p=0.0001) and a greater proportion of medication-free eyes in the Xen63 group compared with the Xen45 group (73.2% vs. 34.1%, p =0.001). Overall, risk of treatment failure was significantly higher in the Xen45 eyes compared to the Xen63 eyes at all IOP thresholds for complete success, with crude HR as high as 2.44 at IOP 6 to 14 mmHg ([95% CI, 1.32–4.51]; p = 0.0033) and adjusted HR as high as 8.81 at at IOP 6 to 14 mmHg ([95% CI, 2.51–30.96]).

The Xen45 results are similar to published outcome data on Xen45. The efficacy and safety profile of Xen45 (standalone and combined with phacoemulsification) has been well documented across several clinical studies, with significant reductions in IOP (baseline: 16–36.1 mmHg to postoperative: 12–17.1 mmHg) and medication use (baseline: 1.9–3.6 to postoperative: 0.2–1.8) noted.[11,15–26] Although limited, early Xen63 clinical studies have also demonstrated good efficacy in terms of IOP and medication use reduction, which was supported by the results of our study.[29–32] Results from the first pilot study, evaluating 34 eyes that underwent Xen63 or Xen140 combined with phacoemulsification to treat open angle, pseudoexfoliative, and pigment dispersion glaucoma, reported an IOP decrease of 31.3% (22.4 ± 4.2 mmHg to 15.4 ± 3.0 mmHg, p <0.0001) and a reduction of 1.6 medications (from 2.5 ± 1.0 to 0.9 ± 1.0) from baseline to 12 months.[29] Long-term data from a prospective, multicentre trial

indicated a 40% reduction in IOP (22.5 ± 4.2 mmHg to 13.4 ± 3.1 mmHg, p <0.001) and a 50% reduction in medication count (2.4 ± 1.3 to 1.2 ± 1.3, p<0.001) at 4-year follow-up. MMC was not used during the surgical procedure of both studies.[30] In the limited trials evaluating the Xen63, the former version of the device was used, which was never made commercially available. The new, commercialized Xen63 device differs from the previous version in numerous ways, including needle gague, injector design, and implantation technique.[33] The incision site for the new Xen63 is decreased compared to the older Xen63, as the newer device is introduced with a smaller 27G needle injector (0.4128 mm outer diameter) compared to the older 25G needle injector (0.5144 mm outer diameter).[33] Early experience with the new Xen63 also suggests good short-term IOP-lowering and adverse event profile.[33]

This study is the first to directly compare the potency and risk profile of the new Xen63 and Xen45, with only one other comparison study published using the older Xen63.[31] Multiple surgeons participated in the study and MMC was used in all cases, making it more generalizable to clinical practice. Adding to this, patients were ethnically diverse with various glaucoma diagnoses on multiple glaucoma medications prior to device implantation. Demographics, and baseline ocular characteristics were well matched across the two treatment groups.

Surgical success rates of Xen45 reported in the literature are wide ranging (15.4% to 90%), likely due to various study populations, designs, and definitions of success and failure.[34] Employing stricter criteria for surgical success, with a requirement of at least 20% IOP reduction from decision IOP, the complete surgical success of Xen45 at 12-months for the IOP threshold 6 to 17 mmHg was 28.6%, which was about half that of Xen63 (59.5%). This study offers that Xen63 has a lower hazard of treatment failure, associated with higher rates of surgical success overall. It is well known that subconjunctival filtering surgery success can vary by surgical

factors like technique and antifibrotic medication use, as well as patient characteristics.[35,36] The intraoperative MMC concentrations were similar among treatment groups, with the majority of patients (>95%) receiving MMC ≥0.4 mg/mL. However, in our study the inclusion of refractory glaucoma cases may have contributed to lower surgical success overall. Although treatment groups were well matched, multivariable analysis revealed the lower risk of failure in the Xen63 group compared to the Xen45 group was maintained and amplified, suggesting perhaps the Xen63 group had more risk factors for failure, yet still preformed better.

