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A European Study of the Performance and Safety of MINIject in Patients With Medically Uncontrolled Open-angle Glaucoma (STAR-II)

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Precis: In this European study (STAR-II), MINIject, a novel, ab-interno, supraciliary minimally invasive glaucoma surgery device, effectively lowered intraocular pressure (IOP) and the need for IOP-lowering medications in patients with primary open-angle glaucoma.

Purpose: This study evaluates the safety and performance of a minimally invasive supraciliary glaucoma drainage device (MINIject DO627) for surgical treatment of primary open-angle glaucoma in patients refractory to topical hypotensive medications.

Methods: In a prospective, interventional, single-arm, multicenter, European study (STAR-II), MINIject was successfully implanted in a stand-alone procedure in 29 of 31 patients in 8 sites in 3 countries. The primary endpoint was the success rate 6 months after surgery $>60\%$ (defined as diurnal IOP ≤ 21 and >5 mm Hg with $\geq 20\%$ IOP reduction from baseline, with/without glaucoma hypotensive medication). ClinicalTrials.gov: NCT03624361.

Results: At the 6-month follow-up, the primary endpoint was fulfilled, with 75.9% of patients reaching prospectively defined success. The mean IOP was reduced by 40.2% (9.9 mm Hg) to 14.7 ± 6.0 mm Hg at 6 months from 24.6 ± 3.8 mm Hg at baseline. The use of IOP-lowering medication ingredients was reduced by 63.4% from 2.9 ± 1.2 at baseline to 1.0 ± 1.3. Furthermore, 79.3% of the patients had mean IOP ≤ 18 mm Hg, 82.8% achieved a $\geq 20\%$ IOP reduction, and 55.2% were medication free at 6 months. Six device-related serious adverse events were reported in the study eye: IOP increase (3/31 patients, 9.7%), and single reports of eye pain, corneal erosion, and chorioretinal folds (1/31, 3.2%), all of which resolved. There was minimal change to corneal endothelial cell density.

Conclusion: Ab-interno supraciliary surgical implantation using MINIject DO627 in a stand-alone procedure significantly lowers IOP by 40% at the 6-month follow-up, while reducing the need for IOP-lowering medication.

Key Words: glaucoma, MIGS, supraciliary, IOP, MINIject

(*J Glaucoma* 2020;29:864–871)

Glaucoma is a chronic, progressive disease and the second leading cause of blindness in the world.[1] Surgical therapies for glaucoma (eg, trabeculectomy, nonpenetrating glaucoma surgery, or shunt implantation) are well-established treatment options with the aim of reducing intraocular pressure (IOP).[2] Key studies have shown that significant reductions in IOP (to at least ≤ 18 mm Hg) can significantly slow the progression of glaucoma and optic nerve damage.[3,4] Investigators from the Collaborative Initial Glaucoma Treatment Study (CIGTS) found that an ~40% reduction in IOP halted the progression of glaucoma in a 5-year study.[5] It is well known, however, that although these traditional procedures can provide significant IOP reductions, they also have high rates of complications, many of which can be sight threatening.[6,7] Such complications commonly restrict the use of bleb-forming surgical therapies only to individuals who have failed medical and laser

Received for publication April 9, 2020; accepted July 14, 2020.

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iSTAR Medical, Wavre, Belgium sponsored the STAR-II study.

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Disclosure: J.G.F.: Santen, Alcon, Glaukos, iSTAR Medical, Thea, AJL. P.D.: Santen, Alcon, Glaukos, iSTAR Medical, Thea, Bausch & Lomb, Allergan. C.H.: SANTEN, iSTAR Medical. F.A.: Alcon, Allergan, Eyetechcare, Glaukos, iSTAR Medical, Santen, Thea. Z.H.: Vice President of Clinical and Regulatory Affairs, at iSTAR Medical. K.L.: Allergan, Ivantis Inc., MicroOptx, Implandata, Sensimed, Thea, Santen, Pfizer. N.P.: Allergan, Ivantis Inc., MicroOptx, Implandata, Sensimed, Thea, Santen, Pfizer. The remaining authors declare no conflict of interest.

