ALLERGAN – CONFIDENTIAL

The following contains confidential, proprietary information
which is the property of Allergan

Study Title:	A Prospective, Multicenter Clinical Trial Designed to Evaluate the Safety and Effectiveness of the XEN45 Glaucoma Treatment System in Patients with Angle Closure Glaucoma
Protocol Number:	Protocol 1924-701-007
Product Name:	XEN45 Glaucoma Treatment System
Development Phase:	Pivotal
Sponsor:	Allergan 2525 Dupont Drive Irvine, California 92612 USA [redacted]
Manufacturer:	Allergan
Safety reporting:	IR-CLINICAL-SAE@Allergan.com Fax +1-714-796-9504 or Back-up Fax +1-714-246-5295

Names and contact information of Allergan study personnel are provided in the supplementary Study Contacts page. Allergan shall maintain an updated list of principal investigators, the coordinating investigator, investigational sites, and other institutions involved in the clinical investigation.

INVESTIGATOR SIGNATURE PAGE

Study Title:	A Prospective, Multicenter Clinical Trial Designed to Evaluate the Safety and Effectiveness of the XEN45 Glaucoma Treatment System in Patients with Angle Closure Glaucoma
Protocol Number:	1924-701-007
Protocol Date:	October 4, 2017
Product Name:	XEN45 Glaucoma Treatment System
Investigator:	
Study Location:	

I agree to:

- Implement and conduct this study diligently and in strict compliance with this protocol, GCP, and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Ethics Committee (EC), or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date
Investigator Printed Name	Signature	Date

RETURN TO ALLERGAN

Synopsis

NUMBER AND TITLE OF STUDY:
1924-701-007

A Prospective, Multicenter Clinical Trial Designed to Evaluate the Safety and Effectiveness of the XEN45 Glaucoma Treatment System in Patients with Angle Closure Glaucoma

DEVELOPMENT PHASE: Pivotal

STUDY CENTERS: Approximately 15 sites in the Asia-Pacific and European Union regions

NUMBER OF PATIENTS: Approximately 65 patients will be unilaterally implanted with the XEN45 Glaucoma Treatment System (hereafter referred to as XEN) either as a stand-alone procedure or in combination with lens extraction. A subset of this population will include a maximum of 10 phakic patients (ie, will not undergo lens extraction at time of XEN surgery) and 10 patients with a history of trabeculectomy or glaucoma shunt implantation, to allow for a representative angle closure glaucoma (ACG) patient population in the study.

OBJECTIVES:

The purpose of the trial is to evaluate the safety and intraocular pressure (IOP)-lowering effectiveness of XEN in up to 65 patients with ACG.

Study design:

This is a prospective, multicenter, single-arm, open-label clinical trial to evaluate the safety and IOP-lowering effectiveness of XEN in patients with ACG.

DIAGNOSIS AND CRITERIA FOR INCLUSION/EXCLUSION:
Adult patients with ACG with uncontrolled IOP after having failed previous medical and/or surgical treatments. If both eyes qualify for inclusion, then the eye with the higher IOP at baseline will be the study eye. If both eyes qualify for inclusion and have the same baseline IOP, then the right eye will be the study eye.

KEY INCLUSION:

- Diagnosis of ACG defined as areas of iridotrabecular contact present in ≥ 2 quadrants and glaucomatous damage to optic disc and visual field, in the study eye.

  Note: Procedures to widen the iridocorneal angle in the target quadrant (eg, goniosynechialysis, lens extraction [clear lens extraction or cataract surgery/phacoemulsification], and intraocular lens [IOL] placement) are permitted on the operative day (Day 1) at the investigator's discretion; however, all procedures must be successful and uncomplicated for patients to receive XEN. A maximum of approximately 10 phakic patients (ie, will not undergo lens extraction at time of XEN surgery) is allowed in the study.
- In the opinion of the investigator, the IOP is uncontrolled in the study eye after having failed previous medical and/or surgical treatment (eg, topical IOP-lowering medications, laser peripheral iridotomy, lens extraction, glaucoma shunt implantation, trabeculectomy)
- IOP of ≥ 20 mm Hg and ≤ 35 mm Hg by Goldmann applanation tonometry in the study eye at screening and baseline (Hour 0)
- Study eye has healthy, free, and mobile conjunctiva in the target quadrant
- Glaucomatous visual field loss with a mean deviation score of at least -1 dB in the study eye that, in the opinion of the investigator, is not functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression are excluded)

