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Coexistent primary open-angle glaucoma and cataract: interim analysis of a trabecular micro-bypass stent and concurrent cataract surgery

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PURPOSE. *To evaluate the safety and efficacy of the iStent Trabecular Micro-bypass Stent in patients undergoing concurrent cataract and glaucoma surgery.*
METHODS. *Prospective, 24-month, uncontrolled, multicenter, multicountry evaluation of 58 patients with uncontrolled primary open-angle glaucoma (including pseudoexfoliation and pigmentary) and cataract. Patients underwent clear cornea phacoemulsification followed by ab interno gonioscopically guided implantation of the iStent. Of the 48 per protocol population, 42 patients completed 12 months of the 24-month study, and their data are included in this interim analysis.*
RESULTS. *At baseline, mean (±SD) intraocular pressure (IOP) was 21.7±3.98 mmHg. At 12 months, mean IOP was reduced to 17.4±2.99 mmHg, a mean IOP reduction of 4.4±4.54 mmHg ($p<0.001$, 18.3%). At baseline, patients were taking a mean 1.6±0.8 medications. By 12 months, the mean number of medications was reduced to 0.4±0.62 ($p<0.001$). Half the patients achieved an IOP ≤18 mmHg and were able to discontinue hypotensive medication by the 12-month visit. The most commonly reported device-related adverse events were the appearance of stent lumen obstruction (7 eyes) and stent malposition (6 eyes). None of the adverse events were deemed serious.*
CONCLUSIONS. *In patients undergoing concurrent cataract and glaucoma surgery, the iStent was safe and efficacious for the reduction of IOP and medication therapy. (Eur J Ophthalmol 2009; 19: 393-9)*

KEY WORDS. *Glaucoma, IOP, Schlemm's canal, Trabecular meshwork*

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INTRODUCTION

Medical therapies that treat glaucoma act either by reducing aqueous production or increasing the outflow of aqueous via the trabecular or uveoscleral pathways. More recently, trabecular bypass has been found to enhance the facility of outflow and reduce intraocular pressure (IOP) to physiologic levels (1). To that end, the iStent (Glaukos Corp., Laguna Hills, CA) was developed to address some of the limitations of current medical and surgical therapies for treating glaucoma, including ocular morbidity, extrusion, hemorrhage, infection, hyphema, and corneal ede-

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ma. The device aims to bypass the trabecular meshwork, which is considered to be responsible for the increased outflow resistance leading to glaucoma, connecting the anterior chamber with Schlemm's canal. The purpose of this study was to evaluate the safety and efficacy of the iStent Trabecular Micro-bypass Stent in patients undergoing concurrent cataract and glaucoma surgery.

METHODS

This study was a prospective, 24-month, nonrandomized, uncontrolled, multicenter, multicountry (4 sites in Germany, 1 each in Spain and Switzerland), clinical evaluation of the safety of the iStent for the treatment of primary open-angle and/or pseudoexfoliation glaucoma in patients with IOP uncontrolled by their current ocular hypotensive medications. The protocol was in compliance with Good Clinical Practices and the Declaration of Helsinki (1996). This study was approved by relevant ethics committees, and study participants gave informed consent prior to initiation of the study.

Included patients were those who had a diagnosis of primary open-angle glaucoma (including pseudoexfoliative glaucoma or pigmentary glaucoma), an IOP of at least 18 mmHg (as measured at last two consecutive office visits), were on at least one glaucoma medication, and had a concurrent diagnosis of cataract requiring cataract surgery and IOL implantation. Patients had to be at least 18 years of age. Patients' scleral spur had to be clearly visible with gonioscopy and patients were required to be available and willing to attend follow-up visits for 2 years study duration.

