ISSN: 2996-0940
Research Article
Science Set Journal of Ophthalmology and Eye Care

Minimally Invasive Micro Sclerostomy (MIMS©): 42-Month Performance and Safety in Open-Angle Glaucoma

Lilit Voskanyan[1, 2*], Iqbal Ike K. Ahmed[3], Hovsep Miroyan[1], Vahan Papoyan[1], Astghik Ghazaryan[1], Haik Babayan[1], Oren Bar-Ilan[4], and Yoseph Glovinsky[5, 6]

[1]*Ophthalmological Center after S.V. Malayan, Yerevan, Armenia*
[2]*Mikhitar Heratsi Yerevan State Medical University, Yerevan, Armenia*
[3]*Department of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada 4DataSights Ltd, Enfield, England, UK*
[5]*Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
[6]*Goldschleger Eye Institute, Sheba Medical Center, Tel Hashomer, Israel*

***Corresponding author:** Lilit Voskanyan Ophthalmological Center after S.V. Malayan, Yerevan, Armenia.

Submitted: 31 May 2025 **Accepted:** 09 June 2025 **Published:** 16 June 2025

https://doi.org/10.63620/MKSSJOEC.2025.1030

Citation: *Voskanyan, L., Ahmed, I. I. K., Miroyan, H., Papoyan, V., Ghazaryan, A., Babayan, H., Bar-Ilan, O., & Glovinsky, Y. (2025). Minimally Invasive Micro Sclerostomy (MIMS©): 42-Month Performance and Safety in Open-Angle Glaucoma. Science Set Journal of Ophthalmology and Eye Care, 4(2), 01-11.*

Abstract

Minimally Invasive Micro Sclerotomy (MIMS) is an ab interno subconjunctival bleb-forming stent-less device designed to reduce intraocular pressure (IOP) in subjects with open- angle glaucoma (OAG). This 42-month prospective follow-up extension study was aimed at reporting the long-term outcomes of MIMS as a standalone procedure or combined with phacoemulsification.

Thirty MIMS-treated eyes for primary OAG or pseudoexfoliative glaucoma (PXFG) with uncontrolled IOP >21 mmHg on tolerated topical medication at baseline that showed ≥20% IOP reduction at Month 12 follow-up visit in the prior trial and additional 18 eyes considered as failures were included in the overall success and survival analysis. The mean (±STD) baseline IOP (27.3±3.2 mmHg) was reduced by 33.0% to 17.8±5.9 mmHg and by 37.4% to 17.0±4.6 mmHg at Month 36 and 42 visits, respectively. Qualified success of ≥20% IOP reduction on the same or fewer hypotensive medications was achieved in 54.2% eyes (47.4% for MIMS stand-alone and 80% for phacoemulsification-MIMS). Complete success of ≥20% IOP reduction with no hypotensive medications was observed in 39.6% of the MIMS-treated eyes (31.6% for MIMS stand-alone and 70.0% for phacoemulsification- MIMS). Between 12 and 42 months, 9.2% eyes were reoperated for glaucoma and 2.5% eyes had 20% endothelial cell loss without corneal edema, attributed to patient's age and health condition.

These findings demonstrate the long-term (up to 3 years) effectiveness and safety of the MIMS device for OAG and PXFG patients, both as a standalone procedure and in combination with phacoemulsification, positioning it as a viable choice for minimally invasive surgical intervention.

Keywords: Glaucoma, Minimally Invasive Micro Sclerostomy, Glaucoma Filtration Surgery, Open-Angle Glaucoma, Long-Term, Minimally Invasive Bleb Surgery

Abbreviations

- **AC:** Anterior Chamber
- **AE:** Adverse Event
- **AAOG:** American Academy of Ophthalmology's Glaucoma
- **BCVA:** Best Corrected Visual Acuity
- **CI:** Confidence Interval
- **CRA:** Clinical Research Associate
- **CRO:** Contact Research Organization

- **CSR:** Clinical Study Report
- **GDD:** Glaucoma Drainage Device
- **EC:** Ethical Committee
- **ECC:** Endothelial Cell Count
- **ECD:** Endothelial Cell Density
- **EGS:** European Glaucoma Society
- **IEC:** Institutional Ethical Committee
- **IOP:** Intraocular Pressure
- **MCID:** Minimal Clinically Important Difference
- **MIBS:** Minimally Invasive Bleb Surgery
- **MIGS:** Minimally Invasive Glaucoma Surgery
- **MIMS®:** Minimally Invasive Micro Sclerostomy
- **OCT:** Optical Coherence Tomography
- **OVD:** Ophthalmic Viscoelastic Device
- **PAS:** Peripheral Anterior Synechiae
- **PCIOL:** Posterior Chamber Intraocular Lenses
- **PEXG:** Pseudo exfoliative Glaucoma
- **PG:** Pigmentary Glaucoma
- **PKP:** Penetrating Keratoplasty
- **PO:** Post Operation/ Post-Index Procedure
- **POAG:** Primary Open Angle Glaucoma
- **PROM:** Patient-Related Outcome Measures
- **RCT:** Randomized Clinical Trial
- **SAE:** Serious Adverse Event
- **SD:** Standard Deviation

Introduction

Glaucoma, the leading cause of irreversible blindness worldwide, is an optic neuropathy characterized by the progressive degeneration of retinal ganglion cells [1,2]. The prevalence of open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) climbed from about 60 million individuals in 2010 to nearly 80 million in 2020 and is anticipated to reach over 110 million by 2040 [3, 4]. Although glaucoma has multiple contributing factors, the only effective way to slow its progression is by lowering the associated elevated intraocular pressure (IOP). The first-step management of glaucoma typically involves topical eye drops and laser trabeculoplasty. While incisional surgeries, such as trabeculectomy and glaucoma drainage device implantation, are effective in reducing IOP, they come with significant drawbacks [5-8]. These include specific surgeons' specialization, extended surgical and recovery periods, frequent follow-up requirements and fluctuating postoperative IOPs [9]. As a result, these surgical approaches are generally reserved for patients with advanced disease requiring more aggressive treatment.

Minimally invasive glaucoma surgery (MIGS) has grown increasingly popular over the past decade. These microsurgical procedures are typically classified based on their mechanism of action: improving aqueous humor outflow through the trabecular meshwork, diverting it to the subconjunctival or suprachoroidal space, or reducing its production. These minimally invasive procedures have shown promising results, delivering effective outcomes with minimal trauma, a high safety profile, short operation times, and rapid patient recovery [10, 11].

MIGS are Often Performed Alongside Cataract Surgery

However, since the reduction in intraocular pressure (IOP) achieved through MIGS is generally less significant than that of trabeculectomy or glaucoma drainage devices (GDDs), its use is typically limited to patients with mild to moderate disease. These patients may have uncontrolled IOP despite medical or laser therapies or face challenges such as poor adherence, intolerance, or restricted access to medical treatments, leaving them with limited options [12, 13]. Surgery may be indicated for people who continue to show progressive vision loss despite maximal medical therapy, are intolerant of glaucoma medications, or have difficulty adhering to medical treatment plans. For moderate to severe glaucoma, minimally invasive bleb surgery (MIBS) or conventional or incisional glaucoma surgery may be performed [14].

The Minimally Invasive Micro Sclerostomy (MIMS), developed by Sanoculis Ltd. (Kiryat Ono, Israel) is an innovative stent-less ab interno subconjunctival bleb-forming stent-less device. As a minimally invasive bleb surgery, the MIMS device creates a new subconjunctival outflow pathway of ~100 microns in diameter for eye fluid drainage, connecting the anterior chamber to the subconjunctival space [14]. MIMS procedure is a less invasive alternative to conventional incisional glaucoma surgery (e.g., trabeculectomy).

Preclinical studies conducted both in vitro and using an experimental porcine model demonstrated consistently high levels of safety, feasibility, and efficacy [15].

