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Two-year outcomes of Xen 45 gel stent implantation in patients with open-angle glaucoma: real-world data from the Fight Glaucoma Blindness registry

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ABSTRACT

Objective To evaluate efficacy and safety outcomes of the Xen 45 gel stent implant over 24 months of follow-up.

Methods A retrospective analysis of prospectively collected data from the Fight Glaucoma Blindness observational registry. Complete success (CS) was defined as intraocular pressure (IOP) reduction ≥20% from preoperative and an IOP ≤18 mm Hg and ≥6 mm Hg with no secondary procedure at 2 years and without IOP-lowering medications. Qualified success (QS) was defined similarly, allowing the use of IOP-lowering medications.

Results The Xen 45 gel stent implant was implanted in 646 eyes of 515 patients. Preoperative IOP was 21.4±7.6 (mean±SD) mm Hg on 2.7±1.3 IOP-lowering medication and mean deviation was −10.2±8.4 dB. After 24-month follow-up, IOP was 16.8±7.3 mm Hg (mean reduction of 21.7%) on 1.2±1.4 IOP-lowering medications. CS and QS rates at 24 months were 26% and 48%, respectively. CS and QS were higher in the Xen stand-alone group (33% and 52%, respectively) than in the Xen+cataract group (16% and 42%, respectively). Bleb needling was performed in 28.4% of cases, and 18% underwent a secondary procedure.

Conclusions The Xen 45 gel stent implant offers acceptable long-term efficacy for the treatment of open-angle glaucoma. However, there is a significant rate of reoperation and needling, and outcomes are less effective if combined with cataract surgery.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Existing publications describe short-term safety and efficacy outcomes of the Xen 45 gel stent implant.

WHAT THIS STUDY ADDS

⇒ This study analysed a large cohort of Xen surgeries followed longitudinally up to 4 years. It showed that complete success was significantly higher for stand-alone Xen surgery versus Xen combined with cataract surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This real-world study supported that Xen 45 gel stent implant is an acceptable surgical approach for open-angle glaucoma. There is a significant rate of reoperation and needling, and outcomes are less effective if combined with cataract surgery.

INTRODUCTION

Glaucoma is the leading cause of irreversible blindness globally[1] and reducing intraocular pressure (IOP) remains the only confirmed treatment.[2 3] In patients with open-angle glaucoma, filtration surgery may be considered when medical therapy is insufficient to control optic neuropathy progression or is poorly tolerated. Gold-standard filtration surgery remains trabeculectomy.[4 5] However, many new procedures have been developed for the last two decades in order to decrease complication of filtering surgery.[6 7] Among all these procedures the Xen 45 gel stent implant (AbbVie, Allergan plc, Dublin, Ireland) is a bleb forming device which has been proposed as an alternative. Many studies with relatively limited follow-up have compared the Xen 45 gel stent implant to other filtration surgeries.[8–12] Data on longer-term outcomes with larger cohorts are required to understand the role of the device in the management of patients with this chronic disease. Primary objective was to report 24 months real-world safety and efficacy outcomes of a large international cohort of patients having Xen 45 surgery stand-alone or combined with cataract surgery.

METHODS

Data source

This retrospective multicentre observational study used anonymised data from the international Fight Glaucoma Blindness (FGB) registry, which is part of the Save Sight Registries group in the University of Sydney.[13] The FGB registry is a web-based platform allowing specialists to capture the data from their routine clinical practice for auditing and research of real-world glaucoma treatments. As this is real-world data, the decisions regarding surgical technique, the frequency of visits and postoperative management were up to the glaucoma surgeon in discussion with each patient. The FGB registry

requires a baseline visit with a minimum dataset that accurately phenotyped patients, along with pertinent clinical measurements such as visual acuity (VA), IOP and previous surgical procedures. The software automatically generates a field requiring the clinician to indicate whether there have been any relevant adverse events if any eye has previously had a procedure. Each follow-up visit included mandatory fields such as VA, IOP, medical treatments, adverse events and additional procedures. A detailed description of this registry have been published previously.[13]

Procedure selection

We identified procedures in the registry that were either Xen stand-alone or Xen combined with cataract surgery. Eyes with a diagnosis of open-angle glaucoma or ocular hypertension were included, while those with angle closure spectrum disease were excluded. Eyes with prior glaucoma filtration surgery were excluded, as were eyes that had IOP measured with a technique other than Goldmann. Patients <18 years old were excluded. Patients with a follow-up <6 months were not included. Results were analysed at a series of follow-up windows which include 6 months, 12 months, 24 months, 36 months and 48 months.

Outcomes

The primary outcome was success defined as IOP ≤18 mm Hg, ≥6 mm Hg and ≥20% reduction from baseline with no secondary procedures, at 24 months. Complete success (CS) was this outcome without any glaucoma medications, and qualified success (QS) was completed with or without glaucoma medications (QS) based on World Glaucoma Association guidelines.[14] Secondary outcomes were similar success measures using different IOP target thresholds (12, 15 and 21 mm Hg). For example, QS for 12 mm Hg was defined as (1) IOP ≤12 mm Hg, (2) IOP ≥6 mm Hg, (3) ≥20% decrease in IOP from baseline, and CS for 12 mm Hg required additional condition of (4) without medications.