KEY EXCLUSION:

- Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the

investigator) or those on pharmacologic blood thinners other than aspirin (up to 100 mg/day)

- History of dermatologic keloid formation

Key Ocular Criteria for Exclusion

- Open angle glaucoma, active acute angle closure attack, congenital glaucoma, juvenile glaucoma, secondary glaucoma (eg, anterior subluxation of the lens, iris or ciliary body cysts, active iris and angle neovascularization, iridocorneal endothelial syndrome, anterior uveitis, drug-induced) in the study eye
- History of following surgeries in the study eye
  - incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions
  - corneal graft including partial grafts such as Descemet's stripping endothelial keratoplasty and Descemet's membrane endothelial keratoplasty
  - previous laser or incisional intraocular surgery that might interfere with the outcome of this trial

  However, previous incisional and laser glaucoma surgeries (eg, trabeculectomy, glaucoma shunt implantation, laser trabeculoplasty, iridotomy, cilioablative procedures) or uncomplicated phacoemulsification with IOL, occurring more than 3 months prior to screening, are allowed in the study eye. A maximum 10 patients with a history of trabeculectomy or glaucoma shunt implantation (away from the target quadrant) is allowed in this study.
- Previous glaucoma shunt implantation in the target quadrant in the study eye
- Visually significant cataract (ie, BCVA 20/40 Snellen equivalent using LogMar chart at screening and baseline) in the study eye that will not be removed at the time of XEN implantation
- Study eye with best-corrected visual acuity (BCVA) worse than 20/100 (Snellen equivalent using LogMar chart) at screening and baseline; fellow (non-study) eye with BCVA worse than 20/200 at screening and baseline. A patient with a cataract in the study eye and BCVA worse than 20/100 in the study eye may be included if, in the opinion of the investigator, the patient is likely to have BCVA of 20/40 or better after cataract surgery that will be performed at the time of XEN implantation.

TEST PRODUCT AND MODE OF ADMINISTRATION:

XEN45 Glaucoma Treatment System, *ab interno* surgical approach and implantation. XEN45 Glaucoma Treatment System is comprised of the XEN Gel Implant (also referred to as Gel Implant) and XEN Injector (also referred to as Injector). The XEN Injector is a sterile, single use mechanical delivery system for the XEN Gel Implant. The needle of the sterile XEN Injector preloaded with the XEN Gel Implant is advanced through the peripheral cornea and across the anterior chamber (ie, *ab interno*) toward the target quadrant.

DURATION OF STUDY: Screening period: 60 days. Follow-up Period: 12 months after device implantation.

RESPONSE MEASURES:

Effectiveness:

- IOP (Hour 0) measured by Goldmann applanation tonometry
- Number of concomitant IOP-lowering medications

Health Outcome Measures:

Patient ocular symptom questionnaire

Safety:

Safety assessments include adverse events (AEs), pregnancy test and ocular parameters as determined through assessments of visual acuity, visual field, pachymetry, biomicroscopic slit lamp, gonioscopy, and ophthalmoscopic examinations

STATISTICAL METHODS:

Sample Size Calculation:

Fifty patients will provide a precision of at least ±0.145 to estimate the proportion of patients achieving an IOP reduction ≥ 20% at 12 months on the same number or fewer IOP-lowering medications compared with baseline based on a 95% exact Clopper-Pearson CI for binomial proportions. Sixty-five patients will be implanted to ensure at least 50 evaluable patients with 12 months of follow-up.

Study Population:

Implanted population: The implanted population will include all patients implanted with XEN. This population will be used for all primary and secondary effectiveness analyses and all safety analyses.