Patients were excluded if they had any type of glaucoma other than primary open-angle glaucoma, pseudoexfoliation, or pigmentary glaucoma, cloudy corneas with opacity determined likely to inhibit gonioscopic view of the nasal angle, history of filtering surgery (trabeculectomy), viscocanalostomy, cyclophotocoagulation, collagen implant, or aqueous shunt, or cataract surgeries in the study eye. Patients with elevated episcleral venous pressure from history of active thyroid orbitopathy, carotid-cavernous fistula, Sturge-Weber syndrome, orbital tumors or orbital congestive disease, a history of any significant ocular disease or condition likely to interfere with study surgery or evaluations (including ocular surface disorders), or a history of trauma to the eye or ocular surface were also excluded. Moreover, patients with existing peripheral anterior synechia (PAS) where PAS was located near enough to the potential implant site to cause problems initially or subsequent to progression of PAS or a prior history of refractive procedures that may prevent accurate IOP measurements (e.g., photorefractive keratectomy, laser-assisted in situ keratomileusis) were also not enrolled. Patients receiving any other secondary surgical interventions were excluded from the efficacy analysis at the time point at which the event occurred but continued to be followed and monitored for safety.

No washout of patients' current ocular hypotensive medications was required. Patients discontinued use of all agents immediately postoperatively and were instructed to resume treatment only if the investigator determined additional IOP lowering was needed. There was no predetermined increase in IOP or percentage increase dictated by the study protocol for resuming medical treatment; all investigators used their own expertise in the decision-making process.

There were 58 patients at 6 sites initially enrolled in this study. Ten were excluded from the efficacy analysis for failure to meet entry criteria, but were included in the safety analysis (the intent-to-treat population). All patients were implanted with the stent between March 2003 and November 2004. Unless otherwise noted, this interim report on the 12-month results on safety includes the intent-to-treat (ITT; n=58) population; efficacy reports include the per-protocol (PP; n=48) study population. Reasons for exclusion from the study protocol included unsuccessful implantation of the stent upon failure to penetrate the trabecular meshwork and inner wall of Schlemm's canal (1 patient), no cataract extraction (6 patients), and preoperative IOP below the baseline requirement of at least 18 mmHg with medication (3 patients).

Surgical procedure

The implantable stent is manufactured from titanium and is heparin-coated. The device is about 1 mm in length. There are two stent designs, one for each eye, so that the stent will direct the fluid to where the largest grouping of collector channels is found. Each implant is attached to a single-use applicator.

On the day of the surgery, patients underwent implantation of the study stent in combination with standard clear cornea cataract surgery.

Implantation of the study stent occurred after cataract extraction and IOL insertion using the same small, temporal,

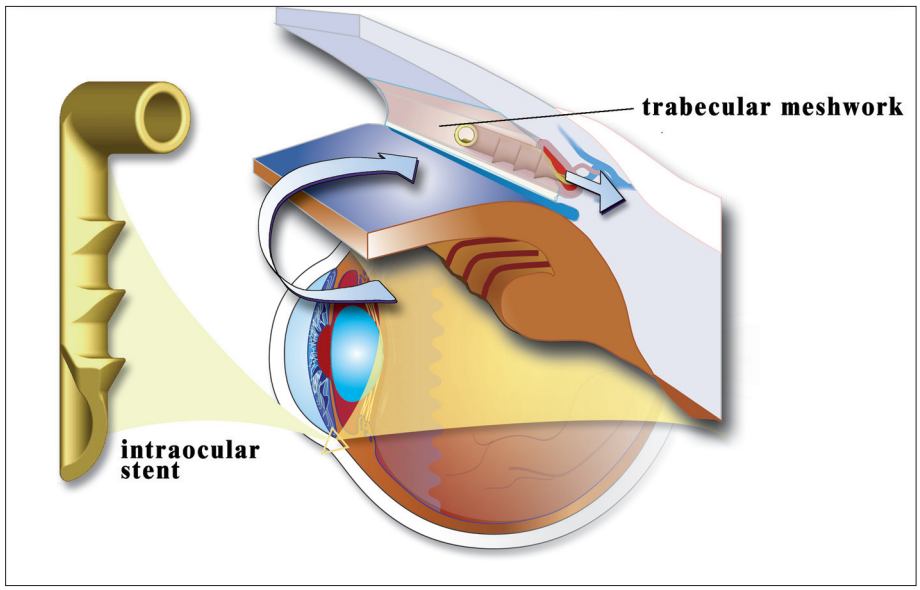

Fig. 1 - *Artist's rendering of the stent and its placement.*

clear-corneal incision (approximately 3 mm) used to perform phacoemulsification and place the IOL. The study stent was guided into Schlemm's canal using ab interno gonioscopy (using a Swan-Jacobs gonioscope) (Figs. 1 and 2).