The secondary outcomes included (1) IOP outcomes (IOP change from baseline, IOP % change from baseline, and the proportion of eyes achieving 20% IOP reduction), (2) medication outcomes (the number of medications and change in the number of medications), (3) adverse events including (VA loss of ≥10 letters, numerical hypotony, hypotony+VA loss of ≥10 letters at the same visit, hypotony maculopathy, choroidal effusions, glaucoma device exposure and endophthalmitis) and (4) secondary glaucoma procedures. We also calculated the primary and secondary outcomes at 6, 12, 36 and 48 months.

We also undertook comparison between Xen stand-alone versus Xen combined with cataract surgery at 24 months. In order to assess a possible difference between groups, we used a slightly different definition of failure that incorporated both IOP efficacy and surgical failure components. Using the outcome of CS at the 18 mm Hg threshold as an example, failure was defined as any of the following:

- Two consecutive visits with IOP >18 mm Hg or IOP reduction <20% from preoperative or any antiglaucoma medications at least 1 month after surgery.
- Any visit with IOP <6 mm Hg and VA loss ≥10 letters at the same visit, at least 1 month after surgery.
- Any secondary glaucoma procedure (excluding bleb needling).
- Loss of light perception.

The failure for different IOP target thresholds (12, 15 and 21 mm Hg) were defined similarly, as was failure for QS, except that antiglaucoma medications were allowed to be used to achieve the relevant outcome.

Statistical analysis

Excluding patients requiring secondary glaucoma procedures would bias the results in favour of the relevant procedure as excluded cases would be more likely to have poor outcomes. We therefore used a 'last observation carried forward' analysis

Table 1 Patient demographic and baseline characteristics

Variable	Overall	6 months*	12 months	24 months	36 months	48 months
Eyes, n	638	431	439	338	245	203
Patients, n		510	361	361	276	192
Male, n	258 (51%)	182 (51%)	185 (51%)	144 (52%)	88 (46%)	67 (45%)
Age, years	72.4 (11.1)	72.0 (11.2)	72.0 (10.8)	71.5 (10.4)	70.3 (10.1)	70.4 (9.3)
Diagnosis at baseline, n						
Normal tension glaucoma	26 (4.1%)	16 (3.7%)	17 (3.9%)	20 (5.9%)	10 (4.1%)	12 (5.9%)
Ocular hypertension	35 (5.5%)	27 (6.3%)	25 (5.7%)	18 (5.3%)	12 (4.9%)	4 (2%)
Primary open angle glaucoma/normal tension glaucoma suspect	54 (8.5%)	41 (9.5%)	47 (11%)	30 (8.9%)	10 (4.1%)	2 (0.99%)
Primary congenital glaucoma	1 (0.16%)	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)	1 (0.49%)
Primary open angle glaucoma	438 (69%)	291 (68%)	291 (66%)	224 (66%)	186 (76%)	162 (80%)
Secondary open angle glaucoma	94 (15%)	65 (15%)	67 (15%)	50 (15%)	30 (12%)	24 (12%)
Best corrected visual acuity, letters	70.0 (18.9)	69.2 (20.7)	69.8 (20.1)	72.1 (17.3)	71.2 (17.7)	70.0 (17.1)
Intraocular pressure, mm Hg	21.4 (7.6)	21.8 (8.0)	21.5 (7.7)	21.1 (7.3)	20.6 (7.0)	19.9 (6.9)
Medications, n	2.7 (1.3)	2.8 (1.3)	2.8 (1.3)	2.8 (1.3)	2.6 (1.2)	2.5 (1.2)
Visual field, mean deviation, dB	−10.2 (8.4)	−9.9 (8.2)	−10.2 (8.2)	−9.7 (8.4)	−10.4 (8.5)	−10.4 (8.7)
RNFL thickness, µm	64.9 (13.1)	64.6 (12.9)	65.7 (12.4)	65.9 (12.3)	66.1 (12.8)	64.3 (10.8)
Central corneal thickness, µm	529.5 (36.8)	530.1 (39.1)	528.6 (36.7)	527.2 (36.3)	529.3 (37.0)	527.8 (34.0)

Data are presented as n (%) or mean (SD).
*Eligible procedures were ones that had at least one visit 6 months (150–335 days) after the procedures themselves were performed. The same applied to the 12 months, 24 months, 36 months and 48 months.
RNFL, retinal nerve fibre layer.

where the IOP and medication values immediately prior to the secondary intervention are carried forward to the relevant follow-up time window. Bleb needling was not included as a secondary glaucoma procedure and therefore did not censor that procedures follow-up.

T-test was used for continuous variables and χ^2 test for categorical variables to compare the baseline characteristics between the Xen and Xen+cataract groups.