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DOI: 10.1097/IJG.0000000000001632

trabeculoplasty therapy, and have already experienced visual field (VF) deterioration. The development of minimally invasive glaucoma surgery (MIGS) has bridged the gap between medical therapy and incisional surgery in the management of patients with glaucoma. To be defined as a MIGS, the procedure itself should fulfill 5 criteria: a microinvasive approach, minimal tissue trauma, at least modest performance, rapid recovery, and a high safety profile. Among MIGS, there are 3 categories into which a procedure can be classified: those involving the trabecular meshwork, the supraciliary space, and those that create a subconjunctival bleb.[8–10]

Recent times have witnessed greater attention paid to MIGS targeting the uveoscleral drainage pathways. Although ab-externo subconjunctival drainage implants have been better studied and used for a longer time, complications inherent to the ab-externo approach, and bleb-related complications, might make it a 2-edged sword. Thus, the supraciliary space, untapped and less well known, has garnered interest for its potentially safer approach, as a bleb-free glaucoma surgery, while promising to be more efficacious than trabecular meshwork treatment options.[11,12] Indeed, some ab-interno supraciliary MIGS devices have been shown to be efficacious in IOP reduction, including CyPass (Alcon, Vernier-Geneva, Switzerland)[13] and iStent Supra (Glaukos Corporation, San Clemente, CA).[14] However, despite promising performance results, the CyPass Micro-Stent has been withdrawn from the market because of safety concerns related to corneal endothelial cell loss in a 5-year safety study.[15–17] As a consequence of optimal IOP reduction using the supraciliary space, and the lack of many options in the market, there has been interest in the development of devices targeting the supraciliary space.

The ab-interno supraciliary MINIject DO627 integrated system (iSTAR Medical SA, Wavre, Belgium) and the STAR material (Fig. 1) have been previously described in preclinical studies in rabbits and in a first-in-human trial conducted in Panama and India (STAR-I).[18,19] This study (STAR-II) is a prospective, open, single-arm, multicenter, interventional European clinical trial with one cohort analyzing the performance and safety of an investigational device, the MINIject DO627 integrated system, in patients with open-angle glaucoma uncontrolled by topical hypotensive medications. This report describes the performance and safety outcomes observed at the primary endpoint, which occurred at the 6-month follow-up. Follow-up will continue for 2 years after implantation.

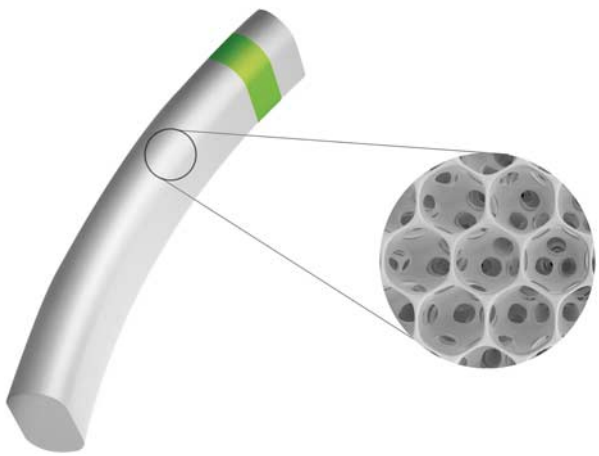

FIGURE 1. MINIject implant and STAR material. © iSTAR Medical, *Source*: https://www.istarmed.com/products/minject-migs/.

METHODS

Patients with primary open-angle glaucoma (POAG) uncontrolled by topical hypotensive medication were enrolled under a standardized treatment protocol (ClinicalTrials.gov identifier: NCT03624361). The premarket trial is monitored by a Medical Monitor and a Safety Monitoring Committee consisting of 3 core members and 1 ad hoc member based in the United States and in Europe (see the Acknowledgments section). The MINIject study protocol was approved by the National Competent Authorities (CA) of each country and the responsible ethics committee (EC) at each hospital and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent before any study procedures were undertaken, and all data were 100% monitored onsite by an independent monitoring company.

All study participants underwent a complete ophthalmic examination preoperatively, including demographic data, medical history, medicated diurnal IOP measurement (Goldmann applanation tonometry), concomitant ocular and non-ocular medication, best-corrected visual acuity (BCVA), gonioscopy, vertical cup/disc ratio, perimetry, pachymetry, slit-lamp examination, dilated funduscopic ophthalmoscopy, and corneal endothelial specular microscopy to measure endothelial cell density (ECD). The inclusion criteria were as follows: male or female 50 years of age or older, diagnosed with POAG with Shaffer Grade 3 or 4 as assessed by clinical gonioscopy, refractive to topical hypotensive medication(s) (or intolerant), and a medicated IOP between 21 and 35 mm Hg. Participants could be either phakic or pseudophakic. Exclusion criteria were as follows: diagnoses of glaucoma other than POAG, previous glaucoma surgery in the study eye (other than laser treatment when performed $\geq$ 90 d before the baseline visit), VF defect in the 10-degree central field, or any clinically significant ocular pathology other than POAG. A single eye per participant was enrolled as the study eye. If both eyes fulfilled the eligibility criteria, the study eye was selected by the investigator. Study eyes were subjected to surgery within 6 weeks after screening. Each site used its standard course of postoperative antibiotics and steroids. No mitomycin C or 5-fluoruracil was used before, during, or after surgery. No medication washout was performed at baseline or at any follow-up visit.

