THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 13 Issue 2

REVIEW ARTICLE

Development of SIBS and the PRESERFLO™ MicroShunt to Treat Advanced Glaucoma: A Review

Leonard Pinchuk, Ph.D., D.Sc. (*h.c.*), NAE, FNAI, F-AIMBE, ICFBSE, 2019 Russ Prize Laureate [1]

[1] Founder and Senior Vice President and Executive Principal Scientist, Polymer Engineer, InnFocus, Inc., a Santen Company; Distinguished Research Professor, Biomedical Engineering, University of Miami, Miami, FL.

OPEN ACCESS

PUBLISHED
28 February 2025

CITATION
Pinchuk, L., 2025. Development of SIBS and the PRESERFLO™ MicroShunt to Treat Advanced Glaucoma: A Review. Medical Research Archives, [online] 13(2).
https://doi.org/10.18103/mra.v13i2.6169

DOI
https://doi.org/10.18103/mra.v13i2.6169

ISSN
2375-1924

ABSTRACT

Polyisobutylene-based biomaterials are elastomeric polymers specifically designed for long-term implant applications. These polymers, which are comprised of only carbon and hydrogen atoms, contain no cleavable groups and are highly purified. Their intrinsic methyl groups interact with tissue, minimizing foreign body reactions. The present review describes the development of a glaucoma micro-shunt made from one of these polymers, poly(styrene-*block*-isobutylene-*block*-styrene) (SIBS). This review also reports recent findings in patients implanted with these PRESERFLO™ MicroShunts.

Keywords: Poly(styrene-*block*-isobutylene-*block*-styrene); SIBS; Glaucoma; MicroShunt; Preserflo; MIGS

Abbreviations:

AGIS, advanced glaucoma intervention study
CE, Conformité Européenne
CI, confidence interval
FDA, US Food and Drug Administration
IDE, investigational device exemption
IOP, intraocular pressure
MMC, mitomycin C
PDMS, polydimethylsiloxane
PMA, premarket approval
PMN, polymorphonuclear leukocytes
PTVT, primary tube versus trabeculectomy
RCT, randomized control trial
SIBS, poly(styrene-*block*-isobutylene-*block*-styrene)
WGA, World Glaucoma Association

Introduction

Polyisobutylene-based biomaterials are both extremely inert and highly flexible and have been applied commercially in medicine for over 25 years. The first commercial application of a polyisobutylene-based material in medicine was the thermoplastic polymer poly(styrene-*block*-isobutylene-*block*-styrene) (SIBS), used as the drug carrier in paclitaxel-eluting coronary stents (Taxus® from Boston Scientific, Natick, MA, USA). SIBS and the processes used to fabricate these stents have been described[1-3]. The second commercial product based on a polyisobutylene-based biomaterial is the PRESERFLO MicroShunt (MicroShunt) (InnFocus/Santen, Miami, FL, USA), a drainage device for the treatment of glaucoma. Other possible applications of polyisobutylene-based polymers are under development.

This review first discusses the development of SIBS, the premise behind its bio-inertness and biocompatibility, and its use in the PRESERFLO MicroShunt. The article then reviews early studies of the clinical development of the MicroShunt, followed by a description of continued improvements in its performance through its implantation in approximately 100,000 eyes world-wide. The article concludes with a discussion on why this well-recognized treatment for advanced glaucoma, i.e., the PRESERFLO MicroShunt, has not yet been approved for sale by the United States Food and Drug Administration (FDA). A goal of the article is to elucidate the nuances of confidence intervals, the criteria of non-inferiority relative to an existing procedure, the learning curve on new devices when compared with frequently-practiced procedures, and the restrictions of performing a clinical study under strict limitations.

Polyisobutylene Chemistry and its Advantages as a Biomaterial: Certain polyisobutylene-based biomaterials have been classified as elastomers, generally defined as materials capable of stretching more than 20% and returning on their own to their original shapes. Work on this specific class of elastomers for long-term medical implants began in the early 1990s, when conventional polyether urethane implantable biomaterials, such as those comprising the insulators on pacemaker leads (Pellethane 2363 80A) and synthetic vascular grafts attracted granulocytes as a consequence of their unintended biodegradation in the body[4]. Macrophages, polymorphonuclear leukocytes (PMNs), and foreign body giant cells migrated towards the device to either wall-off the degraded material by forming thick capsules around it or to remove degraded fragments by phagocytosis. Many pacer lead insulators were, and still are, made from these industrial-grade polyether urethanes that were never designed for long-term applications in the body. Consequently, there remained a need to develop a biostable polymer that met four major criteria. The first was that the polymer be devoid of sites for degradation, including the absence of urethane (carbamate), ether, ester, carbonate, and amide linkages, on its backbone or side-groups. The second was that the backbone, in the event of oxidation by granulocytes, would be unable to form double bonds that could embrittle and degrade the polymer, leading to cracking or deterioration of the backbone when subsequently stretched or bent. The third criterion was that the polymer be composed only of carbon and hydrogen atoms, preferably with tissue interfacing methyl groups, which is a common tissue interface in the body. More specifically, the polymer should not contain silicon or fluorine atoms, which are not found in the human body and could, if introduced, provoke a foreign body reaction. The fourth criterion was that the polymer be purifiable; that is, it must be soluble or extractable in specific solvents to remove oligomers, initiators and other contaminants that can otherwise leach out and cause inflammation.

Figure 1 shows three reaction schemes of polymers, called polyolefins, comprised of only carbon and hydrogen atoms. Carbon atoms attached to one, two, three and four other carbon atoms are defined as primary, secondary, tertiary and quaternary carbon atoms, respectively. Polyethylene (top) is comprised of repeating secondary carbons (methylene groups). In the presence of macrophages that secrete superoxide and hydrogen ions, hydrogens are abstracted from the backbone, leading to free radical formation and its subsequent coupling with the free radical on an adjacent carbon, forming double bonds that embrittle the elastomer and lead to its degradation[1]. Polypropylene (middle) contains alternating secondary and tertiary carbon atoms, and, similar to polyethylene, is oxidized by superoxide and hydrogen ions, leading to double bond formation and deterioration of the polymer. In contrast, the backbone of polyisobutylene (bottom) consists of alternating quaternary and secondary carbons, preventing the formation of double bonds. Any free radical derived from the dissociation of a hydrogen atom on a secondary carbon would be unable to pair with the adjacent quaternary carbon. Carbon-carbon bonds are not readily cleaved by granulocytes. Thus, if the carbon bond is sustained, the quaternary carbon will form five bonds, which cannot occur, preventing its oxidization and degradation in the body. These findings indicate that polyisobutylene is extremely biostable.