We estimated crude difference and 95% CI between the two groups (Xen stand-alone vs Xen+cataract) for (1) IOP at 24 months, (2) IOP change over 24 months, (3) achievement of 20% reduction of IOP over 24 months, (4) the number of medications at 24 months, (5) change in the number of medications over 24 months, (6) QS of 12, 15, 18 and 21 mm Hg at 24 months and (7) CS of 12, 15, 18 and 21 mm Hg at 24 months. Modified linear model was used where each outcome was regressed on the group (Xen stand-alone or Xen+cataract). We estimated adjusted difference and 95% CI using linear mixed model where each outcome was adjusted on gender, age, preoperative IOP and preoperative number of medications, and doctors and eyes were regarded as random effects to take account of the cluster.

The probability curve of qualified and CS (12, 15, 18 and 21 mm Hg) was plotted using Kaplan-Meier estimation. Follow-up started at the surgery date of Xen stand-alone or Xen+cataract. Censoring was defined as the earlier of the date of failure as defined above or the last visit date before March 2023. Crude and adjusted HR (aHR) and 95% CI of failure was estimated with Cox-proportional hazard model. In the adjusted model, sex, age, preoperative IOP, preoperative number of medications were regarded as fixed effects, and doctors and eyes were regarded as random effects to take account of the cluster.

A p value <0.05 was considered statistically significant. All statistical analyses were conducted using R software V.4.2.3 (R Foundation for Statistical Computing).

RESULTS

A total of 638 eyes were eligible. Table 1 shows the baseline characteristics, with 50.5% males and a mean age of 72.4±11.1 years (mean±SD). The most common diagnosis was primary open-angle glaucoma accounting for 69% of cases. Preoperatively, mean IOP was 21.4±7.6 mm Hg, mean number of medications was 2.7±1.3 and the average visual field mean deviation where that was recorded, was −10.2±8.4 dB. There were 12 surgeons contributing to this dataset with a mean number of surgery cases of 24. As a registry study of real-world practice, surgeons enter consecutive patients that they operate on into the registry. This means that there will be a smaller number of patients at each follow-up window. These numbers increase over time as each patient being followed reaches a new time point of follow-up. The number of procedures eligible for analysis at 6 months, 12 months, 24 months, 36 months and 48 months were 431, 439, 338, 245 and 203, respectively.

Table 2 shows an IOP range and medication outcomes. For the primary outcome measure (IOP threshold ≤18 mm Hg), CS and QS rates were 26% and 48%, respectively. At 24 months, CS and QS at the different IOP thresholds of 12, 15 and 21 mm Hg, were 13%, 21%, 27% and 22%, 38%, 50%, respectively.

Table 2 Intraocular pressure outcomes, medication outcomes, qualified success and complete success

Variables	6 months*	12 months	24 months	36 months	48 months
Procedures, n	431	439	338	245	203
IOP outcomes					
Preoperative IOP, mm Hg	21.8 (8.0)	21.5 (7.7)	21.1 (7.3)	20.6 (7.0)	19.9 (6.9)
Final IOP, mm Hg	15.8 (7.0)	16.6 (7.4)	16.8 (7.3)	17.1 (6.8)	16.3 (6.4)
IOP change, mm Hg	−6.0 (9.0)	−4.9 (8.8)	−4.3 (8.9)	−3.4 (7.8)	−3.7 (7.8)
IOP % change	−28.2 (−46.9, 0.00)	−24.4 (−43.6, 0.00)	−21.7 (−41.3, 4.5)	−16.7 (−36.4, 5.3)	−15.8 (−35.7, 5.3)
20% IOP reduction	252 (58%)	248 (56%)	173 (51%)	110 (45%)	90 (44%)
Medication outcomes					
Preoperative medications	2.8 (1.3)	2.8 (1.3)	2.8 (1.3)	2.6 (1.2)	2.5 (1.2)
Final medications	0.77 (1.2)	1.0 (1.4)	1.2 (1.4)	1.4 (1.4)	1.4 (1.4)
Change in No. of medications	−2.0 (1.5)	−1.7 (1.6)	−1.6 (1.7)	−1.2 (1.7)	−1.1 (1.8)
Qualified success					
12 mm Hg	125 (29%)	112 (26%)	76 (22%)	43 (18%)	35 (17%)
15 mm Hg	190 (44%)	183 (42%)	130 (38%)	78 (32%)	63 (31%)
18 mm Hg	230 (53%)	215 (49%)	162 (48%)	98 (40%)	81 (40%)
21 mm Hg	238 (55%)	232 (53%)	168 (50%)	107 (44%)	87 (43%)
Complete success					
12 mm Hg	98 (23%)	70 (16%)	44 (13%)	18 (7.3%)	15 (7.4%)
15 mm Hg	143 (33%)	112 (26%)	70 (21%)	35 (14%)	21 (10%)
18 mm Hg	168 (39%)	131 (30%)	87 (26%)	41 (17%)	23 (11%)
21 mm Hg	170 (39%)	138 (31%)	91 (27%)	46 (19%)	25 (12%)
Failure					
Secondary glaucoma surgery†	43 (10%)	57 (13%)	62 (18%)	45 (18%)	34 (17%)
IOP <6 mm Hg and VA loss ≥10 letters	60 (14%)	53 (12%)	45 (13%)	28 (11%)	15 (7.4%)
Loss of light perception	1 (0.23%)	0 (0%)	2 (0.59%)	1 (0.41%)	1 (0.49%)

Data are presented as n (%), mean (SD) or median (IQR).
*Eligible procedures were ones that had at least one visit 6 months (150–335 days) after the procedures themselves were performed. The same applied to the 12 months, 24 months, 36 months and 48 months.
†Not including bleb needling.
IOP, intraocular pressure; VA, visual acuity.