Effectiveness:

Primary Effectiveness Analysis

The primary effectiveness analysis will estimate the proportion of patients, with corresponding 2-sided 95% CI, that achieve at least a 20% reduction from baseline Hour 0 IOP while on the same number or fewer IOP-lowering medications at Month 12 compared with baseline using a repeated measures logistic regression model. The model will include visit and baseline IOP as fixed effects with data from Months 1, 3, 6, 8, 10, and 12. The primary effectiveness analysis will be performed using the implanted population.

Secondary Effectiveness Analyses

The mean and 2-sided 95% CI for raw IOP with the corresponding change from baseline will be estimated using a mixed-effects model for repeated measurements including all post-baseline visits with visit and baseline IOP as fixed effects. Additionally, the number of IOP-lowering medications will be summarized by visit with descriptive statistics (mean, standard deviation, minimum, maximum) and 2-sided 95% CI for the mean. The secondary effectiveness analyses will be performed using the implanted population.

Safety:

Safety analyses will be performed using the implanted population. The number and percentage of patients reporting AEs will be tabulated regardless of causality. AEs, adverse device effects (ADEs), BCVA, line change in BCVA from baseline, biomicroscopic slit lamp, and ophthalmoscopy findings will be summarized by frequencies at each visit.

Table of Contents

List of Tables

List of Figures

Table 1-1 Schedule of Visits and Procedures

Study Period	Screening[a]	Baseline	Operative day Day 1	Day 2	Day 8	Week 2	Month 1	Month 3	Month 6	Month 8	Month 10	Month 12/ Early exit visit
Visit Window	up to 60 days	Day -5 to Day -7	NA	NA	±2 days	±3 days	±5 days	±10 days	±14 days	±14 days	±14 days	± 14 days
Consent/Authorization	X											
Inclusion/Exclusion Criteria	X	X	X									
Patient Demographics	X											
Medical/Ophthalmic History[b]	X	X										
Patient ocular symptom questionnaire	X							X	X			X
Concomitant Medications, Procedures, Therapies	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (Urine)[c]	X	X										X
Study Treatment			X									
Examinations: Recommended to be performed in the following order from top to bottom												
Manifest refraction[d]	OU	OU						SE				OU
Best-corrected visual acuity (Snellen equivalent using LogMar)	OU	OU					SE	SE	SE	SE	SE	OU
Visual Field[e] test	OU											OU[f]
Biomicroscopic slit lamp examination	OU	OU		SE	SE	SE	SE	SE	SE	SE	SE	OU
Intraocular pressure measurement (tonometry)[g]	OU	OU[h]		SE	SE	SE	SE	SE	SE	SE	SE	OU[h]
Pachymetry	OU											OU
Gonioscopy	OU						SE		SE			OU
Ophthalmoscopy[i]	OU	OU					SE	SE	SE			OU

NA = not applicable; SE = study eye; OU = both eyes

[a] Screening examinations can be completed on more than one visit within the allowable window

[b] Medical history, surgical history, ophthalmic history, and ophthalmic surgical history will be collected

[c] Applicable to females of childbearing potential

[d] Manifest refraction will be performed during any visit if best-corrected visual acuity (BCVA) reduction of ≥ 2 lines is observed since the last BCVA examination.

[e] Visual field test performed up to 6 months prior to operative day (Day 1) is allowed

[f] If the visual field assessment at this visit shows progression of visual field loss from baseline (defined as a worsening of at least 3 dB in mean deviation score), a second visual field test must be performed within one week to confirm the progression. If the second visual field test is not confirmatory or is equivocal, a third test must be performed within a week to confirm results.

[g] Measurement of intraocular pressure (IOP) must be performed at Hour 0; IOP must be completed prior to pachymetry, gonioscopy, and ophthalmoscopy.

