

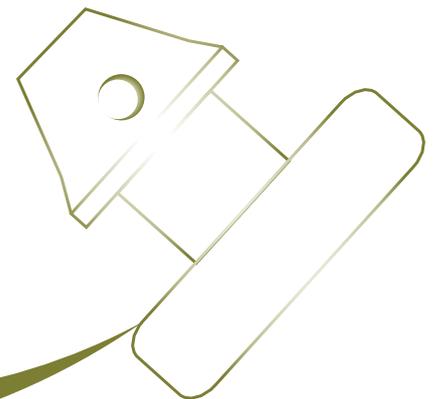


Supplement
December 2019/
January 2020

iStent
inject® W
TRABECULAR
MICRO-BYPASS

A Cataract Surgeon's Guide to iStent *inject* W

Improving Outcomes and Quality of
Life in Cataract Patients with
Mild-to-Moderate Open-Angle Glaucoma



Sponsored by

GLAUKOS®
Transforming Glaucoma Therapy

With about one-in-five cataract patients also needing glaucoma medication ⁽¹⁾, combining cataract and trabecular micro-bypass stent surgery presents a unique opportunity to improve long-term outcomes for select cataract patients with ocular hypertension (OHT) or mild-to-moderate primary open-angle glaucoma, while minimising additional surgical risk and post-surgical complications ⁽²⁾.

Measuring 360 microns deep and wide, iStent *inject W* is one of the smallest medical implants now available. In bypassing the trabecular meshwork, which is often the major impediment to fluid drainage in open-angle glaucoma ⁽²⁾, the stent is designed to restore physiological aqueous outflow directly to Schlemm's canal ⁽³⁾.

Whether combined with cataract surgery or implanted alone, studies show the iStent and iStent *inject* devices significantly reduce intraocular pressure (IOP) ⁽³⁾ as well as the mean number of topical medications needed to control IOP ⁽⁴⁾. In many cases, trabecular bypass stenting eliminates the need for glaucoma medication entirely ⁽⁴⁾.

Reduced reliance on topical medications benefits patients in several ways. "Reduction in topical glaucoma medications, which typically contain the preservative benzalkonium chloride (BAK), can help maintain the quality of tear film and potentially improve refractive outcomes". Complications are not only unpleasant but

also even debilitating for patients. They can reduce medication compliance and cut success rates for future glaucoma procedures, increasing the risk of glaucoma progression and vision loss ⁽⁵⁾.

Trabecular micro-bypass stenting may also reduce diurnal IOP fluctuation, which may reduce progression risk ⁽⁶⁾. At the same time, physiological episcleral backpressure may minimise the risk of hypotony seen with more invasive glaucoma procedures including transscleral devices ^(6, 7).

Placed through a corneal incision, iStent *inject W* is straightforward to implant as a standalone glaucoma procedure or combined with cataract surgery. For combined surgery, trabecular micro-bypass stenting is highly compatible with established cataract surgery workflow. Studies show visual outcomes after combined cataract and trabecular micro-bypass surgery are similar to standalone cataract procedures ⁽⁸⁾.

In this supplement we discuss the clinical case and indications for standalone and combined cataract-iStent *inject W* surgery in select patients, as well as practical advice on how cataract surgeons can add this procedure to their practices. For qualified patients, iStent *inject W* may provide substantial clinical and lifestyle advantages, providing cataract surgeons a new tool to help prevent long-term vision loss.

iStent *Inject W* – Building on Nearly Two Decades of Trabecular Micro-Bypass Success

The product of nearly two decades of development, more than 500,000 iStents and iStent *injects* have been implanted around the world since the original device was CE marked in 2004, noted Thomas W Samuelson MD. Experience with the snorkel-shaped iStent suggested placing two is more effective than one, and a more direct insertion method may be more elegant to learn.

This led to development of the iStent *inject*, which was CE marked in 2010 and FDA approved in 2018. The iStent *inject* device is shaped like an arrow and designed to be inserted through the wall of the trabecular meshwork with the head residing in Schlemm's canal, the flange in the anterior chamber, and a narrower thorax held in place by the trabecular meshwork.

A central lumen 80 microns in diameter enables aqueous flow from the anterior chamber directly to Schlemm's canal, where it exits through four 50-micron side-flow outlets. "People sometimes scoff at the small size, but 80 microns is bigger than the lumen of the most of the commonly implanted glaucoma drainage devices. It's a reasonably sized lumen, fully optimised to carry the necessary volume of aqueous. A lot of outflow can go through there," said Dr Samuelson, who is a founding partner and attending surgeon of Minnesota Eye Consultants, and adjunct professor of ophthalmology at the University of Minnesota, USA.

It is made of surgical grade, nonferromagnetic titanium, and

is heparin coated to promote flow, Dr Samuelson said. Two stents are preloaded into a single-use injector, allowing insertion two to three clock hours apart during cataract surgery, or as a standalone procedure outside the United States. It can be efficiently performed coincident with phacoemulsification through the same incision. The major refinement for the iStent *inject W* device released in 2019 is a wider anterior chamber flange that aids in visualising the device during surgery, Dr Samuelson said. The injector is also redesigned for more predictable insertion and an enhanced retraction button for manipulation.

Because iStent *inject W* is placed within the physiological outflow pathway, natural venous pressure regulates postoperative IOP. "You just don't get hypotony because you have episcleral pressure as a back stop. It's a very elegant system," Dr Samuelson concluded.

iStent *inject W* Patient Selection Guide

- Mild-to-moderate POAG
- Cup-to-disc ratio ≤ 0.8
- Preoperative medicated IOP up to 30mmHg
- Phakic, pseudophakic or undergoing cataract surgery
- Poor medication tolerance or compliance

Source: Samuelson TW, 2019



People sometimes scoff at the small size, but 80 microns is bigger than the lumen of the most of the commonly implanted glaucoma drainage devices

Thomas W Samuelson MD

Why Trabecular Micro-Bypass? Prof Hengerer explains iStent *inject W* mechanism of action

Intraocular pressure is a balance of aqueous humour production with outflow. About 70-to-95% of aqueous leaves the eye through the trabecular meshwork, Schlemm's canal, intrascleral channels

Ocular surface disease increases with topical glaucoma medication use...

