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ORIGINAL RESEARCH

A Prospective Evaluation of the 2-Year Efficacy and Safety of INTERCIL: A Novel Uveal Spacer for Open-Angle Glaucoma

Lilit Voskanyan · Vahan Papoyan · Hayk Babayan · Hovsep Miroyan · Christophe Baudouin

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ABSTRACT

***Introduction*:** Intraocular pressure (IOP) reduction is the most commonly therapeutically modifiable risk factor in glaucoma. Minimally invasive glaucoma surgeries are generally considered safe but ineffective, constrained by physiological pressure. Invasive bleb-forming filtration surgeries are effective, but associated with high risk and high rates of failure. Technologies utilizing uveoscleral rely on creation of a cyclodialysis cleft. This study evaluated a novel supraciliary uveal spacer (INTERCIL®) designed to enhance uveoscleral outflow, avoiding anterior and posterior chamber entry or bleb formation.

***Methods*:** SAFARI 3, a prospective, single-center, single-arm study included adults with mild-to-moderate glaucoma (Shaffer grade 1–4), uncontrolled on 1–4 medications (baseline IOP 21–35 mmHg). Patients underwent standalone ab externo implantation of INTERCIL®. The primary endpoint was mean change in medicated IOP at 24 months. Secondary outcomes included medication reduction, success rates (IOP ≤ 18 mmHg with ≥ 20% reduction), safety, and quality of life.

***Results*:** Twenty-nine patients with primary open-angle glaucoma (POAG) were analyzed (mean age 65.9 years; baseline IOP 23.4 ± 1.9 mmHg; medications 1.9 ± 0.9). At 24 months ($n = 19$), mean IOP decreased to 14.4 ± 3.1 mmHg (39% reduction); medication use decreased to 0.4 ± 0.8 (83% reduction), with 73.7% medication-free. Complete and qualified success rates were 74% and 95%, respectively. All patients achieved ≥ 20% IOP reduction by 12 and 24 months; 94.7% had IOP between 6 and 18 mmHg at 24 months. Adverse events were mild to moderate in severity. One event of inadvertent anterior chamber entry with migration affected one patient. Six cases of cataract, not deemed device- or procedure-related, were reported; causality cannot be excluded, but cataract development is not uncommon after glaucoma surgery. Device position remained stable

Prior Presentation: This analysis with all final data has not been presented publicly previously. An interim analysis from the study was presented by Dr Voskanyan as a free paper presentation at the ESCRS Conference (12–16 September, 2025, Copenhagen ESCRS25-FP-3422). The same interim data were made available in a company white paper, Ciliatech SAS (The INTERCIL Uveal Spacer for Primary Open Angle Glaucoma: The SAFARI 3 Study. Ciliatech White Paper 2025, November, Ref 2025110 6-00).

L. Voskanyan (✉) · V. Papoyan · H. Babayan · H. Miroyan
S.V. Malayan Ophthalmological Center, Yerevan, Armenia
e-mail: lilit.voskanyan@yahoo.com

C. Baudouin
Quinze-Vingts National Ophthalmology Hospital and Vision Institute, Paris, France

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overall, and visual function parameters showed no clinically significant changes.
Conclusions: INTERCIL® provided sustained IOP and medication reduction by potentially harnessing uveoscleral outflow, without surgical risks associated with bleb- or cleft- dependent procedures, suggesting a potential new concept for patients with open-angle glaucoma requiring durable disease control.
Trial Registration: ClinicalTrials.gov identifier, NCT05236439.

Keywords: Glaucoma; Open angle; Intraocular pressure supraciliary; Suprachoroidal; Filtration; Uveal spacer

Key Summary Points

Why carry out this study?

The uveoscleral outflow pathway is not fully understood, but the few available therapeutic options which utilize this pathway provide powerful intraocular pressure reduction in patients with glaucoma.

A novel non-shunting device designed to create space in the uveal tract, and potentially enhance uveoscleral outflow, was developed to treat primary open-angle glaucoma and primary angle-closure glaucoma, in patients with progressing disease.

This study evaluated if the concept of controlled spacing in the uveal tract by implantation of a uveal spacer device had any impact on intraocular pressure, and whether the device can be safely implanted and tolerated in patients with glaucoma.

What was learned from the study?

Twenty-four months after implantation with the uveal spacer, the mean intraocular pressure was reduced by 39%, and medication burden reduced by 83%, compared to baseline.

Surgical implantation of the novel uveal spacer was shown to be safe, and successful, in reducing intraocular pressure and medication burden. More research is needed to further understand the mechanism of action.

The uveal spacer may be an option for patients with glaucoma who require powerful intraocular pressure reduction with minimal disruption to intraocular structures, sparing time, and tissue for later-stage, invasive filtration surgery.

INTRODUCTION

Glaucoma is the second leading cause of blindness worldwide [1]. It is a generally bilateral, progressive condition which if left untreated can cause significant disability. Treatment for primary open glaucoma consists of first-line topical laser or drop therapy [2], before surgery is necessary to control intraocular pressure (IOP), which is the only proven therapeutically targetable risk factor for glaucoma [3–5]. In recent decades there has been a wave of innovation in minimally invasive ab interno surgical treatments for glaucoma, which aim to target the conventional trabecular outflow system with stenting, stripping, or dilating techniques, in an attempt to overcome trabecular outflow resistance, one of the factors contributing to elevated IOP. These treatments have varied levels of success in reducing IOP and medication burden but are generally considered safe, and are routinely performed with concomitant cataract surgery, in mild to moderate disease [6, 7].

Glaucoma inevitably progresses over time in the majority of patients. The next surgical stage after the effects of minimally invasive surgeries have a diminished effect and glaucoma progression is evident—invasive filtration surgery. Trabeculectomy remains the gold standard of glaucoma filtration surgery, which was first described by Cairns, a technique which is relatively unchanged in the last 60 years [8]. Trabeculectomy involves creating an ab externo scleral flap, to redirect aqueous flow from the

anterior chamber into the subconjunctival space via a filtration bleb, where the aqueous may be ultimately reabsorbed through other plexuses. Innovation in the filtration surgery space with the development of silicone or gelatin stents has reduced surgical complexity, yet all these technologies still rely on the principle of a connection between the anterior chamber and the subconjunctival space [9].

The uveoscleral pathway is known as the unconventional aqueous flow pathway in glaucoma. Uveoscleral flow involves seepage through and around muscle and scleral tissue, and through vessels including choroidal, emissaria, and lymph [10]. Bill and Toris have published extensively on the proposed mechanism of uveoscleral outflow [11, 12]. Unlike trabecular outflow, which is limited by episcleral venous pressure, or subconjunctival outflow, requiring access via a bleb, uveoscleral flow is pressure independent, but the mechanism is still not fully understood [13]. Experiments in animal models using cannulation, silicone sponges, or hydrogels by Toris have demonstrated both IOP reduction and a proposed mechanism of uveoscleral flow [14, 15]. The pressure differential between the supraciliary and suprachoroidal space was greater than that shown between the anterior chamber and the supraciliary space, with this pressure differential described as the driving force for uveoscleral outflow. The uveoscleral outflow pathway has consequently also been a challenging target for glaucoma innovation.

Devices targeting uveoscleral outflow generally involve creation of a cyclodialysis cleft: a direct connection between the anterior chamber and the suprachoroidal space. The creation of a cyclodialysis cleft is not new, and was first described by Heine [16]. Ab interno devices targeting the uveoscleral outflow pathway may achieve greater IOP reductions than trabecular minimally invasive glaucoma surgery (MIGS) in non-comparative studies, but no head-to-head randomized controlled trials exist, and indirect comparisons are confounded by differences in study design, baseline IOP, and patient populations. Adverse events reported with ab interno devices which create a cyclodialysis cleft include spontaneous cleft closure, bleeding, endothelial cell loss, very large IOP spikes, or hypotony maculopathy [17–20].