The MINIject DO627 system being investigated in this trial was an integrated system consisting of a minimally invasive glaucoma drainage implant and a dual operator delivery tool (DODT). The DODT was configured for inserting the implant into the subscleral location through an ab-interno, minimally invasive approach. It was single use and the intervention was performed as a stand-alone procedure. The MINIject implant and the delivery tool were manufactured by iSTAR Medical SA, Belgium, as an investigational device for clinical study use only. The MINIject implant provided a controlled fluid path for the aqueous humor to drain from the anterior chamber to the subscleral space of the eye. The MINIject implant leveraged the same silicone-based STAR biomaterial as that used for the STARflo glaucoma implant (iSTAR Medical), which obtained CE-Marking in 2012.[20–22] The MINIject implant was soft and naturally conformed to the eye anatomy. It was porous in nature and has been shown in preclinical studies to be biocompatible with minimal inflammation and

minimal fibrosis.[19] Cell migration into the implant is the likely reason for the lack of fibrotic reaction and minimal encapsulation around the device.[19] The surgical procedure has been previously described.[18]

The primary outcome measure for this study was a responder analysis for success at 6 months >60%, where success is defined as diurnal IOP ≤21 and >5 mm Hg with a minimum 20% diurnal IOP reduction from baseline with or without the concomitant use of allowed glaucoma hypotensive medication. The secondary endpoints included reduction in diurnal IOP between the baseline visit and 6 months after surgery, with or without the use of allowed glaucoma hypotensive medications, and reduction in diurnal IOP between the baseline visit and 6 months after surgery, without the use of any concomitant glaucoma hypotensive medication. Additional secondary endpoints included complete success at 6 months after surgery, defined as mean diurnal IOP ≤21 and >5 mm Hg with a minimum IOP reduction from baseline of 20% without the use of IOP-lowering medications, and the mean reduction in the number of IOP-lowering medications 6 months after surgery compared with the baseline visit. Adverse events and their severity were also included as secondary endpoints. Safety outcomes were monitored by an independent safety monitoring committee. Participants were reassessed at 1 day, 1 and 2 weeks, and 1, 3, and 6 months after surgery. IOP, need for IOP-lowering medication, and BCVA were assessed at every visit and also eye symptoms, dilated fundus, and slit-lamp examination. Optic nerve examination and photography, VF testing, ultrasound biomicroscopy (UBM) to assess implant position, and corneal endothelial specular microscopy were to be performed at several protocol-specified follow-up timepoints. All topical IOP-lowering medications were discontinued at the time of surgery. At each postoperative visit, investigators were permitted to add medications to the patient's treatment regimen as necessary based on IOP (if not reduced by 20% or more, or if deemed to be at an unsafe level) or on progression of disease as manifested by the optic nerve or VF. Similarly, medication could be discontinued at any follow-up visit at the investigator's discretion. Assessments were performed according to the methods below: IOP was measured by an experienced operator using Goldmann applanation tonometry. Two readings were obtained at each timepoint, with the tonometer dial set to 10 mm Hg between each reading. A third reading was obtained if readings differed by >2 mm Hg. At baseline and 6 months after surgery, diurnal IOP was measured at 8:00 AM, 12:00 PM, and 4:00 PM (±1 h), whereas at other follow-up examinations, IOP was measured at a single timepoint. The mean diurnal IOP was calculated as the average IOP considering all 3 timepoints. BCVA was measured at 4 m using the ETDRS chart with either retro-illumination or reflectance illumination. All adverse events identified by investigators or participants were recorded. Prespecified ocular symptoms (blurred vision, glare, halos, dryness, foreign body sensation, other) were evaluated at each visit and were graded as absent, mild, moderate, or severe. Automated perimetry VF testing was performed using either the Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany) or the Octopus perimeter (Haag-Streit AG, Koeniz, Switzerland). VF progression was defined as a 3 dB or more decrease in mean deviation compared with the baseline.[23,24]