	Monotherapy	BitheraPy	TritheraPy	Total
Severe OSD	13%	23%	33%	21%
Mild OSD	25%	31%	38%	30%
No detectable OSD	62%	46%	29%	49%

... and glaucoma severity

	Ocular hypertnesion	Early glaucoma	Advanced glaucoma	Severe glaucoma
Severe OSD	13%	23%	33%	21%
Mild OSD	25%	31%	38%	30%
No detectable OSD	62%	46%	29%	49%

Source: Baudouin et al. *Eur J Ophthalmol*, 2012

and episcleral and conjunctival veins, also known as trabecular, or conventional, outflow. The remainder exits through the iris root, between the ciliary muscles, then through the suprachoroidal-scleral tissues, known as uveoscleral, or unconventional, outflow.

In most cases of open-angle glaucoma, the trabecular meshwork, which normally permits and may even promote aqueous outflow through pulsatile pumping⁽²³⁾, restricts outflow due to a variety of causes, including inflammation, fibrosis and blockage from protein deposition, said Prof Fritz Hengerer MD, Chief Medical Officer and Director of Bürgerhospital Eye Clinic, Frankfurt, Germany. "Looking at the pathology of the trabecular meshwork, the normal structure has large gaps while the trabecular meshwork in glaucoma patients is completely different. The trabecular meshwork is completely blocked and the aqueous cannot find a way out."

Recent research, including high-resolution OCT showing the pumping action of the trabecular meshwork, Schlemm's canal and collector channels⁽²³⁾, along with clinical studies finding a 20-fold increase in trabecular meshwork stiffness in POAG compared with normal eyes⁽²⁴⁾, strongly suggest that loss of flexibility plays a major role in glaucoma progression.

iStent *inject W* is designed to restore the pathway for natural outflow by creating two patent bypass pathways through the trabecular meshwork, Prof Hengerer said. This results in multi-directional flow through Schlemm's canal. Aqueous passes from the anterior chamber down the device's central lumen and exits into Schlemm's canal through four side channels. The resulting increase in aqueous outflow can clearly be seen using aqueous angiography.

"You can see the difference before and after surgery. There are a lot of collector channels filling through the stents in the trabecular meshwork," Prof Hengerer said.

OSD: Why Addressing it is Essential for Long-Term Glaucoma Treatment Success

Every ophthalmologist knows the limitations of eyedrops for treating open-angle glaucoma. They are difficult for many patients to properly instil, they can cause irritation and inflammation, they require daily or multiple daily application to work and even when properly administered may cause IOP fluctuation due to limited corneal dwelling time and penetration. Beyond that, patients complain about eyedrops, and their cost can be burdensome.

In short, topical medications create many barriers to effective glaucoma management, said Prof Christophe Baudouin MD, PhD, FARVO, who is Professor of Ophthalmology and chairman of a large department of Ophthalmology in Quinze-Vingts National

Ophthalmology Hospital, Paris. He also is currently vice president of the French Glaucoma Society.

Beyond degrading quality of life, Prof Baudouin's extensive research indicates that ocular surface disease (OSD) associated with long-term topical medication use may contribute to glaucoma progression. Indeed, up to 60% of medically treated glaucoma patients report OSD symptoms⁽⁹⁾, and increased topical medication use is associated with poorer outcomes.

Trabecular micro-bypass surgery such as implanting the iStent *inject W* has been shown in many studies to consistently and reliably reduce mean IOP while reducing medication burden^(3,4). It is a safe procedure that does not affect visual outcomes or recovery when combined with cataract surgery and spares the conjunctiva, and leaves options open if the patient requires more invasive glaucoma procedures in the future. "For patients using glaucoma medications, this is a good option," Prof Baudouin said.

Topical Medications and OSD

The evidence that topical glaucoma medication promotes ocular surface disease (OSD) is voluminous and consistent, Prof Baudouin said. Consistent observational studies around the world, with similar results. He cited eight observational studies involving about 56,000 patients in studies from Europe and the USA, all similarly concluding that ocular surface issues are present in 40-to-60% of glaucoma patients⁽¹⁰⁻¹⁷⁾. Allergy, toxic immunoinflammatory reactions, chronic irritation and tear film instability are consistent findings.



Looking at the pathology of the trabecular meshwork, the normal structure has large gaps while the trabecular meshwork in glaucoma patients is completely different. The trabecular meshwork is completely blocked and the aqueous cannot find a way out

Prof Fritz Hengerer MD

Verifiable allergic reactions are not the most common, as they are sometimes delayed and difficult to identify, appearing only after immunoinflammatory toxins accumulate, Prof Baudouin said. Chronic irritation without an identifiable specific cause is a problem for many more patients, he added. And even though it isn't typically thought of as a surface problem per se, tear film instability is an even more common sign of ocular surface distress.

"Compared with saving the optic nerve, tear film stability doesn't seem to be very important. However, below the tear film there are infiltrates of inflammatory cells; an accumulation of inflammatory cytokines and matrix protease activation," Prof Baudouin said. Indeed, dry eye, burning and discomfort from medication can be more bothersome to patients than the glaucoma itself. In addition to quality of life, it affects quality of vision and future surgical outcomes.

Prof Baudouin's research has found that OSD is both more common and more likely to be severe as patients increase the number of topical therapies. In a study involving 516 patients, 13% of patients on monotherapy had severe OSD compared with 23% and 33% for those using two and three therapies, respectively. Only 38% on monotherapy reported any OSD, compared with 71% on tritherapy. "One medication may not be a problem but if you have two, three or four, OSD is more likely to become a problem"

Similarly, the prevalence and severity of OSD increased with glaucoma severity, Prof Baudouin found. About 10% percent of patients with ocular hypertension suffer severe OSD and 30% any kind of OSD, compared with 34% severe OSD and 64% any OSD for patients with severe glaucoma.⁽¹⁸⁾ "It's logical because those severe glaucoma patients are likely to be older, have more years in therapy and use more medications."

Overall, severe OSD complications, such as keratoconjunctivitis and pterygium, are quite rare, but lesser symptoms including hyperaemia, chronic irritation and tear film instability increase over time, with about half of all glaucoma patients reporting at least mild symptoms, Prof Baudouin said. However, the variability of patient sensitivity to topical glaucoma medications complicates the decision to implant a trabecular bypass micro-stent, particularly patients early in the disease course when 70% or more have no

OSD symptoms, Prof Baudouin noted. "We don't know which of the asymptomatic patients after a few years will become symptomatic and evolve into more involved disease."