The basic science, however, and work on uveoscleral outflow by Toris and Bill indicate that a transciliary approach of aqueous flow following augmentation of the supraciliary space itself reduces IOP [14]. There is no disruption of the iris root with this approach. Until recently, there were no supraciliary devices commercially available on the market to substantiate this hypothesis of IOP reduction without a cyclodialysis cleft, nor a filtration bleb, in humans. Various technologies, either currently or previously available in various parts of the world, have been positioned in the supraciliary space, all of which target the uveoscleral outflow pathway. One such device includes an intrascleral ciliary sulcus suprachoroidal microtube technique, using a modified tube extender sutured to the sclera directing aqueous from the posterior ciliary sulcus to the suprachoroidal space, first reported by Laroche [21]. Current commercially available suprachoroidal devices, inserted ab interno and utilizing a cyclodialysis cleft, include the MINIject® (iStar Medical, Wavre, Belgium) and AlloFlo™ Uveo (Iantrek Inc. USA). There remains a significant unmet need to find a safe and suitable way to harness the power of the uveoscleral outflow pathway for patients suffering from glaucoma.

As a novel uveal spacer, INTERCIL® (Ciliatech SAS, Annecy, France) potentially changes this paradigm, representing a new option in the glaucoma treatment pathway. The uveal spacer, a sterile, non-bioabsorbable synthetic polymer device CE marked in August 2025, is designed to be implanted in the supraciliary space (between the ciliary muscle/body and the sclera) for the restoration of aqueous humor outflow and subsequent reduction of IOP as part of treatment for patients suffering from glaucoma. INTERCIL® is an anatomically shaped flat plate, generally trapezoidal in shape (6.0 × 7.0 × 3.4 mm), with a thickness varying from 0.4 mm at the anterior edge to 0.6 mm at the posterior edge. Without entering the anterior chamber, it presents a beveled anterior edge to maximize aqueous humor collection, and a hollowed-out surface on the face exposed to sclera for free circulation. On the opposite side, the face exposed to the

ciliary body is flat to avoid any stress on the ciliary body and contains through-holes to allow aqueous humor to circulate through the device (Fig. 1). This paper reports on the clinical trial performed at S.V. Malayan Ophthalmological Center, to evaluate the safety and efficacy of the INTERCIL® uveal spacer, model SV22 in patients with glaucoma.

METHODS

Study Design and Participants

The SAFARI 3 ("*S*upr*A*ciliary *F*iltration *A*lone *R*educes *I*OP") study was a single-center, single-surgeon prospective single-arm study evaluating safety and performance of INTERCIL® (version SV22) in adult (age 18 or over) patients with primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). The study was conducted in accordance with the Declaration of Helsinki 1964, revised in 2013 and 2024, and all ethical principles, guidelines and procedures required for responsible conduct of clinical investigations. Ethical approval was provided by the Malayan Eye Center Ethical Committee. Written informed consent was obtained for all patients included in the study. The study was performed in accordance with the relevant local government laws of Armenia. The clinical trial was held at Malayan Eye Center, Yerevan. A data and safety monitoring board consisting of five independent physicians in France and Spain was set up to oversee the safety and welfare of participants. The ClinicalTrials.gov identifier is NCT05236439. Informed consent was sought by the authors from all participants using an ethical committee-approved consent form. Patients were evaluated at screening, baseline, and surgery, followed by postoperative assessments on days 1, 7, and 30, and at months 3, 6, 12, 18, 24, and 36. The primary endpoint was assessed at month 24.

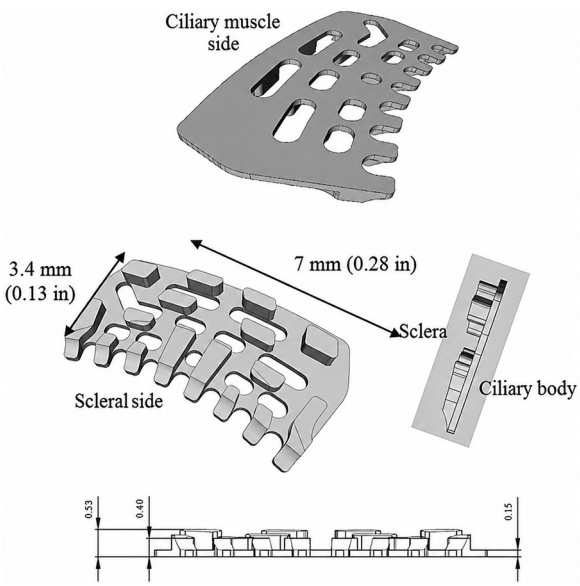


Fig. 1 INTERCIL® uveal spacer

Inclusion criteria permitted patients with a glaucoma diagnosis, primary in nature, with an angle grade of Shaffer grade 1–4. Patients with narrow angles were required to have a patent peripheral iridotomy in place (or in absence of this, an iridotomy was performed no less than 1 week prior to the study implantation), and never have experienced an attack of acute angle closure. As INTERCIL® is implanted ab externo, with no entry into the anterior chamber, there was no additional risk considered to enroll patients with narrow angles. This is a differentiating factor to many other glaucoma devices which have been studied, which generally require expertise in intraoperative gonioscopy, an open angle, and clearly identifiable angle structures for implantation. INTERCIL® implantation does not require this specific expertise.

Glaucoma needed to be mild to moderate in stage, with visual field loss no worse than 15 dB loss on automated static perimetry and a cup/disc ratio no greater than 0.9. Central corneal thickness was required to be in the normal range (480–620 µm). Subjects were eligible if their glaucoma was uncontrolled on one to four ocular hypotensive agents and between 21 and 35 mmHg at screening and baseline, rendering them suitable for surgical intervention with a standalone implant (without concomitant cataract surgery). There was no medication washout performed in the study owing to the necessity for patients to have a further surgical intervention. Phakic and pseudophakic patients were allowed to be enrolled, as long any cataract

surgery that had taken place was uncomplicated, and consisted of cataract surgery alone, without any concurrent surgeries, which are common in some practices, such as minimally invasive glaucoma procedures including stenting or canaloplasty. All other glaucoma laser and glaucoma surgical procedures (including standalone MIGS or filtration surgery) were excluded. Extremely long or short eyes, eyes with prior retinal laser or surgery, or other surgery within the previous 6 months prior to enrollment, eyes with abnormal angle anatomy, clinically significant dry eye, or visually significant cataract, or any other ocular or systemic condition or prescribed medication, which may confound outcomes, rendered subjects ineligible. Secondary glaucomas were not permitted with the exception of pseudoexfoliative and pigmentary glaucoma.