The trial uses a 1-stage design[25,26] for the primary endpoint. In this design, a formal decision rule allows for concluding whether the treatment device has efficacy due to the proportion of successes being above a certain cut-off, or unworthy due to being below this cut-off. The cut-off was determined using hypotheses of interest as determined by clinical experts and regulatory authorities with a type I error of $\alpha = 5\%$ and a type II error of $\beta = 20\%$. The type I error inflation by performing this type of multiple testing was taken into account using a fixed sequence hierarchical test procedure. Using these assumptions, the sample size in the study was set to 30 patients, so that 25 patients would be available for the analysis of the primary endpoint. The prospectively defined responder analysis primary endpoint was calculated by counting the number of patients who achieved success. The device would be considered to have sufficient efficacy if >15 successes were noted among 25 patients (>60%). The secondary IOP endpoints were compared statistically using a paired-sample *t* test, 2-sided, with a significance level of 5% and a power of 90%. The intention-to-treat (ITT) population was used for primary inference, and the results were confirmed in the per-protocol (PP) population.

RESULTS

Between May 2018 and May 2019, 31 eyes of 31 individuals were enrolled in 8 centers in Germany, France, and Spain. Demographic information is presented in Table 1. Safety analysis included all 31 patients based on investigator-reported adverse events. Two patients discontinued study participation because implantation of the device was aborted during surgery. In 1 case, an investigator's first MINIject case, physiological resistance was felt during the implantation procedure and the patient experienced ocular pain due to the decreased effect of the anesthesia; thus, the surgery was terminated. In the second case, the implant could not be fully released with the delivery tool (a device deficiency with the DODT) and so the surgery was aborted. These 2 patients completed the 1-month safety follow-up visit without any safety issues and then left the study as prospectively defined in the protocol. The ITT population consisted of the remaining 29 patients, all of whom were available for follow-up at 6 months. In the PP population, 5 patients were excluded from the ITT data set, resulting in 24 patients. The reasons for excluding the patients from the PP population were as follows: 1 patient

TABLE 1. Demographic Characteristics (Safety Population, N = 31)

	MINIject CS627 Implant (N = 31) [n (%)]
Age (y)	
Mean (SD)	69.5 (10.9)
Median (minimum, maximum)	71.0 (36, 85)
Sex	
Male	9 (29.0)
Female	22 (71.0)
Ethnic origin	
Black	4 (12.9)
Caucasian	25 (80.6)
Other*	2 (6.5)
Study eye	
OD (right)	15 (48.4)
OS (left)	16 (51.6)

*No ethnic information provided.

was too young and so did not fulfill the inclusion criteria for age, 3 patients (3/31, 9.7%) had undergone additional glaucoma surgery before the 6-month visit, and in 1 patient, the implant was placed partially in the wrong space. The analysis carried out in this report is based on the entire ITT population of 29 patients.

In the present study, at 6 months, the primary endpoint responder analysis of success >60% was successfully met and was achieved in 75.9% of patients (22/29 patients) in the ITT population. This result was both clinically relevant and statistically significant, and was confirmed in the PP analysis (18/24 patients, 75.0%).

A key secondary endpoint was the reduction in the mean diurnal IOP, with or without the use of concomitant hypotensive medication, assessed at month 6 compared with the diurnal IOP at baseline. IOP at baseline was 24.6 ± 3.7 mm Hg (mean ± SD) and the mean number of topical medication ingredients was 2.9 ± 1.2. The reduction in IOP at every timepoint for the ITT population can be found in Table 2 and Figure 2. At month 6, the mean relative reduction in diurnal IOP was 40.2% (9.9 mm Hg), which was statistically significant ($P < 0.0001$; 95% confidence interval: −12.1, −7.6 mm Hg) and clinically relevant. The mean diurnal IOP at month 6 was 14.7 ± 6.0 mm Hg, and the mean medication usage decreased by 63.4% to a mean of 1.0 ± 1.3. Of the 29 eyes evaluated at 6 months, 79.3% achieved an IOP ≤18 mm Hg, 82.8% achieved an IOP reduction ≥20%, and 55.2% of the patients were medication free.

Another secondary endpoint was the reduction in the mean diurnal IOP, without the use of concomitant hypotensive medication, assessed at month 6 compared with the diurnal IOP at baseline. At the 6-month timepoint, 44.8% (13/29) achieved complete success (diurnal IOP ≤21 and >5 mm Hg with a minimum 20% IOP reduction from baseline without the need for any glaucoma hypotensive medication). The mean diurnal IOP for those patients not taking IOP-lowering medication at month 6 (16 patients) was reduced by 13.0 mm Hg (51.5%) compared with baseline IOP for this subset (24.6 mm Hg), which was statistically significant ($P < 0.0001$; 95% confidence interval: −16.0, −10.0 mm Hg) and clinically relevant. The mean diurnal IOP for this patient subset at month 6 was 12.6 ± 6.4 mm Hg.