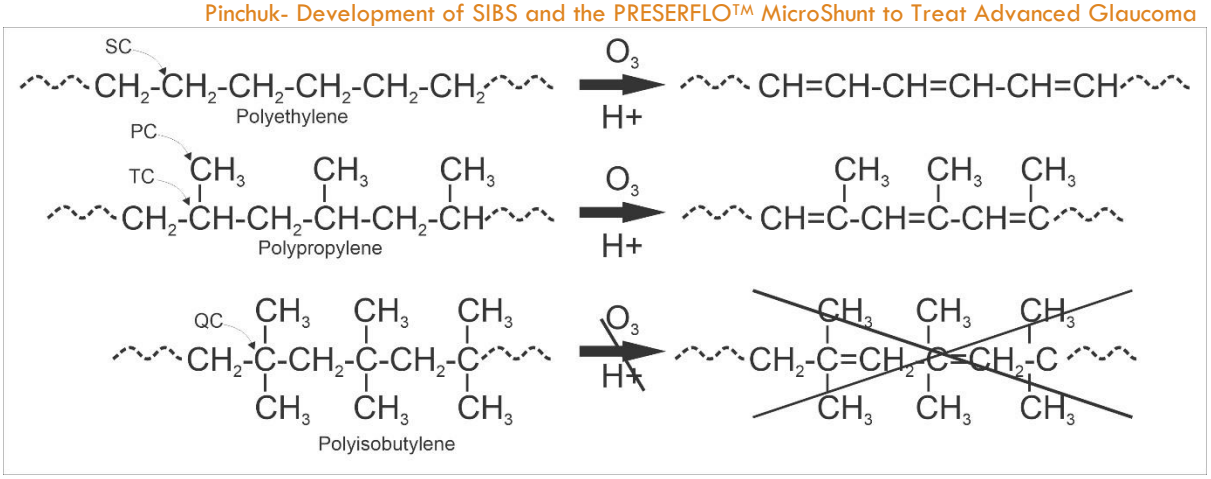

Figure 1: Top, polyethylene with secondary carbons (SC) showing oxidation to conjugated double bonds; Middle, polypropylene with primary (PC), secondary (SC) and tertiary carbons (TC) showing oxidation and double bond formation; Bottom, polyisobutylene with alternating secondary and quaternary carbons (QC) showing no ability to form double bonds on the backbone as carbon cannot support 5 bonds.

Polyisobutylene is a gum, with many types of chewing gum comprised of naturally-derived polyisobutylene from natural sources (Figure 2, left). Conversion to a processable elastomer (e.g., for injection molding or extrusion) requires its crosslinking with meltable or solvent-dissolvable crosslinks. In SIBS, the polyisobutylene center block is capped on both sides with polystyrene (Figure 2, right). During melting or in solution, the polystyrenes combine and segment due to hydrophobic interactions, and, when cooled or removed from solution, the polystyrene end-groups crystallize into glassy segments that hold the polyisobutylene ends together, with the product being a meltable crosslinked elastomer.

The type of chemistry used to synthesize polyisobutylene and SIBS (Figure 2) was developed by Dr. Joseph P. Kennedy and his team at the University of Akron (Akron, OH, USA)[5,6], with the products being refined, purified and patented for specific implantable use by the present author[7].

Polymers comprised of crosslinked collagen, such as those used in XEN Gel-Stents (AbbVie, Dublin, Ireland), contain both amides and many unprotected carbons, with no alternating quaternary carbons[8]. These properties are thought to be responsible for the slow embrittlement and degradation of XEN Gel-Stents.[8]

Design of the PRESERFLO MicroShunt: The development began on a glaucoma shunt in 2003, when SIBS disks 3-mm in diameter and 1-mm thick were implanted in the corneal stroma, as well as under the conjunctiva and Tenon's capsule of New Zealand white rabbits' eyes[9]. For comparison, disks made of silicone rubber (polydimethylsiloxane [PDMS]) were implanted alongside the SIBS disks. After 2 months, there were no myofibroblasts or angiogenesis in the vicinity of the SIBS disks or integral capsules surrounding these disks[10]. In contrast angiogenesis, myofibroblasts, and significant capsules were observed in the vicinity of the PDMS control disks. These findings suggested that SIBS was very inert and innocuous in rabbit eyes. Moreover, the absence of clinically significant fibrous capsule formation suggested that SIBS could theoretically be used for a plateless glaucoma shunt to lower intraocular pressure (IOP) and thwart vision loss due to glaucoma[9].

Anatomical features require that SIBS tubes be at least 8 mm long (8.5 mm was selected) to shunt from the anterior chamber to the mid-posterior eye. The lumen serves as a flow restrictor to prevent the pressure in the eye from dropping to below approximately 6 mmHg for a prolonged period of time, as this deflation of the eye (hypotony) could lead to retinal detachment and other serious pathologies. Based on a normal aqueous humor flow rate of 2.5 µL/min and a desired IOP drop of 12 mmHg, the Hagen-Poiseuille equation suggests a lumen diameter of approximately 55 µm. Due to the high surface tension of SIBS, the desired flow was difficult to obtain at this lumen diameter; therefore, the lumen was increased to approximately 70 µm to allow flow at physiological pressures. The flow characteristics of the PRESERFLO MicroShunt have been comprehensively analyzed in vitro[11]. Implantations into rabbit eyes[12,13] confirmed that these requirements were satisfied by a nominal lumen diameter of 70 µm. To prevent kinking and to allow the tube to be pushed through a needle tract formed by a 25-G or 27-G needle inserted under the limbus, the outer diameter of the tube was set at 350 µm, providing a tough tube with a wall thickness of 140 µm.

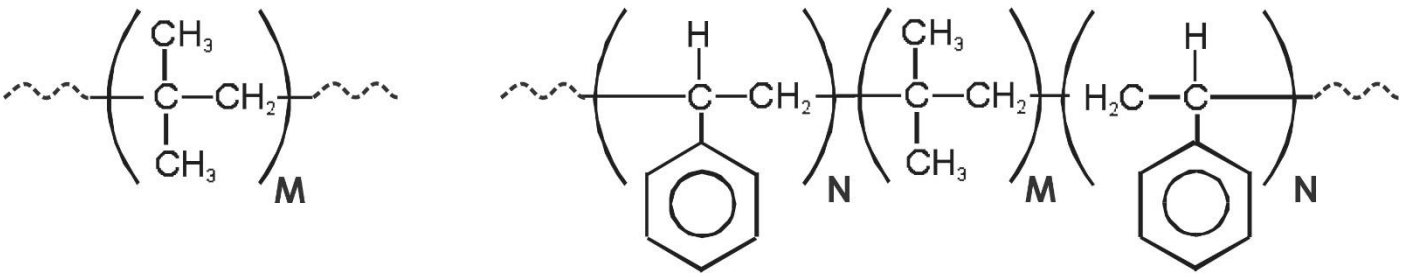

Figure 2: Chemical formulas of polyisobutylene (left) and poly(styrene-*block*-isobutylene-*block*-styrene) (SIBS) (right), where M>>N.

A fin located halfway down the tube length was required as an additional design feature, as a simple tube lacking a fin often migrated into the anterior chamber of rabbit eyes. The surgical technique now requires incising a shallow 1 mm wide, 1 mm long pocket in the sclera, and then following through with a needle tract parallel to the iris, under the limbus, and terminating in the anterior chamber. The pocket serves to wedge the 1.1 mm fins in the 1 mm pocket. The pocket and fins (1) serve as a "cork" to seal the device in the pocket and prevent leakage around the tube; (2) serve as a stopper to prevent the device from migrating into the eye; (3) the pocket prevents the fins from turning and eroding the conjunctiva; and (4) serve as a mechanism of orienting the device such that the bevel in the anterior chamber faces the cornea, enabling the surgeon to visualize whether the lumen at the proximal end of the device is free of debris. In some markets, both the pocket and needle tract are formed by a continuous stab incision into the anterior chamber using a manufacturer-supplied double stepped knife.

Figure 3 shows a schematic of the PRESERFLO MicroShunt and its placement in the anterior segment of the eye. The design of the tube, where it is placed, the surgical procedure, and the drug regimens used before, during, and after implantation took approximately 4 years to develop.

First Clinical Implants of the PRESERFLO MicroShunt: The MicroShunt was first implanted in humans in January 2006, predominantly in French patients who failed incisional glaucoma surgery. The lack of the intraoperative antifibrotic mitomycin C (MMC) resulted in a surgical success rate of only 42%, whereas a subsequent study, which included 0.2 mg/mL, MMC, improved the surgical success rate to 67%[9]. A study in the Dominican Republic of 23 patients in a pre-dominant Afro-Caribbean population with primary open-angle glaucoma (POAG) and no previous conjunctival surgery who had failed maximum tolerated glaucoma medication found that MicroShunt implantation, accompanied by a 3-minute intraoperative application of 0.4-mg/mL MMC, resulted in a qualified success rate of 100%, with a 55% drop in IOP from baseline at 1 year. The results of these four independent clinical trials in France and the Dominican Republic, which led to the final design and method of implantation of the MicroShunt, have been summarized[14]. Follow-up of the patients in the Dominican Republic showed prolonged success at 3 and 5 years[15,16].