Preoperatively, the subject was directed to use a fluoroquinolone antibiotic QID for 1 day with one additional drop 30 minutes before surgery. The eye was anesthetized per standard hospital procedures and a 3-mm self-sealing corneal incision was created.

Because the stent is designed for nasal placement and surgery was performed from the temporal side of the head rather than the top of the patient's head, the patient's head was repositioned after the IOL was placed. If no complications occurred during phacoemulsification, acetylcholine was injected in the anterior chamber after the IOL implantation to constrict the pupil. The implant and applicator tip were rinsed with sterile balanced salt solution. The anterior chamber was then filled with a viscoelastic agent to reform the anterior chamber and provide more clearance in the angle. Surgeons ensured that the orientation of the stent on the applicator was appropriate for the desired nasal implantation and inspected the angle with a gonioprism to ensure good view at nasal implant location. The gonioscope was placed on the cornea and the surgical microscope was repositioned as needed to visualize the trabecular meshwork through the gonioprism on the nasal side of the eye.

The anterior chamber was traversed with the applicator (the implant was on the tip of applicator) and the trabecular meshwork located. The leading edge of the device was gently slid through the trabecular meshwork and into Schlemm's canal at the nasal position (3 to 4 o'clock for the right eye; 9 to 8 o'clock for the left eye) with the tip of

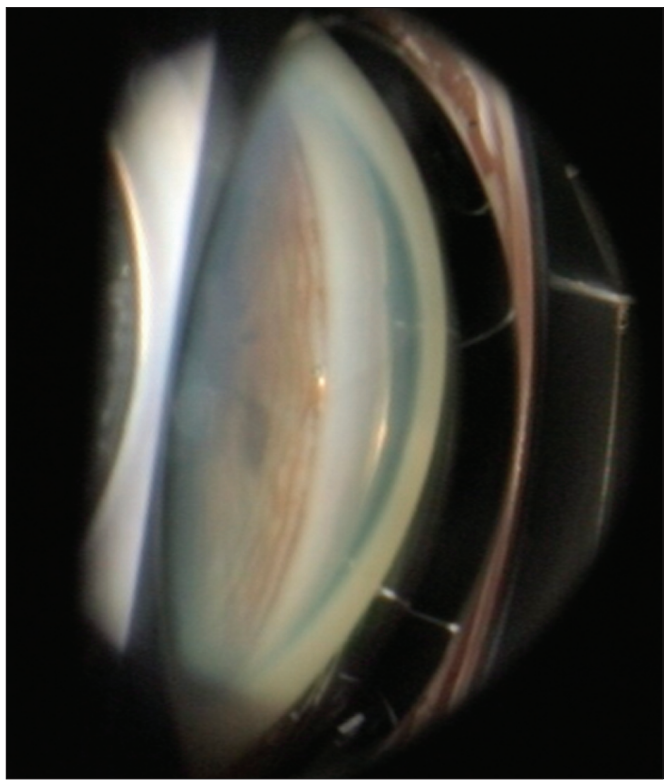

Fig. 2 - *Postoperative stent position, noting location of stent in Schlemm's canal.*

the implant directed inferior. If difficulty was encountered with the insertion at the primary location, surgeons were to try inserting about 0.5 clock hour inferior, and continue to move inferior as needed for subsequent attempts. Next, the device was released by pushing the button on the applicator, position of the stent was verified, and the applicator was withdrawn.

At the end of the procedure, the anterior chamber was flushed of any refluxed blood. A high-magnification examination was performed to confirm that the base of the implant was parallel with the circumferential axis of Schlemm's canal. Gently nudging the snorkel confirmed that the snorkel axis was parallel with the iris plane and that the base was well seated and fully through the trabecular meshwork.

The surgeon at the end of the procedure was asked to rate the ease of the implantation using a scale from 1 (least difficult) to 5 (most difficult) and to note the attempts of implantation.