It is clear that Xen63 offers benefits in terms of IOP lowering and reduction of medication burden. In keeping with previous studies there was a 35% and 50% reduction in IOP at 12-months in Xen45 eyes and Xen63 eyes, respectively. Nonetheless, the most important impact of MIBS is to maintain low IOP on fewer medications.[37] Medication adherence drops significantly when patients are on multiple glaucoma medications, with resulting consequences for glaucoma progression in the form of visual field loss.[4,38] Our study demonstrates that both Xen63 and Xen45 are effective in reducing medication use, but eyes implanted with Xen63 have a greater chance of eliminating medications. Although utilizing the older Xen63 device, Fernandez-Garcia et al. also confirmed Xen63 significantly reduces IOP compared to Xen45 at 12-months, with more stable reductions in IOP-lowering medications over 3-years.[31]

Serious adverse events were rare among the two groups. Although the Xen63 group had more early adverse events, these were largely transient and minor. There were no cases of treatment failure as a result of persistent hypotony in Xen63 eyes. However, hypotony remains an important consideration, as hypotony-related adverse events like choroidal occurred at a greater rate in the Xen63 group compared to Xen45 group (23.8% vs. 4.8%). Early hypotony was a common adverse event in previous Xen63 studies, although these studies were not able to directly compare hypotony rates with Xen45 cases.[12,30]

The larger lumen size of Xen63, lowers resistance to flow and increases flow volume overall. In accordance with Poiseuille's law, the resistance to flow of Xen63 is 3.8 times lower than Xen45.[32] This results in a lower potential IOP across the devie and bleb, and a higher theoretical risk of hypotony in Xen63 eyes.[29] Choroidal effusions occur in the setting of hypotony as there a reversal of the hydrostatic pressure gradient. In the postoperative setting, low IOP providing little opposition to the suprachoroidal osmotic pressure, coupled with excessive protein leakage from the choriocapillaris secondary to an inflammatory response, may lead to choroidal effusion.[39,40]

Most patients with choroidal had documented IOPs of less than 6 mmHg, and those that did not presumably had an unreported episode of hypotony. The majority of cases (91.7%) resolved with conservative management or observation alone, with one Xen63 case requiring multiple AC reformations with air fill and subsequent bleb revision for persistent hypotony. However, in general, it is reassuring that there were no long-term complications due to hypotony in our study population.

Overall, it is not surprising that greater rates of adverse events in the Xen63 treatment group was coupled with higher intervention and reoperation rates (21.4% vs 14.3%). This is not insignificant, as it predisposes to patients to greater harm and the system to higher costs.

There are several limitations to this study. Although the sample size is small, to our knowledge, it is the largest cohort of Xen63 patients reported on. Having a greater number of cases would have increased the explanatory power of the study. The statistical power limits our safety assessment and the scope of multivariable analysis to assess for measured confounders. Given the low rate of serious complications, and a reassuring initial safety profile, the evaluation the

new Xen63 relative to the conventional Xen45 should continue. There are additional limitations inherent to the design of this retrospective study with a matched cohort. Confounding by indication is a primary concern for this study type. The concern arises when a new intervention (Xen63) is chosen for a patient with a greater likelihood of success and the older intervention (Xen45) chosen for those with more complicated cases. Although previous incisional surgery was not an exclusion criterion in our study, due to the limited number of Xen63 cases available, baseline analysis of the study population suggests that this effect did not occur, with most patients with a history of incisional surgery getting implanted with Xen63. However, the inclusion of such cases may have limited the surgical success rates of both treatments overall. In addition, the inclusion of two different surgical approaches (open and closed conjunctiva) creates some variability when evaluating surgical success, although the treatment groups were also well matched in this regard. We maintain that the matched cohort method is an approach allows us to take advantage of the large cohort of Xen45 patients and match most optimally to the smaller pool of patients in the Xen63 group. The post treatment IOP was compared to decision IOP with no prior washout period, limiting the ability to definitively evaluate IOP reduction attributable to the devices. Importantly, IOP, which is used as a marker of glaucoma stability, is only a surrogate metric.

Further research is needed to compare these two treatments. Larger, multicenter observational studies, with long-term surveillance, will be important to better assess safety outcomes, including endothelial cell loss rates. Although these observational studies allow for greater generalizability, randomized control trials comparing the two devices should also be conducted to control confounding factors.

In conclusion, this study adds to the limited information available on the novel Xen63 device. Treatment of glaucoma patients with Xen63 was associated with a lower risk of treatment failure

compared to the conventional Xen45 and demonstrated superior IOP and medication reduction. Although there were greater rates of early adverse events, particularly those that were hypotony-related, these were often transient. Nonetheless, the trade-off for greater potency appears to be more adverse events and subsequent interventions These results are promising for the risk/benefit profile of Xen63, but further evaluation is required.