The MicroShunt was marked as Conformité Européenne (CE) on January 9, 2012, in Europe and is available in 35 countries world-wide. It was initially used in European, Middle Eastern and African countries in 2018, followed by Canada and Australia in 2021 and Japan in 2022. To date, however, the MicroShunt has not been approved for sale in the United States.

Several studies by investigators in the Dominican Republic, Europe and Canada helped define the advantages and limitations of the PRESERFLO MicroShunt[14,17-20]. A thorough overview of the MicroShunt has been provided[21], and a consensus on the use of the PRESERFLO MicroShunt for the treatment of glaucoma has been summarized by a Delphi Panel of expert users of this device[22]. In brief, the Delphi Panel sought consensus on 25 statements, including: the MicroShunt is suited to those with a failed trabeculectomy, hypermetropia, high pre-operative IOP or with contact lenses. In addition, the MicroShunt allows for rapid post-operative visual recovery, the posterior position of the bleb can minimize device erosion. Blebs may potentially be revived by needling or removing scar tissue, often described by surgeons as a loosely adherent fibrous sock surrounding the MicroShunt. The incidence of flare is lower with the PRESERFLO MicroShunt than with other devices and treatments used in the eye[23]. A recent meta-analysis found that the magnitude of IOP decrease is lower with the MicroShunt than with trabeculectomy, but that the two had a similar safety profile and the MicroShunt had a lower reintervention rate[24].

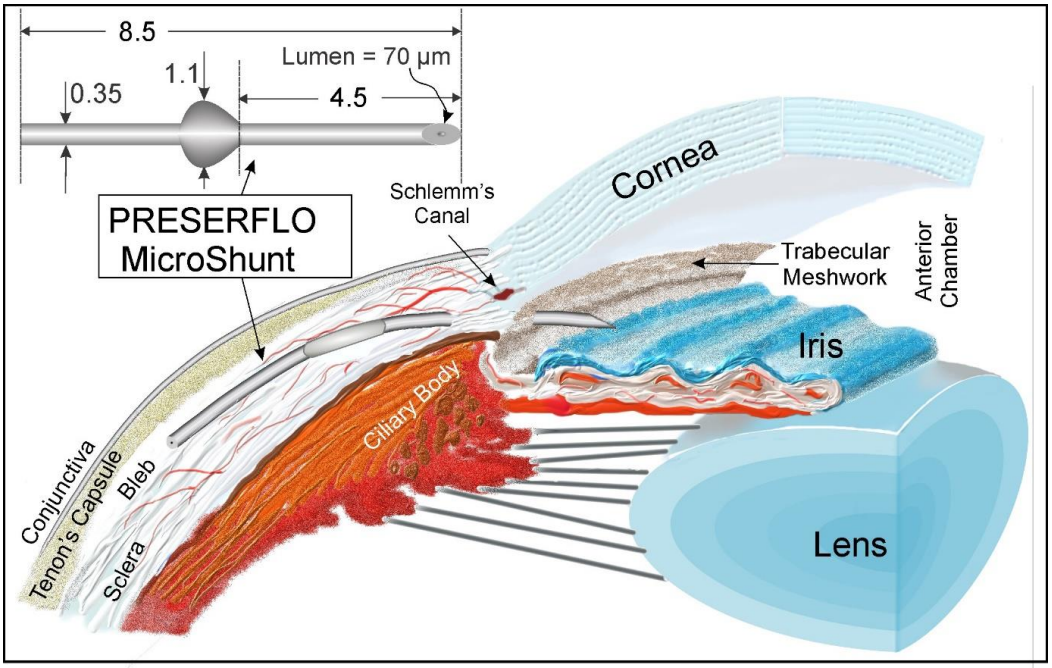

Figure 3: Schematic of the PRESERFLO MicroShunt showing its dimensions (mm) (top left) and its placement in the eye, shunting fluid from the anterior chamber to a bleb (small blister) formed between the conjunctiva/Tenon's capsule and the sclera in the mid-posterior eye.

Delayed Approval of the PRESERFLO MicroShunt in the USA

InnFocus was granted an Investigational Device Exception (IDE) by the U.S. Food and Drug Administration (FDA) in May 2013 to begin clinical testing of the MicroShunt in the U.S. (herein called the "IDE" study). The FDA required a two-year, prospective, randomized, multicenter, non-inferiority study (NCT01881425) comparing the MicroShunt with primary trabeculectomy in the United States and Europe. The study population consisted of 527 patients, uncontrolled on maximum tolerated glaucoma medication at 29-sites, with 395 eyes in the MicroShunt group and 132 in the control group, who underwent primary trabeculectomy. The study was completed in 2019[25].

The one-year results of this IDE trial have been reported[20]. The data obtained on patients who underwent MicroShunt implantation with intraoperative 0.2 mg/mL MMC were consistent with previous findings (Table 1)[16-18]. From baseline to 1-year, non-washout IOP decreased from 21.1 ± 4.9 mmHg to 14.3 ± 4.3 mmHg (32%) and the number of glaucoma medications decreased from 3.1 to 0.6 in the MicroShunt group[20]. In the trabeculectomy group, non-washout IOP decreased from 21.1± 5.0 mmHg to 11.1± 4.3 mmHg (47%) and the number of glaucoma medications decreased from 3.0 to 0.3 from baseline to 1 year. Rates of post-operative interventions, cataract progression and hypotony were lower in the MicroShunt than in the trabeculectomy group.

Of importance, the PRESERFLO MicroShunt did not fail due to bad MicroShunt data. Rather, the trabeculectomy control arm performed better than in any previously published randomized control trial (RCT) of primary trabeculectomy. The FDA has guidelines for "Non-Inferiority Studies"[26], including a "C*onstancy Assumption*", which states that results in the control group must be statistically similar to previously reported results to allow their use in determining non-inferiority. The Primary Tube versus Trabeculectomy (PTVT) study[27] was the only study of primary trabeculectomy available prior to the IDE study and differed from the IDE study in regard to inclusion criteria, baseline IOP and mitomycin C dose. At 1 year, the mean ± SD IOP for trabeculectomy in the PTVT study was 12.4 ± 4.4 mmHg (n=105), which was significantly higher (p = 0.023) than the mean IOP (11.1 ± 4.3 mmHg) in the trabeculectomy group of the IDE study (n=132). Thus, for all the above reasons, the control group in the IDE study failed the C*onstancy Assumption,* casting doubt on the overall appropriateness of this RCT.

The IDE trial had two endpoints. Endpoint #1 was defined as a responder (non-failure) rate of the MicroShunt group being within 15% of the responder rate of the trabeculectomy group, whereas Endpoint #2, was defined as an IOP of the MicroShunt group at 1 year being within 2.5 mmHg of the IOP of the trabeculectomy group. Meeting both endpoints would therefore suggest that the MicroShunt was non-inferior to trabeculectomy.

It is important to understand the implications of the non-inferior margins in regard to a CI of 95%. For example, if the responder rates of the MicroShunt and trabeculectomy were 65.1% and 73.5%, respectively, with the difference being -8.4%, then this difference would be within a margin of 15%, indicating that Endpoint #1 would be met. Unfortunately, this was not the case. The term "non-inferior", as defined by the FDA, required that the 15% difference between groups be within a 95% confidence interval (CI), indicating that with a sample size of 527 eyes, the difference would have to be within 6%, not 15%. To state it statistically, to be 95% confident that the difference between the MicroShunt and trabeculectomy is within 15%, the difference in population responder rate, for the number of patients enrolled, would have to be less than 6%.