An initial screening visit, informed consent was obtained and IOP was measured, followed by a comprehensive baseline examination. A flowchart of subject accountability is shown in Fig. 2. At baseline and most follow-up visits, assessments included best corrected visual acuity (BCVA), slit lamp biomicroscopy, endothelial cell density, pachymetry, perimetry, gonioscopy, fundoscopic examination, patient quality of life (EQ-5D and VAS pain score), and adverse events. A surgeon ease-of-use questionnaire was collected following surgery. IOP was measured by Goldmann applanation on a calibrated tonometer, using an observer-masked method (one person turning the dial, another evaluating the mires). A single measurement was performed at

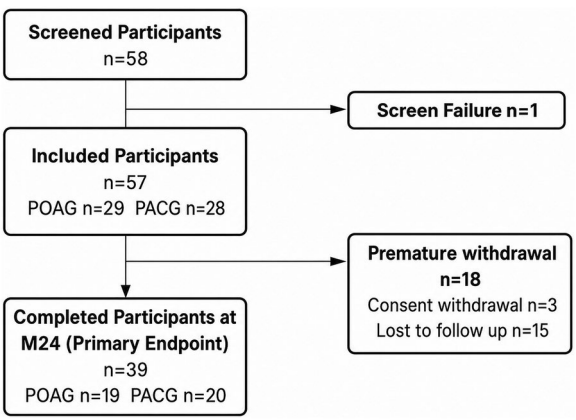


Fig. 2 Enrollment flowchart

screening, surgery, days 7 and 30, and months 3 and 18. Diurnal measurement was performed at baseline and months 6, 12, 24, and 36.

Surgical Technique

INTERCIL is implanted ab externo for permanent placement in the supraciliary space, in a standalone setting. The implant creates a localized gap between the ciliary muscle and the sclera. The study involved one operating investigator previously experienced in implantation with INTERCIL® from early proof-of-concept trials with prior device designs, ran at the same center. Topical and/or local subtenon anesthetics were used in all patients, and in all cases the implantations were performed in the superior quadrant at either the 10 or 2 o'clock meridians.

The surgical procedure involved performing two conjunctival incisions, separated by 8 mm, 2 mm posterior to the limbus, following which two full-thickness scleral incisions were performed, one incision being 3.0 mm long, the second 1.5 mm with the visual marker being the change in color from the white of the sclera to the brown color of outer edge of the ciliary body. Care was taken to avoid incising conjunctival or intrascleral vessels. Any bleeding from vessels was managed by light cautery. Cohesive viscoelastic (Healon) was injected between the sclera and the ciliary body on each side to gently separate the ciliary body from the sclera and then to create a pocket for INTERCIL® implantation. A paracentesis was performed to lower IOP as required following a digital palpation check, prior to INTERCIL® implantation. The device was removed from the package and placed on the surface next to the long incision. A pair of non-toothed vitreoretinal forceps was inserted through the opposing incision, passed through the subscleral pocket, and used to grasp INTERCIL®, which was then maneuvered into the pocket. The forceps and the OVD were gently removed. Scleral incisions were sutured watertight with two or three 10-0 Nylon sutures with a buried knot to avoid any subconjunctival filtration or bleb formation. Conjunctival incisions were sutured watertight, with two or three 10-0 Vicryl sutures. All preoperative

IOP-lowering treatments were discontinued on the day of surgery. Postoperative treatment consisted of standard regimen of topical antibiotics and non-steroidal anti-inflammatory agents for up to 15 days postoperatively. Postoperative reintroduction of ocular hypotensive agents was prohibited, unless the principal investigator deemed medication reintroduction necessary for patient safety reasons.

Primary Effectiveness Criteria and Statistical Analysis

The sample size of 57 patients was calculated for the primary endpoint of mean change in medicated IOP across the whole cohort at month 24 set with 80% power, an alpha of 0.05, and a loss to follow-up rate of up to 30%, based on loss to follow-up rates in prior pilot studies at the same center. Descriptive statistical analyses were planned with all endpoints in the full analysis set, which included all patients implanted with the device during the study. Recruitment started in May 2022 and completed within 7 months, with the last patient surgery taking place in December 2022. Success was determined at 24 months postoperative. Complete success was determined as a medication-free subject with an IOP of 18 mmHg or less and a greater than or equal to 20% reduction in IOP from baseline. Qualified success used the same IOP criteria, but included subjects who were not medication-free. Failure criteria were not determined in the protocol.

Secondary Effectiveness and Safety Outcomes

Postoperative outcomes for IOP and clinical examinations evaluated performance, safety, and quality of life. IOP control was further assessed by determining the proportion of patients achieving ≥ 20%, ≥ 30%, ≥ 40%, and > 50% reductions from baseline at long -term postoperative timepoints, as well as the proportion of eyes achieving IOP between 6 and 18 mmHg and between 6 and 16 mmHg at the same timepoints.

Procedural characteristics, including operative time and ease of each implantation, were assessed using an ordinal three- or four-point categorical scale (e.g., “very difficult”, “difficult”, “easy”, “very easy”) to evaluate surgical feasibility and the learning curve. Patient-reported outcomes were captured through assessments of postoperative pain and discomfort using VAS scales, and quality of life, using the EQ-5D instrument. Safety outcomes included a descriptive change from baseline analysis for BCVA, slit lamp examination findings, corneal pachymetry, endothelial cell density (CellChek, Konan Medical USA, Irvine, California) fundoscopy, UBM assessment of device positioning (ABSolu, formerly Quantel Medical, now Lumibird Medical, Lannion, France), and visual field mean deviation using the Humphrey Visual Field Analyzer (Carl Zeiss Meditech AG, Jena, Germany) or the Octopus Visual Field Analyzer (Haag-Streit AG, Koeniz, Switzerland). As the device, by design, does not require a subconjunctival filtration bleb, the number of postoperative interventions which may indicate the existence of these was collected by forced choice questions, and quantified. Outcomes assessing secondary interventions for glaucoma control included the incidence of selective laser trabeculoplasty, gonipuncture, or bleb needling (if inadvertent bleb was present), along with the proportion of eyes with evidence of subconjunctival filtration, or the presence of inadvertent bleb.

RESULTS

Baseline Characteristics

Fifty-seven patients with glaucoma were enrolled and underwent implantation of the device in this study. As the device is, by design, intended to avoid anterior chamber entry and the iridocorneal angle, this study protocol permitted inclusion of patients with Shaffer grade 1–4, in order to evaluate potential safety and performance across angle subtypes. Outcomes of the Shaffer grade 3–4 group (hereafter labeled the “POAG” group) and Shaffer grade 1–2 group (hereafter labeled the “PACG”

group) were similar. The cohort of 29 patients with POAG only are reported in this paper. The global incidence of POAG far exceeds that of PACG, where POAG comprises 75% of all glaucoma cases [22], common in the Western world with most glaucoma innovation taking place to treat POAG. Reporting on the POAG group in this paper enables a direct comparison to outcomes for POAG using other techniques and clinical trials in the surgical landscape, and to enable generalization to other patient populations with POAG. Many of the products used today for PACG are not indicated for this condition or have little evidence of effectiveness. This does not minimize the importance or incidence of PACG, which is prominent in Asia, which has a reported 87% of the global cases of ACG [23].

The study was powered for all 57 patients, who were enrolled with an equal mix of POAG and PACG, so evaluation of patients with POAG as a subgroup alone may be underpowered, impacting the ability to draw meaningful conclusions about device performance. POAG and PACG, however, have different disease spectrums, with alternative treatment pathways.

All available data for the 29 patients with POAG were included in the final analysis set for all outcomes, with no imputation for missing data, per the prespecified statistical analysis plan. Pseudoexfoliation and pigment dispersion phenomenon were permitted in the inclusion criteria, but there were no patients enrolled with either condition. Ethnicity was not collected during the study. However, 100% of the patients in the trial were those living in Yerevan and surrounding towns. The population of Armenia is reported as homogenous with ethnic makeup estimated from official records as 98.1% population Armenian, Yezidi 1.1%, Other 0.8% (2022 est.) [24]. Female patients were predominant, representing 62% of the patients with POAG (Table 1). Eighteen of the 29 patients with POAG were phakic when entering the study, of which five had early cataract, not deemed at screening to be visually significant. The mean age of patients in the study was 65.9 years. Mean IOP at baseline was 23.4 ± 1.9 mmHg and medication burden was 1.9 ± 0.9 (Table 1).