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Figure Captions

Figure 1. Kaplan-Meier survival curves for complete and qualified success at various IOP thresholds plus at least 20% IOP reduction from baseline in Xen63 and Xen45 eyes. Complete success with IOP thresholds of A. 6 mmHg to 14 mmHg, B. 6 mmHg to 17 mmHg, C. 6 mmHg to 21 mmHg. Qualified success with IOP thresholds of D. 6 mmHg to 14 mmHg, E. 6 mmHg to 17 mmHg, F. 6 mmHg to 21 mmHg.

Figure S2. Forest plots showing risk factors for surgical failure overall. Crude (Left) and adjusted (Right) hazard ratios for surgical failure with 95% confidence intervals are shown. [1]Poor preop vision refers to preoperative best-corrected visual acuity of 0.4 logMAR or worse. [2]Moderate or advanced disease stage versus mild disease based on visual field mean deviation (-6 dB cutoff). Preop = preoperative; IOP = Intraocular pressure; LPI = laser peripheral iridotomy.

Figure 3. **A.** Intraocular pressure (IOP), and **B.** Medication count from baseline to 12-months in Xen63 and Xen45 eyes. IOP and medication count, for both Xen63 and Xen45 eyes, decreased significantly over time from baseline ($p < 0.001$). There were significant differences in mean IOP and medication count at postoperative month 3, 6, and 12 between Xen63 and Xen45 eyes. The error bars represent standard deviations. Preop = preoperative; POM = postoperative month.

Figure 4. Box and whisker plot of preoperative to postoperative IOP. The middle lines indicate the median; the lower and upper ends of boxes indicate the lower and upper quartiles; the whisker ends from the 1st to the 99th percentile. The error bars represent standard deviations. *

indicates statistical significance in intraocular pressure between the Xen45 and Xen63 eyes. Preop = preoperative; POM = postoperative month.

Figure 5. A. Intraocular pressure (IOP). B. Assessment of IOP and medication count at 12 months for Xen45 eyes and Xen63 eyes. A. Compared with preoperative IOP, both Xen45 and Xen63 eyes had a significant reduction in IOP. B. Both groups significantly reduced medication use compared with preoperative values. The difference in change was significantly greater in the Xen63 group for both IOP and medication count. The error bars are standard deviations.

Figure 6. The percentage of eyes using 0, 1, 2, or 3 or more medications at 12 months in Xen45 and Xen63 groups.

Figure S7. BCVA from baseline in Xen63 or Xen45 eyes. There is no significant difference in the BCVA at POM12 compared to baseline in both groups. BCVA = best corrected visual acuity; Preop = preoperative; POM = postoperative month.

Statements

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Author Contributions

Table S1. International Committee of Medical Journal Editors (ICMJE) Authorship Criteria

Author Initials	A) Information Procurement			B) Dissemination		C) Approval of Final Draft	D) Accountable for Final Content
	Concept	Acquisition	Interpretation	Drafting	Revising		
IMH		x	x	x	x	x	x
TDF			x	x	x	x	x
IIKA	x	x	x		x	x	x

http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html
To qualify, an author must have participated in at least one aspect of each category (A, B, C, and D). Additionally, authors should be able to identify which co-authors are responsible for specific other parts of the work and should have confidence in the integrity of the contributions of their co-authors.