[h] Diurnal IOP measurements: Three IOP measurements taken over an eight-hour period on the same day approximately four hours apart, at Hour 0 (± 1 hour), Hour 4 = Hour 0 + 4 hours (± 30 minutes), and Hour 8 = Hour 0 + 8 hours (± 30 minutes)

[i] Non-dilated ophthalmoscopy may be performed if the investigator believes that pupil dilation may put the patient at risk. When dilation is used, ophthalmoscopy should be the last examination.

1. Abbreviations and Terms

Term/Abbreviation	Definition
ACG	angle closure glaucoma
ADE	adverse device effect
AE	adverse event
ALPI	argon laser peripheral iridoplasty
BCVA	best-corrected visual acuity
BID	twice daily
EC	Ethics Committee
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GON	glaucomatous optic neuropathy
IC	informed consent
ICH	International Conference on Harmonisation
IDFU	investigational directions for use
IOL	intraocular lens
IOP	intraocular pressure
ISO	International Organization for Standardization
ITC	iridotrabecular contact
LPI	laser peripheral iridotomy
OAG	open angle glaucoma
PAC	primary angle closure
PACG	primary angle closure glaucoma
PACS	primary angle closure suspect
PAS	peripheral anterior synechiae
POAG	primary open angle glaucoma
SADE	serious adverse device effect
SITA	Swedish interactive thresholding algorithm
TID	three times daily
USADE	unanticipated serious adverse device effect
QID	four times daily
QD	once daily
WOCF	worst observation carried forward
XEN	XEN45 glaucoma treatment system

2. Background, Risk and Benefit, and Clinical Rationale

2.1 Background

Glaucoma is the second leading cause of visual impairment and blindness worldwide and a significant healthcare problem, with a substantial humanistic and economic burden that increases with disease progression. More than 79 million people are projected to suffer from glaucoma by 2020, and approximately 25% of all these cases will be angle closure glaucoma (ACG) (Quigley 2006). ACG carries a heavier burden of visual morbidity than open angle glaucoma (OAG) (Foster 2002). The prevalence of ACG differs among different ethnic groups with the highest rates reported in Inuit, Chinese, and other Asian populations (Marchini 2015).

ACG is a group of diseases characterized by the apposition of the peripheral iris against the trabecular meshwork, resulting in the obstruction of aqueous outflow. Based on the etiology, angle closure can be primary, secondary to another eye disease, or drug-induced (American Association of Ophthalmology 2013). The current international classification of angle closure includes 3 conceptual stages corresponding to the progression of the disease (Weinreb 2006). Primary angle closure suspect (PACS) is characterized by iridotrabecular contact (ITC), normal intraocular pressure (IOP), absence of peripheral anterior synechiae (PAS), and no evidence of glaucomatous optic neuropathy (GON). Primary angle closure (PAC) involves ITC resulting in raised IOP and/or PAS, and no evidence of GON. Primary angle closure glaucoma (PACG) is defined by presence of ITC plus evidence of GON; however, PAS and raised IOP may be absent at the time of initial examination. In this classification scheme, the extent of ITC in each stage was originally defined to be ≥ 3 quadrants; however, recent guidelines have reduced the ITC diagnostic threshold to ≥ 2 quadrants to avoid under-diagnosis of patients along this ACG spectrum (Weinreb 2006; European Glaucoma Society 2014). The glaucomatous optic neuropathy defined in this classification include structural (eg, optic disc) and functional (eg, visual field) abnormalities consistent with glaucoma. In cases where there is advanced vision loss and automated perimetry cannot be performed, glaucoma diagnosis is based on structural damage to the optic disc. Conversely, in cases where the optic disc cannot be visualized, glaucoma can be diagnosed on the basis of visual acuity < 3/60 and either IOP > 24 mm Hg or signs of previous filtering surgery (Weinreb 2006).

Other classifications of ACG have been used in the past, such as the subcategories of acute, subacute/intermittent, and chronic, which are based on the presence or absence of symptoms; however, a major flaw in this scheme is the lack of emphasis on visual function. Furthermore,

this classification often assigns all the subgroups as "glaucoma," regardless of whether there is glaucomatous optic neuropathy. ACG can also be categorized based on the 4 levels of anatomic mechanisms of angle closure, including, iris (eg, pupillary block), ciliary body (eg, plateau iris), lens (eg, phacomorphic), and posterior to the lens (eg, malignant glaucoma), and this scheme can be used in combination with disease stage to determine the optimal treatment approach.