Follow-up evaluations

Postoperative study visits were at day 1, week 1, and months 1, 2, 3, 6, and 12. Additional study visits have been scheduled for months 18 and 24. Every study visit included IOP measurement with Goldmann applanation tonometry, slit lamp examination, evaluation of number of glaucoma medications, and adverse event assessment. Additionally, stent location and condition was evaluated gonioscopically. Patients were considered to have had a successful outcome if any of the following criteria were observed at the 1-year postoperative follow-up examination: clinically significant reduction in IOP from screening baseline with or without glaucoma medications; IOP ≤18 mmHg with or without glaucoma medications; or reduction in baseline drug regimen. Efficacy was determined by IOP reductions and hypotensive medication reductions 1 year after surgery compared with baseline screening. The primary efficacy success measure was the proportion of subjects with an IOP ≤18 mmHg with or without medications.

Data analysis

The primary outcome measure was IOP as measured by Goldmann applanation tonometry. The secondary outcome measure was number and type of glaucoma medications preoperatively and postoperatively. Comparison of mean IOP at each study visit was evaluated using a paired-sample *t*-test. The a priori level of significance was 0.05. All analyses were performed with SAS software (version 9.1.3, SAS Institute, Cary, NC).

RESULTS

Patient demographics

The patient demographics are shown in Table I. All patients were diagnosed with concomitant glaucoma and cataract. Of all the patients (n=58), primary open-angle glaucoma was diagnosed in 43, pseudoexfoliation was diagnosed in 10, and pigmentary glaucoma was diagnosed in 5. Nine patients also had macular degeneration. Three patients had past central vein occlusion or venostasis.

Fifty-eight patients were enrolled in this study; 48 received the surgical treatment and met the study inclusion criteria, comprising the PP cohort (one patient did not have a stent implanted, 6 patients did not have cataract surgery, and 3 patients did not meet the inclusion criteria because their IOP was too low). Of the 48 patients in the PP cohort, 42 are part of the 12-month efficacy analysis. (Two patients underwent trabeculectomy after stent implantation at 11 days and 6 months, respectively; two other patients had died before 12-month data could be compiled; and two subjects missed their 12-month follow-up visit.)

IOP-lowering efficacy

At month 12, the mean IOP reduction from the medicated screening ranged from 3.4 to 5.9 mmHg (14.2% to

TABLE I - PATIENT DEMOGRAPHICS: PER-PROTOCOL POPULATION (N=47)

Characteristics	Values
Age, y, mean ± SD	76.2±6.7
Gender, n (%)	
Male	18 (38)
Female	29 (62)
Race, n (%)	
Caucasian	46 (98)
Hispanic	1 (2)
Medical history, n (%)	
Vascular disease	6 (13)
Systemic hypertension 2	6 (55)
Diabetes	5 (11)

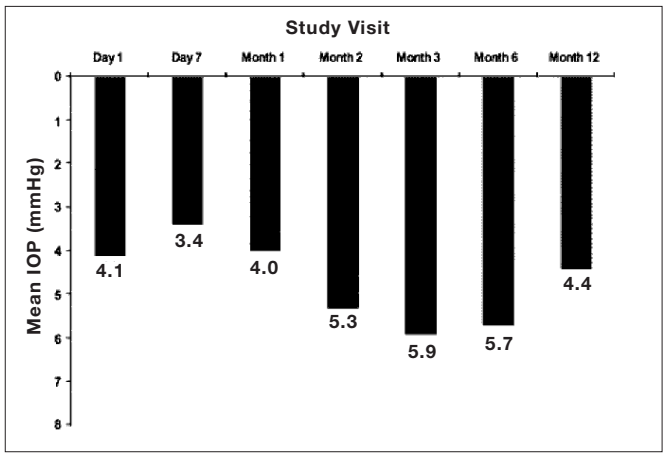

Fig. 3 - *Mean intraocular pressure reduction (in mmHg) at each study visit through month 12.*

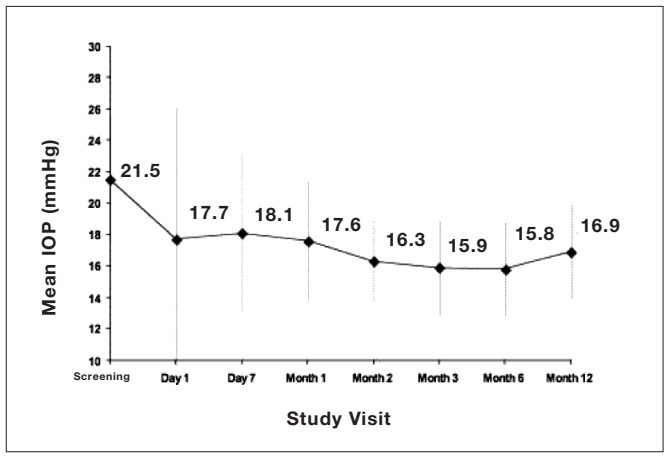

Fig. 4 - *Mean intraocular pressure from baseline through month 12 in per-protocol patient group.*