Table 1. Baseline Characteristics

Characteristic	Total	Xen63	Xen45	P Value
Eyes, n	84	42	42	
Demographic				
Age, Median (IQR), years	69.9 (58.0 – 75.3)	67.0 (57.0–75.0)	71.2 (64.4–76.8)	0.12
>70 years old, n (%)	43 (51.2)	19 (45.2)	24 (57.1)	0.38
Left Eye, n (%)	47 (56.0)	25 (59.5)	22 (52.4)	0.66
Female, n (%)	43 (51.2)	23 (54.8)	20 (47.6)	0.66
Diabetes, n (%)	22 (26.2)	9 (21.4)	13 (31.0)	0.46
Ethnicity, n (%)				0.21
Caucasian	53 (63.1)	22 (52.3)	31 (73.8)	
East Asian	6 (7.1)	5 (11.9)	1 (2.4)	
South Asian	13 (15.5)	7 (16.7)	6 (14.3)	
African	6 (7.1)	3 (7.1)	3 (7.1)	
Caribbean	4 (4.8)	3 (7.1)	1 (2.4)	
Middle Eastern	2 (2.4)	2 (4.8)	–	
Vision				
Preoperative VA (logMAR), median (IQR)	0.3 (0.1–0.5)	0.4 (0.2–0.6)	0.3 (0.1–0.4)	0.15
Preoperative BCVA 0.4 logMAR or worse, n (%)	27 (32.1)	17 (40.5)	10 (23.8)	0.16
Decision IOP*				
>21 mmHg, n (%)	50 (59.5)	24 (57.1)	26 (61.9)	0.82
Median (IQR), mmHg	23.0 (19.0–28.0)	24.0 (19.0–29.0)	23.0 (19.0–26.0)	0.51
Decision medication classes, median (IQR)*	4.0 (3.0–4.0)	4.0 (3.0–5.0)	4.0 (3.0–4.0)	0.07
Glaucoma type and severity				
Disease type, n (%)				0.85
Primary open angle	51 (60.7)	28 (66.7)	23 (54.8)	
Pseudoexfoliative	11 (13.1)	4 (9.5)	7 (16.7)	
Pigment dispersion	6 (7.1)	2 (4.8)	4 (9.5)	
Primary angle closure	6 (7.1)	3 (7.1)	3 (7.1)	
Combined mechanisms	7 (8.3)	3 (7.1)	4 (9.5)	
Angle recession	2 (2.4)	1 (2.4)	1 (2.4)	
Other	1 (1.2)	1 (2.4)	–	
Cup-to-disc ratio, median (IQR)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.48
Preoperative MD, median (IQR)	-11.7 (-23.6 to -6.7)	-11.1 (-22.5 to -6.9)	-12.1 (-24.2to -5.3)	0.95
Disease severity, n (%)†				0.30
Mild	19 (22.6)	7 (16.7)	12 (28.6)	

Moderate	23 (27.4)	14 (33.3)	9 (21.4)	
Advanced	42 (50.0)	21 (50.0)	21 (50.0)	
Previous ocular laser/surgery, n (%)				
Laser peripheral iridotomy	12 (14.3)	6 (14.3)	6 (14.3)	1.0
Laser trabeculoplasty	52 (61.9)	26 (62.0)	26 (62.0)	1.0
ECP	1 (1.2)	1 (2.4)	–	1.0
GSL	1 (1.2)	–	1 (2.4)	1.0
Trabeculotomy/Trab. Stents	9 (10.7)	4 (9.5)	5 (11.9)	1.0
Previous cataract surgery	40 (47.6)	18 (42.9)	22 (52.4)	0.51
Previous Subconjunctival Surgery				
Trabeculectomy	4 (4.8)	3 (7.1)	1 (2.4)	0.62
Xen	2 (2.4)	2 (4.8)	–	0.49
Cypass	3 (3.6)	1 (2.4)	2 (4.8)	1.0
Surgical Details, n (%)				
Combined with cataract surgery	22 (26.2)	11 (26.2)	11 (26.2)	1.0
Open surgical approach	44 (52.4)	22 (52.4)	22 (52.4)	1.0
Surgeon				0.22
1	49 (58.3)	28 (66.7)	21 (50.0)	
2	33 (39.3)	13 (31.0)	20 (47.6)	
3	2 (2.4)	1 (2.4)	1(2.4)	
Intraoperative MMC				0.62
MMC 0.2 mg/mL	3 (3.6)	1 (2.4)	2 (4.8)	
MMC 0.4 mg/mL	79 (94.1)	39 (92.9)	40 (95.2)	
MMC 0.5 mg/mL	2 (2.4)	2 (4.8)	–	

*At which time the decision was made to proceed with surgery.
†Based on mean deviation on visual fields: mild, 0 dB to more than −6 dB; moderate, −6 dB to more than −12 dB; advanced, −12 dB or worse.
BCVA = best-corrected visual acuity; ECP = endoscopic cyclophotocoagulation; GSL = goniosynechialysis; IOP = intraocular pressure; IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; MD = mean deviation (dB); MMC = mitomycin C; SD = standard deviation; VA = visual acuity.

Table 3. Crude and adjusted hazard ratios for failure in Xen45 relative to Xen63 eyes.