At 1 year, the success rates in the MicroShunt and trabeculectomy groups were 53.9% (n=333) and 72.7% (n=113), respectively, a difference of -18.8%, indicating a failure to meet the primary endpoint[20]. The Farrington-Manning test using the above data showed that the 95% CI was -28.6% to -9.0% (see Figure *4*). To meet the 95% CI, the -15% value would have to be outside the range of -28.6% to -9.0%, a function of the null hypothesis, which is why the primary endpoint was not met.

However, the definition of "responder rate" in the comparison of MicroShunt and trabeculectomy[20] in the IDE study differed from that provided by the World Glaucoma Association (WGA) guidelines[28]. If defined according to WGA guidelines, the difference would have been significantly lower. The failure rate for the primary endpoint, as defined in the IDE study[20], was IOP <5 mmHg or <20% reduction in IOP compared with baseline, with no increase in glaucoma medications, reoperation for glaucoma, or loss of light perception vision at 1 year. In contrast, the WGA guidelines defined failure rate as an IOP >21 mmHg or a less than 20% reduction below baseline at two consecutive follow-up visits after 3 months, an IOP ≤5 mmHg at two consecutive follow-up visits after 3 months, reoperation for glaucoma, or loss of light perception vision[28]. That is, the standard WGA guidelines allow patients to be placed back on medication, with a single >20% responder rate drop not considered a failure. This study did not allow for the patients being placed back on medications in order to be considered a success. Moreover, if IOP was not at target in patients who underwent trabeculectomy, suture lyses could be performed to further reduce IOP, indicating a bias in favor of the trabeculectomy arm.

Confidence Interval	Z	Farrington-Manning Equation				
80%	1.28					
85%	1.44	Input		Output		
90%	1.65					
95%	1.96	95% Confidence Interval	z=	1.96		
99%	2.58			MicroShunt		Trabeculectomy
99.50%	2.81	Responder Rate %	x1=	53.9	x2=	72.7
99.90%	3.29	Number of patients	n1=	333	n2=	113
		Responder Rate, x/100	p1=	0.539	p2=	0.727
		sqrt([p1*(1-p1)/n1] + [p2*(1-p2)/n2])=			0.050	
		Z*sqrt([p1*(1-p1)/n1] + [p2*(1-p2)/n2])=			0.098	
		p1-p2 ± Z*sqrt([p1*(1-p1)/n1] + [p2*(1-p2)/n2])=		-0.3		-0.1
		100*[(p1-p2) ± Z*sqrt([p1*(1-p1)/n1] + [p2*(1-p2)/n2]))]=		-28.6		-9.0

Figure 4: Farrington-Manning test for non-inferiority at a 95% CI using the non-responder data comparing the MicroShunt with trabeculectomy[20]. *(Feel free to contact the author for an Excel version of this test).*

Post hoc reanalysis of success according to WGA guidelines showed that the responder rates in the MicroShunt and trabeculectomy groups at Year-1 were 65.1% and 73.5%, respectively, a difference of -8.4%. According to the Farrington-Manning test (Figure *4*) for 95% CI, recalculated using the 65.1% and 73.5% responder rates, the range was -17.3% to 0.5%, again indicating an endpoint failure because -15% was within this range. If, however, the CI was 85% (Z=1.44), the range would be -14.9% to -1.9%, which would meet the criteria as -15% is outside this range. Further, if the patient population was doubled, the 95% CI would be -14.7 to 2.1, thereby meeting the primary endpoint.

The primary reason for the large discrepancy in responder rate in comparisons of the MicroShunt and trabeculectomy groups for both endpoints was largely due to many trabeculectomy patients having IOPs <6 mmHg at 1 year. If all <6 mmHg data from both arms of the study were removed, the responder rates in the MicroShunt and trabeculectomy groups using the WGA definition would be 82.4% (n=329) and 86.8% (n=102), respectively, a difference of -4.4% with a 95% CI of -12.2% to 3.4% thereby meeting the primary Endpoint.

The large number of patients in the trabeculectomy group with IOP < 6 mmHg at 1 year may have been due to the recruitment of these patients by surgeons with extensive experience in performing trabeculectomy. These patients were deemed by the surgeons as able to undergo the risk of hypotony. In contrast, the PRESERFLO MicroShunt was a new device, with surgeons having little knowledge of the device or methods to optimize its performance. For example, the first approximately 100 procedures were performed with the MicroShunt implanted at 12 o'clock, which was reported to be suboptimal by several surgeons. Rather, implanting the device in the superior quadrant of the eye at 11 or 1 o'clock to avoid the rectus muscles is now preferred. In addition, a higher MMC dose of 0.4 mg/mL is preferred, by glaucoma surgeons for filtering surgeries, over the 0.2 mg/mL dose previously approved for commercial use by the FDA. According to the Advanced Glaucoma Intervention Study (AGIS)[29], the control of IOP to < 14 mmHg in the majority of patients suggests that glaucomatous progression of vision loss would be unlikely. There are no definitive data suggesting that control of IOP to < 6 mmHg provides further benefit; rather, it places patients at higher risk of pathological hypotony.

Table 1 provides a summary review of 11 additional studies of IOP and glaucoma medication use over time in patients who underwent MicroShunt implantation (upper table) and trabeculectomy (lower table). Success rates were omitted from Table 1 due to variations in the definition of success. Cumulative averages were computed as (Σ(n*A))/T, where n is the number of eyes per study, A is the average of the event measured with this number of eyes and T is the total number of eyes in all of the studies. The average IOPs at an average follow-up of 1.7 years in patients who underwent MicroShunt implantation and trabeculectomy were 13.7 mmHg and 11.7 mmHg, respectively, a difference of 2 mmHg. The 1-year IOPs in the MicroShunt and trabeculectomy groups in the FDA clinical trial were 14.3 mmHg and 11.1 mmHg, respectively, a difference of 3.2 mmHg[20] which exceeded the non-inferiority margin set for this endpoint at 2.5mmHg.

Post Market Surveillance

A post-market surveillance review performed internally by InnFocus (not published) has found that the 12-month complaint rate for the PRESERFLO MicroShunt, ending September 2024, was 0.62%, based upon approximately 48,000 implants. The most frequently reported device failure was lack of flow during implantation. Thorough analysis of the returned devices by InnFocus found that most of these devices demonstrated flow. The absence of flow at implantation may result from clinical factors, such as pinching/closure of the lumen by the forceps used to implant it, leakage around the outside of the device, or blockage of the tube due to insertion of the tip in the iris. Adverse events included hyphema, increased IOP, choroidal detachment, and hypotony. These are anticipated risks and are routinely addressed in the company's Failure Mode and Risk Analysis documentation in the context of filtering surgeries and characterized well in company sponsored clinical studies and real-world evidence. A review of clinical data from this internal Post Market Surveillance period suggests that the risks associated with the PRESERFLO MicroShunt were acceptable when weighed against patient benefits, with this 0.62% complaint rate falling well below the 2% safety threshold commonly associated with medical devices of this nature.

Table 1. Summary of studies evaluating pre- and post-operative IOP and glaucoma medication use in patients who underwent PRESERFLO MicroShunt implantation (upper panel) or trabeculectomy (lower panel).