Current ACG treatment consists of IOP-reducing laser procedures, lens extraction, medications, and incisional surgeries. The first line treatments involve establishing the target pressure, usually by relieving pupillary block using laser peripheral iridotomy (LPI) and/or lens extraction (Azuara-Blanco 2011; Azuara-Blanco 2016). When indicated, argon laser peripheral iridoplasty (ALPI) may also be used to further open an appositionally closed angle. LPI alone is often not effective in preventing progression from PACS and PAC to PACG (Sun 2017). Furthermore, the vast majority of patients with ACG, with reports as high as 94 to 100% in both Asian and North American patients, require additional IOP control with topical medications (Rosman 2002). The IOP is controlled for approximately 40% of PACG patients on a combination of LPI and topical medications, and the remaining proportion of patients require additional laser (eg, ALPI) or incisional surgical interventions (eg, filtering surgery) (Rosman 2002).

The most commonly performed filtering surgery is trabeculectomy. Although effective, trabeculectomy is an invasive, resource-intensive procedure that has been associated with high rates of significant post-surgical complications, treatment failure, and vision-threatening adverse effects, and a long-term IOP control may still require hypotensive medications post-surgery (Chen 2009; Sun 2017). Lens extraction may also be performed in combination with a filtering procedure to allow for angle-widening and greater IOP-lowering (Chen 2015; Murthy 2006; Wang 2012). Although phacoemulsification and lens extraction alone can be an ACG treatment, current literature suggests combination phacotrabeculectomy and trabeculectomy in patients with PACG have similar long-term efficacy results at 1 to 2 years, including similar IOP reduction, complete success rate, rate of functioning blebs, number of IOP-lowering medications, and surgical complications (Murthy 2006; Wang 2012).

Goniosynechialysis, which can also be performed in combination with lens extraction, might also be used as surgical treatment in cases with extensive PAS to strip PAS from the trabecular surface in the angle and improve trabecular flow. Although it is effective in opening a closed angle and lowering IOP with an overall success rate of 80% (Fang 2010; Qing 2012), it does not have long-term effectiveness and may be associated with

complications. Glaucoma drainage devices (eg, Baerveldt implant, Ahmed valve) may be considered in PACG when medication and/or trabeculectomy fail to control IOP, but are also associated with numerous postoperative complications (Gedde 2012; Marchini 2015; Saheb 2014). Unlike OAG treatment options, there are no minimally invasive glaucoma surgery options available for ACG, due to unsuitable device designs, to serve as a safer and less invasive alternative to be used earlier in the treatment paradigm.

XEN45 Glaucoma Treatment System (referred to as XEN), comprised of the XEN Gel Implant (also referred to as the Gel Implant) and the XEN Injector (also referred to as the Injector) potentially alleviates this unmet need. Approximately 6 mm long and as wide as a human hair, this soft gelatinous stent is implanted via an *ab interno* surgical approach through a small, self-sealing corneal incision, to facilitate aqueous humor drainage from the anterior chamber to the subconjunctival space. The gelatin imparts hydrophilic properties that allow the Gel Implant to conform to the ocular tissue by expanding when hydrated upon contact with the aqueous humor. This expansion might minimize issues such as migration, erosion, and corneal endothelial damage observed in stents with synthetic materials.

The *ab interno* surgical approach for XEN is less invasive than traditional glaucoma surgeries and has several other advantages, including minimal trauma to the conjunctiva, maintenance of the natural drainage pathways, reduced scarring response, and the ability to accurately place the device under direct visualization of anatomy. Minimizing damage to the conjunctiva allows the possibility of future glaucoma surgery.