Primary Effectiveness: Mean IOP and Medication Reduction

The primary endpoints of IOP and medication burden both showed a substantial reduction. Mean IOP reduced from 23.4 ± 1.9 mmHg at baseline ($n = 29$) to 14.4 ± 3.1 mmHg at 24 months postoperative ($n = 19$), demonstrating a 39% reduction (Fig. 3). IOP reduction was stable and consistent through the 24-month period. Mean medication burden was reduced from 1.9 ± 0.9 medications at baseline ($n = 29$) to 0.4 ± 0.8 medications at 24 months postoperative ($n = 19$), demonstrating an 83% reduction, with 73.7% of patients medication-free at 24 months (Fig. 3). Five of 19 patients (26.3%) were not medication-free at month 24. The maximum number of medications prescribed at month 24 was two.

The proportion of patients that completed the 24-month endpoint were included in the success criteria evaluation ($n = 19$). The pairwise mean IOP and medication burden at baseline (pairwise used for the success criteria evaluation) was 23.3 ± 1.1 mmHg on 1.9 ± 1.0 medications, reducing to 14.4 ± 3.1 mmHg on 0.4 ± 0.8 medications at month 24, representing a 38.1% IOP reduction, and a 78.9% medication reduction, from baseline. The proportion meeting the absolute success criteria (measured by the proportion of patients medication-free at 24 months postoperative, with an IOP of 18 mmHg or less and a 20% IOP reduction from baseline) was 74%. Ninety-five percent of the cohort met the qualified success criteria (Fig. 4).

Proportion of Patients Achieving Prespecified IOP Outcomes

The proportion of patients achieving IOP ≥ 20%, ≥ 30%, ≥ 40%, and > 50% reductions from baseline at postoperative month 6, 12 and 24 are shown in Fig. 5. By postoperative months 12 and 24, 100% of patients in the study achieved at least a 20% reduction in IOP. As only five patients in the dataset required reintroduction of ocular hypotensive medication by postoperative month 24, and the implantation of INTERCIL®

Table 1 Baseline characteristics of the POAG (primary open-angle glaucoma) group in SAFARI 3

	N (%)	Mean ± SD	Median	Range
Age at screening (years)	29	65.9 ± 10.7	65.2	36.6–84.8
IOP (mmHg)	29	23.4 ± 1.9	23.2	21.5–31.2
Number of medications	29	1.9 ± 0.9	2	1–4
BCVA (decimal)	28	0.8 ± 0.3	0.9	0.2–1.0
VF mean deviation (dB)	24	− 7.4 ± 4.6	− 7.8	− 14.2 to − 0.8
Corneal pachymetry (μm)	29	541.4 ± 34.2	541.0	475.0–630.0
Endothelial cell count	29	2214.9 ± 423.4	2240	1097–2818
Cup/disc ratio	29	0.7 ± 0.1	0.7	0.5–0.9
Study eye				
Left	13 (44.8)			
Right	16 (55.2)			
Total	29 (100.0)			
Sex				
Female	18 (62.1)			
Male	11 (37.9)			
Total	29 (100.0)			
Lens status				
Phakic	18 (62.1)			
Pseudophakic	11 (37.9)			
Total	29 (100.0)			
Cataract status (phakic eyes)				
Initial	5 (27.8)			
None	13 (72.2)			
Total	18 (100.0)			

was performed as a standalone implantation, the results show consistent and durable IOP lowering, generally beyond 30% through postoperative month 24. The proportions of patients with eyes achieving IOP between 6 and 18 mmHg at postoperative months 6, 12, and 24 were 93.1%, 90.9%, and 94.7%, respectively. The proportions of patients with eyes achieving IOP between 6 and 16 mmHg at postoperative months 6, 12, and 24 were 70.4%, 70.0%, and 68.4%, respectively.

Ease of Implantation, Postoperative Management, and Patient Quality of Life

A single surgeon performed all surgeries in the study, under topical anesthetic (topical and/

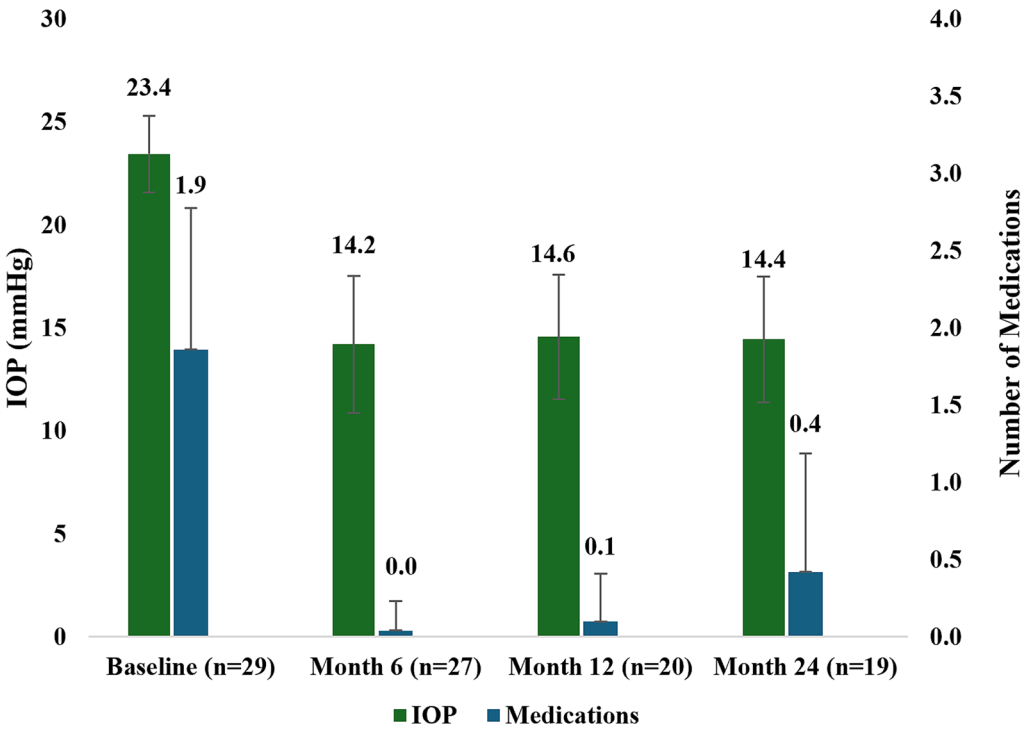


Fig. 3 Mean (± standard deviation) intraocular pressure and medication through month 24 in SAFARI 3