Intraocular Pressure and Glaucoma Medication: PRESERFLO® MicroShunt						
Study	**No. of Eyes (n)**	**Pre-op IOP (mmHg) (A)**	**Pre-op Drugs**	**Follow-Up Final (yrs)**	**IOP (mmHg)**	**Post-op Drugs**
Riss et al. (2015) [30]	23	23.8	2.6	1	10.7	0.3
Schlenker et al. (2015) [17]	164	21.4	3.4	1	13.3	0.5
Beckers et al. (2017) [31]	91	24.3	2.4	1	13.3	0.4
Batlle et al. (2021) [16]	23	23.8	2.4	5	12.4	0.4
Martinez-de-la-Casa (2021) [32]	58	21.5	2.3	1	14.6	0.2
Beckers et al. (2022) [19]	81	21.7	2.5	2	14.1	0.5
Fili et al. (2022) [33]	150	23.5	2.5	1	12.9	0.4
Van Lancker et al. (2023) [34]	64	24.3	3.4	1	14.0	0.5
Tanner et al. (2023) [37]	104	23.4	3.4	1	14.7	0.7
Gubser et al. (2023) [38]	70	21.7	3.5	2	15.5	1.1
Cumulative Averages	**828**	**22.8**	**2.9**	**1.6**	**13.7**	**0.5**
Intraocular Pressure and Glaucoma Medication: Trabeculectomy						
Study	**No. of Eyes**	**Pre-op IOP (mmHg)**	**Pre-op Drugs**	**Follow-Up Final (yrs)**	**IOP (mmHg)**	**Post-op Drugs**
Gedde et al. (2020) [39]	89	23.9	3.2	3	12.1	1.2
Van Lancker et al. (2023) [34]	58	25.4	3.6	1	12.5	0.6
Fili et al. (2022) [33]	150	22.0	2.7	1	11.4	0.6
Gubser et al. (2023) [38]	87	24.1	3.3	2	11.4	0.5
Cumulative Averages	**384**	**23.4**	**3.1**	**1.8**	**11.7**	**0.7**

The PRESERFLO MicroShunt Learning Curve:

Once the PRESERFLO MicroShunt was approved for use, many surgeons optimized their own procedural techniques. ***The reader should be aware that InnFocus/Santen cannot condone or encourage the use of these off-label procedures.***

- Use of 0.4 mg/mL MMC: Compared with 0.2 mg/mL MMC, 0.4 mg/mL MMC was found to result in a lower IOP and generally better clinical outcomes[16,19,35,36]. The MicroShunt drains to the mid-posterior Tenon's capsule, which is thicker than the anterior Tenon's capsule, the site of trabeculectomy. The mid-posterior Tenon's capsule contains larger numbers of fibroblasts and smooth muscle cells than the anterior Tenon's capsule, which is thin and relatively devoid of smooth muscle cells[37].

  A recent meta-analysis compared the efficacy and safety of 0.2 mg/ml and 0.4 mg/ml MMC in 450 eyes of 441 patients that underwent MicroShunt implantation alone, without phacoemulsification, including 335 eyes that received 0.2 mg/ml MMC and 115 eyes that received 0.4 mg/ml MMC[40]. The primary outcome was complete success rate, defined as no two consecutive IOPs >17 mmHg, no clinical hypotony, ≥20% IOP reduction from baseline, and no use of glaucoma medications. At 1 year, the complete success rate was significantly higher (71.3% vs. 50.5%, P <0.001) and the median IOP was significantly lower (13.0 vs. 14.2 mmHg, P <0.05) in eyes that received 0.4 mg/ml than 0.2 mg/ml MMC. Rates of needling (7% vs. 18.8%, P = 0.002) and surgical revision (4.3% vs. 13.7%, P=0.0087) were significantly lower in the 0.4 mg/ml MMC group. Adverse event rates were similar in the 0.4 and 0.2 mg/ml MMC groups (29.6% vs, 26.6%, P = 0.46), with most adverse events being early and transient. This evidence suggests that one might expect more meaningful outcomes with a high concentration of MMC, although this needs to be studied further in a prospective randomized clinical trial.

- Surgical implant site: Initially, in the first 100 implants in the IDE clinical study, the MicroShunt was implanted at the 12 o'clock position. Implantation superiorly at the 11 or 1 o'clock position was later found by the surgeons in this study to be optimal, as it avoided the superior rectus muscle.

- Single versus double MicroShunts: A recent retrospective analysis compared outcomes in glaucoma patients who underwent single (n=29) or double (n=28) MicroShunt implantation[41]. Although mean preoperative IOP was significantly higher in patients who underwent double than single implantation (29.4 ± 10.0 vs. 21.7 ± 8.2 mmHg, P = 0.003), mean postoperative IOP was significantly lower in the double implantation group at 1 day, 1 week and 3 and 6 months (all P <0.021). In the 17 patients who underwent a two-stage procedure, mean IOP lowering was similar after both procedures, with a longer sustainable effect observed after the second procedure. These findings suggest that double MicroShunt implantation was safe and effective in lowering IOP in glaucoma patients. although the risk of hypotony was higher when two devices were implanted in the same eye.

- Stenting the MicroShunt: Beginning in 2022, the MicroShunt has been stented by inserting a suture, generally polypropylene or Nylon, 9.0 or 10.0, at the time of surgery, 2 to 3 mm into the posterior lumen of the MicroShunt, inhibiting short-term flow to prevent hypotony[42-46]. The free end of the suture has often been placed close to the limbus to ensure later access to the "ripcord," with the suture-ripcord pulled 2 to 6

weeks after MicroShunt implantation[45]. The outflow pathways in the eye and through several MIGS devices, including the MicroShunt, have been modeled[47], and studies are assessing the effects of stenting.

- Maintenance of the bleb: Several methods have been described for maintenance of the bleb, including filling the bleb with Ologen containing MMC. Ologen is a porous collagen–glycosaminoglycan copolymer matrix used to modulate wound healing in connective and epithelial tissues[48,49]. At 6 months, however, IOP reductions in groups with and without Ologen implantation did not differ significantly.
  Beta radiation provides another non-invasive method of modulating fibrosis[50-53]. Trabeculectomy with a single adjunctive dose of 1000 rad β radiation in Chinese eyes with POAG was found to achieve a qualified success rate of 88.4% at 7 years[50]. Annual prophylactic exposure of the bleb area to β radiation for 20 seconds may prevent long-term bleb fibrosis[51,52].
  Administration of a biodegradable wafer infused with MMC to rabbit eyes yielded results similar to a controlled dose of MMC applied intraoperatively after one month[53]. These rabbit eyes, however, were not glaucomatous, preventing assessment of the true efficacy of the biodegradable wafer. In addition, many practitioners inject MMC and 5-FU periodically after surgery, as well as performing needling and bleb revisions[21].

- MicroShunt implantation in conjunction with cataract surgery: The PRESERFLO MicroShunt has been implanted into eyes undergoing cataract surgery. An evaluation of 35 eyes that underwent MicroShunt implantation alone and 23 eyes that underwent MicroShunt implantation in combination with phacoemulsification found no between-group differences in reduction of IOP and glaucoma medications at 12 months[32]. Overall mean IOP dropped from 21.5 ± 3.3 mmHg at baseline to 14.6 ± 3.5 mmHg at 12 months, and the average number of glaucoma medicines dropped from 2.3 at baseline to 0.2 at 12 months. The complete success rates in these two groups were 68.6% (24/35 eyes) and 52.2% (12/23 eyes), respectively.
  Similarly, an evaluation of 51 eyes that underwent MicroShunt implantation alone and 13 that underwent MicroShunt implantation with phacoemulsification found no significant between-group differences in the number of IOP-lowering medication (0.2 ± 0.08 vs. 0.1 ± 0.1; P =0.2)[54]. In the overall study population, mean IOP decreased significantly from 22.03 ± 0.7 mm Hg at baseline to 12.7 ± 0.4 mm Hg at the final visit (mean follow-up: 11 ± 1.4 months) (P <0.0001), and the mean number of ocular hypotensive medication was reduced significantly from 2.7 ± 0.7 to 0.2 ± 0.5 (P <0.0001).