Impact on Vision

While discomfort and pain can significantly affect patients' quality of life, OSD also can degrade visual quality, Prof Baudouin said. In a study he participated in involving 136 eyes in 72 patients, a direct correlation between optical quality evaluated by objective scatter index (OSI) and dry eye clinical test results and symptoms was observed, particularly tear film break-up time (TBUT). In addition, poor optical quality observed in patients with DED correlated with its clinical severity.

While many of these patients have normal best corrected visual acuity, they also complain of blurred or fluctuating vision because of tear film instability and/or poor tear quality, and the aberrations and light scattering induced. "It's true for post-refractive surgery dry eye, it's true for post-cataract surgery dry eye and it is true for our glaucoma patients with dry eye – the quality of vision is impaired."⁽¹⁹⁾

Impact on Glaucoma Surgery

Of more concern for surgeons, the more glaucoma medications a patient has been exposed to, the greater the chances filtration surgery will fail, Prof Baudouin added. He cited a 2013 study involving 128 patients who had trabeculectomies that found increased preoperative exposure to ophthalmic solutions preserved with benzalkonium chloride (BAK) is a risk factor for earlier surgical failure, independent of the number of medications used.⁽²⁰⁾

Similarly, the more pre-op inflammation, the more post-op fibrotic response, Prof Baudouin said. In filtration surgery this can lead to overuse of anti-metabolites such as mitomycin-C and 5-fluorouracil to overcome fibrosis, which in turn can lead to bleb complications. "We have to choose between using too little or too much."

More topical glaucoma meds = higher glaucoma surgery failure

Avoiding complications related to topical drug use

To reduce the risk of OSD and related complications that can result from long-term exposure to topical glaucoma medications and their preservatives, Prof Baudouin recommended the following:

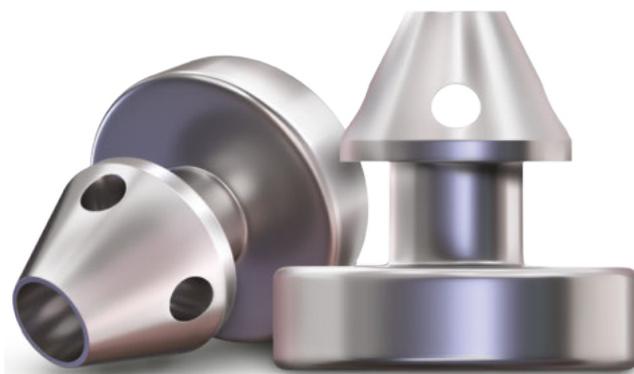
- Propose trabecular micro-bypass surgery in the early stages of glaucoma – Early surgery can improve long-term IOP control, potentially slowing glaucoma progression
- Respect the ocular surface – Reducing dependence on topical glaucoma drugs can reduce OSD symptoms that can degrade patient adherence, and reduce chronic inflammation that complicates later glaucoma surgery
- Prioritise alternative glaucoma surgeries with a trabecular micro-bypass approach first – In addition to reducing topical medication need, implanting a trabecular micro-bypass device spares conjunctiva for potential future glaucoma surgery

Cataract Surgery Alone is Not an Effective Long Term POAG Treatment: Why Prof Baudouin uses iStent *inject*

It is widely known that cataract surgery alone reduces mean intraocular pressure in patients with primary open-angle glaucoma, with some studies suggesting the effect persists for five years or more. However, evidence is accumulating that the IOP-lowering effect of cataract surgery alone is both unpredictable and usually insufficient to reduce dependence on topical medications to control IOP, Prof Baudouin said.

For example, a recent retrospective analysis by Prof Baudouin and colleagues of 70 eyes of 40 POAG patients undergoing phacoemulsification cataract surgery found a mean IOP reduction of just 1.15 ± 3.0 mmHg, or 6%, along with an insignificant mean reduction of 0.1 topical medications one year after surgery. The IOP reduction ranged from 1 mmHg to 8 mmHg and was unpredictable, especially in eyes with narrow angles or big lenses. Moreover, 20% of cases experienced postoperative IOP spikes, with 12.9% exceeding 30 mmHg, Prof Baudouin reported.⁽²¹⁾ "Removing the cataract does not treat glaucoma," he said.

By contrast, adding a trabecular micro-bypass device, such as iStent *inject* W, directly treats glaucoma by reducing aqueous outflow resistance, significantly reducing IOP and topical medication dependence beyond cataract surgery alone, Prof Baudouin said. He cited another retrospective study by his



iStent inject W

group involving 41 eyes of 31 patients with mild-to-moderate POAG who received both phacoemulsification and two iStent *inject* implants in a combined procedure. Mean IOP dropped about 2.0 mmHg, or 13%, along with a 30% reduction in topical medications after three months.⁽²²⁾

Other studies in phakic POAG patients confirm the efficacy of trabecular micro-bypass for treating glaucoma independent of cataract surgery. One study involving 57 POAG patients using one topical medication before surgery found a mean 41% drop in unmedicated IOP, with 97% requiring no topical medication at 18 months.⁽³⁾

In summary, Prof Baudouin explained why he, as both a cataract and a glaucoma surgeon, started using the iStent *inject* in cataract patients: "To avoid more-invasive combined filtration surgery."

More important is why he continues to use iStent *inject* today. Trabecular micro-bypass surgery protects the ocular surface of his cataract patients with glaucoma, provides a better quality of life for his patients, is an elegant procedure, predictably lowers IOP and has minimal effect on visual outcomes of cataract surgery, Prof Baudouin concluded.