Table 3 24 months outcomes stratified by Xen stand-alone and Xen+cataract groups

Variables	Xen stand-alone	Xen+cataract	Crude difference (95% CI)*	P value	Adjusted difference (95% CI)*	P value
Procedures, n	199	139				
IOP outcomes						
Preoperative IOP, mm Hg	22.0 (7.4)	19.7 (7.1)				
Final IOP, mm Hg	17.4 (8.1)	15.9 (6.0)	1.5 (−0.1 to 3.1)	0.052	1.1 (−0.6 to 2.9)	0.21
IOP change, mm Hg	−4.6 (9.7)	−3.8 (7.7)	−0.8 (−2.8 to 1.1)	0.39	1.1 (−0.6 to 2.9)	0.21
IOP % change	−25.6 (−43.7, 2.8)	−16.7 (−35.8, 8.2)				
20% IOP reduction	109 (55%)	64 (46%)	8.7% (−2.1% to 19.6%)	0.11	−1.1% (−12.6% to 10.5%)	0.85
Medication outcomes						
Preoperative medications	2.9 (1.3)	2.6 (1.2)				
Final medications	1.1 (1.5)	1.3 (1.3)	−0.2 (−0.5 to 0.1)	0.14	−0.2 (−0.5 to 0.2)	0.37
Change in No. of medications	−1.8 (1.7)	−1.3 (1.6)	−0.5 (−0.8 to −0.1)	0.011	−0.2 (−0.5 to 0.2)	0.37
% change in No. of medications	−100.0 (−100.0, −20.0)	−50.0 (−100.0, 0.00)				
0 medications	116 (58%)	56 (40%)	18.0% (7.3% to 28.7%)	0.001	15.1% (2.8% to 27.3%)	0.016
1 medication	19 (9.5%)	19 (14%)	−4.1% (−11.0% to 2.8%)	0.24	−3.3% (−10.7% to 4.0%)	0.37
2 medications	28 (14%)	44 (32%)	−17.6% (−26.3% to −8.9%)	<0.001	−12.9% (−22.8% to −3.1%)	0.01
≥3 medications	36 (18%)	20 (14%)	3.7% (−4.4% to 11.8%)	0.36	1.5% (−7.3% to 10.3%)	0.74
Qualified success						
12 mm Hg	50 (25%)	26 (19%)	6.4% (−2.7% to 15.5%)	0.16	0.1% (−10.2% to 10.3%)	0.99
15 mm Hg	83 (42%)	47 (34%)	7.9% (−2.7% to 18.5%)	0.14	0.4% (−11.6% to 12.4%)	0.95
18 mm Hg	103 (52%)	59 (42%)	9.3% (−1.5% to 20.2%)	0.092	−0.1% (−12.1% to 12.0%)	0.99
21 mm Hg	107 (54%)	61 (44%)	9.9% (−1.0% to 20.7%)	0.074	1.5% (−10.4% to 13.3%)	0.81
Complete success						
12 mm Hg	34 (17%)	10 (7.2%)	9.9% (2.6% to 17.2%)	0.005	6.1% (−2.5% to 14.6%)	0.16
15 mm Hg	54 (27%)	16 (12%)	15.6% (6.9% to 24.3%)	<0.001	11.7% (1.9% to 21.6%)	0.02
18 mm Hg	65 (33%)	22 (16%)	16.8% (7.5% to 26.2%)	<0.001	12.1% (1.6% to 22.7%)	0.024
21 mm Hg	68 (34%)	23 (17%)	17.6% (8.1% to 27.1%)	<0.001	11.9% (1.2% to 22.7%)	0.029

Crude outcomes are presented as n (%), mean (SD) or median (IQR).
*Reference is the Xen+cataract group.
IOP, intraocular pressure.

Mean IOP change was −4.3±8.9 mm Hg, median IOP % change was −21.7% and the proportion of achieving 20% reduction in IOP was 51%. The mean number of medications at 24 months was 1.2±1.4, a mean reduction of 1.6 medications. The proportion of eyes who were completely off all glaucoma medications was 51%. There was a trend for a reduction in the success rate over time. The proportion of eyes achieving CS at the 18 mm Hg threshold at 6, 12, 24, 36 and 48 months were 39%, 30%, 26%, 17% and 11%, respectively.

Table 3 shows the 24 months outcomes stratified by Xen stand-alone (n=199) and Xen+cataract groups (n=139). After adjusting for baseline characteristics, at 24 months there was no significant difference in IOP outcome (IOP at the last visit, IOP change or 20% IOP reduction) between the two groups. More eyes in the Xen stand-alone group were glaucoma medications free (58% vs 40%, p=0.016). More eyes in the Xen stand-alone group achieved CS than in the Xen plus cataract; for a target pressure of 15 mm Hg (27% vs 12%; p=0.02), 18 mm Hg (33% vs 16%; p=0.024) and 21 mm Hg (34% vs 17%; p=0.029).