IOP criteria	Hazard Ratio (95% confidence interval)	
	Crude	**Adjusted**
Complete Success		
6–14 mmHg + ≥20% reduction	2.44 (1.32–4.51)	8.81 (2.51–30.96)
6–17 mmHg + ≥20% reduction	2.28 (1.21–4.32)	7.90 (2.12–29.43)
6–21 mmHg + ≥20% reduction	2.28 (1.21–4.30)	7.85 (2.10–29.23)
Qualified Success		
6–14 mmHg + ≥20% reduction	2.32 (1.20–4.50)	6.65 (2.14–20.64)
6–17 mmHg + ≥20% reduction	1.86 (0.91–3.78)	5.47 (1.46–20.56)
6–21 mmHg + ≥20% reduction	1.75 (0.85–3.58)	4.89 (1.30–18.35)

IOP = Intraocular pressure.

Table 4. Early and late postoperative adverse events in Xen63 and Xen45 eyes up to 1 year

Adverse Event	Xen63, n = 42		Xen45, n = 42	
	Early (<3 months)	Late (≥3 months)	Early (<3 months)	Late (≥3 months)
Minor, n (%)				
Choroidals or choroidal folds	10 (23.8)	–	2 (4.8)	–
Shallow AC	5 (11.9)	–	1 (2.4)	1 (2.4)
Hyphema*	5 (11.9)	–	3 (7.1)	–
Iritis	3 (7.1)	1 (2.4)	2 (4.8)	1 (2.4)
Diplopia	1 (2.4)	–	–	–
Seidel	1 (2.4)	–	1 (2.4)	–
Dellen	–	–	1 (2.4)	–
Iridocorneal touch	1 (2.4)	–	–	–
Vitreous hemorrhage	–	1 (2.4)	2 (4.8)	–
Macular Edema	–	1 (2.4)	1 (2.4)	–
Xen-iris touch	2 (4.8)	1 (2.4)	–	–
Xen-cornea touch	–	–	–	1 (2.4)
Migrated Xen	1 (2.4)	–	1 (2.4)	–
Serious, n (%)				
Corneal Decompensation	–	–	–	1 (2.4)
Malignant Glaucoma	1 (2.4)	–	1 (2.4)	–
Total	30	4	15	4

*Hyphema measuring < 2 mm
AC = anterior chamber.

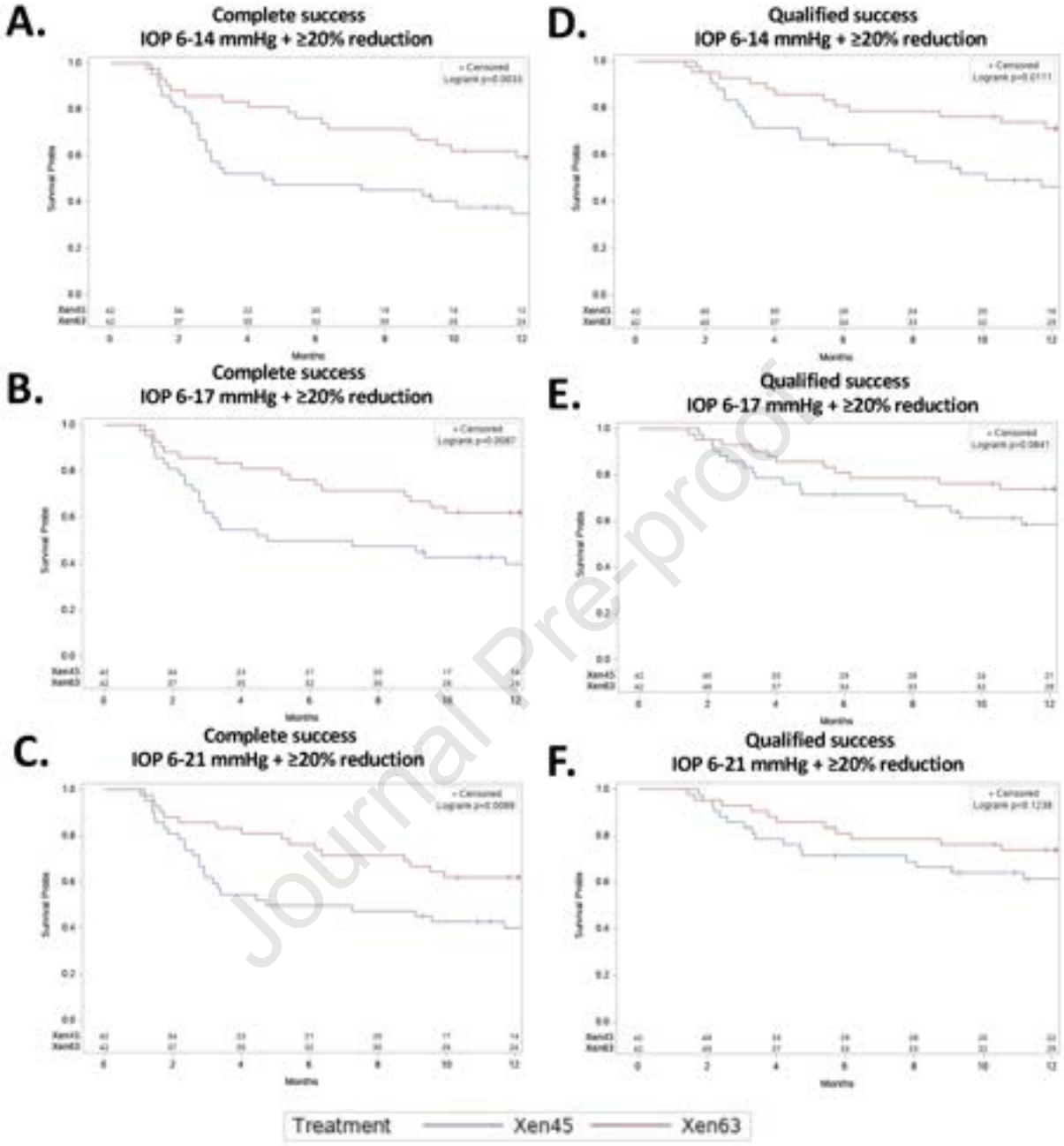
Table 5. Postoperative interventions in Xen63 and Xen45 eyes up to 1 year