Subsequently, a prospective, open-label, single-arm trial was conducted, involving 120 patients who underwent either a standalone MIMS procedure (n = 100) or a combined phacoemulsification-MIMS procedure (n = 20). The 12-month results indicated that MIMS procedure is a relatively efficacious and safe for patients with OAG and uncontrolled IOP and may be considered in cases requiring surgical intervention [16, 17]. The current study aims to expand upon the conclusions of that clinical trial by further evaluating the safety, performance, and efficacy of MIMS for an extended follow-up period of up to 42 months.

Methods

Setting and Design

This is a prospective, observational, follow-up extension study, registered at ClinicalTrials.gov, for subjects originally treated as part of a prospective, single-arm, single-center (Ophthalmologic Center after S.V. Malayan, Yerevan, Armenia), open-label study with intra-subject comparisons (ClinicalTrials.gov Identifier: NCT04503590). The design was based on prior preclinical and clinical experience with the MIMS device, which has undergone exhaustive preclinical and clinical testing, as well as the published recommendations of the World Glaucoma Association (WGA) guidelines on design and reporting of glaucoma surgical trials, and ANSI Z80.27-2014(R2019) Standard for Implantable Glaucoma Devices. The study was approved by the local Independent Ethics Committee of S. Malayan Eye Center, Yerevan, Armenia, and conducted in accordance with the Declaration of Helsinki, Good Clinical Practice, ISO 14155:2020 standard, and the local/national guidelines and regulations of the S. Malayan Eye Center.

Patient Selection

The cohort consisted of patients who fulfilled the following criteria: prior MIMS surgery; 18– 85 years old; ability and willingness to attend at least one of the scheduled follow-up visits, (optionally all), understanding and signing the informed consent. Subjects were excluded if met any of the following criteria: withdrawal from the previous study; any ocular surgery since the MIMS surgery in the study eye; severe trauma in the study eye

since the MIMS surgery in the study eye; current participation in another investigational drug or device clinical trial or participation in such trial within the last 30 days before enrollment into the study; pregnant or lactating women. Eligible subjects attended the 36- and 42-month post- treatment follow-up visits between 02 December 2022 and 13 August 2023. Additional 18 eyes defined as failures in the prior 1-year study, although not being invited for additional assessments during the course of this study, were included in the 3-year performance / effectiveness analysis of success rates and the Kaplan-Meyer survival analysis. Thus, in total, 48 eyes, including 38 eyes treated with MIMS® alone and 10 eyes treated with combined MIMS®-phacoemulsification, were included in these two analyses.

MIMS Procedure

The full methods used in the prior 12-months study have been previously published [16, 17]. To briefly recap, the marketed CE-marked (under MDD, 93/42/EEC) MIMS device was provided by Sanoculis Ltd, comprising a sterile, disposable surgical device (A32-000) and a repeated-use activation device (AS1000 or AS1001) that manages the activation pulse duration and rotations per minute, a motor, and a footswitch. In all cases, whether as a stand-alone procedure or in combination with clear corneal incision cataract surgery using phacoemulsification and posterior-chamber IOL implantation a subconjunctival injection of 0.1 mL Mitomycin C (MMC) 0.02% was given 1 h before the procedure. Ocular viscoelastic agent (Viscoat, Alcon Laboratories, Inc., Fort Worth, TX) was injected into the subconjunctival space at the superonasal quadrant for potential accommodation of the protruded surgical tool during the procedure.

A temporal paracentesis of 1.5 mm was created. The MIMS device was then inserted ab-interno into the anterior chamber through the small clear temporal corneal incision, with the tip positioned at the superior angle, above the trabecular meshwork. A thin cylinder of sclero-corneal tissue was removed, creating a drainage channel connecting the anterior chamber to the subconjunctival space.

Study Protocol

The study eyes were evaluated at the following postoperative visits: Month 36 (± 3 months) and Month 42 (± 3 months), with all data recorded within the Case Report Forms per visit. Measurements performed at all visits included automated refraction test, best-corrected visual acuity (BCVA) evaluation using an ETDRS chart, a comprehensive biomicroscopic examination including IOP, gonioscopy, a dilated fundus examination with optic disc assessment, and a thorough retinal examination directed toward identifying pathologies. Complications / adverse events were documented per visit.

All IOP measurements were performed using a calibrated Goldmann applanation tonometer (Haag Streit, Berne, Switzerland) during the morning hours. Two IOP measurements were taken at each study visit and the average was recorded; a third IOP measurement was taken if the difference between the first two was more than 3 mmHg and the average of the two closest measurements was recorded.

Outcome Measures

The selected outcome measures were designed to evaluate performance based on well- established and widely recognized efficacy and safety criteria for surgical treatments of glaucoma. The primary efficacy endpoint was the IOP levels at Months 36 and 42.

Further assessment of efficacy was based on the proportion of patients meeting the criteria of different definitions of complete (with no medications) and qualified success (on the same or fewer medications), not requiring any reoperation for glaucoma or having hypotony (IOP<5 mmHg). For all eyes, for calculating the surgical success rates, the last visit data was included in the "3-year" data analysis, as the worst-case scenario, i.e., the data collected from Month 36 and Month 42 visits were pooled into the 3-year performance analysis, based on the assumption that the performance outcomes at Month 42 are either stable or have worsened compared to Month 36.

The secondary efficacy endpoints were the proportion of subjects achieving ≥20% reduction in IOP from baseline at 3 years. A 20% reduction in IOP serves as the effectiveness endpoint recommended by the United States Food and Drug Administration (FDA) for implantable MIGS devices [18]. Additional success criteria were included based on the recommendations of the expert panel of American Academy of Ophthalmology's Glaucoma (AAOG) Preferred Practice Pattern® (PPP) Committee, which has suggested to define the clinically meaningful endpoint for reporting in clinical trials with standalone MIGS as surgical success of at least 50% with IOP of 21 mmHg or less and reduced by 20% or more from baseline without an increase in glaucoma medications, additional laser or incisional glaucoma surgery, loss of light perception vision, or hypotony, or a minimum of 50% medication free subjects, the European Glaucoma Society (EGS) Guide on Surgical Innovation for Glaucoma 2023 target IOP recommendations for the minimal clinically important difference (MCID) for surgical interventions for glaucoma, including the use of more than one set of criteria in presentation of data, or a minimum of 20%-30% medication free subjects, and the WGA Guidelines on Design and Reporting of Glaucoma Surgical Trials [19-21].

The EGS- recommended additional success criteria included the proportion of subjects achieving≥25% reduction in IOP from baseline, proportion of subjects achieving a mean IOP ≤ 21 mmHg and a ≥25% reduction in IOP from baseline and proportion of subjects achieving a mean IOP ≤ 18 mmHg and a ≥30% reduction in IOP from baseline, at 3 years. Additional criteria were the proportion of subjects achieving ≥20% reduction in IOP from baseline or IOP ≤21 mmHg, proportion of subjects achieving a mean IOP ≤ 18 mmHg and a ≥20% reduction in IOP from baseline, proportion of subjects achieving a mean IOP ≤ 18 mmHg or a ≥20% reduction in IOP from baseline, proportion of subjects achieving a mean IOP ≤ 18 mmHg or a ≥25% reduction in IOP from baseline and proportion of subjects achieving a mean IOP ≤ 14 mmHg or a ≥30% reduction in IOP from baseline, at 3 years.

Additional post-hoc analyses were performed based on target IOP recommendations from the EGS Guide on Surgical Innovation for Glaucoma [20]. The analyses included the mean change in medications for glaucoma from baseline at Months 36 and 42 and the proportion of the medication free subjects.

Failure was defined by any of the following criteria: final IOP outside the aforementioned range, development of any serious complication, severe loss of vision, or need to undergo addition-

al glaucoma surgery other than bleb needling or laser iridoplasty to retract the iris from the internal ostium of the channel.