- Pseudoexfoliation glaucoma: A retrospective, single-center study compared the safety and efficacy of the PRESERFLO MicroShunt with trabeculectomy in patients diagnosed with pseudoexfoliation glaucoma[55]. Thirty-one eyes underwent MicroShunt implantation, and 29 underwent trabeculectomy. Surgical success was defined as an IOP between 5 mmHg and 17 mmHg at one-year, no need for surgical revisions or secondary glaucoma surgery, and no loss of light perception. Mean IOP decreased from 20.8 ± 5.9 mmHg at baseline to 12.4 ± 2.8 mmHg ($p < 0.0001$) in the MicroShunt group and from 22.3 ± 6.5 mmHg to 11.1 ± 3.7 mmHg ($p < 0.0001$) in the trabeculectomy group. The mean number of glaucoma medications showed similar reductions in the two groups, from 2.7 ± 1.2 to 0.2 ± 0.7 ($p < 0.0001$) in the MicroShunt group and from 2.9 ± 1.2 to 0.3 ± 0.9 ($p < 0.0001$) in the trabeculectomy group. Complete and qualified success rates were 83.9% and 90.3%, respectively, in the MicroShunt group and 82.8% and 93.1%, respectively, in the trabeculectomy group. Postoperative complications were comparable in the two groups. These findings indicated that MicroShunt implantation had a non-inferior efficacy and safety profile compared with trabeculectomy at 1 year in patients with pseudoexfoliation glaucoma.

- Refractory glaucoma: Patients with refractory glaucoma have been defined as those with POAG who have failed incisional glaucoma surgery or presented with severe forms of secondary glaucoma (e.g., after penetrating keratoplasty or globe penetrating injury). The efficacy of MicroShunt implantation has been assessed in 40 eyes of 38 patients with refractory glaucoma, with complete success defined as reaching the target IOP (>6 mm Hg and <14 mm Hg) without additional IOP-lowering medication and qualified success defined as reaching the same target IOP regardless of changes in medication[56]. The complete success rate after 12 months was 85.7%, with an average IOP of 10.5 ± 2.0 mm Hg, without the use of glaucoma eye drops. The average IOP reduction from baseline was 58.4%. Five (12.5%) eyes experienced failure, with these eyes requiring revision surgery.
  Another study evaluated the effects of MicroShunt implantation in 47 eyes with uncontrolled IOP despite maximally tolerated medical therapy and at least one previous failed glaucoma surgery [57]. At baseline, the mean preoperative IOP was 30.1 ± 7.1 mmHg, the mean number of glaucoma medications was 3.4 ± 1, and the mean number of previous surgeries was 2.3 ± 1.3. One year after MicroShunt implantation, the mean IOP was significantly reduced to 18.8 ± 4.6 mmHg, with the mean number of medications significantly reduced to 1.4 ± 1.2. Complete success was achieved in 35% of eyes, and qualified success in 60%. Moreover, 55% of eyes showed a ≥30% reduction in IOP. Needling or bleb repair was performed in 49% of eyes. Complications were minimal and transient, except for one eye that presented with tube extrusion, and another eye with a transected tube. Repeat glaucoma surgery was performed in 17% of eyes. These findings indicated that the PRESERFLO MicroShunt provided moderate success but a significant reduction in IOP, with a good safety profile after 1 year of follow-up, in eyes at high risk for failure of filtering surgery.
  Treatment of 21 consecutive patients with uncontrolled refractory uveitic glaucoma with MicroShunt

implantation and intraoperative MMC yielded success rates after 1, 2, and 3 years of 68%, 47% and 47%, respectively[58]. Relative to baseline, mean IOP decreased 26.5%, 33.5% and 30.1% at postoperative years 1, 2 and 3, respectively ($p < 0.001$). The number of glaucoma medications decreased from 4.1 ± 0.9 at baseline to 0.9 ± 1.2 at the final follow up ($p = 0.0005$). No sight-threatening complications were reported by 3 years, indicating that the MicroShunt was safe and effective in the treatment of refractory uveitic glaucoma in this patient population.

- Refractory childhood glaucoma: MicroShunt implantation into 12 eyes of 12 children, aged 15 months to 14 years, with mean preoperative IOP of 22.72 ± 4.8 mmHg and taking a mean 3.3 ± 0.65 glaucoma medications, showed that none of these eyes experienced any intraoperative complications[59]. Of the eyes followed-up for ≥1 year (range 12-23 months), nine were successfully controlled, with IOP decreasing from 21.6 ± 4.9 mm Hg preoperatively to 11.9 ± 3.8 mmHg at 1 year, a decrease of 45%. Seven patients were off glaucoma medications at 12 months, and two required two medications (fixed-combination dorzolamide-timolol). Three eyes failed, requiring additional surgery. These results, in which patients were administered 0.4 mg/mL MMC, suggest that the device is safe and effective in patients with refractory childhood glaucoma. A prospective, multicenter trial is planned.

  MicroShunt implantation was also analyzed in 14 patients, 8 (57%) males and 6 (43%) females, of mean age 27.5 ± 13.5 years[60]. Nine patients (64%) had undergone at least two trabeculectomies, and six (43%) had undergone at least one trabeculectomy and a glaucoma drainage implant. One year after MicroShunt implantation, the mean IOP change from baseline was 11.3 ± 4.9 mmHg, with 12 patients (86%) showing a ≥ 20% reduction in IOP and 11 (79%) showing a ≥ 30% reduction. The mean number of glaucoma medications decreased from 3.9 ± 0.7 at baseline to 0.7 ± 1.3 at 12 months. No intraoperative complications or adverse events were observed. None of these patients required secondary filtration surgery, although one required bleb needling 1 month after surgery.

Conclusion

The development of the PRESERFLO MicroShunt was an educated iterative process that occurred over 10 years. The process required formulating a long-term indwelling thermoplastic glaucoma shunt using chemistry and engineering principles. The chemistry and design of the SIBS MicroShunt yielded an atraumatic flow-restrictor tube that minimized foreign body reactions, with few reports of erosion or expulsion of the tube from the eye. Draining to under the conjunctiva and Tenon's capsule is important because the shunt bypasses areas of high resistance in the drainage path for aqueous humor, including the trabecular meshwork, Schlemm's canal, the collector channels, the aqueous veins, and the episcleral veins. In addition, the bleb formed in the posterior eye is thicker-walled and potentially less prone to adverse events such as device erosion than blebs formed in the anterior part of the eye. However, the posterior drainage site also contains more fibroblasts and smooth muscle cells, which often necessitate a higher dose of MMC. The MicroShunt is suited to eyes with a failed trabeculectomy, hypermetropia, high pre-operative IOP or contact lenses. Results also suggest that the MicroShunt may be useful in the treatment of childhood glaucoma, pseudoexfoliation glaucoma and other types of refractory glaucoma. In addition, innovations in the field, such as increased MMC dosing, bleb management, stenting the MicroShunt or insertion of a second MicroShunt, may further improve MicroShunt performance. Finally, the MicroShunt allows for rapid post-surgery visual recovery with little risk of corneal decompensation.

Acknowledgments:

Editorial assistance with referencing and formatting was provided by BelMed Professional Resources supported by Santen Inc. according to Good Publication Practice guidelines (link).

Author Disclosure Statement:

No competing financial interests exist other than being an employee of Santen. No funding was received for this article.