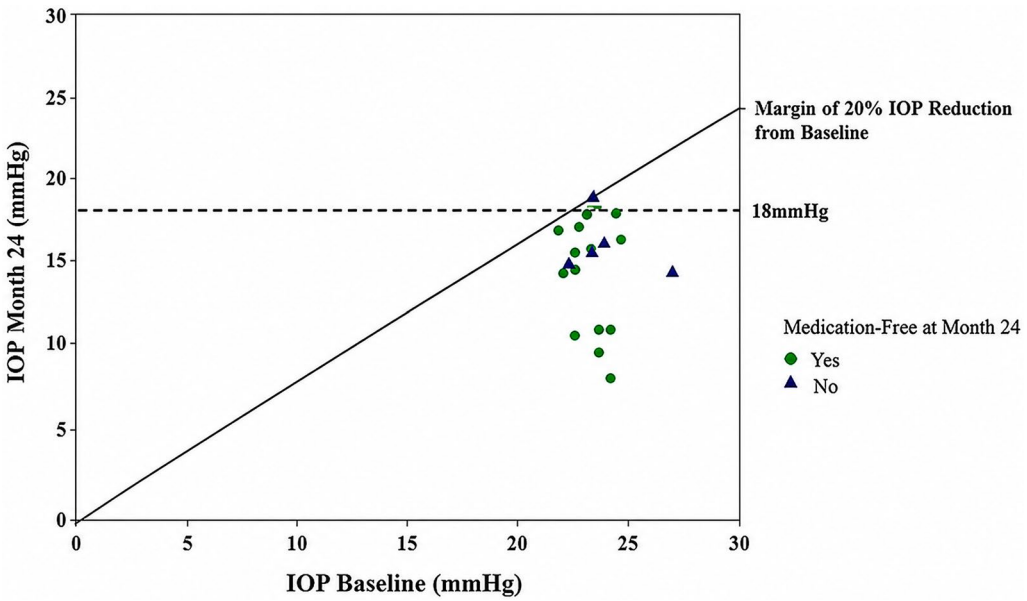
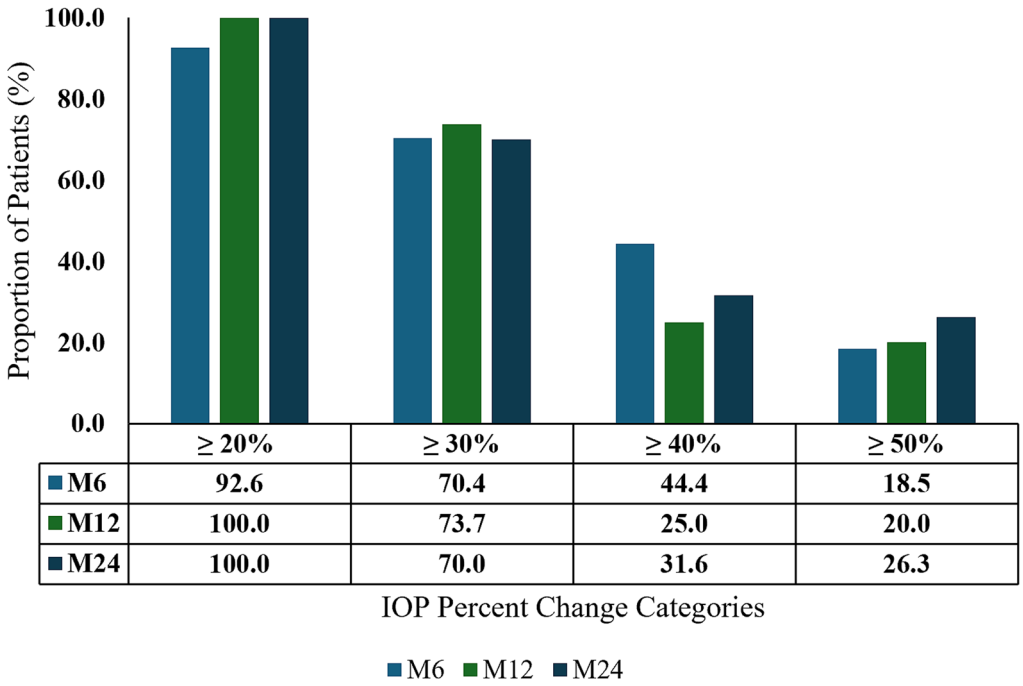


Fig. 4 Scatterplot showing complete and qualified success in SAFARI 3



	≥ 20%	≥ 30%	≥ 40%	≥ 50%
M6	92.6	70.4	44.4	18.5
M12	100.0	73.7	25.0	20.0
M24	100.0	70.0	31.6	26.3

Fig. 5 Secondary effectiveness analyses: proportion of eyes with mean diurnal intraocular pressure reduction ≥50%, ≥ 40%, ≥ 30%, and ≥ 20% at postoperative month 6, 12, and 24

or local sub-Tenon), rating each one using prespecified usability metric on an ordinal categorial scale. Surgeon experience is reported for the entire cohort, which did not change between the POAG or the PACG groups The surgeon rated handling and positioning of the device similarly for the entire cohort, rating it "good" in 59.6% of cases ($n=34$ of 57 cases) and "very good" in 40.4% of cases ($n=23$ of 57 cases). There were no difficulties encountered during product use and no intraoperative complications recorded during the time of surgery. The postoperative management burden did not require any surgical reinterventions during the early postoperative period out to the first 30 days following surgery. Surgeon satisfaction level was very high, with 70.2% ($n=40$ of 57 cases) of cases meeting the "very satisfied" outcome measure, and the remaining 29.8% ($n=17$ of 57 cases) of cases meeting the "satisfied" measure. Patient comfort scores compared to before surgery increased by almost 10% throughout the postoperative time period on a VAS scale, from 80.7 ± 9.9 at day 7 postoperative to 89.4 ± 11.4 at month 24, which may correlate with the limited postoperative treatment burden, and resultant ocular relief from a reduction in topical drop therapy. Global patient satisfaction following device implantation, assessed using a VAS scale, showed a small increase from 84.9 ± 7.8 at postoperative day 7 to 89.2 ± 14.2 at postoperative month 24. There were no reductions in any of the quality-of-life indices seen on the EQ-5D instrument between baseline and postoperative month 24.

Safety Outcomes and the Adverse Event Profile

Safety in the POAG group was highly favorable during the study with no unanticipated adverse device effects reported. There were no clinically meaningful numerical changes from baseline in the prespecified safety outcome parameters (Table 2). Slit lamp examinations revealed a quiet postoperative course, with no anterior chamber flare using the SUN working group grading system [25] identified in 100% of patients at all postoperative timepoints. Slit lamp examinations of the conjunctiva and

Table 2 Safety outcomes from baseline through month 24 in the study population

	Baseline Mean ± SD		Month 24 Mean ± SD		Mean pairwise change from baseline though month 24 [95% CI]
BCVA (decimal)	0.8 ± 0.3	*n* = 28	0.7 ± 0.3	*n* = 19	0.10 [− 0.06, 0.28]
VF mean deviation (dB)	− 7.4 ± 4.6	*n* = 24	− 9.4 ± 7.1	*n* = 19	1.83 [− 1.38, 5.03]
Corneal pachymetry (μm)	541.4 ± 34.2	*n* = 29	539.2 ± 45.8	*n* = 19	8.66 [− 4.23, 21.56]
Endothelial cell count	2214.9 ± 423.4	*n* = 29	2260.56 ± 552.62	*n* = 18	48.9 [− 127.9, 225.8]
Cup/disc ratio	0.73 ± 0.1	*n* = 29	0.77 ± 0.09	*n* = 19	− 0.02 [− 0.04, − 0.00]

cornea showed no evidence of subconjunctival filtration or evidence of filtration bleb, nor any corneal findings of epithelial or stromal edema. Progression of cataract was noted over time seen by a change in lens grading, mostly by the postoperative month 12 timepoint, but there was no overall change in mean BCVA in the study cohort. There were no changes to the lens status of any pseudophakic patients (no tilt, decentration, or opacification). Any visual field progression, corneal pachymetry, endothelial cell density, and cup/disc ratio change from baseline to postoperative month 24 were all within normal physiological limits. There were no new fundoscopic findings nor progression of any pre-existing retinal conditions. UBM examination, performed at each postoperative timepoint, showed overall positional stability of the device with no early postoperative subclinical inflammation, nor any long-term fibrosis around the implant. One patient required a secondary glaucoma procedure during the 24-month postoperative period, which was a device repositioning (following penetration to the anterior chamber during the initial surgery, not due to any postoperative migration). There were no reports of any patient losing light perception, or experiencing sustained hypotony. The protocol did not prespecify failure criteria, but these three criteria (secondary procedures, loss of light perception, and sustained hypotony) are normally considered grounds for treatment failure in international guidelines [26]. As there was one patient who underwent a glaucoma procedure, and no incidence of the other two criteria, the margin of failure may be considered as very low in this study.