The need to reintroduce ocular hypotensive medications was determined at the physician's discretion. Participants acted as their own control over time through repeated observations, thereby minimizing intersubject variability. As spontaneous improvement in IOP was not anticipated, the treatment outcomes associated with the MIMS device were unlikely to be influenced by the natural progression of the disease. Safety endpoints encompassed the occurrence of adverse events associated with the MIMS device or procedure, including changes in visual acuity and postoperative complications, and were evaluated across all participants from the original cohort (N=120) [17].

Statistical Analysis

Data from each visit were compared to baseline values obtained during the prior 12-month study [17]. Two-sided 95% Clopper–Pearson confidence intervals (CIs) were calculated for all measured parameters. Adverse events were categorized by severity, their association with the device or procedure, and their resolution status, with both their number and percentage reported.

In this study, the sample size was adequate to ensure that clinically meaningful differences / endpoints (taking into account the lower limit of the 95% confidence interval) could be identified, in accordance with the recommendations of the EGS consensus expert panel for IOP reductions of 2–3 mmHg and 20–30% medication-free subjects, as well as the guidance provided by the AAOG PPP Committee expert panel, at both follow-up visits [19,20].

For surgical success rates (as described above), the data from the two visits pooled into the "3-year" performance analysis for surgical success rates (as described above).

For data analysis, continuous variables were described by means and standard deviations (SD). Dichotomous variables were presented as percentages with 95% confidence interval. Wilcoxon signed rank test for paired observations was used for paired comparisons. P- values < 0.05 were considered statistically significant.

Results

The baseline characteristics and demographics of the original 120 eyes from 120 subjects have been detailed in prior research [17]. In this study, efforts were made to reach all 93 participants who completed 12 months of follow-up during the prior study and were not defined as surgical failures. Of these, 30 provided consent to participate, while others were not included in the follow-up due to trabeculectomy (11 participants) or other reasons (34 participants; including lack of interest, limited or no communication, travel abroad), health issues (9 participants; e.g., cataract or trauma-related surgery) or death (6 participants). On Month 36 and 42 visits, 19 and 25 eyes were assessed, respectively.

The cohort in this follow-up extension study consisted of 30 eyes, including 29 eyes that were defined as success at the end of the prior 12-month study (i.e., ≥20% IOP reduction on the same or fewer number of medications) and 1 eye had a ≥20% IOP reduction on a higher number of medications. Of them, 27 were diagnosed with POAG and 3 with PXFG, with baseline characteristics similar to the original cohort (age: 63.2± 13.5 [range: 22 – 85] years; male: 53.3%; right eye operated: 40%; phakic 63%). The mean baseline IOP was 27.3 ± 3.2 (95% CI: 26.2–28.5) mmHg. At baseline, subjects were treated with an average of 1.87 ± 0.68 (95% CI: 1.62–2.12) ocular hypotensive medications.

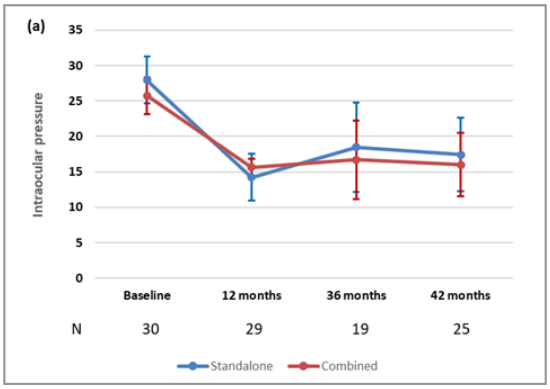
Efficacy

IOP and Medication Reduction

Table 1 presents the mean (± SD) IOP measurements and the mean (± SD) number of hypotensive medications being used at all consecutive study visits, for the whole cohort of this extension study and by type of procedure (stand-alone MIMS or combined phacoemulsification-MIMS). Mean IOP at baseline was 27.3 ± 3.2 mmHg, dropping to 14.7 ± 2.9 mmHg at Month 12, 17.8 ± 5.9 mmHg at Month 36 and 17.0 ± 4.6 mmHg at Month 42. At baseline, patients were using 1.87 ± 0.7 hypotensive medications, dropping to 0.17 ± 0.47 at Month 12, 0.63±1.01 at Month 36 and 0.40±0.76 at Month 42 (Figure 1). Statistical analysis upon completion of the study showed that the difference from baseline for IOP and medication was statistically significant (P < 0.05 for all).

Table 1: Mean IOP and mean number of hypotensive medications during follow-up in patients treated with MIMS

Group	Study Visit	N	IOP (mmHg), mean ± SD [95% CI]	P value (vs. baseline)	No. of medications, mean ± SD [95% CI]	P value (vs. baseline)
All patients	Baseline	30	27.3 ± 3.2 [26.2 - 28.5]	-	1.87 ± 0.7 [1.62 - 2.12]	-
	Month 12	29*	14.7 ± 2.9 [13.7 - 15.7]	< 1e-5	0.17 ± 0.47 [0 - 0.35]	< 1e-5
	Month 36	19	17.8 ± 5.9 [15.2 - 20.5]	< 1e-5	0.63 ± 1.01 [0.18 - 1.08]	< 1e-4
	Month 42	25	17.0 ± 4.6 [15.0 - 18.9]	< 1e-5	0.40 ± 0.76 [0 - 0.80]	< 1e-4
Stand-alone MIMS	Baseline	21	28.0 ± 3.3 [26.6 - 29.4]	-	2.10 ± 0.54 [1.87 - 2.33]	-
	Month 12	20	14.3 ± 3.3 [12.6 - 15.7]	< 1e-4	0.15 ± 0.37 [-0.01 – 0.31]	< 1e-4
	Month 36	12	18.5 ± 6.3 [14.9 - 22.1]	0.007	0.67 ± 1.07 [0.06 - 1.27]	0.009
	Month 42	17	17.4 ± 5.2 [15.0 - 19.9]	<0.001	0.47 ± 0.80 [0.09 - 0.85]	<0.001
Phacoemulsification-MIMS	Baseline	9	25.8 ± 2.6 [24.1 - 27.5]	-	1.33 ± 0.71 [0.87 - 1.79]	-
	Month 12	9	15.7 ± 1.2 [14.9 - 16.5]	0.008	0.22 ± 0.67 [-0.22 - 0.66]	0.018
	Month 36	7	16.7 ± 5.5 [12.6 - 20.8]	0.017	0.57 ± 0.98 [-0.16 - 1.29]	0.043
	Month 42	8	16.0 ± 4.5 [12.9 - 19.1]	0.012	0.25 ± 0.71 [-0.24 - 0.74]	0.028



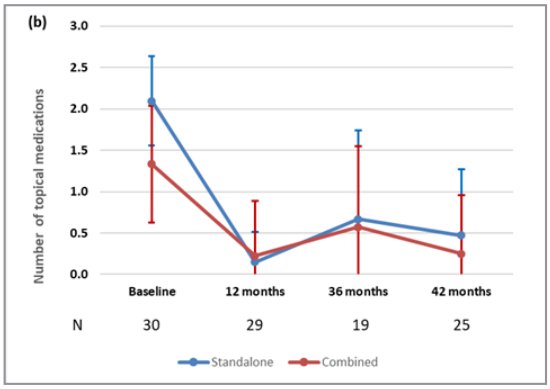


Figure 1 a Mean±SD (mmHg) intraocular pressure of study participants at all study visits, in stand-alone MIMS patients and MIMS combined with phaco-emulsification and IOL implantation. b Mean±SD number of topical hypotensive medications of study participants at all study visits, in stand-alone MIMS patients and MIMS combined with phacoemulsification and IOL implantation

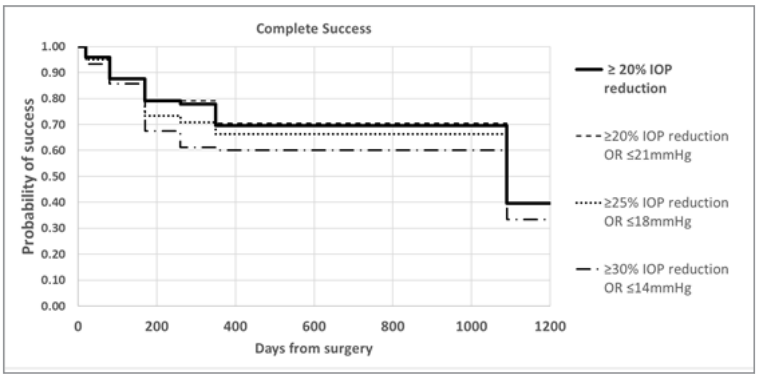
Success and Failure

Table 2 presents the cumulative success rates and 95% confidence intervals, as defined by eight criteria, in the whole cohort. Table 3 presents the same for the stand-alone subgroup. Survival curves for complete and qualified success are shown in Figure 2.