References

1. Pinchuk L, Wilson GJ, Barry JJ, Schoephoerster RT, Parel JM, Kennedy JP. Medical applications of poly(styrene-block-isobutylene-block-styrene) ("SIBS"). Biomaterials 2008;29(4):448-460. doi:10.1016/j.biomaterials.2007.09.041
2. Pinchuk L, Boden M, Bluestein D. In: SIBS in Medicine. Macromolecular Engineering: Design, Synthesis and Application of Polymers, edited by Lubnin and Erdodi, 2021. 978-0-12-821998-0, Chapter 11, Section V, Disruptive Medical Applications.
3. Boden M, Richard R, Schwarz MC, Kangas S, Huibregtse B, Barry JJ. In vitro and in vivo evaluation of the safety and stability of the TAXUS paclitaxel-eluting coronary stent. J Mater Sci Mater Med 2009;20(7):1553–1562. doi:10.1007/s10856-009-3705-5
4. Pinchuk L. A review of the biostability and carcinogenicity of polyurethanes in medicine and the new generation of "biostable" polyurethanes. J Biomater Sci Polym Ed 1994;6(3):225-267. doi:10.1163/156856294X00347
5. Kennedy JP, Puskas JE, Kaszas G, Hager WG. Patent. Thermoplastic Elastomers of Isobutylene and Process of Preparation. US Patent No. 4946899. 7 August 1990.; 1990.
6. Storey RF, Chisholm BJ, Masse MA. Morphology and physical properties of poly(styrene-b-isobutylene-b-styrene) block copolymers. Polymer 1996;37(14):2925-2938.
7. Pinchuk L. Patent. Biostable Elastomeric Polymers Having Quaternary Carbons. US Patent No. 5741331. 21 April 1998.
8. Widder RA, Kühnrich P, Hild M, Rennings C, Szumniak A, Rossler GF. Intraocular degradation of XEN45 Gel Stent 3 years after its implantation. J Glaucoma 2019;28(12):e171–e173. Doi:10.1097/IJG.0000000000001364
9. Pinchuk L, Riss I, Batlle JF, et al. The development of a micro-shunt made from poly(styrene-block-isobutylene-block-styrene) to treat glaucoma. J Biomed Mater Res B Appl Biomater 2017;105(1):211-221. doi:10.1002/jbm.b.33525.
10. Acosta AC, Espana EM, Yamamoto H, et al. A newly designed glaucoma drainage implant made of poly(styrene-b-isobutylene-b-styrene): biocompatibility and function in normal rabbit eyes. Arch Ophthalmol 2006;124(12):1742-1749. doi:10.1001/archopht.124.12.1742
11. Ibarz Barberá M, Hernandez-Verdejo JL, Bragard J, et al. Evaluation of the ultrastructural and in vitro flow properties of the PRESERFLO MicroShunt. Transl Vis Sci Technol 2021;10(13):26. Doi:10.1167/tvst.10.13.26.
12. Fantes F, Acosta AC, Carraway J, et al. An independent GLP evaluation of a new glaucoma drain, the Midi. Invest Ophthalmol Vis Sci. 2006;47(13):3547.
13. Arrieta EA, Aly M, Parrish R, et al. Clinicopathologic correlations of poly-(styrene-b-isobutylene-b-styrene) glaucoma drainage devices of different internal diameters in rabbits. Ophthalmic Surg Lasers Imaging 2011;42(4):338-345. doi:10.3928/15428877-20110603-01
14. Pinchuk L, Riss I, Batlle JF, et al. The development of SIBS in the InnFocus MicroShunt®. In: Samples JR, Knepper PA, eds. Glaucoma Research and Clinical Advances 2018–2020. Amsterdam, The Netherlands: Kugler Publications; 2018.
15. Batlle JF, Fantes F, Riss I, et al. Three-year follow-up of a novel aqueous humor microshunt. J Glaucoma 2016;25(2):e58-e65. doi:10.1097/IJG.0000000000000368
16. Batlle JF, Corona A, Albuquerque R. Long-term results of the PRESERFLO MicroShunt in patients with primary open-angle glaucoma from a single-center nonrandomized study. J Glaucoma 2021;30(3):281–286. doi:10.1097/IJG.0000000000001734
17. Schlenker MB, Durr GM, Michaelov E, Ahmed IIK. Intermediate outcomes of a novel standalone ab externo SIBS Microshunt with mitomycin C. Am J Ophthalmol 2020;215:141–153. Doi:10.1016/j.ajo.2020.02.020
18. Pillunat KR, Herber R, Haase MA, Jamke M, Jasper CS, Pillunat LE. PRESERFLO™ MicroShunt versus trabeculectomy: first results on efficacy and safety. Acta Ophthalmol 2021;100(3):e779–e790. Doi:10.1111/aos.14968
19. Beckers HJM, Aptel F, Webers CAB, et al. Safety and effectiveness of the PRESERFLO MicroShunt in primary open-angle glaucoma: results from a 2-year multicenter study. Ophthalmol Glaucoma 2022;5(2):195–209. Doi:10.1016/j.ogla.2021.07.008
20. Baker ND, Barnebey HS, Moster MR, et al. Ab-externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: one-year results from a 2-year randomized, multicenter study. Ophthalmology 2021;128(12):1710–1721. Doi:10.1016/j.ophtha.2021.05.023
21. Gambini G, Carla MM, Giannuzzi F, et al. PreserFlo® MicroShunt: an overview of this minimally invasive device for open-angle glaucoma. Vision (Basel) 2022;6(1):12. Doi:10.3390/vision6010012
22. Khawaja AP, Stalmans I, Aptel F, et al. Expert consensus on the use of the PRESERFLO MicroShunt device in the treatment of glaucoma: a modified delphi panel. Ophthalmol Ther 2022;11(5):1743–1766. Doi:10.1007/s40123-022-00529-4
23. Ranjit A, Patel B, Sherman TEJ, et al. Evaluating post-operative flare in glaucoma surgery: Miniject, Microshunt, Baerveldt tube, cataract & ECP and trabeculectomy. Invest Ophthalmol Vis Sci 2024;65(7):3522 (abstract).
24. Khan A, Khan AU. Comparing the safety and efficacy of Preserflo Microshunt implantation and trabeculectomy for glaucoma: A systematic review and meta-analysis. Acta Ophthalmol 2024;102(4):e443–e451. Doi:10.1111/aos.16658
25. Panarelli JF, Moster MR, Garcia-Feijoo J, et al. Ab-externo MicroShunt versus trabeculectomy in primary open-angle glaucoma: two-year results from a randomized, multicenter study. Ophthalmology 2024;131(3):266–276. Doi:10.1016/j.ophtha.2023.09.023
26. Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry, U.S. Department

of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), November 2016, Clinical/Medical