We don't know which of the asymptomatic patients after a few years will become symptomatic and evolve into more involved disease

Prof Christophe Baudouin MD, PhD, FARVO

Combined Phaco-iStent *inject* Lowers IOP and Medication use More Than Cataract Surgery Alone in POAG Patients

	Cataract surgery alone (N=70)	Cataract surgery with two iStent inject stents (N=41)
Mean IOP change	-0.96 mmHg (5%)* @ 3 months -1.15 mmHg (6.0%) @ 12 months	2.0 mmHg (13%) @ 3 months
Mean topical medication change	+0.3* @ 3 months -0.1* @ 12 months	-0.6 (-30%) @ 3 months
Source	Majstruk L et al, 2019	Cela D et al, 2019

*not statistically significant

iStent *inject* Relieves Glaucoma Medication Burden – two case studies

Prof Fritz Hengerer MD sees the benefits trabecular micro-bypass surgery brings individual patients, including relief from OSD symptoms that may result in glaucoma progression. He shared

two recent iStent *inject* cases from his practice at Bürgerhospital Eye Clinic, Frankfurt, Germany, where he is chief medical officer and director.

Case #1 – Progression Halted, Medication Eliminated

2013: A 71-year-old male presented with glaucoma, with maximum IOP of 22mmHg OD and 24mmHG OS.

2014: Despite commencing prostaglandin analogue in both eyes, progression in cup-to-disc ratio to 0.9 was seen in both eyes, with visual field mean deviation progressing to -3.5db on the right and -3.2db on the left. Medication compliance declined due to allergic reactions.

2017: Cataract progression noted with medicated pressures of 14/12mmHg right/left. Phaco and iStent *inject* procedure in the right eye.

2018: Phaco and iStent *inject* procedure in the left eye.

Post-surgery IOP without medication, right/left:

- **Feb 2018:** 11/12mmHg
- **Aug 2018:** 12/11mmHg
- **Mar 2019:** 11/12mmHg
- **July 2019:** 09/09mmHg uncorrected visual acuity 1.0/1.0 with no progression in visual field mean deviation or cup-to-disc ratio.

iStent *inject* outcome: 18+ months after surgery the patient's glaucoma was stable with no medication.

Case #2 – Medication burden reduced 9X

2018: A 54-year-old phakic male with 15-year glaucoma history presented with IOP of 28/27mmHg right/left. Medication compliance was low and several medications were not tolerated.

Aug 2018: iStent *inject* implanted in both eyes

Post-surgery IOP right/left, and medication course:

- **Sept 2018:** 21/23 mmHg, carbonic anhydrase inhibitor (CAI) 3X daily, right and left
- **Oct 2018:** 18/17
- **Nov 2018:** 19/18
- **Dec 2018:** 18/18
- **Feb 2019:** 15/16mmHg, CAI 2X daily, right and left
- **Apr 2019:** 14/14, CAI 1X daily, right and left
- **June 2019:** 13/14, CAI once every two days, right left
- **Aug 2019:** 14/13, CAI once every three days, OCT stable, no visual field changes

iStent *inject* outcome: 12 months after surgery IOP controlled and patient stable with medication reduced from 3X daily to once every three days.

Who Can Benefit From Trabecular Micro-Bypass Surgery? A glaucoma treatment algorithm

The range of glaucoma treatments, from medications to lasers, to surgical options now available for treating open-angle glaucoma complicates early surgical treatment decisions. For Thomas W Samuelson MD, it comes down to balancing the potential benefits of surgery against the risk – and helping patients decide, particularly in cases that could benefit from either approach.

Rather than getting lost in the details of each device, in counselling patients, Dr Samuelson starts with an explanation of the two general options. "We can operate on the natural outflow system and improve it, or completely bypass the natural system and create a new pathway."

The benefit of enhancing aqueous flow to Schlemm's canal is "exquisite safety", Dr Samuelson said. The risk is potentially not achieving a desired IOP target, which may require additional medication or procedures to adequately control IOP.

The advantage of a subconjunctival approach is tremendous efficacy in lowering IOP, but substantially more risk of infection and complications from using antimetabolites, managing blebs, hypotony and potentially limiting future surgical options. "It's hard to estimate how much more risk – 10 times, 20 times more?" Dr Samuelson said. "Patients understand that difference and, given the option, almost always go for the safer procedure."

So, for which patients do the benefits of a subconjunctival approach outweigh the risks? In general, patients with mild-to-moderate open-angle glaucoma are candidates for trabecular micro-bypass surgery, while refractory patients or those requiring very low IOP to slow progression may be better served with a subconjunctival procedure. "There's an art to having that conversation with the patient," Dr Samuelson said. It should cover the following:

Safety – "For a patient at low risk for blindness from glaucoma, with mild-to-moderate disease who is not a rapid progressor, who is not in a severe glaucoma state, we really want to emphasize safety," Dr Samuelson said. He generally prefers trabecular micro-

bypass surgery for these patients because intraoperative and both short- and long-term postoperative complications, are minimal, as confirmed by the US FDA approval pivotal study for iStent *inject*⁽⁶⁾.

Efficacy – “We obviously want efficacy because without it, why bother?” Dr Samuelson said. Patients who are not progressing at moderate IOP, who can reasonably be expected to remain stable with a post-treatment pressure of middle teens or less with one or less topical medications are good candidates for trabecular micro-bypass surgery. Cataract-glaucoma patients who can reach this target with a 20% or so IOP reduction from preoperative baseline are usually good candidates^(6, 17).

Predictability and patency – Trabecular micro-bypass provides consistent, sustained IOP over multiple years, Dr Samuelson said. “What I love about trabecular micro-bypass surgery, and iStent *inject* particular, is I am almost never surprised by an unexpected adverse outcome. I almost never have anything particularly worrisome other than maybe moving on to medical therapy. A surprise negative outcome is something I almost never have to deal with.”

Practice efficiency – Trabecular micro-bypass surgery enhances practice offerings for cataract surgeons, with no difference in visual rehabilitation⁽⁶⁾. “We schedule procedures two weeks apart, and it’s really nice that I can be certain that within two weeks the patient will be seeing well and I can go on with surgery in the other eye. With some of the other glaucoma surgical interventions we have we can almost never plan on surgery in two weeks because the patient is still recovering and pressure is still stabilising.”

In addition, research suggests that maintaining the natural outflow pathway avoids atrophy of Schlemm’s canal, Dr Samuelson added⁽⁷⁾. “Trabecular micro-bypass surgery is my foundational therapy for mild-to-moderate disease.”