There were no non-ocular adverse events reported in the POAG group. In the study eye, the median time to adverse event onset (*n* = 15 adverse events, 7 event terms, affecting 9 patients) was 6.7 months postoperative. The most common adverse event reported through the 24-month follow-up was cataract, which occurred and was operated on in six patients by postoperative month 24. The study protocol allowed subjects who were indicated for cataract surgery after device implantation; five of the six patients had cataract surgery between postoperative month 12 and month 24. Two of the six patients had pre-existing cataract at baseline; the causality for three patients was deemed age-related and not related to the study procedure or device, with causality assessments fully examined independently by the data and safety monitoring board (DSMB). Dilated lens assessments were not performed at every postoperative visit per the protocol, and a standardized lens grading system was not used in this study. Interobserver variability may account for changes in lens status and the lack of standard reference may be a contributing factor to the increased reporting of cataract progression, coupled with the socioeconomic factors described. A single incidence of cataract was likely due to a concurrent adverse event of anterior chamber penetration and steroid usage. There were no device-related adverse events reported, and the causative factors for cataract described are reasonable and plausible, notwithstanding that there is a risk of cataract

Table 3 Adverse events and surgical reinterventions in the study eye reported through month 24 postoperative

	N events	Incidence in study population (*n* eyes in study = 29)
Adverse events		
Cataract[a]	6	20.7%
Low IOP (numerical hypotony)	4	13.8%
Eye dryness	1	3.4%
Eye redness	1	3.4%
BCVA decrease with transient choroidal detachment	1	3.4%
Penetration of device into AC	1	3.4%
Total	15	
AE onset timing		
Early (≤ 1 month postoperative)	0	0.0%
Mid (> 1 month < 3 months postoperative)	4	13.8%
Late (≥ 3 months postoperative)	11	37.9%
Total	15	
AE severity		
Mild	2	6.9%
Moderate	13	44.8%
Severe	0	0.0%
Total	15	
Surgical reinterventions for glaucoma		
Device repositioning	1	3.4%
Total	1	3.4%

[a]Six patients underwent cataract surgery prior to month 24. Two of the six patient had pre-existing cataract

development after any glaucoma surgery, which is not fully understood [27]. However, any causal relationship with the device or procedure cannot be completely ruled out, however miniscule the risk. All adverse events were classified as mild or moderate (Table 3). There were no early adverse events reported (early defined as the first 30 days following surgery).

The surgical procedure took on average 15 min to complete and was mostly complication-free. One patient had an inadvertent iatrogenic penetration of the device into the anterior chamber, which was only identified postoperatively during UBM imaging and not identified during the surgery. The penetration into the anterior chamber was in an oblique direction, with a small part of the device penetrating into the AC. The same patient also recorded adverse events in the study eye of cataract, reduction of BCVA, and a choroidal detachment in the 3 months following surgery, which resolved without sequelae. The transient choroidal detachment developed at 3 months postoperative in the setting of borderline

hypotony (IOP 6 mmHg) accompanied by myopic shift (2.00 D from baseline). The choroidal detachment resolved by 6 months with medical management, following the typical course for post-glaucoma surgery choroidal effusions [28–31]. These findings are consistent with ciliochoroidal effusion causing anterior displacement of the lens–iris diaphragm [32]. The myopic shift magnitude of − 2.00 D falls within the range typically associated with ciliochoroidal pathology after glaucoma surgery [33]. Choroidal detachment occurs in approximately 18–35% of patients after glaucoma drainage device surgery and is typically associated with hypotony [30–32]. The development of cataract was considered related to the treatment with steroids for the concurrent adverse events. The patient underwent successful, uncomplicated cataract surgery and device repositioning 1 year later, which involved reopening of one of the scleral incisions and the implant moved posteriorly into the originally desired position, with a spatula. The device was not sutured in place. The patient also recorded an adverse event of cataract in the fellow eye. The patient had no further sequelae following the device repositioning and cataract surgery, the IOP remained controlled, and there were no additional adverse events noted to the study eye. The patient achieved excellent long-term IOP reduction, despite the initial complication, with unmedicated mean diurnal IOP ranging from 6 to 8.5 mmHg throughout follow-up, representing a 67–75% reduction from baseline. BCDVA returned to baseline (20/20) by 6 months and remained stable through 24 months.

This serious adverse event of penetration into the anterior chamber and its associated adverse events were directly attributed to the learning curve effect in this single case. The surgical technique used in this case included the anterior push towards the iris root. This anterior push is no longer used in clinical trials nor is it on the current device label bearing the CE mark, for commercial use, which represents a minor change to the procedure. There were no other changes to the procedure, nor to the device design, following initial CE marking. No other injuries to intraocular structures during implantation were reported in the study. No other anterior chamber penetrations were reported during the study.

There were four cases of numerical hypotony (IOP < 6 mmHg with no associated complications) which occurred in the first 3 months (mean time of onset 2.8 ± 0.4 months) which resolved without sequalae and did not meet the definition of clinical hypotony (IOP < 6 mmHg associated with choroidal detachment and/or with hypotony maculopathy and/or with AC depth reduction; or IOP < 6 mmHg for which surgery to reverse hypotony-related complications was performed). Patients were treated with short-course topical steroids and cycloplegics as required to treat hypotony. No postoperative IOP spikes (elevated IOP ≥ 10 mmHg above baseline) were reported in the implanted eyes.

DISCUSSION

The INTERCIL® uveal spacer is a device which demonstrates sustained IOP and medication burden reduction following implantation in the supraciliary space, with no entry into the anterior chamber nor reliance on subconjunctival filtration via a bleb. There has been limited clinical experience with deliberate separation of the ciliary body from the sclera, without deliberate creation of a cyclodialysis cleft. Most investigations related to ciliary body separation are confined to theoretical or experimental laboratory settings or animal models, notably by Brubaker et al. in 1979 [34]. Early clinical exploration was reported by Alper [35], who performed ab externo ciliary body detachment as a treatment for glaucoma, with partial initial success; however, in Alper's small series, the IOP-lowering effect was not sustained, and patients required resumption of medical therapy within 6 months. While ciliochoroidal detachment, often associated with hypotony, has been described in clinical practice, such cases are typically secondary in nature, most commonly arising owing to trauma, complications of intraocular surgery, or in the context of systemic disease—rather than the result of controlled, intentional separation [36–38].

The controlled separation and carefully constructed surgical technique used for INTERCIL® in the SAFARI 3 study, along with a device design and material specifically intended to conform to the geometry of the globe, may represent a new, safe iteration of this concept, indicated by the durable, long-term, medication-free IOP reduction seen through 6, 12, and 24 months. There were cases of numerical hypotony seen in the present study, but cases were not chronic, nor were any cases of hypotony maculopathy identified. The mechanism of increasing outflow remains to be understood from either experimental or clinical work, but this study provides evidence that uveoscleral outflow may be increased in humans, with the resulting reduction in IOP, adequate to control glaucomatous progression in this patient population. The proposed mechanism of IOP reduction based on the theory of creation of space to increase the pressure gradient in the supraciliary space, resulting in enhanced uveoscleral outflow, was demonstrated in this study. An area of hypoechogenicity was seen in the supraciliary-suprachoroidal space surrounding or posterior to the implant on UBM imaging in this study (Fig. 6), which may provide evidence to further support the theory. The actual mechanism by which uveoscleral outflow may increase postoperatively could be due to this theoretical pressure differential, but other factors may be responsible, which are known to decrease IOP such as leak from the anterior or posterior chamber, partial ciliary body shutdown, aqueous suppression, molecular or chemical changes in aqueous humor, or choroidal expansion [11, 39, 40].