25.9%, n=42, Fig. 3). Mean IOP is illustrated in Figure 4. Patients were also more likely to reach low target levels of IOP 12 months after implantation of the study stent with fewer topical ocular hypotensive agents than were needed prior to implantation. After implantation of the study stent, 61.9% had an IOP ≤18 mmHg, 26.2% had an IOP ≤15 mmHg, and 2.4% had an IOP ≤12 mmHg. Moreover, 69.1% (29/42) had IOP ≤21 mmHg without the use of any ocular hypotensive medications.

Reduction in glaucoma medication

At screening, the mean number of medications was 1.6±0.8 for the patients in the PP arm and 1.7±0.9 for the ITT arm. Postoperatively, the mean number of medications in the PP group decreased to between 0.3 and 0.5, without substantial diminution of effect (Fig. 5). The mean decrease from the number of medications at screening throughout 12 months of postoperative evaluation ranged from 1.0 to 1.3, with a mean decrease of 1.2±0.7 at month 12 ($p<0.0001$).

Safety

The safety analysis included the ITT study population. There were two intraoperative surgical adverse events. Anterior chamber collapse was observed in one patient; no treatment was required and the event resolved at time of surgery. In one patient, the surgeon was unable to implant the stent. There was no touching of the endothelium, no excessive bleeding, no iris damage, or hyphema

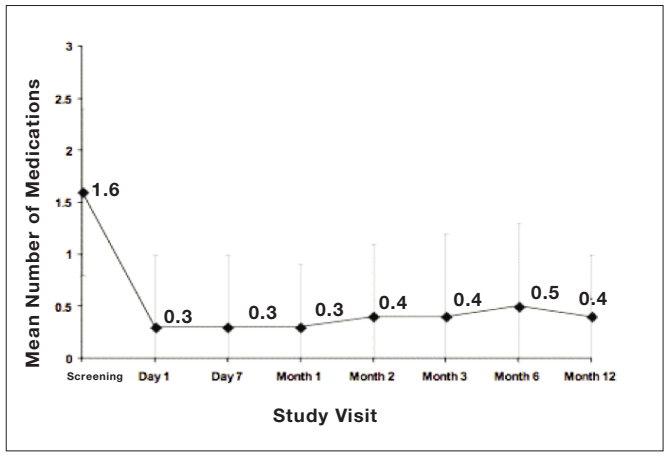

Fig. 5 - *Mean number of ocular hypotensive medications from baseline through month 12.*

observed. There was no reported incidence of hypotony, postsurgical flat chambers, and/or choroidal effusion, and no significant reductions in visual acuity were reported at 12 months.

One patient had a postoperative complication associated with the cataract surgery. A vitreous wick was incarcerated in the paracentesis inferiorly and was removed by vitrectomy at 1 day postoperatively. Two other patients had posterior capsulotomy for posterior capsule opacification.

Implantation of the stent could be achieved in one attempt in 50% and in one or two attempts in 84%. Moreover, 66% of the surgeons rated the ease of implant procedure as either 1 or 2 (1 least difficult, scale 1–5).

At 1 month postoperatively, one patient underwent corneal paracentesis to reduce IOP. Three patients underwent secondary surgical intervention for stent malposition to either reposition the stent (n=1) or replace the stent (n=2).

For 6 patients, the stent was perceived as malpositioned but no secondary surgical intervention was performed. For most of these patients, it seemed as though the stent was actually functioning, since the patients experienced a reduction in IOP and number of medications from baseline.

The stents appeared obstructed in 7 patients. For one patient, argon laser was used to remove iris tissue that was in contact with the lumen of the stent. Two patients underwent injection of recombinant tissue plasminogen activator in an attempt to clear the lumen of the stent; however, both of them had a trabeculectomy performed later on. The remaining 4 subjects improved in both IOP and number of medications, suggesting that the stents were functional in these patients. Two patients died during the course of the study due to reasons unrelated to the stent implantation.