Considerations for Treating Mild-To-Moderate OAG with iStent *inject* W Trabecular Micro-Bypass

Safety

- First do no harm
- Minimal intraoperative, short- and long-term postoperative sequelae

+

Efficacy

- Ideal post-treatment target pressures of ≤ middle teens with ≤ 1 glaucoma medication

+

Predictability/Patency

- Consistent, sustained IOP reduction over multiple years
- ≥ 20% IOP reduction from preoperative baseline⁽²⁵⁾

+

Practice efficiency

- Enhances practice offering
- Minimal disruption related to post-surgical sequelae, visual rehabilitation

Source: Samuelson TW, 2019

Adding Trabecular Micro-Bypass to a Cataract Practice

Dr Gundersen finds early success with iStent inject

About 20% of cataract patients at Kjell Gunnar Gundersen MD, PhD’s Ifocus Eye Clinic in Haugesund, Norway, are either glaucoma suspects or under treatment for glaucoma. But they still have the same high expectations for cataract surgery outcomes – spectacle independence, low optical side-effects and safety.

Plus, they want to get off glaucoma medication. “Taking daily IOP-lowering drugs for some patients may be experienced as reduced quality of life,” said Dr Gundersen, a cataract and refractive surgeon who has done 40,000+ cataract procedures in 27 years.

With trabecular micro-bypass, cataract surgery now provides an opportunity to do something for glaucoma other than drugs or lasers, Dr Gundersen said. But to remain competitive in the cataract and refractive market, he needed a glaucoma surgery option that did not interfere with visual outcomes.

Dr Gundersen found that option in iStent *inject*. He did his first combined surgery in January 2018.

So far, the results have lived up to his expectations, Dr Gundersen said. Not only are visual outcomes of combined procedures and secondary procedures in pseudophakic patients similar to cataract surgery alone, the prospect of reducing or eliminating glaucoma medication with trabecular micro-bypass makes his practice more attractive to a large group of patients needing cataract surgery and treatment for mild-to-moderate open-angle glaucoma.

The Learning Curve

While some of the iStent *inject* W procedure is on familiar ground for cataract surgeons – the device is implanted in the anterior chamber through a corneal incision – it is not cataract surgery and there is a learning curve. “It is a straightforward procedure to learn theoretically, but to use it as a practical procedure you have to train,” Dr Gundersen said. He took the following steps:

- Read and study anatomy – Understanding the location and function of Schlemm’s canal and outlet channels, and being able to accurately recognise and target them in surgery is critical for success
- Instructional visit and video – Techniques for implanting iStent *inject* W have been developed over several years, and learning them can improve outcomes
- Hands-on surgery with a Glaukos instructor assisting for 10 cases – “This is a very controlled education of the potential iStent *inject* W surgeon,” Dr Gundersen said “After that, you are certified. Then practice! Because with experience your results will become even better,” Dr Gundersen added.



It is a straightforward procedure to learn theoretically, but to use it as a practical procedure you have to train

Gunnar Gundersen MD

The Procedure

Dr Gundersen started with a temporal incision approach, which provides maximum access. The procedure requires visualising and accessing the angle, which entails tilting the patient's head away from and the microscope toward the surgeon by about 35 degrees. After learning in this position, Dr Gundersen switched to a 12 o'clock approach for most cases. This is consistent with his usual cataract approach and also takes advantage of learning from previous SLT practice that the space in the chamber is deepest at the bottom.

The preloaded injector is introduced into the eye through the cataract incision. The trocar is placed through the centre portion of the trabecular meshwork and into the back wall of Schlemm's canal, where the first stent is deployed. The injector is then moved two-to-three clock hours and the second stent deployed.

The procedure itself is bimanual, requiring holding a gonioscope in one hand to visualise the angle while using the other to introduce the trocar and implant the device. "The key is to visualise the trabecular meshwork," though this may be an unfamiliar move that takes some practice to master, Dr Gundersen said.

Once the implant is properly in place, blood may reflux through it, confirming it is in the correct position. "I think this is the only occasion where ophthalmic surgeons are glad to watch blood coming up," Dr Gundersen said.

Challenges include deep-set eyes and patients who are unable to comply. "You are asking them to direct their gaze in a certain direction so they have to be able to comply with the surgeon's direction."

Dr Gundersen began his studies on October 2017, did his first 10 cases from January to March 2018 and was certified in April 2018. Over the next 16 months he did 68 combined and 12 secondary iStent *inject* implants.

Currently, about 80% of his cases are combined procedures, with the rest secondary implants in patients with previous cataract surgery, extending the benefits of trabecular micro-bypass surgery. "iStent *inject* delivers procedural predictability and precision to meet the needs of your patients and your practice," Dr Gundersen said.

iStent *inject* W pearls from Dr Samuelson

Experienced iStent surgeon and trainer Thomas W Samuelson MD recommends:

Getting started

- Start with straightforward cases. "Pick a case where you could reasonably perform cataract surgery alone without a glaucoma procedure, don't pick a case with very high pressures or rapid progression."
- Choose the eye you are ergonomically most comfortable with. "If you prefer the right eye for cataract surgery you'll probably prefer the right eye for iStent *inject* W, at least initially."

Visualisation

- Practice gonioscopy and positioning the head for a clear view throughout the insertion procedure.
- For the best view, the goniolens should be positioned so that the injector appears in the middle of the window. Visualisation is critical.

iStent *inject* Outcomes: Consistently lower IOP in the hands of new and experienced surgeons alike

One advantage of the precision and refined surgical technique of the iStent *inject* W system is surgeons can get excellent results whether they are new or veterans of hundreds of procedures.

For example, for his first 25 cases in 15 patients, cataract and refractive surgeon Kjell Gunnar Gundersen MD, PhD, director of Ifocus Eye Clinic in Haugesund, Norway, saw mean IOP drop from 22.0mmHg with 1.5 medications preoperatively to 16.1mmHg on 1.0 medications one month after surgery – a reduction of 27% in IOP and 33% in medications – with an 80% success rate. Of these, 19 cases were combined cataract-iStent *inject* procedures and six were secondary iStent *inject* implants in patients with previous cataract surgery. A cohort of five patients saw further reductions to 14.6mmHg and 0.8 medications after three months.

These results are similar to those reported for large, long-term retrospective studies, said Thomas W Samuelson MD, of Minnesota, USA. For example, a study by experienced surgeons in Brazil reported a 27% reduction in IOP for 35 eyes treated with iStent *inject*, and a 16% reduction for 38 treated with the original iStent six months after implantation combined with cataract surgery⁽²⁶⁾.