Table 2: Success criteria at multiple IOP levels at study endpoints– whole study cohort

IOP Levels (mmHg)	Success Criteria	1 year n/N (%) [95% CI]	3 years n/N (%) [95% CI]
≥ 20% IOP reduction	Complete [b]	66/95 (70%) [59.2–78.5%]	19/48 (40%) [25.8–54.7%]
	Qualified [a]	77/95 (81%) [71.7–88.3%]	26/48 (54%) [39.1–68.6%]
5 < IOP ≤ 21 OR ≥20% reduction	Complete	67/95 (71%) [60.3–79.4%]	19/48 (40%) [25.8–54.7%]
	Qualified	78/95 (82%) [72.9–89.2%]	26/48 (54%) [39.1–68.6%]
5 < IOP ≤ 18 OR ≥25% reduction	Complete	63/95 (66%) [55.9–75.7%]	19/48 (40%) [25.8–54.7%]
	Qualified	73/95 (77%) [67.1–84.9%]	26/48 (54%) [39.1–68.6%]
5 < IOP ≤ 14 OR ≥30% reduction	Complete	57/95 (60%) [49.4–69.9%]	16/48 (33%) [20.4–48.4%]
	Qualified	65/95 (68%) [58.1–77.6%]	21/48 (44%) [29.5–58.8%]
5 < IOP ≤ 18 AND ≥20% reduction	Complete	54/95 (57%) [46.3–67.0%]	18/48 (38%) [24.0–52.6%]
	Qualified	61/95 (64%) [53.7–73.8%]	21/48 (44%) [29.5–58.8%]
≥ 25% IOP reduction	Complete	62/95 (65%) [54.8–74.7%]	18/48 (38%) [24.0–52.6%]
	Qualified	72/95 (76%) [65.9–84.0%]	25/48 (52%) [37.2–66.7%]
5 < IOP ≤ 21 AND ≥25% reduction	Complete	59/95 (62%) [51.6–71.8%]	18/48 (38%) [24.0–52.6%]
	Qualified	68/95 (72%) [61.4–80.4%]	24/48 (50%) [35.2–64.8%]
5 < IOP ≤ 18 AND ≥30% reduction	Complete	50/95 (53%) [42.1–63.0%]	15/48 (31%) [18.7–46.3%]
	Qualified	57/95 (60%) [49.4–69.9%]	18/48 (38%) [24.0–52.6%]

[a] Qualified surgical success. [b] Complete surgical success - refers to medication-free eyes, out of all evaluable study eyes. [c] Data from 2S eyes defined as success, 1 eye with ≥20% IOP reduction and larger number of medications, and 18 eyes defined as failure in the prior 12-month study



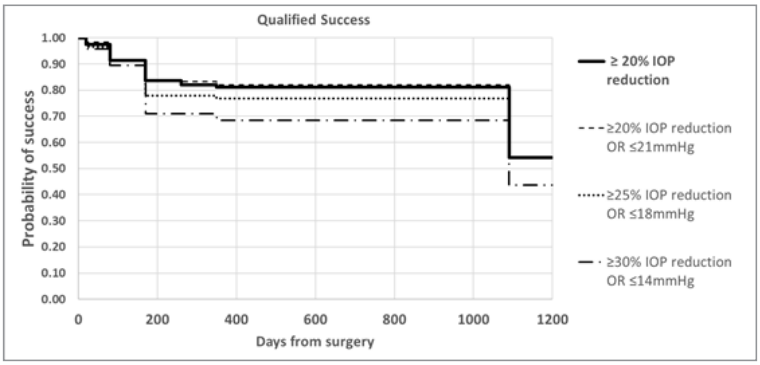


Figure 2 Survival curves for complete (top) and qualified (bottom) success for the secondary success criterion in this follow-up extension study (>20% IOP reduction) and the success criteria from the prior 12-month study (>20% IOP reduction or <21mmHg), >25 % IOP reduction or <18mmHg, and >30 % IOP reduction or <14mmHg)

Table 3: Success criteria at multiple IOP levels at study endpoints – standalone procedure

IOP Levels (mmHg)	Success Criteria	1 year n/N (%) [95% CI]	3 years n/N (%) [95% CI]
≥ 20% IOP reduction	Complete [b]	50/78 (64%) [52.4–74.6%]	12/38 (32%) [17.5–48.6%]
	Qualified [a]	62/78 (79%) [68.1–87.5%]	18/38 (47%) [31.0–64.2%]
5 < IOP ≤ 21 OR ≥20% reduction	Complete	50/78 (64%) [52.4–74.7%]	12/38 (32%) [17.5–48.6%]
	Qualified	62/78 (80%) [68.8–87.8%]	18/38 (47%) [31.0–64.2%]
5 < IOP ≤ 18 OR ≥25% reduction	Complete	47/78 (60%) [48.5–71.2%]	12/38 (32%) [17.5–48.6%]
	Qualified	56/78 (72%) [60.5–81.4%]	18/38 (47%) [31.0–64.2%]
5 < IOP ≤ 14 OR ≥30% reduction	Complete	41/78 (63%) [40.9–64%]	11/38 (29%) [15.4–46.0%]
	Qualified	48/78 (62%) [49.8–72.3%]	16/38 (42%) [26.3–59.2%]
5 < IOP ≤ 18 AND ≥20% reduction	Complete	38/78 (49%) [37.2–60.3%]	12/38 (32%) [17.5–48.6%]
	Qualified	44/78 (56%) [44.7–67.6%]	15/38 (40%) [24.0–56.6%]
≥ 25% IOP reduction	Complete	46/78 (59%) [47.5–70.0%]	12/38 (32%) [17.5–48.6%]
	Qualified	55/78 (71%) [59.1–80.3%]	18/38 (47%) [31.0–64.2%]
5 < IOP ≤ 21 AND ≥25% reduction	Complete	43/78 (55%) [43.4–66.4%]	12/38 (32%) [17.5–48.6%]
	Qualified	51/78 (65%) [53.8–75.8%]	18/38 (47%) [31.0–64.2%]
5 < IOP ≤ 18 AND ≥30% reduction	Complete	34/78 (44%) [32.4–55.3%]	11/38 (29%) [15.4–45.9%]
	Qualified	40/78 (51%) [36.7–62.8%]	14/38 (37%) [21.8–54.0%]

[a] Qualified surgical success. [b] Complete surgical success - refers to medication-free eyes, out of all evaluable study eyes. [c] Data from 21 eyes defined as success and 17 defined as failure in the prior 12-month study

Safety

No serious ocular or systemic adverse events were reported during the original study over the first 12 months. All adverse events were considered as mild to moderate. The most common was iris plugging of the internal ostium of the channel which occurred in 18 patients. In 7 cases it occurred early (≤ 12 weeks postoperatively) and in 11 late (> 12 weeks postoperatively). Treatment with topical pilocarpine drops followed by laser application on the adherent iris synechia led to complete resolution in all but 3 patients in whom persistent iris plugging was observed at the 12-months visit.

There were 15 cases with an IOP spike (> 30mmHg) on postoperative day one. This was attributed to retained viscoelastic material in the anterior chamber. All resolved at the slit- lamp by partial removal of the viscoelastic material by a gentle pressure on the posterior lip of the temporal paracentesis. All the above cases ended-up without sequelae, with or without topical treatment. One patient had 20% endothelial cell loss without corneal edema after a combined phacoemulsification-MIMS procedure which was attributed to the high nuclear density of the cataract, requiring high mean intraoperative cumulative dis- sipated energy during phacoemulsification.