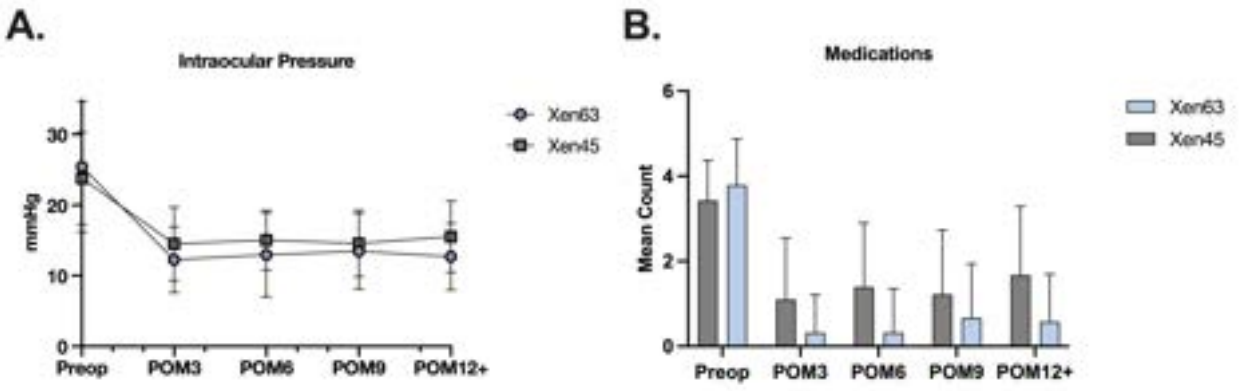
Intervention, n (%)	**Xen63, n = 42**	**Xen45, n = 42**
Needling	5 (11.9)	5 (11.9)
AC tap	5 (11.9)	3 (7.1)
AC reformation	3 (7.1)	–
Laser to ostomy	5 (11.9)	3 (7.1)
5-FU Injection	6 (14.3)	6 (14.3)
MMC Injection	–	1 (2.4)
Xen reposition	–	1 (2.4)
Slit lamp GSL	1 (2.4)	–
SLT	–	1 (2.4)
IZH	1 (2.4)	1 (2.4)
Iris sweep	1 (2.4)	–
Conjunctival suturing	1 (2.4)	–
Total	28	21