Figure 1 shows the Kaplan-Meier curve for CS at the 18 mm Hg threshold. Among the eyes followed for 24 months, the most common adverse event was a loss of ≥10 letters of VA from baseline (online supplemental table S1). This occurred in 31% of eyes within the first 6 months after surgery. We analysed these cases in relation with hypotony, defining numerical hypotony or symptomatic hypotony (IOP <6 mm Hg and at the same visit VA reduced by >10 letters from preoperative). The corresponding rates of longer-term hypotony (onset from 12 months to 24 months postsurgery) was numerical hypotony of 1.5% and symptomatic hypotony of 1.2%. Exposure of the glaucoma device occurred in 1.8% (n=6) of cases, four of these were within 6 months of the original surgery. Online supplemental tables S1 and S2 provide summary details on adverse events and secondary procedures.

Bleb needling was performed in 28.4% of cases, 19% of these occurring within the first 6 months after the procedure, 5% between 6 and 12 months and 4.4% between 12 and 24 months. Among the eyes followed up for 24 months (online supplemental table S2), 18% underwent a secondary procedure, the most common of these being bleb revision (7.5%). This included either bleb revision alone, or revision combined with cataract surgery. In addition, 5.1% of eyes underwent trabeculectomy following Xen within the first 24 months.

As part of data entry into the registry, when Xen surgery was performed, there was a requirement to state whether the surgery was performed abinterno or abexterno, and whether the conjunctiva was opened or left closed. In this cohort of patients who reached 24-month follow-up, 86% of eyes had abinterno surgery with closed conjunctiva and 13% of patients had abinterno surgery where the conjunctiva was opened. Almost all patients had surgery with MMC 0.2 mg/mL and surgeons applied 0.1 mL. So the number of cases with other MMC concentrations was too limited to undertake a meaningful statistical comparison.

Table 4 shows the crude and aHR of failure for Xen stand-alone group (vs Xen+cataract group). The Xen stand-alone group showed significantly lower aHR of failure for all IOP

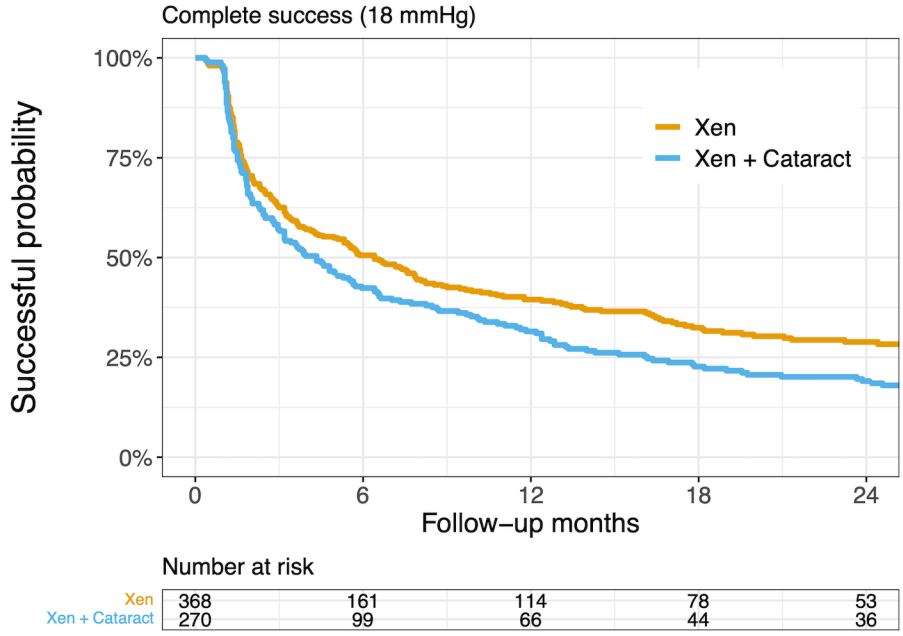

Figure 1 The Kaplan-Meier curve for complete success at the 18 mm Hg threshold.

thresholds (CS): aHR was 0.79 (95% CI 0.62 to 0.99), 0.68 (0.53 to 0.88), 0.71 (0.54 to 0.92) and 0.70 (0.54 to 0.92), respectively. Meanwhile, the failure rate for QS was similar between the two groups.

DISCUSSION

This international multicentre retrospective real-world study provides a large dataset of longitudinal outcomes regarding safety and efficacy of the Xen 45 gel stent implant. The primary outcome measure of complete and QS at 24 months were 26% and 48%, respectively.