Four patients had early corneal edema which spontaneously resolved, and there were single events of mild hyphema, choroidal effusion, ciliary body detachment, and branch retinal vein occlusion. Overall, BCVA decreased over the study period by ≥ 2 lines in 11 patients (9.2%), all due to cataract progression, with no cases of irreversible vision loss. At 12 months post-surgery,

post- operative interventions were reported in 2 patients who underwent trabeculectomy procedure due to bleb scarring and elevated IOP (both considered as failure). One patient underwent a successful needling procedure with MMC.

During the course of this follow-up extension study, from 12 months up to 42 months post- surgery, 3 patients (2.5%) had 20% endothelial cell loss without corneal edema after a combined phacoemulsification-MIMS procedure, which was attributed to the patients' age and health condition and 11 patients (9.2%) undergone reoperation for glaucoma. No events of induced astigmatism or new events of BCVA decrease were reported. One event of retinal edema / epiretinal membrane was reported in a fellow eye, not related to device / procedure.

Discussion

This extension study reports long-term IOP-lowering performance and safety of the MIMS® device, discussed in comparison with the literature on the gold standard of surgical approach, i.e., the MMC-trabeculectomy, and the marketed subconjunctival bleb-forming devices.

In the original study of this cohort [17], 93 subjects were followed up for up to 12 months, achieving a mean reduction in IOP of 38.0% in MIMS-treated eyes (37.4% for MIMS stand-alone, and 40.6% for phacoemulsification-MIMS), and a mean reduction in number of glaucoma medications of 85.1% (83.9% for MIMS stand-alone, and 91.6% for MIMS- phacoemulsification). These values are comparable to those reported in the studies included in the 2017 systematic review and meta-analysis of Lavia et al. investigating the effect of surgery with different MIGS devices on IOP and need for glaucoma medica- tions at 1 year [22]. In the current extension study, the IOP lowering effect was predominantly sustained during the long term. At 36 months, a mean reduction in IOP of 33.0% in MIMS- treated eyes (32.8% for MIMS stand-alone, and 33.8% for phacoemulsification-MIMS) and a mean reduction in number of glaucoma medications of 62.0% (59.7% for MIMS stand- alone, and 75.0% for MIMS-phacoemulsification). At 42 months, a mean reduction in IOP of 37.4% in MIMS-treated eyes (37.0% for MIMS stand-alone, and 38.3% for phacoemulsification-MIMS) and a mean reduction in number of glaucoma medications of 77.1% (78.6% for MIMS stand-alone, and 75.0% for MIMS-phacoemulsification).

The observed long-term IOP performance of the MIMS surgery is consistent with the 3-year mean IOP reduction rates reported with the marketed subconjunctival bleb-forming devices, such as XEN® gel implant (XEN45) (28.4% - 38.5%) and PRESERFLO MicroShunt 35.3% - 47.8%), and lower to some extent than the rates reported with the MMC-trabeculectomy (44% - 55%) [23–33]. Furthermore, the observed mean reduction of over 73% in the number of IOP-lowering drops at 3 years post MIMS® surgery is consistent with (or potentially larger than) the effects reported for to the MMC- trabeculectomy procedure (72% - 96%) and for XEN45 gel stent (72% - 87.5%) and PRESERFLO MicroShunt (72.6%) [24-33]. Furthermore, the number of medication- free subjects (70%) by 3 years post-MIMS® surgery is substantially than that reported at 3 years after implantation of XEN45 gel stent (42.4%) and PRESERFLO MicroShunt (53%) [23-26].

To evaluate the success of the procedure, either complete (with no medications) or qualified (on the same or fewer medications), not requiring any reoperation for glaucoma or having hypotony (IOP<6 mmHg), we used several sets of criteria, in order to be able to compare to the broadest set of existing long-term evidence with MMC-trabeculectomy and marketed subconjunctival bleb-forming devices, and also to illustrate the change in the MIMS performance compared to its 1-year performance. Qualified success of ≥ 20% IOP reduction on the same or fewer number of medications and no reoperation for glaucoma was achieved in 54.2% MIMS-treated eyes through the 3-year period (47.4% for MIMS stand-alone and 80% for phacoemulsification-MIMS). As anticipated, the 3-year qualified success of MIMS surgery (either standalone or combined with phacoemulsification) was lower than that reported for conventional MMC-trabeculectomy (71% - 88.9%) [32–36].

Trabeculectomy filtration surgery, using antimetabolites, such as mitomycin C (MMC) is still considered the gold standard of surgical approach for patients, which is highly effective in sustained IOP lowering for long-term periods [36].

However, it has a relatively high-risk profile, as perioperative and long-term postoperative complications and side effects are associated with this procedure [37–39]. Similar to conventional trabeculectomy, the MIMS® device is a subconjunctival bleb-forming procedure, creating a drainage channel in the sclero-corneal junction [40, 41]. But, as compared to trabeculectomy, the MIMS surgery, by forming a small size sclerostomy, allows for a less invasive, ab-interno, implant-free surgical intervention to improve the facility of outflow of aqueous humor from the eye, thus enabling a reduced risk of injury to the surrounding ocular tissues, as evidenced by the safety outcomes of the MIMS surgery reported in this study (see discussion below). Noteworthy, the proportion of the MIMS eyes with qualified success reduced by approximately 34% from 1 to 3 years; this is consistent with 23% reduction rate reported from 1 to 3 years after MMC-trabeculectomy, indicating a similar tendency in the post-operative tissue responses to control IOP levels. Finally, comparing the qualified success criterion of ≥20% IOP reduction to similar marketed subconjunctival bleb-forming devices, the 3-year success of the standalone MIMS surgery was found to be higher than that reported for XEN45 gel stent (~28%) [32-42]. The 3-year complete success of ≥20% IOP reduction was observed in 39.6% of the MIMS®- treated eyes (31.6% for standalone and 70.0% for combined MIMS surgery). This result is consistent the long-term data reported for subconjunctival bleb-forming procedures: at 3 years, complete success was reported in 44% eyes following MMC-trabeculectomy and in 51.1% eyes with XEN45 gel stent, with the majority (71.7%) of the eyes undergoing the XEN45 procedure combined with phacoemulsification [24-32]. Moreover, this result is consistent with the international recommendations for the minimal clinically important difference for surgical interventions for glaucoma, with a minimum 20%-30% medication free subjects proposed by the EGS expert group [20].

Additional analyses of the 3-year surgical success rates of the MIMS® surgery revealed comparable long-term results reported with the similar marketed subconjunctival bleb-forming devices. Specifically, at 3 years, the target IOP of >5 mmHg and

≤21 mmHg with a minimum 20% reduction from baseline on the same or less medical therapy was achieved in 52.1% of the MIMS® eyes, similar to 52.4% eyes with XEN45 gel stent and lower to some extent than in the eyes with PRESERFLO MicroShunt (68%) [26-34]. Moreover, Nouri- Mahdavi et al reported a 48% probability of success after 3 years using the same combined criterion in OAG patients who underwent trabeculectomy without antimetabolites [43].

Complete long-term success rates following the MIMS surgery (39.6%) are consistent with the literature on XEN45 gel stent (42.9%) and PRESERFLO MicroShunt implantation (49%) [26-34]. Following MMC-trabeculectomy, the 3-year success rates were reported to be higher or similar, ranging between 72.2% - 86% and 41.7% - 64% for qualified and complete criteria, respectively [44–46].

Using the success criterion of IOP ≤18 mmHg and IOP reduction of ≥20%, the outcomes of the MIMS® procedure (43.8%) are in line with the results reported for XEN45 gel stent (36.9%) [24]. Complete success rate with the MIMS procedure (37.5%) seems to be higher or comparable with the reported rates with XEN45 gel stent (27.3% - 31.5%) [23, 24].