A number of device deficiencies were reported with the dual-operator delivery tool used to deliver the MINIject implant due to transportation issues, incorrect coupling, and inability to fully retract the sheath. The EC and CA in Germany withdrew their initial trial approval, after patient enrollment was already completed, but agreed that investigators should continue to follow the safety of patients according to the study protocol until trial completion. Patients were informed accordingly. There was no change to the trial status by the ECs and CAs in France and Spain. All patients in the study are being followed up to 2 years as intended.

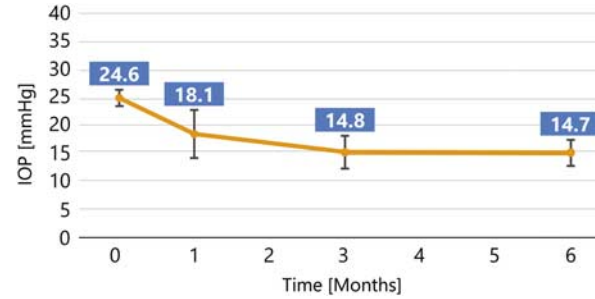

FIGURE 2. Mean intraocular pressure (IOP) over various timepoints up to the 6-month follow-up in the intention-to-treat population (n = 29). Error bars are 95% confidence intervals.

There were no sight-threatening intraoperative complications. Proper implant positioning was confirmed via UBM observation at week 1 and reconfirmed at month 6, confirming no implant migration. Example UBM images are shown in Figure 3. Ocular adverse events in the study eye are listed in Table 3. The most frequently reported ocular events in the study eye (irrespective of the causality assessment by the investigator to the device, surgical implantation procedure, or neither) included increase in IOP (15/31 patients, 48.4%), for which 2 patients (6.5%) satisfied the protocol definition of substantial IOP increase, which is a ≥10 mm Hg increase after month 1; visual acuity reduced (9/31, 29.0%); hyphema (7/31, 22.6%); vision blurred (7/31, 22.6%); dry eye (6/31, 19.4%); and VF defect (6/31, 19.4%). Of the 2 patients with substantial increase in IOP, 1 patient had MINIject implanted too posteriorly, without any portion of the implant in the anterior chamber, and thus the device was not able to work as expected. The other patient had an increase in IOP resulting from an injection of viscoelastic (Healon) due to chorioretinal folds coming from low IOP; the increase in IOP was deemed not to be related to the device or procedure. The majority of cases with reduction of visual acuity occurred in the first week after surgery and were transient. There were 2 cases ongoing at the 6-month follow-up: one was a result of secondary glaucoma surgery just before the 6-month visit, and the second was due to cataract progression according to slit-lamp findings. Both of these were deemed not to be related to the device or the surgery. Of the 7 patients with blurred vision, 3 were transient in the immediate postoperative period and were assessed as related to the procedure only. The other 4 cases were deemed not to be related to the device or the procedure. In 2 patients, apparent VF loss reported as a defect was not maintained across successive visits, and as such loss did not persist. Of the 4 patients with persistent VF defects at 6 months, 2 were deemed possibly

TABLE 2. Mean IOP and Medication-use at Each Timepoint in the Intention-to-treat Population (n = 29)

	Baseline	Day 1	Week 1	Week 2	Month 1	Month 3	Month 6
n	29	28	29	28	29	29	29
IOP [mean (SD)] (mm Hg)	24.55 (3.75)	13.30 (7.23)	12.55 (5.20)	16.11 (10.17)	18.09 (11.16)	14.81 (7.45)	14.68 (6.00)
IOP reduction [mean (SD)] (mm Hg)	NA	11.33 (7.66)	12.00 (6.62)	8.48 (10.68)	6.47 (11.70)	9.74 (8.95)	9.89 (5.86)
IOP reduction (%), mean	NA	45.52	47.73	33.52	25.10	37.79	40.17
No. medications per eye [mean (SD)]	2.9 (1.16)	0.2 (0.77)	0.2 (0.69)	0.3 (0.71)	0.4 (0.82)	1.0 (1.24)	1.0 (1.30)

IOP indicates intraocular pressure; NA, not applicable.