Similarly, a prospective study of iStent *inject* by Fritz Hengerer MD, Chief Medical Officer and Director of Bürgerhospital Eye Clinic, Frankfurt, Germany, found IOP was reduced by 37% in eyes undergoing combined phaco and iStent, and 42% in eyes undergoing iStent *inject* alone three years after surgery. Medication use also declined significantly, by 68% in the combined surgery group and 80% in the iStent *inject* standalone group.

A data set including 165 eyes operated by five surgeons in Australia showed a similar IOP reduction one year after implanting iStent *inject*. Mean IOP fell from 18.3 to 14.0, or 23%⁽²⁷⁾.

iStent *inject* Reduces IOP and Medication Burden for Experienced Surgeons...

	Mean IOP/meds, combined	Mean IOP/meds, standalone iStent <i>inject</i>
Preop	22.6/2.5	25.3/3.0
Year 1	14.8	15.0
Year 2	14.5	15.0
Year 3	14.3/0.8	14.6/0.6

Source: Hengerer F, 2019

...newcomers...

	Mean IOP	Mean medications
Pre-op N=25	22.0	1.5
Month 1 N=24	16.1	1.0
Month 3 N=5	14.6	0.8

First 25 iStent *inject* cases by cataract and refractive surgeon

Source: Gundersen, G, 2019

... and a large pooled data set

Standalone Results

In a study of iStent *inject* as a standalone procedure in 57 patients, mean unmediated IOP dropped 41% at 18 months⁽³⁾

	Mean IOP. mmHg
Pre-op	19.5
BL	24.4
Month 1	14.3
Month 3	14.2
Month 6	14.6
Month 12	14.2
Month 18	14.4

Source: Lindstrom et al, 2016

Stand-Alone iStent *Inject* vs Two Meds

In a prospective study, iStent *inject* implanted in a standalone procedure reduced IOP in unmedicated eyes similarly to eyes treated with two medications in OAG eyes not controlled on one medication out to 12 months⁽²⁷⁾.

Visual Outcomes

Of particular concern for cataract surgeons, studies also show that adding iStent *inject* does not affect visual outcomes. For example, a study comparing 76 combined surgeries with 50 cataract-only surgeries found no significant difference in the percentage of eyes within 0.25, 0.5 or 1.0 dioptre of refractive target.⁽²⁹⁾ "There's satisfaction when you know you are not adversely affecting visual outcomes," Dr Samuelson said.

While many of these results are for the iStent *inject*, early iStent *inject* W results are similar, which is to be expected given the designs are nearly identical save the wider flange on the iStent *inject* W, Dr Samuelson noted.

Safety

Clinical studies of iStent and iStent *inject* have found low incidence of complications. For example, Prof Hengerer reported no intraoperative complications, or hypotony, peripheral anterior synechiae, choroidal haemorrhage or effusion, and five additional surgeries for glaucoma progression in 125 cases. Lindstrom reported no intraoperative or post-operative adverse events related to iStent

inject in 57 cases followed for 18 months. And the US FDA approval study found no unanticipated adverse events and a similar rate of adverse events in the combined cataract surgery-iStent *inject* and cataract surgery-alone control groups.

Cost-Effectiveness

In addition to excellent efficacy and safety, iStent *inject* has been found to be a cost-effective treatment in several studies. For example, an analysis of costs in France found that iStent *inject* improved patient quality of life as measured by Quality Adjusted Life Years by 0.65 at a cost of €529 per patient over their lifetimes.

"The cost of iStent *inject* is partially offset by the decreased medication costs, lower rate of secondary procedures, decreased transportation and disability costs. Together with the quality of life gains expected with iStent *inject*, it is a cost-effective treatment option for patients with mild-to-moderate open-angle glaucoma in France," the study concluded.⁽³⁰⁾ Similar cost-effectiveness has been found by studies in Germany and Spain.^(31, 32)

Conclusion – The Future Of Micro-Scale Injectable Glaucoma

A substantial body of evidence and user experience shows that iStent and iStent *inject* have demonstrated efficacy and safety in treating mild-to-moderate open-angle glaucoma, Thomas W Samuelson said. "The new iStent *inject* W is built on the same proven safe and effective technologies," he added.



The wider flange on iStent inject W allows for advanced visualisation during implantation



iDose, a unique drug delivery device

The treatment is straightforward and designed to restore natural outflow, while preserving the trabecular meshwork. It may allow for glaucoma medications to be reduced or eliminated at the discretion of eyecare professionals. With a safety profile similar to cataract surgery alone, it provides a very favourable benefit-to-risk ratio.

The precision of the technology and its proven efficacy combined with cataract surgery make it a treatment option that meets both patient and practice needs.

The next goal is extending the safety of micro-scale injectable therapy approach further up the disease intensity scale, potentially to treat advanced and refractory cases, Dr Samuelson said. Glaukos has several products in development that may be suitable.

On the device side, these include iStent infinite for advanced glaucoma, which allows injection of three stents. "Studies suggest that additional stents are associated with increased efficacy," Dr Samuelson noted. On the medication side, iDose Travoprost is a titanium implant for delivering continuous microdoses of medication over long periods, with a refillable reservoir. It is currently in clinical trials.⁽³³⁾

"When I started my glaucoma practice 30 years ago, we had medicines, lasers and trabs with nothing in between. To have procedures that we can offer patients that are so safe and do not adversely affect phaco outcomes, and may be synergistic with some new medications is truly transforming glaucoma practice," Dr Samuelson concluded.

References

(1) Shrivastava A et al. Analysis of US Medicare data. ASCRS presentation, 2017.
 (2) Samuelson TW et al. Randomized evaluation of the trabecular micro-bypass stent in patients with glaucoma and cataracts. *Ophthalmology* 2011;118:459-467.
 (3) Lindstrom R et al. Outcomes Following Implantation of Two Second-Generation Trabecular Micro-Bypass Stents in Patients on One Medication: 18-Month Follow-Up. *Adv Ther* 2016;33:2082-2090.
 (4) Hengerer FH. Personal experience with second-generation trabecular micro-bypass stents in combination with cataract surgery in patients with glaucoma: 3-year follow-up. ASCRS 2018 Presentation.
 (5) Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. *Arch Ophthalmol* 1994; 112: 1437-45. II. The outcome of filtration surgery. *Arch Ophthalmol* 1994; 112: 1446-54.
 (5.1) Zimmerman TJ et al. The impact of ocular adverse effects in patients treated with topical prostaglandin analogs: changes in prescription patterns

and patient persistence. *J Ocul Pharmacol Ther* 2009; 25:145-52.