Following MMC-trabeculectomy, as anticipated, the surgical success rates at 3 years were reported to be higher or similar, at the ranges of 72.2% - 86% and 40% - 64% for qualified and complete successes, respectively [37-48]. As mentioned above, evidence suggests that while MMC-trabeculectomy may achieve a more substantial and sustained IOP reduction, as compared to other less invasive subconjunctival bleb-forming devices, such as XEN45 gels stent, it is associated with a higher rate of postoperative complications and interventions [23].

Pertaining to long-term safety, in this clinical study the MIMS procedure resulted in few complications, all were anticipated and non-serious. Substantially increased IOP was the most common early postoperative finding (12.5%), comparable to 13% reported for XEN45 [24]. The incidence of other postoperative adverse events following the MIMS surgery was comparable or lower than that reported with the marketed subconjunctival bleb-forming devices/procedures. There were no adverse events at long term related to MIMS device/procedure, with no hypotony (IOP <6 mmHg) events were reported throughout the whole follow up period. Glaucoma reoperation was the most common reason for failure (72.2% of the total reasons for failure). The other reason for failure was inadequate IOP reduction (defined as intraocular pressure reduced <20% below baseline). The overall rate of reoperations for glaucoma in this study over the 3-year follow-up period was 10.8% (13 out of 120 patients), which is close to the lower boundary of the range (7% to 30%) of secondary surgical interventions reported following implantation of XEN45 and RESERFLO MicroShunt [23-49]. Bleb failure is suggested to be the most common cause of IOP elevation at long-term follow up after glaucoma filtration surgery [50, 51]. Excessive fibrous reaction around the bleb appears to be the major cause of long-term failure for trabeculectomy and GDD devices [50, 51].

Overall, MIMS® surgery had no significant side effects on either the visual acuity, endothelial cell density (ECD) or induced astigmatism after 3 years in patients with open- angle glaucoma. Few events (2.5%) of notable endothelial cell loss were not associated with irreversible corneal edema or corneal decompensation and were attributed to the subjects' older age and disease condition, in line with previous reports on the age as a risk factor for greater ECD loss [52].

Comparing the safety profile of the MIMS surgery over 3 years with similar subconjunctival bleb-forming devices, other late postoperative events (which were not observed in MIMS study) were reported over 2-3 years following implantation of XEN45 stent gel and PRESERFLO MicroShunt. For instance, XEN45 stent gel implantation was associated with stent problems (1.1% - 3.4%), macular hemorrhage (1.1%), choroidal detachment (4.3% - 17.6%), tenon cyst (11.1%), hyphema (5.9% - 7.9%), hypotony (4.3%), subconjunctival hemorrhage (4.3%), encapsulated filtration bleb (4.3%) and Seidel (2.9% - 3.2%) [23- 49]. Recent studies with PRESERFLO MicroShunt with the same follow-up period reported hyphema (8.7%), vitreous hemorrhage (4.3%), exposed Tenon's capsule (8.7%), choroidal effusion or detachment (8.7%), anterior uveitis (2%), iris incarceration (1%), tube obstruction (4.3%), device removal (1%), corneal decompensation (1%) [26-53].

Compared to the MIMS surgery and subconjunctival bleb-forming implants (XEN45 stent gel and PRESERFLO MicroShunt), a higher incidence of complications is commonly observed after standard MMC-trabeculectomy. Over 3 years, MMS-trabeculectomy was reported to be associated with encapsulated or cystic bleb (3% - 12%), persistent diplopia (3%), shallow or flat anterior chamber (1% - 6.8%), dysesthesia (3%), late hypotony (21%), hypotony maculopathy (1%-4%), iritis (1%), persistent corneal edema (2%), hyphema (6%-25%), vitreous hemorrhage (3%), choroidal detachment (1% - 24.6%), wound / bleb leak (1% - 17.8%), anterior bleb migration/irregular astigmatism (1%), blebitis / endophthalmitis (0.4% - 3%), pseudophakic bullous keratopathy (1%) [32- 46].

The MIMS procedure has a short learning curve and is exceptionally quick to perform, with a mean duration of 2 min per procedure. With the rising costs of glaucoma treatment, the brief duration of the procedure makes MIMS a comparatively cost-effective option, particularly when performed alongside cataract surgery [42,43].

Study Limitations

Firstly, due to the missed visits caused by the COVID-19 pandemic and ensuing lockdowns, 20.8% of our patients did not comply with the complete follow-up protocol during the first year after surgery [44-46]. Consequently, these patients were included solely in the safety analysis and excluded from the performance analysis, potentially introducing a negative bias in both efficacy and safety. This bias is likely linked to the tendency of patients with poorer outcomes to be more motivated to attend follow-up examinations.

Other shortcomings of our study were the lack of a comparator, its open-label design and the study population consisting exclusively of eyes from individuals of Caucasian descent. Although there is evidence that ethnicity may influence outcomes of glaucoma surgery, mainly due to the increased risk of fibrosis at the conjunctival–scleral interface, survival of glaucoma surgery im-

proves with use of Mitomycin C, with no significant differences between Asian, American and Caucasian groups in cumulative survival, and rates of surgical success, failure, complication, hypotony, and vision decrease [54,55].

Moreover, no statistically significant impact of ethnicity (European, African and Asian descents) on 3- year performance outcomes in glaucoma patients undergoing PreserFlo MicroShunt surgery was previously reported [26]. Notably, differences in trabeculectomy flap scarring (as opposed to subconjunctival scarring) that most likely to drive variations in success rates by ethnicity can be considered as an irrelevant factor in minimally invasive bleb surgery, such as MIMS surgery, where no scleral flap is created [56].

In addition, whereas our findings were evaluated in comparison with the literature, the baseline characteristics of patients eligible for surgery in previously reported trials varied significantly regarding glaucoma severity, IOP levels and the number of glaucoma medications. Furthermore, washout IOP values differed among studies, and washout was not considered in all studies, including ours, primarily due to ethical considerations.

Finally, the combined surgeries could also serve as a confounding factor, given the IOP- lowering effect of phacoemulsification. Hence, future standardized controlled studies comparing MIMS to other filtration procedures are warranted to further evaluate its long- term efficacy and safety.

Conclusion

In conclusion, this extended 3-year study, building upon the 1-year findings of the previous research, indicates that the MIMS provides a viable option to adjust an uncontrolled IOP in adult primary open angle and pseudo exfoliative glaucoma accompanied by reduced topical glaucoma medication in the long-term period, with a relatively safe conjunctival approach.

Funding

The study was supported by grants from Sanoculis Ltd. The funding organization participated in data collection, data management, and data analysis.

Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval and Consent to Participate

The study protocol was approved by the local ethics committee (Ophthalmological Center after S.V. Malayan, MMS EEU-1, SN 27102023). Written informed consent for participation in the study was obtained from all participants.

Consent for Publication

Not applicable.

Competing Interests

Authors Lilit Voskanyan and Iqbal Ike K Ahmed received a research grant from Sanoculis Ltd., Kiryat Ono, Israel. Oren Bar-Ilan received consultation payments from Sanoculis Ltd., Tel Hashomer, Israel. Yoseph Glovinsky received research grants and consultation payments from Sanoculis Ltd., Tel Hashomer, Israel. The remaining authors declare that they have no conflict of interest.

Author Contributions

L.V., I.A., V.P., A.G., H.B., and O.B.I. performed the measurements and processed the experimental data. Y.G. and H.M. were involved in planning and supervising the work, O.B.I. performed the analysis. All authors aided in interpreting the results, made critical revision for intellectual content, discussed the results and commented on the manuscript.

Acknowledgements

The authors very much appreciate the support from Mr. Nir Israeli and Mr. Vadim Shmukler from Sanoculis Ltd. The authors would like to thank Mrs. Ani Babayan who professionally coordinated the clinical trial. Medical writing support was provided by Anna Sterkin, Israel, funded by Sanoculis Ltd, Israel.