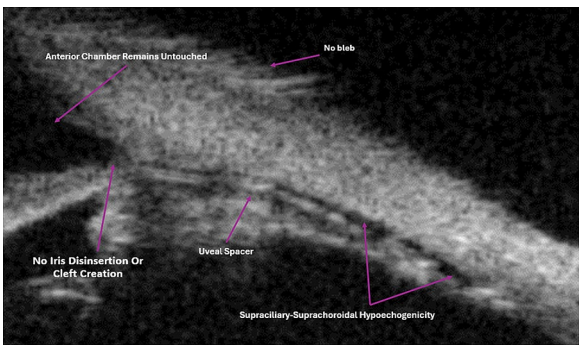


Fig. 6 Ultrasound biomicroscopic image of an implanted uveal spacer surrounding by area of hypoechogenicity

Uveoscleral outflow represents a significant component of aqueous humor drainage under physiological conditions, accounting for approximately 3–60% of total outflow [12]. Procedures which provide a direct access route for aqueous from the anterior chamber to the supraciliary space are known to be effective, but the potential for a device to facilitate the same effect, without direct shunting via a conduit (physical lumen or physiological disruption of the anatomy) was the rationale for INTERCIL®, explored in this study over a 24-month period, and successfully demonstrated. Devices evaluating the effectiveness of devices utilizing the uveoscleral outflow pathway via a cyclodialysis cleft have demonstrated potent IOP lowering, either in the context of cataract surgery or as a standalone procedure. A decade ago, the COMPASS study by Vold et al. reported a randomized controlled clinical trial enrolling 505 patients, evaluating the CyPass Microstent (Alcon Inc.) (combined with phacoemulsification or using phacoemulsification alone) in POAG, and which achieved approximately 7.4 mmHg mean IOP reduction (vs. 5.4 mmHg for phaco alone) at 24 months [17]. Despite commercial success, the product was withdrawn because of concerns of endothelial cell loss. Endothelial cell density for INTERCIL® was reported as stable throughout the postoperative period to 24 months (Table 2), which is a differentiating factor, based on the device design of avoiding entering the anterior chamber. Calvo more recently reported on a newly emerged, commercially available (in some regions only), bio-interventional, cleft-based procedure (AlloFlo Uveo, Iantrek Inc.) which uses scleral allografts to reinforce a deliberate cyclodialysis cleft, with the objective of enhancing uveoscleral outflow [41]. A real-world case series of 31 patients at 2 years showed a 34% reduction in IOP. All procedures reported were done in combination with cataract surgery and were not done in the context of a study, so a direct comparison to INTERCIL® is not appropriate. Dick et al. reported a recent meta-analysis of trials using a similar device implanted in the supraciliary space after creation of a cyclodialysis (MINIJect®. iStar Medical, Wavre, Belgium)

[42]. The analysis reported a similar IOP reduction (39.3% at 2 years) but the medication-free rate was much lower at 37.9% compared to 73.7% with INTERCIL. A comparison of the data in the study should be treated with caution because the surgical technique, like other supraciliary devices available globally, requires an ab interno cyclodialysis to insert the device; the meta-analysis combined data from three different trials, performed with slightly different delivery systems, and with different statistical analysis methods. The medication-free rates differ between MINIJect® and INTERCIL, but the trials had different mean baseline medication burden (2.4 medications compared to 1.9 medications with the INTERCIL® trial). The data from the MINIJect and AlloFlo studies, despite not being directly comparable to Intercil, provide a valuable insight into the interest and continued potential of the supraciliary space to reduce IOP.

INTERCIL® demonstrated in the current study a greater IOP reduction than seen in a bio-interventional study, which may support the theory of enhancing uveoscleral outflow without requiring a cyclodialysis cleft creation. Laroche reported 1-year results in a cohort of 36 patients using a different approach to access the supraciliary space, via a ciliary sulcus suprachoroidal silicon microtube technique [21]. The study population included patients with refractory glaucoma with a high baseline medication burden (mean 4.2 medications), much higher than the mean 1.9 medications seen in the study with INTERCIL® and different glaucoma diagnoses. The results demonstrated a 37% IOP reduction at 12 months with no sight-threatening complications, although further incisional glaucoma surgery was required in some cases. The IOP-lowering ability of the ciliary sulcus microtube was very similar to that reported in the present study with INTERCIL®, which provides encouragement when considering the supraciliary-suprachoroidal pathway in glaucoma and highlighting that INTERCIL® is differentiated from all others by not employing a physical conduit in the form or a tube or cleft to reduce IOP.

Alternative procedures to treat mild to moderate glaucoma targeting the trabecular outflow pathway—which have become a generally considered safe mainstay of glaucoma surgical innovation in recent years—remain inherently limited by episcleral venous pressure [13]. By comparison, the uveoscleral outflow is independent of episcleral venous pressure, providing an alternative route for aqueous drainage. Surgical strategies that exploit the uveoscleral pathway therefore have the potential to achieve greater IOP reduction, commonly in the range of ≥ 40%, by bypassing the physiological constraints of the conventional trabecular system. Minimally invasive bleb-forming devices (MIBS), which may be categorized into the broader category of glaucoma filtration surgery, utilize subconjunctival drainage and afford powerful IOP control in the region of 35–50% reduction, in patients with moderate to severe disease, who may be at risk of faster progression of disease [20, 43]. However, the risk–benefit ratio of ab externo filtration procedures requires scrutiny, as the burdens of frequent postoperative management in the early phase and a high reported incidence of early postoperative failure, or safety concerns, such as inflammation, infection, IOP spikes (the cause of which is multifactorial but include blockage of filtration device lumen, retained viscoelastic, or steroid responses) or hypotony, should not be underestimated [44]. The ability for the INTERCIL® uveal spacer to provide consistent efficacy closer to these cleft-based or filtration procedures, but with a conceivably advantageous safety profile, may support an unmet need in the marketplace for a device to provide potent, durable efficacy utilizing the supraciliary space, supported by data in this study and a credible hypothesized mechanism of pressure gradient modulation. The INTERCIL® uveal spacer does utilize conjunctival dissection and a full-thickness scleral flap but does not require a filtration bleb. Conjunctival dissection and manipulation is minimal however, with no peritomy or cytotoxic agents utilized as with traditional filtration surgeries. The use of cytotoxic agents during filtration surgery, while providing meaningful anti-scarring support to enable a successful aqueous flow channel, has its own side effects, including conjunctival thinning. This thin conjunctiva can preclude further surgery or raise the risk of failure in the same region. Conjunctiva closure and wound health after INTERCIL® seen in the

clinical trial was stable, with no inadvertent bleb, scarring, or conjunctiva-related adverse events during the reported study period. Therefore, despite the ab externo approach, the risks identified in other surgeries using the same region or similar conjunctival and scleral dissection requiring cytotoxic agents may be reduced, preserving tissue integrity. The device may be used as a middle step between truly conjunctival-sparing, ab interno MIGS, and as such it is not directly comparable.