Reitsamer *et al*[15] reported 24 months outcomes for Xen surgery with and without cataract surgery. For the eyes with 24 months follow-up, clinical success was 65.8% defined as an IOP reduction >20% and no increase in medications or reoperations. Using our least stringent success measure (QS, IOP threshold of ≤21 mm Hg), we observed a success rate of 50% at 2 years. Indeed, the comparison of different series is most often difficult because of various definitions of success.[16] Mansouri *et al*[17] also reported a series of patients with 24-month follow-up, and they found CS (requiring >20% IOP reduction) of 18.2% at the final IOP threshold of ≤12 mm Hg and 44.4% for IOP ≤15 mm Hg.

Table 4 HR for failure in Xen stand-alone group (vs Xen+cataract group)

	Crude HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Qualified success				
12 mm Hg	0.84 (0.70 to 1.01)	0.061	0.89 (0.70 to 1.13)	0.34
15 mm Hg	0.85 (0.70 to 1.04)	0.11	0.90 (0.69 to 1.16)	0.41
18 mm Hg	0.91 (0.74 to 1.11)	0.34	1.01 (0.78 to 1.32)	0.93
21 mm Hg	0.91 (0.74 to 1.12)	0.36	1.02 (0.79 to 1.33)	0.87
Complete success				
12 mm Hg	0.84 (0.70 to 0.998)	0.048	0.79 (0.62 to 0.996)	0.046
15 mm Hg	0.77 (0.64 to 0.92)	0.004	0.68 (0.53 to 0.88)	0.003
18 mm Hg	0.77 (0.64 to 0.93)	0.006	0.71 (0.54 to 0.92)	0.011
21 mm Hg	0.76 (0.63 to 0.92)	0.005	0.70 (0.54 to 0.92)	0.011

With this definition, our success rate in our series is in the same range 13% and 38%, respectively. Our 2-year success rate (IOP ≤18 mm Hg) of 26% is in line with a number of smaller studies reporting success rates of 27.4%,[18] 27%[19] and 34%.[20]

Although our primary analysis was at 2 years, we also have data on over 200 eyes completing at least 48 months of follow-up. Using the same primary success outcome of IOP ≤18 mm Hg and >20% reduction at this time point, QS was 40% and CS was 11%, therefore lower than at the 24 months outcomes, 48% and 26%, respectively. To date there are few studies reporting 48-month follow-up and more. Gillmann *et al*[21] showed a higher success rate at 3 years with 29% of eyes achieving IOP ≤15 mm Hg without treatment, with 44% of eyes achieving a >20% IOP reduction from preoperative. Torbey *et al* presented 5-year outcomes of Xen gel stent in 80 eyes.[22] CS was achieved (IOP threshold of ≤15 mm Hg) in 33.5% and QS (IOP threshold of ≤15 mm H) in 44.7%.

The Xen gel stent was FDA approved through the 510k pathway which does not require any randomised controlled trial and so limited high-quality data is available comparing outcomes with trabeculectomy. Schlenker *et al*[12] undertook a retrospective cohort study of trabeculectomy versus Xen gel stent outcomes at 1 year, and found no significant difference between the two groups in success, although the Xen group had both a higher needling rate (43.2% vs 30.8%) and secondary intervention rate (10.3% vs 5.3%, p=0.11). To compare longer-term outcomes, the primary TvT study reported 3-year outcomes for their trabeculectomy arm.[23] Using success as defined as IOP <21 mm Hg and >20% reduction, CS was 44% and 71% were complete or QSs. In contrast, the comparable success rates for the Xen gel stent in this study were 19% and 44%. Secondary procedures were undertaken in 9% of trabeculectomy cases, less than the equivalent 18% for the Xen 45 gel stent implant in our study. In contrast, they found a higher rate of long-term symptomatic hypotony around 6% versus 1.5% in this cohort.

In our subgroup analysis looking for differences between Xen stand-alone and Xen combined with cataract, we did not find any difference in mean IOP between the two groups. However, there was a difference in the medication reduction parameters,

with the Xen stand-alone group having a greater effect. Indeed the CS was higher in the Xen stand-alone compared with the Xen+cataract group at all IOP thresholds. Yang *et al*[24] also found a more substantial decrease in mean IOP in stand-alone MIGS group. Other studies have shown no significant difference in outcomes between these two groups.[25] Torbey *et al*[22] also reported no significant differences in success rates between the Xen stand-alone group and combined cataract+Xen procedure. Poorer outcomes with phacotrabeculectomy versus trabeculectomy alone have been reported[26] with a possible explanation being that cataract surgery leads to disruption of the blood-aqueous barrier, and that secreted inflammatory material could adversely affect the function of the filtration bleb.

Relatively high rates of bleb needling have been reported in prior Xen gel stent publications. At 2 years, needling was performed in 28.4% of eyes in our study, most within the first 6 months. This is consistent with some studies[27] but higher rates have been reported in other studies ranging from 41% to 62%.[20 21] We found a rate of secondary glaucoma procedures at 18%, which is comparable to other studies with a shorter follow-up (12 months).[28 29] This rate of secondary glaucoma surgery appears to be focused within the first 2 years after the surgery.