References

1. Cook, C., & Foster, P. (2012). Epidemiology of glaucoma: What's new? Canadian Journal of Ophthalmology, 47(3), 223–226.
2. Quigley, H. A. (2011). Glaucoma. Lancet, 377(9774), 1367–1377.
3. Tham, Y.-C., Li, X., Wong, T. Y., Quigley, H. A., Aung, T., & Cheng, C.-Y. (2014). Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. Ophthalmology, 121(11), 2081–2090.
4. Quigley, H. A., & Broman, A. T. (2006). The number of people with glaucoma worldwide in 2010 and 2020. British Journal of Ophthalmology, 90(3), 262–267.
5. Anderson, D. R., Drance, S. M., & Schulzer, M. (1998). The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. American Journal of Ophthalmology, 126(4), 498–505.
6. Blackwell, B., Gaasterland, B., & Ederer, F. (2002). The Advanced Glaucoma Intervention Study (AGIS): 12. Baseline risk factors for sustained loss of visual field and visual acuity in patients with advanced glaucoma. American Journal of Ophthalmology, 134(4), 499–512.
7. Heijl, A., Leske, M. C., Bengtsson, B., Hyman, L., Bengtsson, B., Hussein, M., & Early Manifest Glaucoma Trial Group. (2002). Reduction of intraocular pressure and glaucoma progression: Results from the Early Manifest Glaucoma Trial. Archives of Ophthalmology, 120(9), 1268–1279.
8. Samples, J. R., Singh, K., Lin, S. C., Francis, B. A., Hodapp, E., Jampel, H. D., & American Academy of Ophthalmology. (2011). Laser Trabeculoplasty for Open-Angle Glaucoma: A Report by the American Academy of Ophthalmology. Ophthalmology, 118(11), 2296–2302.
9. Bettin, P., & Di Matteo, F. (2017). Postoperative Management of Penetrating and Nonpenetrating External Filtering Procedures. In Developments in Ophthalmology (Vol. 59, pp. 53–66). S. Karger AG.
10. Kerr, N. M., Wang, J., & Barton, K. (2017). Minimally invasive glaucoma surgery as primary stand-alone surgery for glaucoma. Clinical & Experimental Ophthalmology, 45(4), 393–400.

11. Sarkisian, S. R. J., Radcliffe, N., Harasymowycz, P., Vold, S., Patrianakos, T., Zhang, A., & Micro-Bypass Stent in Cataract Surgery Study Group. (2020). Visual outcomes of combined cataract surgery and minimally invasive glaucoma surgery. Journal of Cataract & Refractive Surgery, 46(2), 264–272.
12. Bloom, P., & Au, L. (2018). "Minimally Invasive Glaucoma Surgery (MIGS) Is a Poor Substitute for Trabeculectomy"—The Great Debate. Ophthalmic Therapy, 7(2), 203–210.
13. Agrawal, P., & Bradshaw, S. E. (2018). Systematic literature review of clinical and economic outcomes of micro-invasive glaucoma surgery (MIGS) in primary open-angle glaucoma. Ophthalmic Therapy, 7(1), 49–73.
14. Wang, M., Thomas, S., Holubowich, C., Higgins, C., Rios, D., Gajic-Veljanoski, O., et al. (2024). Minimally Invasive Bleb Surgery for Glaucoma: A Health Technology Assessment. Ontario Health.
15. Gershoni, A., Glovinsky, Y., Rotenberg, M., Barayev, E., Segal, O., & Geffen, N. (2021). MIMS Procedure: Concept and Evaluation of Safety, Feasibility, and Efficacy in a Porcine Experimental Model. Journal of Glaucoma, 30(7), e246–e251.
16. Geffen, N., Kumar, D. A., Barayev, E., Gershoni, A., Rotenberg, M., Zahavi, A., et al. (2022). Minimally Invasive Micro Sclerostomy (MIMS) Procedure: A Novel Glaucoma Filtration Procedure. Journal of Glaucoma, 31(3), 191–200.
17. Voskanyan, L., Ahmed, I. I. K., Gershoni, A., Barayev, E., Papoyan, V., Ghazaryan, A., et al. (2024). Minimally invasive micro sclerostomy (MIMS) procedure in the treatment of open-angle glaucoma. BMC Ophthalmology, 24(1), 122.
18. U.S. Food and Drug Administration. (2015). Premarket studies of implantable minimally invasive glaucoma surgical (MIGS) devices.
19. Gedde, S. J., Vinod, K., Bowden, E. C., Kolomeyer, N. N., Chopra, V., Challa, P., et al. (2024). Reporting Clinical Endpoints in Studies of Minimally Invasive Glaucoma Surgery. Ophthalmology. Advance online publication. https://doi.org/10.1016/j.ophtha.2024.07.030
20. European Glaucoma Society (EGS). (2023). European Glaucoma Society - A guide on surgical innovation for glaucoma. British Journal of Ophthalmology, 107(Suppl 1), 1–114.
21. Shaarawy, T. M., Sherwood, M. B., & Grehn, F. (2009). WORLD GLAUCOMA ASSOCIATION (WGA) Guidelines on Design and Reporting of Glaucoma Surgical Trials. Kugler Publications.
22. Lavia, C., Dallorto, L., Maule, M., Ceccarelli, M., & Fea, A. M. (2017). Minimally-invasive glaucoma surgeries (MIGS) for open angle glaucoma: A systematic review and meta-analysis. PLoS One, 12(8), e0183142.
23. Rauchegger, T., Krause, S.-M., Nowosielski, Y., Huber, A. L., Willeit, P., Schmid, E., et al. (2024). Three-year clinical outcome of XEN45 Gel Stent implantation versus trabeculectomy in patients with open angle glaucoma. Eye, 38(7), 1084-1092.
24. Gillmann, K., Bravetti, G. E., Rao, H. L., Mermoud, A., & Mansouri, K. (2021). Combined and stand-alone XEN 45 gel stent implantation: 3-year outcomes and success predictors. Acta Ophthalmologica, 99(4), e531–e539.
25. Marcos-Parra, M. T., Mendoza-Moreira, A. L., Moreno-Castro, L., Mateos-Marcos, C., Salinas-López, J. A., Figuerola-García, M. B., et al. (2022). 3-year outcomes of XEN implant compared with trabeculectomy, with or without phacoemulsification for open angle glaucoma. Journal of Glaucoma, 31(10), 826–833.
26. Mercieca, K., Bhayani, R., Martinez-de-la-Casa, J. M., Figus, M., Klabe, K., Rabiolo, A., & MicroShunt European Study Group. (2024). 3-year safety and efficacy results of PreserFloTM Microshunt in glaucoma patients: A multicentre European cohort study. AJO International, 1(2), 100054.
27. Batlle, J. F., Corona, A., & Albuquerque, R. (2021). Long-term results of the PRESERFLO MicroShunt in patients with primary open-angle glaucoma from a single-center nonrandomized study. Journal of Glaucoma, 30(4), 281–286.
28. Kiddee, W., Orapiriyakul, L., Kittigoonpaisan, K., Tantisarasart, T., & Wangsupadilok, B. (2015). Efficacy of adjunctive subconjunctival bevacizumab on the outcomes of primary trabeculectomy with mitomycin C: A prospective randomized placebo-controlled trial. Journal of Glaucoma, 24(8), 600–606.
29. Gedde, S. J., Chen, P. P., Heuer, D. K., Singh, K., Wright, M. M., Feuer, W. J., & Primary Tube Versus Trabeculectomy Study Group. (2018). The Primary Tube Versus Trabeculectomy Study: Methodology of a Multicenter Randomized Clinical Trial Comparing Tube Shunt Surgery and Trabeculectomy with Mitomycin C. Ophthalmology, 125(5), 774–781.
30. Matlach, J., Dhillon, C., Hain, J., Schlunck, U., Grehn, F., & Klink, T. (2015). Trabeculectomy versus canaloplasty (TVC study) in the treatment of patients with open-angle glaucoma: A prospective randomized clinical trial. Acta Ophthalmologica, 93(8), 753–761.
31. Wudunn, D., Cantor, L. B., Palanca-Capistrano, A. M., Hoop, J., Alvi, N. P., Finley, C., & Glaucoma Clinical Research Group. (2002). A prospective randomized trial comparing intraoperative 5-fluorouracil vs mitomycin C in primary trabeculectomy. American Journal of Ophthalmology, 134(4), 521–528.
32. Gedde, S. J., Feuer, W. J., Lim, K. S., Barton, K., Goyal, S., Ahmed, I. I. K., & Primary Tube Versus Trabeculectomy Study Group. (2020). Treatment outcomes in the primary tube versus trabeculectomy study after 3 years of follow-up. Ophthalmology, 127(3), 333–345.
33. Baker, D. N., Barnebey, H. S., Moster, M. R., Stiles, M. C., Vold, S. D., Khatana, A. K., & Santen. (2021). Ab-Externo MicroShunt versus Trabeculectomy in Primary Open-Angle Glaucoma: One-Year Results from a 2-Year Randomized, Multicenter Study. Ophthalmology, 128(12), 1710–1721.
34. Nuzzi, R., Gremmo, G., Toja, F., & Marolo, P. (2021). A retrospective comparison of trabeculectomy, baerveldt glaucoma implant, and microinvasive glaucoma surgeries in a three-year follow-up. Seminars in Ophthalmology, 36(7-8), 839–849.
35. Koh, V., Chen, D., Aquino, C. M., Aduan, J., Sng, C., Chee, L. S., & Perera, S. A. (2017). Success rates of 2-site phacoemulsification combined with fornix-based trabeculectomy using mitomycin C for primary angle-closure glaucoma and primary open-angle glaucoma in an Asian population. Japanese Journal of Ophthalmology, 61(3), 245–252.