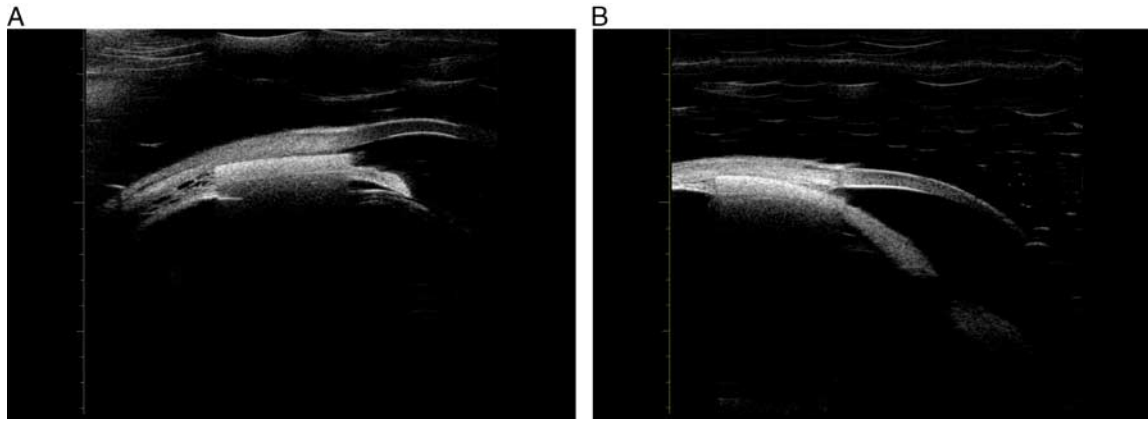

FIGURE 3. Ultrasound biomicroscopy pictures of the MINIject implant in situ at 1 week postsurgery (A) and at 6 months (B). Figure 3 can be viewed in color online at www.glaucomajournal.com.

related to the procedure, and 2 were not related to the device or the procedure. One of these patients had cup-to-disc worsening from 0.7 at baseline to 0.9 at the 6-month follow-up. No further action was taken in any of these patients. All cases of hyphema were resolved by the 6-month follow-up. Three patients had transient corneal edema, all resolving. None of these were deemed to be related to the device, and one was related to the procedure, which was mild. Two patients had chorioretinal folds. One was due to hypotony as described above. The second was not due to hypotony, was transient (duration of 6 d), and resolved with no action taken. There were no suprachoroidal hemorrhages.

Six serious adverse events related to the device were reported in the study eye: increase in IOP (3/31 patients, 9.7%), eye pain (1/31 patients, 3.2%), corneal erosion (1/31 patients, 3.2%), and chorioretinal folds (1/31 patients, 3.2%), and all were resolved. There was no significant mean change (−2%) to central ECD for matched patients (n = 25) between baseline (2235 ± 419) and 6 months (2120 ± 467).

TABLE 3. List of Adverse Ocular Events in the Study Eye in the Safety Population (N = 31), Where n > 1

Adverse Event	n (%)
Intraocular pressure increased	15 (48.4)
Visual acuity reduced	9 (29.0)
Vision blurred	7 (22.6)
Hyphema	7 (22.6)
Visual field defect	6 (19.4)
Dry eye	6 (19.4)
Pupillary deformity	4 (12.9)
Vital dye staining cornea present	3 (9.7)
Conjunctival hemorrhage	3 (9.7)
Conjunctival hyperemia	3 (9.7)
Corneal edema	3 (9.7)
Eye pain	3 (9.7)
Photophobia	3 (9.7)
Postprocedural hemorrhage	2 (6.5)
Intraocular pressure decreased	2 (6.5)
Anterior chamber disorder	2 (6.5)
Chorioretinal folds	2 (6.5)
Conjunctivochalasis	2 (6.5)
Ocular discomfort	2 (6.5)
Conjunctivitis	2 (6.5)

DISCUSSION

Proposed alternative routes to the traditional outflow pathway include the uveoscleral pathway, where aqueous drains across the sclera to be resorbed by orbital vessels; another pathway where aqueous humor enters the choroid to drain through the vortex veins[27]; and a third "uveolymphatic" route that uses the ciliary body lymphatic vessels.[28] Recent evidence has indicated that uveoscleral outflow may account for ~50% of aqueous drainage in normal human eyes and is thought to be higher in glaucomatous patients, in whom redirection toward the uveoscleral pathway occurs.[29–31] There is also evidence that supraciliary microstenting has significant IOP-lowering capabilities[11,13,32,33] and does not face the IOP-lowering limitation of episcleral venous pressure that is encountered when targeting the conventional outflow pathways such as during trabecular bypass. However, it is also known that supraciliary devices may cause a scarring reaction that may limit success rates.[8,29,32] The use of suitable materials that minimize and prevent tissue scarring and foreign body reactions has been suggested by Gigon and Shaarawy.[29] In preclinical studies in rabbits, the MINIject implant produced limited fibrous encapsulation around the device, and caused minimal inflammatory reaction in an animal model that is known for aggressive ocular fibrosis. The ingrowth of healthy cells within the pores of the STAR biomaterial (biointegration) may further assist in the outflow of fluid, and this process may be responsible for limiting capsule formation.[18,19] The implant was seen to exert minimal stress on surrounding tissues as it conforms to the eye anatomy.[18,19] It may be possible to infer the response of surrounding ocular tissues to the MINIject implant in human eyes upon examination of long-term clinical results.