Limitations

The gold standard in clinical trials methodologies of new technologies for glaucoma is a randomized, controlled design. This is a limitation of the present study, as it was uncontrolled and non-randomized. However, the novel design of the device and its fit in the surgical landscape does not easily render it suitable for any particular control arm in a randomized setting. The surgical technique with full-thickness scleral incisions is unique, and the majority of other devices are not comparable because of known differences in mechanism (trabecular or cleft-based uveoscleral outflow, or subconjunctival drainage) or material (no other device is made of hydrophilic acrylic material positioned in the supraciliary space). A full-thickness scleral incision includes a potential risk of bleeding from scleral vessels or choroidal structure, or very low IOP if the scleral incisions are incorrectly placed, connecting to the anterior or posterior chamber. None of these complications were seen in the study and therefore this limitation, when the surgical training is performed correctly, is unlikely. The closest comparator may be ab externo deep sclerectomy, but this procedure is not widely performed, and like other filtration procedures, involves only partial thickness scleral incisions. This study inclusion criteria required patients who were medically uncontrolled and were suitable candidates for surgery, so randomization against pharmacological agents acting on the uveoscleral pathway, without requirement for a cleft, such as prostaglandins, was also not an appropriate design. This study was performed a single center with all 57 surgeries performed by a single surgeon, which provides value to inform the surgical training curve, and future developments, but itself may be a limitation when generalizing findings to the wider population and the performance of the device in other surgeons' hands. The risk of migration of the device could be considered a limitation, but the risk of this occurring is very low. The supraciliary space is a potential space. No migration was identified on UBM imaging in this study. Prior studies performed at the same center included suturing the implant to sclera, and as part of the development of the surgical technique, this study protocol reported in this paper removed the requirement to suture the device to sclera.

Another limitation to this study is that the primary endpoint of diurnal IOP was compared to a medicated baseline. Clinical trials of new glaucoma surgical technologies indicated for mild to moderate glaucoma have historically included a prespecified rule to stop all ocular hypotensive medications prior to surgery (a "washout"), in order to adequately identify a baseline value, and conclude the effect of device performance alone, without confounding of residual effects of medications [45]. Washout was not suitable in this study because patients were only eligible as a result of their disease state being uncontrolled on pharmacologic agents, so stopping these for up to 6 weeks prior to surgery could have introduced an unacceptable safety risk of progression. A lack of washout may have a perceived advantage of more closely representing the likely real-world clinical utilization of a device.

Additional limitations include the loss to follow-up rate of 34.5%. The proposed overall sample size was calculated with a 30% anticipated loss to follow-up rate, so this rate was slightly increased. The explanation for this was ongoing political instability in the study country, including an active war zone with the neighboring country, compounded by post-pandemic socioeconomic hardships and unreliable communication technology infrastructure in this low-income country. Three patients withdrew consent by the postoperative month 24 visit, with 18 further patients lost to follow-up, likely due to the aforementioned

factors. Each patient had a minimum of three documented contact attempts before being considered lost to follow-up. Contact methods included mobile phone, email, and, where available, postal mail. The socioeconomic issues may also have contributed to the higher-than-average cataract surgery incidence in this study, in comparison to other global regions, or indeed other clinical trials. Armenia has limited access to healthcare or advanced technologies, beyond participation in clinical trials, and a high smoking rate [46, 47]. Both these factors may have contributed to increase rates of cataract surgery. The incidence of cataract was not deemed directly related to the study procedure or device in all but one case (with known etiology explained previously in this paper), although it cannot be ruled out, especially with patients who experienced numerical hypotony and were treated with steroids, which are cataractogenic.

Cataract surgery alone is known to reduce IOP [48, 49], and combined procedures with minimally invasive, ab interno interventions targeting the trabecular or uveoscleral outflow pathways provide a modest additional IOP-lowering effect. One study by Fea et al. reported the additive IOP-lowering effect to be as little as a 1.7-mmHg reduction from baseline at 12 months postoperative, in a study comparing a cataract surgery alone with implantation of a trabecular microbypass stent combined with cataract surgery, with not statistically significant differences between the two groups [50]. In the present study, the cohort comprised both phakic ($n=18$) and pseudophakic ($n=11$) patients at baseline; six phakic patients subsequently underwent cataract surgery during follow-up, leaving 12 patients who remained phakic at month 24. Notably, the INTERCIL® uveal spacer evaluated in this study demonstrated a robust IOP-lowering effect from day 1 following standalone implantation, which was sustained through month 24. This effect was observed even among patients who remained phakic at month 24, thereby potentially minimizing any confounding influence of this limitation of cataract surgery performed at 12 or 24 months post-implantation, although caution is warranted in inference from the relatively small sample.

Future studies in experimental or clinical settings could aim to further elucidate the underlying physiology through quantitative outflow measurements, to validate the hypothesis of the proposed mechanism of INTERCIL, and to study the performance of the device in a larger population in countries where the device is already available commercially, as limitations of clinical trial designs always include sample size considerations, and risk of bias such as randomization. This study was sufficiently powered to evaluate performance in the entire study cohort (consisting of patients with POAG and PACG), and there are signals that the technique is safe and effective; however, this paper reports the POAG subset, and the slightly higher loss to follow-up ratio than expected means any conclusions that might be made may be underpowered and treated as early indicators of performance, with larger, adequately powered clinical trials required to appropriately draw any conclusions of excellence in performance.

CONCLUSION

The development of the INTERCIL® uveal spacer to enhance and restore uveoscleral outflow in patients with open-angle glaucoma is based on the theory of controlled supraciliary spacing efficacy, and subsequent modulation of the pressure gradients based on experimental work by Toris et al. The concept is shown to be safe and effective in a single-arm study, demonstrating a clinically meaningful reduction at postoperative month 24 in IOP (mean reduction from baseline – 9.0 mmHg, 39%), and medication burden (mean reduction from baseline – 1.5 medications, 78.9%). The safety profile was favorable, with a reproducible surgical technique and minimal postoperative events. The results of this study may give an early indicator that this novel uveal spacer could present a realistic alternative for patients with moderate glaucoma, who require potent disease control beyond what the trabecular outflow pathway can offer, but are not candidates for other ab externo filtration procedures, which carry a higher risk–benefit burden. Future investigations will be critical

in confirming whether the observed IOP reduction is primarily driven by enhanced uveoscleral drainage, in a specific and powered patient population, and in defining and understanding the role of this technique, which is the only one of its kind and may represent a truly new approach to glaucoma management, within the broader surgical management of glaucoma to fill the large unmet need of controlling this chronic, lifelong disease, that still exists today.

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Data Availability. The datasets generated/analyzed during the current study are not publicly available due ongoing review by international regulatory authorities as part of submission/s for market approval.

Declarations

Medical Writing/Editorial Assistance. Editorial assistance for this article was provided by Stephanie Jones and Priya Patel, both employees of Ciliatech US Corp. Conceptualization and study design was performed by Olivier Benoit and Philippe Sourdille of Ciliatech SAS. Statistical analysis was conducted by Hugo Lacour of Heva Data SAS. All editorial assistance was funded by Ciliatech SAS.

Conflict of Interest. Lilit Voskanyan received financial support from Ciliatech for her work as an investigator in this study. Vahan Papoyan, Hayk Babayan, and Hovsep Miroyan were employed as investigators in the study at S.V. Malayan Ophthalmological Center, and do not have any financial disclosures for this study. Christophe Baudouin received financial support from Ciliatech as chair of the data and safety monitoring board.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki 1964, revised in 2013 and 2024, and all ethical principles, guidelines and procedures required for responsible conduct of clinical investigations. Ethical approval was provided by the Malayan Eye Center Ethical Committee. Written informed consent was obtained for all patients included in the study.

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