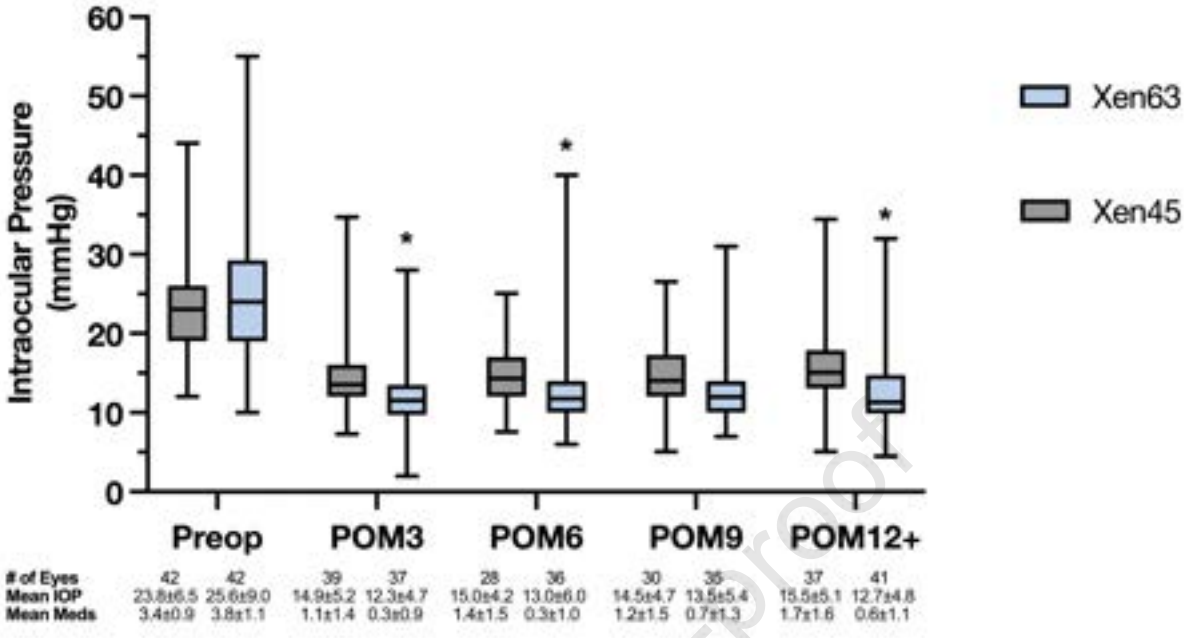
AC = Anterior chamber; 5-FU = 5-Fluorouracil; GSL = Goniosynechialysis; IZH = Iridozonulovitrectomy.

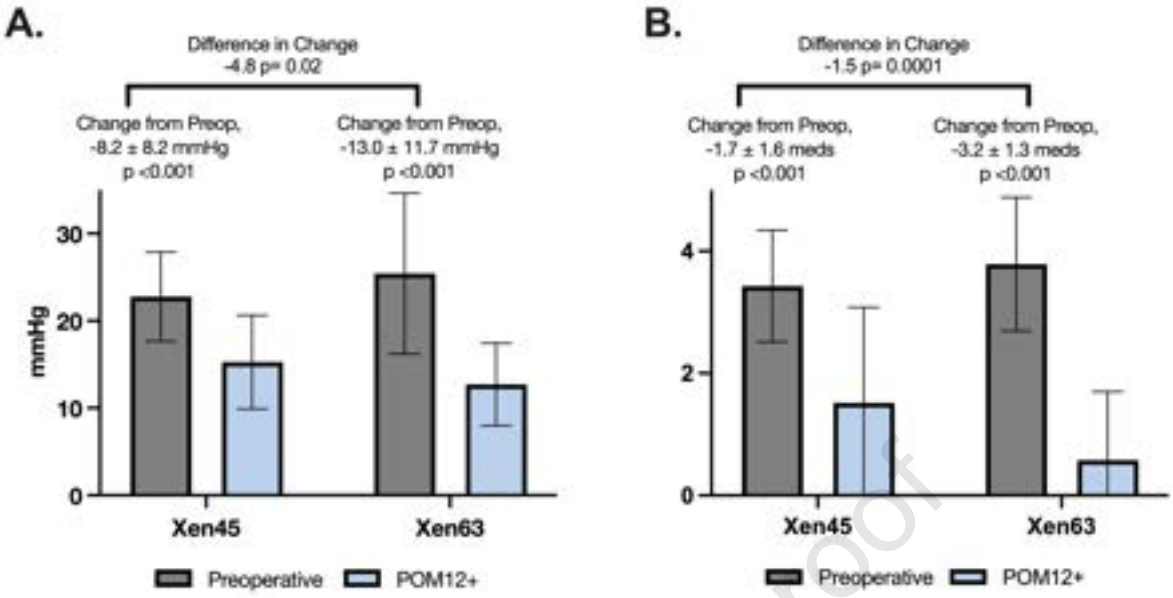
Table 6. Postoperative revisions and reoperations in Xen63 and Xen45 eyes up to 1 year