27. Gedde SJ, Chen PP, Heuer DK, et al. The Primary Tube Versus Trabeculectomy Study: Methodology of a multicenter randomized clinical trial comparing tube shunt surgery and trabeculectomy with mitomycin C. Ophthalmology 2018;125(5):774–781. Doi:10.1016/j.ophtha.2017.10.037.
28. World Glaucoma Association. In: Shaarawy T, ed. Guidelines on Design and Reporting of Glaucoma Surgical Trials. Amsterdam: Kugler; 2009. 22.
29. The AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration. Am J Ophthalmol 2000;130(4):429-440. doi:10.1016/S0002-9394(00)00538-9
30. Riss I, Batlle J, Pinchuk L, Kato YP, Weber BA, Parel JM. One-year results on the safety and efficacy of the InnFocus MicroShunt™ depending on placement and concentration of mitomycin C. J Fr Ophtalmol 2015;38(9):855–860. Doi:10.1016/j.jfo.2015.05.005
31. Beckers HJM, Kujovic-Aleksov S, Webers CAB, Riss I, Batlle J, Parel JM. One-year results of a three-site study of the MicroShunt®. Acta Ophthalmol 2017;95(S258):28-29. Doi:10.1111/aos.13419
32. Martínez-de-la-Casa JM, Saenz-Frances F, Morales-Fernandez L, et al. Clinical outcomes of combined Preserflo Microshunt implantation and cataract surgery in open-angle glaucoma patients. Sci Rep 2021;11(1):15600. Doi:10.1038/s41598-021-95217-x
33. Fili S, Kontopoulou K, Vastardis I, Perdikakis G, Kohlhaas M. PreserFlo MicroShunt versus trabeculectomy in patients with moderate to advanced open-angle glaucoma: 12-month follow-up of a single-center prospective study. Curēus 2022;14(8) e28288. Doi:10.7759/cureus.28288.
34. Van Lancker L, Saravanen A, Abu-Bakra M, et al. Clinical outcomes and cost analysis of PreserFlo versus trabeculectomy for glaucoma management in the United Kingdom. Ophthalmol Glaucoma 2023;6(4):342–357. Doi:10.1016/j.ogla.2022.11.006
35. Tanner A, Haddad F, Fajardo-Sanchez J, et al. One-year surgical outcomes of the PreserFlo MicroShunt in glaucoma: a multicentre analysis. Br J Ophthalmol 2023;107(8):1104–1111. Doi:10.1136/bjophthalmol-2021-320631
36. Abegao Pinto L, Sunaric Megevand G, Stalmans I, et al. European Glaucoma Society – A guide on surgical innovation for glaucoma. Br J Ophthalmol 2023;107(Suppl 1):1–114. Doi:10.1136/bjophthalmol-2023-egsguidelines
37. Kakizaki H, Takahashi Y, Nakano T, et al. Anatomy of Tenons capsule. Clin Exp Ophthalmol 2012;40(6):611–616. Doi:10.1111/j.1442-9071.2011.02745.x
38. Gubser PA, Pfeiffer V, Hug S, et al. PRESERFLO MicroShunt implantation versus trabeculectomy for primary open-angle glaucoma: a two-year follow-up study. Eye Vis (Lond) 2023;10(1):50. Doi:10.1186/s40662-023-00369-8.
39. Gedde SJ, Feuer WJ, Lim KS, et al. Treatment outcomes in the primary tube versus trabeculectomy study after 3 years of follow-up. Ophthalmology 2020;127(3):333–345. Doi:10.1016/j.ophtha.2019.10.002
40. De Francesco T, Armstrong JJ, Hussein IM, Costa MP, Ahmed IIK. Mitomycin 0.2 mg/ml versus mitomycin 0.4 mg/ml during the implantation of an ab externo polystyrene-isobutylene-styrene microshunt: a mega-analysis. Ophthalmol Glaucoma 2024;7(5):454-465. Doi:10.1016/j.ogla.2024.06.001
41. Dervos T, Gugleta K, Scholl HPN, Gatzioufas Z, Enz TJ. Single versus double PreserFlo MicroShunt implantation in glaucoma patients: a retrospective cohort study. Ophthalmic Res 2023;66(1):1362-1375. Doi:10.1159/000535276
42. Lupardi E, Laffi GL, Moramarco A, Barboni P, Fontana AL. Systematic Preserflo MicroShunt intraluminal stenting for hypotony prevention in highly myopic patients: a comparative study. J Clin Med 2023;12(4):1677. Doi:10.3390/jcm12041677
43. Ophthalmology Unit Researchers Provide New Data on Clinical Medicine (Systematic Preserflo MicroShunt Intraluminal Stenting for Hypotony Prevention in Highly Myopic Patients: A Comparative Study). NewsRX LLC, 2023. Print.
44. Aguilar-Munoa S, Tham YH, Barton K. A simple surgical solution for the treatment of persistent postoperative hypotony after PRESERFLO MicroShunt implantation. Eye (Lond) 2023;37(10):2126–2129. Doi:10.1038/s41433-022-02301-1.
45. Verma-Fuehring R, Dakroub M, Bamousa A, Kann G, Hillenkamp J, Kampik D. The use of intraluminal PRESERFLO stenting in avoiding early postoperative hypotony. Graefes Arch Clin Exp Ophthalmol 2024, in press. Doi:10.1007/s00417-024-06567-x
46. Lupardi E, Laffi GL, Ciardella A, Bartoni P, Fontana L. Ab-externo intraluminal stent for prolonged hypotony and choroidal detachment after Preserflo implantation. Eur J Ophthalmol 2023;33(5):NP63–NP66. Doi:10.1177/11206721221137166
47. Farrar N, Yan DB, Johnson M. Modeling the effects of glaucoma surgery on intraocular pressure. Exp Eye Res 2021;209:108620. Doi:10.1016/j.exer.2021.108620.
48. Lüke JN, Enders P, Lappa A, Dietlein TS. Revision of the PRESERFLO MicroShunt with ologen and mitomycin C. Ophthalmologie 2023;120(4):440-442. Doi:10.1007/s00347-023-01816-6
49. Vastardis I, Fili S, Perdikakis G, et al. Preliminary results of Preserflo Microshunt versus Preserflo Microshunt and ologen implantation. Eye Vis (Lond) 2021;8(1):33. Doi:10.1186/s40662-021-00253-3
50. Lai JSM, Poon ASY, Tham CCY, Lam DSC. Trabeculectomy with beta radiation: long-term follow-up. Ophthalmology 2003;110 (9):1822–1826. Doi:10.1016/S0161-6420(03)00561-X
51. Constable PH, Crowston JG, Occleston NL, Cordeiro MF, Khaw PT. Long term growth arrest of human Tenon's fibroblasts following single applications of beta radiation. Br J Ophthalmol 1998;82(4):448–452. Doi:10.1136/bjo.82.4.448

52. El Mazar HM, Mandour SS, Mostafa MJ, Elmorsy OA. Augmented subscleral trabeculectomy with beta radiation and mitomycin C in Egyptian glaucoma patients. J Glaucoma 2019;28(7):637–642. Doi:10.1097/IJG.0000000000001255
53. van Mechelen RJS, Wolters JEJ, Fredrich S, et al. A degradable sustained-release drug delivery system for bleb-forming glaucoma surgery." Macromol Biosci 2023;23(10):e2300075. Doi:10.1002/mabi.202300075
54. Ibarz Barberá M, Martinez-Galdon F, Caballero-Magro E, Rodriguez-Pinero M, Tana-Rivero P. Efficacy and safety of the Preserflo Microshunt with mitomycin C for the treatment of open angle glaucoma. J Glaucoma 2022;31(7):557–566. Doi:10.1097/IJG.0000000000002052
55. Fea AM, Laffi GL, Martini E, et al. Effectiveness of MicroShunt in patients with primary open-angle and pseudoexfoliative glaucoma: a retrospective European multicenter study. Ophthalmol Glaucoma 2022;5(2):210–218. Doi:10.1016/j.ogla.2021.08.005.
56. Seuthe AM, Erokhina M, Szurman P, Haus A. One-year results of the Preserflo MicroShunt implantation for refractory glaucoma. J Glaucoma 2023;32(5):414–419. Doi:10.1097/IJG.0000000000002178
57. Majoulet A, Scemla B, Hamard F, et al. Safety and efficacy of the Preserflo® Microshunt in refractory glaucoma: a one-year study. J Clin Med 2022;11(23):7086. Doi:10.3390/jcm11237086.
58. Triolo G, Wang J, Aguilar-Munoa S, Jayaram H, Barton K. Preserflo Microshunt implant for the treatment of refractory uveitic glaucoma: 36-month outcomes. Eye (Lond) 2023; 37(12) 2535–2541. Doi:10.1038/s41433-022-02368-w
59. Brandt JD. Use of a novel Microshunt in refractory childhood glaucoma: initial experience in a compassionate use/early access cohort. Am J Ophthalmol 2022;239:223–229. Doi:10.1016/j.ajo.2022.03.021
60. Burgos-Blasco B, Garcia-Feijoo J, Gines-Gallego C, et al. Efficacy and safety of the PreserFlo implant with nitomycin C in childhood glaucoma after previous failed glaucoma surgeries. Graefes Arch Clin Exp Ophthalmol 2023;261(5):1349–1357. Doi:10.1007/s00417-022-05939-5