We found a relatively high rate of VA loss of ≥10 letters within the first 6 months after surgery (31%). This is quite different from other studies reporting equivalent rates in the range of 2%–6.2%.[17 21 28] It is likely that methodological factors are at play with this result; as a registry-based study, we enter every visit the patient attended. With more follow-up visits available, and by requiring a VA to be entered at every visit, there is more opportunity to include a visit with VA loss. It seemed that this rate was not associated with future cataract surgery.

We assessed both early (<12 months) and late hypotony (12–24 months) and differentiated between 'numerical hypotony' and 'symptomatic hypotony'. Within the first 6 months after surgery, 27% of patients experienced numerical hypotony, but only 15% had VA loss. Rates of late hypotony were low with 1.5% numerical and 1.2% symptomatic hypotony, which is comparable to other studies.[15 21]

The rate of other adverse events was low, including device exposure of 1.8% and no cases of endophthalmitis. This is lower than in other studies and may relate to the dose of MMC used. The majority of patients had surgery with MMC 0.2 mg/mL but the number of cases with other MMC concentrations was too limited to undertake a meaningful statistical comparison.

The limitations of this study are those inherent with real-world studies. There was no standardisation of approach to treatment; surgery was undertaken as per the individual surgeon's preference, and medications were added or removed in a similar way. Most of the population was Caucasian and therefore these findings may not externally generalise to other ethnicities. Similarly, most of the patients presented with primary open-angle glaucoma.

In conclusion, the Xen 45 gel stent implant provides acceptable efficacy at 24-month follow-up, at the cost of relatively high rates of bleb needling and secondary procedures. Greater CS was achieved with Xen stand-alone surgery.

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Table S1. Adverse events.

Variable	6M	12M	24M	36M	48M
Procedures, n	431	439	338	245	203
VA Loss ≥10 Letters 0-6M (%)	174 (40%)	140 (32%)	106 (31%)	75 (31%)	43 (21%)
VA Loss ≥10 Letters 6-12M (%)		54 (12%)	39 (12%)	23 (9.4%)	15 (7.4%)
VA Loss ≥10 Letters 12-24M (%)			41 (12%)	25 (10%)	16 (7.9%)
Bleb Needling 0-6M (%)	93 (22%)	81 (18%)	65 (19%)	42 (17%)	29 (14%)
Bleb Needling 6-12M (%)		21 (4.8%)	17 (5%)	14 (5.7%)	7 (3.4%)
Bleb Needling 12-24M (%)			15 (4.4%)	12 (4.9%)	7 (3.4%)
Bleb Needling 24-36M (%)				2 (0.82%)	2 (0.99%)
Bleb Needling 36-48M (%)					2 (0.99%)
Hypotony 0-6M (%)	133 (31%)	114 (26%)	92 (27%)	58 (24%)	37 (18%)
Hypotony 6-12M (%)		4 (0.91%)	3 (0.89%)	3 (1.2%)	0 (0%)
Hypotony 12-24M (%)			5 (1.5%)	4 (1.6%)	1 (0.49%)
Hypotony 24-36M (%)				1 (0.41%)	1 (0.49%)
Hypotony 36-48M (%)					0 (0%)
Hypotony 0-6M+VA Loss ≥10 Letters 0-6M (%)	74 (17%)	64 (15%)	50 (15%)	30 (12%)	15 (7.4%)
Hypotony 6-12M+VA Loss ≥10 Letters 6-12M (%)		2 (0.46%)	2 (0.59%)	2 (0.82%)	0 (0%)

Hypotony 12-24M+VA Loss ≥10 Letters 12-24M (%)			4 (1.2%)	4 (1.6%)	1 (0.49%)
Hypotony 24-36M+VA Loss ≥10 Letters 24-36M (%)				1 (0.41%)	1 (0.49%)
Hypotony 36-48M+VA Loss ≥10 Letters 36-48M (%)					0 (0%)
Hyphaema 0-6M (%)	20 (4.6%)	15 (3.4%)	12 (3.6%)	10 (4.1%)	6 (3%)
Hyphaema 6-48M (%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Glaucoma Device Malposition 0-6M (%)	10 (2.3%)	8 (1.8%)	7 (2.1%)	3 (1.2%)	4 (2%)
Glaucoma Device Malposition 6-12M (%)		1 (0.23%)	1 (0.3%)	1 (0.41%)	1 (0.49%)
Glaucoma Device Malposition 12-48M (%)			0 (0%)	0 (0%)	0 (0%)
Choroidal Effusions 0-6M (%)	21 (4.9%)	16 (3.6%)	13 (3.8%)	4 (1.6%)	4 (2%)
Choroidal Effusions 6-12M (%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Choroidal Effusions 12-24M (%)			1 (0.3%)	0 (0%)	0 (0%)
Choroidal Effusions 24-48M (%)				0 (0%)	0 (0%)
Corneal Decompensation 0-6M (%)	4 (0.93%)	3 (0.68%)	3 (0.89%)	3 (1.2%)	3 (1.5%)
Hyphaema 0-6M+VA Loss ≥10 Letters 0-6M (%)	13 (3%)	9 (2.1%)	8 (2.4%)	6 (2.4%)	3 (1.5%)
Hypotony Maculopathy 0-6M (%)	7 (1.6%)	6 (1.4%)	7 (2.1%)	4 (1.6%)	3 (1.5%)
Shallow AC 0-6M (%)	9 (2.1%)	8 (1.8%)	5 (1.5%)	4 (1.6%)	2 (0.99%)
Glaucoma Device Exposure 0-6M (%)	6 (1.4%)	4 (0.91%)	4 (1.2%)	2 (0.82%)	2 (0.99%)
Glaucoma Device Exposure 6-2M (%)		2 (0.46%)	1 (0.3%)	0 (0%)	0 (0%)
Glaucoma Device Exposure 12-24M (%)			1 (0.3%)	1 (0.41%)	0 (0%)