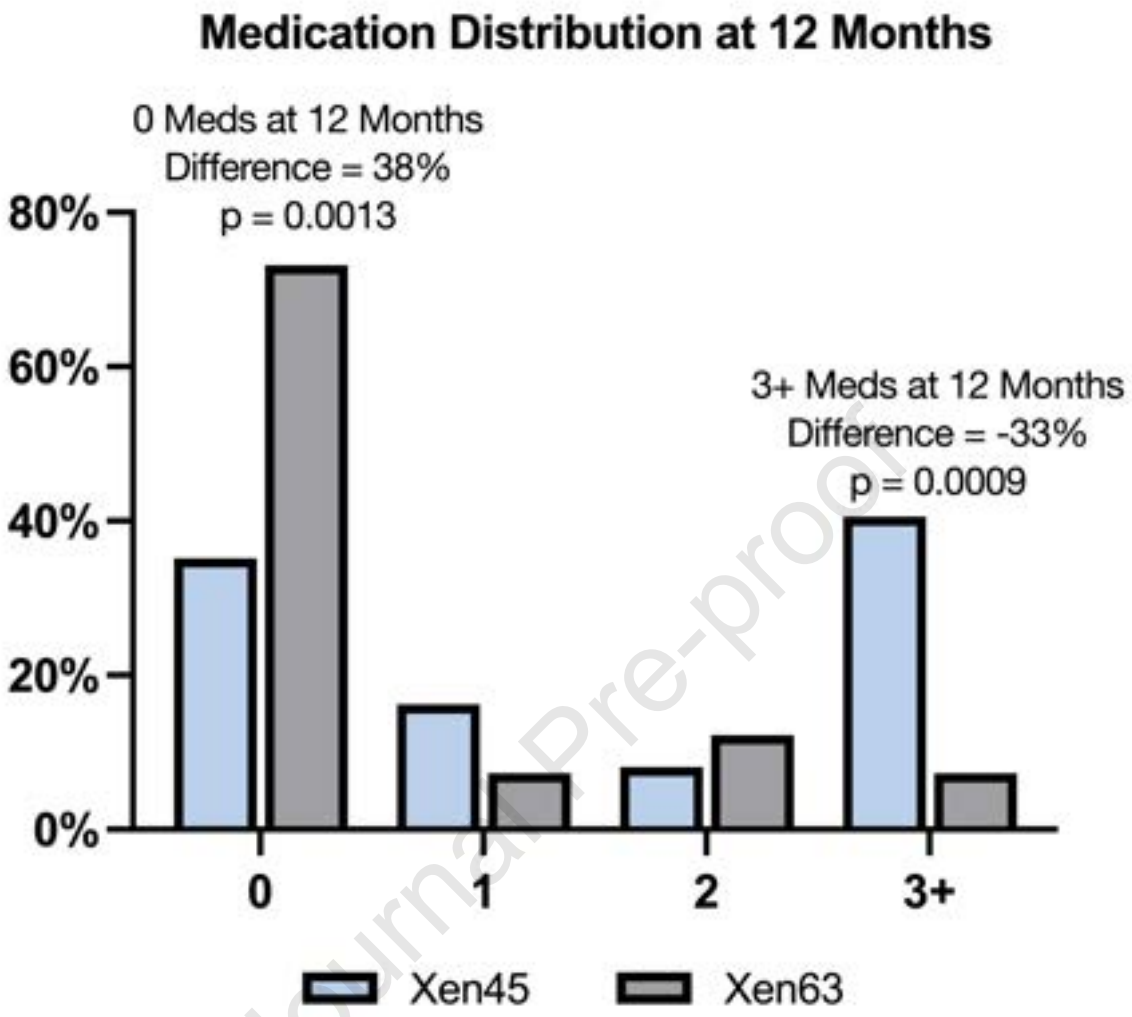
Intervention, n (%)	**Xen63, n = 42**	**Xen45, n = 42**
Xen revision	1 (2.4)	2 (4.8)
Additional Xen implantation	2 (4.8)	1 (2.4)
Bleb compression	1 (2.4)	–
Baerveldt tube shunt	2 (4.8)	1 (2.4)
Ahmed valve	3 (7.1)	2 (4.8)
Total	9	6











Précis

The 63µm gelatin microstent showed benefit over the 45µm gelatin microstent in improving surgical success, reducing intraocular pressure, and medications, although tempered by more adverse events.