(6) Konstas AG et al. Diurnal and 24-h Intraocular Pressures in Glaucoma: Monitoring Strategies and Impact on Prognosis and Treatment. *Adv Ther* 2018; 35(11): 1775-1804.

(7) Rosenquist R et al. Outflow resistance of enucleated human eyes at two different perfusion pressures and different extents of trabeculectomy. *Curr Eye Res* 1989;8:1233-40.

(8) PMA P170043: FDA Summary of Safety and Effectiveness. US FDA, June 21, 2018. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170043b.pdf

(9) Moss E et al. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmology* 2000;118(9):1264-1268.

(10) Pisella PJ et al. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. *Br J Ophthalmol* 2002;86:418-423.

(11) Jaenen N et al. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. *Eur J Ophthalmol*. 2007 May-Jun;17(3):341-9.

(12) Erb C et al. German register for glaucoma patients with dry eye. I. Basic outcome with respect to dry eye. *Graefes Arch Clin Exp Ophthalmol*. 2008 Nov;246(11):1593-601.

(13) Leung EW et al. Prevalence of ocular surface disease in glaucoma patients. *J Glaucoma*. 2008 Aug;17(5):350-5.

(14) Fechtner RD et al. Prevalence of ocular surface complaints in patients with glaucoma using topical intraocular pressure-lowering medications. *Cornea* 2010;29(6):618-21.

(15) Baudouin C et al. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. *Eur J Ophthalmol*. 2012;23:47-54. (reference 10 in original draft v0.0)

(16) Rossi GC et al. Risk factors to develop ocular surface disease in treated glaucoma or ocular hypertension patients. *Eur J Ophthalmol*. 2013 May-Jun;23(3):296-302.

(17) Lemij H et al. Patient satisfaction with glaucoma therapy: reality or myth? *Clin Ophthalmol*. 2015; 9: 785-793.

(18) Baudouin C et al. Prevalence and risk factors for ocular surface disease among patients treated over the long term for glaucoma or ocular hypertension. *Eur J Ophthalmol*. 2012;23:47-54.

(19) Herbaut A et al. Impact of Dry Eye Disease on Vision Quality: An Optical Quality Analysis System Study. *TVST* 2018; Vol.7, 5. doi:10.1167/tvst.7.4.5

(20) Boimer C, Birt CM. Preservative exposure and surgical outcomes in glaucoma patients: the PESO study. *J Glaucoma* 2013; 22: 730-735.

(21) Majstruk L et al. Long term effect of phacoemulsification on intraocular pressure in patients with medically controlled primary open-angle glaucoma.

BMC Ophthalmology 19, Article number: 149 (2019)

(22) Cela D et al. Safety and efficacy of iStent Inject® trabecular micro-bypass stents during phacoemulsification for open-angle glaucoma associated with cataract. Poster presentation, ESCRS, September 2019

(23) Xin C et al. OCT Study of Mechanical Properties Associated with Trabecular Meshwork and Collector Channel Motion in Human Eyes. PLoS ONE 2016; 11(9): e0162048.

(24) Last JA et al. Elastic modulus determination of normal and glaucomatous human trabecular meshwork. Invest Ophthalmol Vis Sci. 2011;52(5):2147–52.

(25) Caprioli J et al. Special Commentary: Supporting innovation for Safe and Effective Minimally Invasive Glaucoma Surgery. Ophthalmology, 2015;122(9):1795–1801

(26) Guedes RAP et al. Intermediate results of iStent and iStent inject implantation combined with cataract surgery in a real-world setting: a longitudinal retrospective study. Ophthalmol Ther March 2019;8(1):87–100.

(27) Clement Cl et al. One-year outcomes following implantation of second-generation trabecular micro-bypass stents in conjunction with cataract surgery for various types of glaucoma or ocular hypertension: Multi-centre, multi-surgeon study. Clin Ophthalmol 2019;13:491–499.

(28) Fea A et al. Clin Ophthalmol 2014;8:875–882.

(29) Hengerer F et al. Prospective, non-randomised, 36-month Study of Second-Generation Trabecular Micro-Bypass Stents with Phacoemulsification in Eyes with Various Types of Glaucoma. Ophthalmol Ther 2018, doi.org/10.1007/sc40123-0152-8.

(30) Schweitzer C et al. A cost-utility analysis of the iStent inject® trabecular micro-bypass system plus cataract surgery in patients with mild-to-moderate open-angle glaucoma in France. ESCRS presentation, 2019.

(31) Bucholz PM et al. A Budget-impact Analysis of the iStent inject® Trabecular Micro-Bypass System vs Trabeculectomy for the Treatment of Glaucoma From a German Payer Perspective. ESCRS poster, 2019

(32) Garcia-Feijoo J, Teus M. Cost-effectiveness analysis of iStent inject® implantation for the treatment of open-angle glaucoma in Spain. ESCRS poster, 2019

(33) The iStent infinite and the iDose Travoprost are both currently in clinical trials

Economic benefits of iStent *inject* for treating OAG

As health services consume an ever-growing slice of national income, cutting treatment costs is critical. Several recent studies show that iStent *inject*'s favourable efficacy and safety profile contribute to reduced need for postoperative medication and follow-up. This saves money and time for patients, their families, physicians and society at large – making iStent *inject* a cost-effective treatment option for many patients with mild-to-moderate open-angle glaucoma.

A comparison of the costs of cataract surgery alone with combined cataract and iStent *inject* in France found the combined procedure improved patient quality of life as measured by Quality Adjusted Life Years (QALY) by 0.065 at a cost of €75 per patient over their lifetimes. That works out to €1,154 per QALY gained, making it a bargain at less than 4% of the ~€30,000 the UK's National Health Service considers a reasonable cost per QALY gained.