36. Kirwan, J. F., Lockwood, A. J., Shah, P., Macleod, A., Broadway, D. C., King, A. J., & Glaucoma Surgery Outcome Study Group. (2013). Trabeculectomy in the 21st century: A multicenter analysis. Ophthalmology, 120(12), 2532–2539.
37. Fontana, H., Nouri-Mahdavi, K., Lumba, J., Ralli, M., & Caprioli, J. (2006). Trabeculectomy with Mitomycin C. Outcomes and Risk Factors for Failure in Phakic Open-Angle Glaucoma. Ophthalmology, 113(6), 930–936
38. Palanca-Capistrano, A. M., Hall, J., Cantor, L. B., Morgan, L., Hoop, J., & WuDunn, D. (2009). Long-term outcomes of intraoperative 5-fluorouracil versus intraoperative mitomycin C in primary trabeculectomy surgery. Ophthalmology, 116(2), 185–190.
39. Law, S. K., Shih, K., Tran, D. H., Coleman, A. L., & Caprioli, J. (2009). Long-term outcomes of repeat vs initial trabeculectomy in open-angle glaucoma. American Journal of Ophthalmology, 148(5), 685–695.e1.
40. Allam, R. S. H. M., Raafat, K. A., & Abdel-Hamid, R. M. (2020). Trabeculectomy with Extended Subscleral Tunnel Versus Conventional Trabeculectomy in the Management of POAG: A 1-Year Randomized-controlled Trial. Journal of Glaucoma, 29(6), 473–478.
41. Eslami, Y., Mohammadi, M., Khodaparast, M., Rahmanikhah, E., Zarei, R., Moghimi, S., & Fakhraie, G. (2012). Sutureless tunnel trabeculectomy without peripheral iridectomy: A new modification of the conventional trabeculectomy. International Ophthalmology, 32(5), 449–454.
42. Gedde, S. S., Feuer, W. J., Shi, W., Lim, K. S., Barton, K., Goyal, S., & Primary Tube Versus Trabeculectomy Study Group. (2018). Treatment Outcomes in the Primary Tube Versus Trabeculectomy Study after 1 Year of Follow-up. Ophthalmology, 125(5), 650–663.
43. Nouri-Mahdavi, K., Brigatti, L., Weitzman, M., & Caprioli, J. (1995). Outcomes of Trabeculectomy for Primary Open-angle Glaucoma. Ophthalmology, 102(12), 1760–1769.
44. Kopsinis, G., Tsoukanas, D., Kopsini, D., & Filippopoulos, T. (2021). Intracameral bevacizumab versus sub-Tenon's mitomycin C as adjuncts to trabeculectomy: 3-year results of a prospective randomized study. Journal of Clinical Medicine, 10(9), 2054.
45. Qin, Z. X., Ying, X., Han, Q., Wang, L., Tan, L., Xu, Y. F., & Ran, S. B. (2023). Outcomes and risk factors for failure of trabeculectomy in glaucomatous patients in Southwest China: A 325 eyes analysis. International Journal of Ophthalmology, 16(3), 367–374.
46. Esfandiari, H., Pakravan, M., Yazdani, S., Doozandeh, A., Yaseri, M., & Conner, I. P. (2018). Treatment outcomes of mitomycin C-augmented trabeculectomy, sub-tenon injection versus soaked sponges, after 3 years of follow-up: A randomized clinical trial. Ophthalmology Glaucoma, 1(2), 66–74.
47. Gedde, S. J., Schiffman, J. C., Feuer, W. J., Herndon, L. W., Brandt, J. D., Budenz, D. L., & Tube Versus Trabeculectomy Study Group. (2009). Three-year follow-up of the Tube Versus Trabeculectomy Study. American Journal of Ophthalmology, 148(5), 670–684.
48. Gonzalez-Rodriguez, J. M., Trope, G. E., Drori-Wagschal, L., Jinapriya, D., & Buys, Y. M. (2016). Comparison of trabeculectomy versus Ex-PRESS: 3-year follow-up. British Journal of Ophthalmology, 100(9), 1269–1273.
49. Cappelli, F., Cutolo, C. A., Olivari, S., Testa, V., Sindaco, D., Pizzorno, C., & Travi, S. (2022). Trabeculectomy versus Xen gel implant for the treatment of open-angle glaucoma: A 3-year retrospective analysis. BMJ Open Ophthalmology, 7(1), e000830.
50. Schlunck, G., Meyer-ter-Vehn, T., Klink, T., & Grehn, F. (2016). Conjunctival fibrosis following filtering glaucoma surgery. Experimental Eye Research, 142, 76–82.
51. Ayyala, R. S., Duarte, J. L., & Sahiner, N. (2006). Glaucoma drainage devices: State of the art. Expert Review of Medical Devices, 3(4), 509–521.
52. Higashide, T., Nishino, T., Sakaguchi, K., Yamada, Y., & Sugiyama, K. (2019). Determinants of Corneal Endothelial Cell Loss After Trabeculectomy With Mitomycin C. Journal of Glaucoma, 28(1), 61–67.
53. Batlle, J. F., Fantes, F., Riss, I., Pinchuk, L., Albuquerque, R., Kato, Y. P., & Shute. (2016). Three-year follow-up of a novel aqueous humor microshunt. Journal of Glaucoma, 25(1), e58–e65.
54. Wilkins, M., Indar, A., & Wormald, R. (2005). Intraoperative Mitomycin C for glaucoma surgery (Review). The Cochrane Library. https://doi.org/10.1002/14651858.CD002897.pub2
55. Law, S. K., Modjtahedi, S. P., Mansury, A., & Caprioli, J. (2007). Intermediate-term comparison of trabeculectomy with intraoperative mitomycin-C between Asian American and Caucasian glaucoma patients: A case-controlled comparison. Eye, 21(1), 71–78.
56. Schlenker, M. B., Gulamhusein, H., Conrad-Hengerer, I., Somers, A., Lenzhofer, M., Stalmans, I., & Migration Study Group. (2017). Efficacy, Safety, and Risk Factors for Failure of Standalone Ab Interno Gelatin Microstent Implantation versus Standalone Trabeculectomy. Ophthalmology, 124(11), 1579–1588