Glaucoma Device Exposure 24-48M (%)				0 (0%)	0 (0%)
Bleb Dysaesthesia 0-6M (%)	2 (0.46%)	2 (0.46%)	2 (0.59%)	0 (0%)	0 (0%)
Bleb Dysaesthesia 6-12M (%)		1 (0.23%)	0 (0%)	0 (0%)	0 (0%)
Bleb Dysaesthesia 12-24M (%)			2 (0.59%)	1 (0.41%)	1 (0.49%)
Stent Obstruction 0-6M (%)	9 (2.1%)	8 (1.8%)	5 (1.5%)	3 (1.2%)	0 (0%)
Stent Obstruction 6-24M (%)		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Corneal Epithelial Toxicity From Antimetabolite 0-6M (%)	2 (0.46%)	1 (0.23%)	0 (0%)	0 (0%)	0 (0%)
Infectious Endophthalmitis 0-6M (%)	1 (0.23%)	1 (0.23%)	0 (0%)	0 (0%)	0 (0%)
Conjunctival Leak 0-6M (%)	2 (0.46%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

M = month.

Data are presented as n (%)

[a] Eligible procedures were ones that had at least one visit 6 months (150–335 days) after the procedures themselves were performed. The same applied to the 12M, 24M, 36M. and 48M.

None of the following adverse events were observed: binocular double vision, blebitis, blebitis with endophthalmitis, cyclodialysis cleft, Intraocular lens dislocation, malignant glaucoma, peripheral anterior synechiae associated with stent, postsurgical scleritis, ptosis, reformation of anterior chamber, or suprachoroidal haemorrhage.

Table S2. Secondary glaucoma procedures after Xen stand-alone or Xen+Cataract surgery.

	6M	12M	24M	36M	48M
Procedures, n	431 (100%)	439 (100%)	338 (100%)	245 (100%)	203 (100%)
Any of the below Procedures	43 (10%)	57 (13%)	62 (18%)	45 (18%)	34 (17%)
Trabeculectomy 0-6M	6 (1.4%)	5 (1.1%)	4 (1.2%)	1 (0.41%)	2 (0.99%)
Trabeculectomy 6-12M		6 (1.4%)	7 (2.1%)	2 (0.82%)	2 (0.99%)
Trabeculectomy 12-24M			6 (1.8%)	4 (1.6%)	3 (1.5%)
Trabeculectomy 24-36M				8 (3.3%)	5 (2.5%)
Trabeculectomy 36-48M					5 (2.5%)
Revision Of Glaucoma Device 0-6M	19 (4.4%)	16 (3.6%)	12 (3.6%)	10 (4.1%)	7 (3.4%)
Revision Of Glaucoma Device 6-12M		7 (1.6%)	6 (1.8%)	4 (1.6%)	2 (0.99%)
Revision Of Glaucoma Device 12-24M			2 (0.59%)	2 (0.82%)	1 (0.49%)
Revision Of Glaucoma Device 24-48M				0 (0%)	0 (0%)
Xen Implant 0-6M	3 (0.7%)	3 (0.68%)	3 (0.89%)	1 (0.41%)	1 (0.49%)
Xen Implant 6-48M		0 (0%)	0 (0%)	0 (0%)	0 (0%)
Revision Of Glaucoma Device Cataract 0-12M	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Revision Of Glaucoma Device Cataract 12-24M			2 (0.59%)	1 (0.41%)	1 (0.49%)
Revision Of Glaucoma Device Cataract 24-48M				0 (0%)	0 (0%)
Revision Trabeculectomy_0-6M	3 (0.7%)	0 (0%)	1 (0.3%)	0 (0%)	0 (0%)

Revision Trabeculectomy 6-12M		2 (0.46%)	1 (0.3%)	0 (0%)	0 (0%)
Revision Trabeculectomy 12-24M			1 (0.3%)	0 (0%)	0 (0%)
Revision Trabeculectomy 24-48M				0 (0%)	0 (0%)
Revision Trabeculectomy Cataract 0-6M	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Revision Trabeculectomy Cataract 6-12M		1 (0.23%)	1 (0.3%)	0 (0%)	0 (0%)
Revision Trabeculectomy Cataract 12-48M			0 (0%)	0 (0%)	0 (0%)

[a] Eligible procedures were ones that had at least one visit 6 months (150–335 days) after the procedures themselves were performed. The same applied to the 12M, 24M 36M and 48M.