"iStent *inject* implantation in conjunction with cataract surgery offers a mechanism for IOP reduction that is more effective than cataract surgery alone while reducing the need for medication use and its associated side-effects. ... [And] can be considered cost-effective in patients with mild-to-moderate OAG by improving the patient's quality-of-life at very low incremental costs," the French study concluded. ⁽¹⁾

A similar comparison in Spain found that combined iStent *inject* cataract surgery cost the Spanish National Health System an additional €1,002 over cataract surgery alone, for a cost per QALY gained of €13,077. When the cost of informal caregiver time was included, the combined procedure actually reduced overall societal costs. "iStent *inject* translates ... provides good value for money in patients with mild-to-moderate OAG," the Spanish study concluded. ⁽²⁾

iStent *inject* may also be more cost-effective than procedures creating a subconjunctival aqueous channel in eligible mild-to-moderate OAG patients. One study found that substituting iStent *inject* combined with cataract surgery for 41% of current Xen gel stents (Allergan)-cataract combined surgeries would save the Spanish National Health System more than €3 million annually by reducing complications and follow-up costs. ⁽⁴⁾

Likewise, substituting iStent *inject* with or without cataract surgery for trabeculectomy would save the German statutory health insurance system about €300 per patient for inpatient iStent procedures and more than €1,800 for outpatient iStents over a three-year period. Overall, substituting iStent *inject* for 10% of trabeculectomies would save German insurers about €17 million. ⁽²⁾ Together, these studies suggest that a compelling economic case can be made for using iStent *inject* in suitable patients.

Citations

(1) Schweitzer C et al. A cost-utility analysis of the iStent inject® trabecular micro-bypass system plus cataract surgery in patients with mild-to-moderate open-angle glaucoma in France. ESCRS presentation, 2019.

(2) Bucholz PM et al. A Budget-impact Analysis of the iStent inject® Trabecular Micro-Bypass System vs Trabeculectomy for the Treatment of Glaucoma From a German Payer Perspective. ESCRS poster, 2019

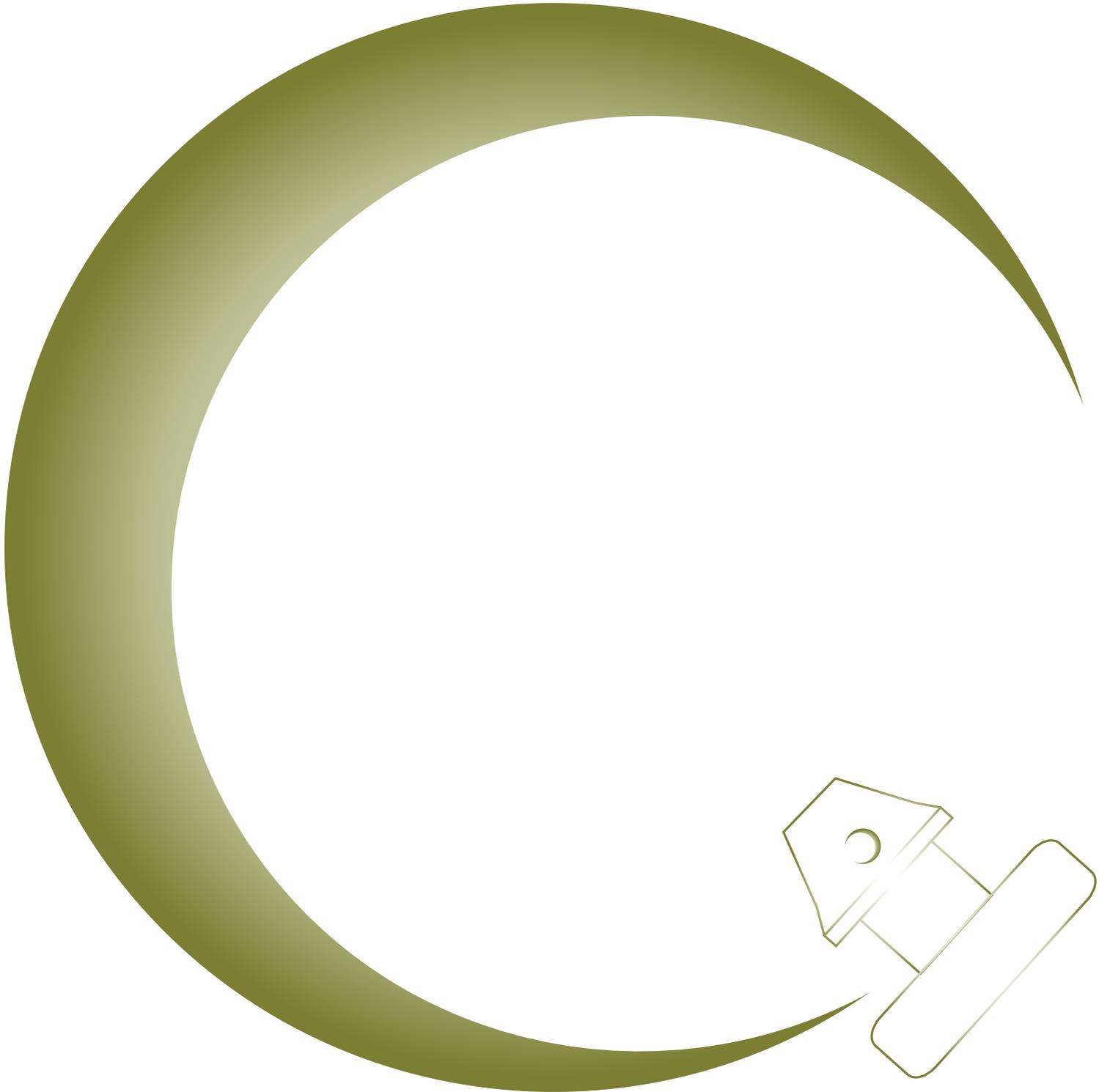
(3) Garcia-Feijoo J, Teus M. Cost-effectiveness analysis of iStent inject® implantation for the treatment of open-angle glaucoma in Spain. ESCRS poster, 2019

(4) Belda JI et al. Budget impact analysis of the iStent inject® implant for OPEN ANGLE GLAUCOMA treatment in Spain. ESCRS poster, 2019



Supplement
December 2019/
January 2020

iStent
inject[®] w.
TRABECULAR
MICRO-BYPASS



Sponsored by an educational grant from

GLAUKOS[®]
Transforming Glaucoma Therapy