A first-in-human study (STAR-I) of the safety and performance of the MINIject DO627 integrated system in 25 patients with medically uncontrolled POAG has been previously published.[18] The mean diurnal IOP was reduced from 23.2 ± 0.6 mm Hg at baseline using 2.0 ± 1.1 IOP-lowering medication classes to 14.2 ± 0.9 mm Hg with 0.3 ± 0.7 medications 6 months after surgery. This was equivalent to a reduction of 9.0 mm Hg or 39.1% ($P < 0.0001$). In total, 87.5% of patients were medication free, and 95.8% achieved a ≥ 20% IOP reduction from baseline. There were no serious adverse events related to the device or procedure, and no

additional glaucoma surgery was required. No device-related adverse events were reported.[18]

Similar results have been achieved in the present study (STAR-II). All of the primary and secondary efficacy endpoints were fulfilled based on an analysis of 6-month data of the ITT population including an evaluation of IOP (diurnal and single-point measurements), success rates, and a reduction in the use of concomitant hypotensive medications (number of patients using medications and active medication ingredient use by patient). In summary, at the 6-month follow-up, 75.9% of patients achieved qualified success. A mean relative IOP reduction of 40.2% (9.9 mm Hg) to 14.7 ± 6.0 mm Hg was achieved, whereas the mean medication usage was reduced by 63.4% to 1.0 ± 1.3. In addition, 55.2% of patients were medication free at the 6-month follow-up. Additional incisional glaucoma surgery was required in 9.7% of patients. These results, although in a much smaller study, attain a similar level of IOP reduction as that observed in the CIGTS study, in which the progression of glaucoma was halted in a 5-year study.[5]

The minimally invasive delivery of MIGS represents a safety advantage compared with other treatment options that are surgically implanted through an ab-externo approach and/or require a bleb. Complications that are typically reported after bleb-forming glaucoma procedures, such as those reported in the Tube versus Trabeculectomy study,[7,34] include choroidal effusion (3.8%), bleb encapsulation (5.7%), bleb leak (4.8%), persistent corneal edema (5.7%), hypotony maculopathy (3.8%), and blebitis (2.9%). In the Tube versus Trabeculectomy study, the total number of patients with serious complications was found to be 27% for trabeculectomy and 17% for tube shunt implantation surgery. Similar complications and rates were reported in the CIGTS.[35] Bleb-related complications are also typically found in newer subconjunctival surgeries such as XEN Gel (Allergan, Dublin, Ireland)[36] and Preserflo Microshunt (Santen, Osaka, Japan).[37–39] Bleb encapsulation, choroidal detachments, anterior chamber reformation, late-stage needling, and early bleb leak are some of the complications that have been described. The lack of these complications with devices placed in the trabecular meshwork and in the supraciliary space, as a bleb is not required, is a factor to consider when deciding which procedure to choose. Device implantation using an ab-interno supraciliary procedure is minimally invasive, which greatly reduces iatrogenic trauma to ocular tissues. In particular, the procedure leaves the conjunctiva and trabecular meshwork intact for future traditional glaucoma surgical interventions, such as trabeculectomy or drainage device implantation, and trabecular approaches such as canaloplasty and canal expanders, if needed.

Ab-interno MIGS devices that do not create a filtering bleb are considered to have a safety advantage over the ab-externo and subconjunctival procedures listed above. There are, however, only a few published studies using stand-alone trabecular MIGS devices that explore their efficacy without the confounder of cataract surgery. One of them is the COMPARE study, which compared 2 different stand-alone trabecular MIGS procedures, the Hydrus Microstent (Ivantis Inc., Irvine, CA) versus 2-iStent Trabecular Micro-Bypass Stent Systems (Glaukos Corporation), at 12 months.[12] In this study, preoperative medicated IOP values for the Hydrus and 2-iStent groups were 19.0 and 19.1 mm Hg, respectively, much lower than those in the current study. The approximate mean medicated IOP at the 6-month follow-up was 18 mm Hg for both devices. At the 12-month follow-up, the study showed that 46.6% of Hydrus patients and 24.0% of 2-iStent patients were medication free ($P = 0.006$).