Mean visual acuity at month 12 was significantly improved from baseline: mean best-corrected visual acuity was (logMar) 0.45 at baseline and 0.15 at month 12 ($p<0.001$). Additionally, no subjects lost more than one line of Snellen visual acuity.

DISCUSSION

In the present study, the implantation of the stent in combination with the extraction of cataract and implantation of an IOL resulted in a statistically significant mean IOP reduction of 4.4 mmHg ($p<0.001$), even from a medicated baseline. This reduction in IOP is greater than IOP reductions previously reported for cataract surgery alone. Numerous studies have shown a reduction in IOP after uncomplicated clear corneal phacoemulsification surgery, primarily ranging from 2–3 mmHg in eyes that also had glaucoma (2-4).

Reducing IOP is the only proven method of slowing or halting glaucomatous progression and every millimeter of IOP lowering counts. The EMGT trial demonstrated that every 1 mmHg decrease in IOP equates to a 10% risk reduction in glaucomatous progression (5). Although difficult to extrapolate, the magnitude of IOP lowering seen in the present study suggests that the iStent may substantially reduce the risk of glaucomatous progression in patients with primary open-angle glaucoma.

The stent significantly reduced the mean number of medications needed to control IOP at 1 year (1.2 fewer medications, $p<0.001$) and allowed most patients to completely discontinue all glaucoma medications. As patient compliance is an ongoing concern for most glaucoma physicians, eliminating or reducing the patient's reliance on medications or daily instillations is a key clinical factor in controlling progression of glaucoma. The reduction in topical medications seen in the present study is also likely to improve patients' ocular surface integrity as chronic use of glaucoma medications can result in corneal damage and inflammation (6). In addition, other potential benefits include improved convenience for patients, increased quality of life, decreased potential for drug interaction, and decreased healthcare costs as a result of fewer requisite prescriptions and office visits.

Implanting the stent via the same small temporal clear corneal incision used to perform phacoemulsification and place the intraocular lens resulted in no additional ocular trauma. In addition, the ab interno gonioscopic and conjunctival-sparing procedure was less invasive than traditional ab externo procedures. Initial surgeon learning curves may have contributed to the number of secondary surgeries required and the initial number of implantation difficulties.

The stent implantation does require some technical abilities in order for this procedure to be successful. The surgical protocol necessitates the surgeon to be familiar with gonioscopy and the angle appearance and correctly visualize the angle structures before attempting the implantation. Slight angle bleeding is expected during stent implantation and confirms stent placement in the canal and was not found to interfere with the success in this study. The study stent required very little additional time to implant beyond the time requirement of phacoemulsification.

The IOP-lowering efficacy of the stent observed in the present study supports earlier theoretical and in vitro work in which Zhou introduced a hypothesis that evaluated the effect of a theoretical channel created through the trabecular meshwork (a trabecular bypass) on the facility of outflow and IOP and Bahler and associates confirmed Zhou's finding in the laboratory when they conducted an in vitro study. The result from placing a single stent was that IOP was lowered from 21.4±3.8 mmHg to 12.4±4.2 mmHg ($p<0.001$). This corresponds to an 84% increase in facility of outflow (7).

This study is not without limitations. First, a randomized, controlled trial is warranted to demonstrate the IOP-lowering efficacy of the stent relative to phacoemulsification alone. Currently a trial with this design as part of a submission to the US Food and Drug Administration has been undertaken. In addition, longer duration of follow-up is needed to truly evaluate the safety and efficacy of the device. This report is of a 12-month interim analysis. Patients were followed for 24 months in this trial and these data will be presented in subsequent reports.

CONCLUSION

In this interim 12-month analysis of subjects with glaucoma and cataracts, the stent provided significant reductions in IOP and reduced patient reliance on topical ocular hypotensive medications throughout the follow-up period. The amount of IOP lowering exceeded the IOP levels that have been reported by cataract surgery alone (2-4). The stent was well tolerated and biocompatible in patients and most adverse events were related to the surgical procedure. While these results are promising, longer-term follow-up and additional clinical studies are warranted and ongoing.

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