As previously mentioned, the potential of the supraciliary space for efficacious IOP reduction has been documented by other devices that target the uveoscleral pathway, such as the CyPass Micro-Stent. When García Feijoó et al[11] studied the CyPass Micro-Stent as a stand-alone procedure in POAG patients refractory to medical therapy, a significant reduction in IOP was documented: from 24.5 ± 2.8 mm Hg at baseline to 17.3 mm Hg at 6 months (−29.3%, $P < 0.0001$). The mean number of topical treatments was also reduced from 2.2 ± 1.1 at baseline to 1.3 medications at the 6-month follow-up ($P = 0.0003$). Additional incisional surgery was required in 16.9% of patients at the 12-month follow-up. The reductions in IOP obtained with CyPass standalone appears to be greater than those obtained with trabecular bypass devices described above, and the present study may also confirm the potential efficacy of the supraciliary space as an outflow pathway to reduce IOP, with a 40.2% IOP reduction 6 months after MINIject implantation, although these are early data.

Based upon a review of 6-month data, the MINIject implant is reasonably safe and well tolerated, despite some device-related issues found in relation to the delivery tool. Lessons learned from the deficiencies of the device in this study led the company to develop a newly designed single-operator delivery tool, which overcomes the deficiencies of the DODT seen in this study and improves ease of use. Some of the improvements made include modifying the tip shape, enhancing the packaging of the sheath to reduce movement of the implant during transportation, making the handle more ergonomic, and increasing operator control during implant release. The single-operator delivery tool will be used in future studies; the MINIject implant remains the same. It is particularly important to note that the mean ECD count for MINIject is not significantly different at 6 months compared with the baseline; however, 6 months is still an early timepoint for evaluating ECD loss. This important safety endpoint will continue to be followed until study completion.

The current study has some limitations. This is a single-arm study, without randomization, and thus far, only 6-month results are available. All comparisons with other procedures have been made with reference to historical controls from other studies evaluating other surgical approaches. Although study participant retention until the primary endpoint at 6 months was excellent (100% of implanted eyes), the study was limited to 29 patients. Nevertheless, the varied number of sites and investigators (8) in 3 different countries allow some variability of surgical technique. As this study required implantation in a stand-alone procedure, outcomes with concomitant cataract surgery were not the purpose of this study. Being an open-label study, VF and IOP measurements were performed unmasked at follow-up visits. The protocol did not allow medication "wash-out" at baseline or follow-up visits, due to the need to protect patient vision and prevent IOP spikes in this patient population; thus, analysis of device performance independent of medication-use could not be fully carried out. Performance data reported in this manuscript contain data up to the 6-month follow-up, whereas safety data include adverse events up until the last recorded patient visit at the time the data were exported, and thus some adverse events relate to a longer follow-up period than

6 months. The decision as to when additional surgery was performed was left to the investigator's discretion, which may have resulted in variations between study centers. The MINIject system used in this study was the MINIject dual-operator DO627 integrated system, which has since been superseded by the manufacturer with the MINIject single-operator SO627 integrated system.

Overall, in this single-arm study, the outcomes for patients with the MINIject implant are promising and can avoid a group of glaucoma-surgery complications that are associated with classical blebs. MINIject could be considered a potential alternative to existing MIGS and conventional glaucoma surgical treatments in patients suffering from POAG requiring low target pressures. Longer term data up to 2 years are anticipated.

ACKNOWLEDGMENTS

The study investigators would like to thank the independent members of the Safety Monitoring Committee: A.G. Jünemann MD (Rostock University, Rostock, Germany); R.D. Fechtner MD (SUNY Upstate Medical University, NY); R.A. Eiferman MD (University of Louisville, Louisville); and L.H. Silver PhD (Silver Pharma Consulting Inc., El Paso, TX). The authors acknowledge statistical consultation by Marc Buyse ScD (IDDI, Louvain-la-Neuve, Belgium), study monitoring by CC Clinical research Consultants (led by Myra Daridan PhD, Paris, France), clinical trial management and writing by Anne Kroker PhD (iSTAR Medical, Wavre, Belgium), and writing and editorial assistance provided by Katherin Awad, BSc, MBA.

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