XEN is cleared in the United States for the management of refractory glaucomas, including cases when previous surgical treatment has failed, cases of primary open angle glaucoma (POAG), and pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to maximum tolerated medical therapy. XEN is approved in multiple countries worldwide to reduce IOP in patients with POAG when previous medical treatments have failed.

XEN was prospectively studied in the United States in a multicenter, single-arm, open-label, clinical trial to evaluate its safety and effectiveness (XEN P13-001 Clinical Study Report; Grover 2017). This 12-month study was conducted in patients with refractory glaucoma when previous filtering or cilioablative procedures failed, or by experience was known to not provide satisfactory results, or IOP was unresponsive to maximally tolerated medication. Of the 65 subjects implanted (intent-to-treat population), at baseline, 85% of subjects had failed prior glaucoma procedures, 85% were using $\geq$ 3 hypotensives, and mean medicated IOP (SD) was 25.1 (3.7) mm Hg. At Month 12, 76% of subjects achieved $\geq$ 20% IOP reduction from

baseline on the same or fewer medications; mean IOP reduction (SEM) was 6.4 (1.1) mm Hg (95% CI: 4.2, 8.7). Mean medication use (SD) decreased from 3.5 (1.0) at baseline (N = 65) to 1.7 (1.5) at Month 12 (n = 52). At 12 months, 13.8% of subjects required secondary surgery. There were no intraoperative complications. Ocular adverse events (AEs) were mostly mild to moderate resolving without sequelae; hypotony and needling procedures were most frequently reported. Of the 16 hypotony cases, 13 occurred on Day 1 and resolved by Day 27; none required surgical intervention. Of the 21 subjects who required needling, 17 experienced no complications.

The safety and efficacy of XEN has also been previously tested in a study conducted outside the United States at two clinical sites in 23 eyes of 20 subjects (mean age, 64.5 ± 14.4 years) (R-008 Clinical Study Report). The majority (16/20, 70%) of subjects had a diagnosis of POAG, 4 subjects (13%) had a diagnosis of pigmentary glaucoma and 1 subject (4%) had a diagnosis of pseudoexfoliative glaucoma. At baseline, the mean medicated IOP was 24.3 mm Hg (range, 18.0 - 42.5 mm Hg), and the mean number of medications of 2.8 (± 1.3) and the median at baseline being 3.0 medications. The 12-month results indicated that XEN provides a safe means to reduce IOP in subjects with glaucoma. The primary effectiveness outcome (change in mean IOP from baseline to 12 months) indicated that XEN lowered IOP by a mean of 47% while also reducing the number of IOP-lowering medications by a mean of nearly 2 medications. In addition, the mean IOP at 12 months was reduced to 12.1 mm Hg from a medicated baseline IOP of 24.3 mm Hg. This study further supports the safety and effectiveness of XEN.

Furthermore, retrospective case study experience has demonstrated its clinical feasibility in patients with PACG/narrow angles (Millan 2017). This study was performed outside the United States in 13 patients with PACG. The Gel Implant (referred to as Gel Stent) was implanted in 14 eyes (93.3%) immediately after cataract extraction, and in 1 eye (6.7%) as a standalone procedure. At the 12-month follow-up, the mean IOP decreased from 19.5 mm Hg at baseline (n = 15) to 13.0 mm Hg (n = 8). All eyes with available data at Month 12 achieved ≥ 20% IOP reduction (mean IOP reduction, −6.5 mm Hg). The mean number of medications decreased from 3.3 preoperatively to 0.9 (72% decrease) at Month 12. One patient was considered a non-responder at Month 12, requiring an additional glaucoma-related surgical intervention. Transient postoperative hyphema (microscopic, 1 eye; Grade I, 2 eyes) was the most common postoperative complication, followed by cystoid macular edema (1 eye, after combined surgery). These results provide supportive evidence for safety and effectiveness of XEN in patients with ACG/narrow angles.

The current study is a prospective, multicenter, single arm, open-label clinical trial in patients with ACG. Approximately 65 patients will be unilaterally implanted with XEN and followed for 12 months to evaluate its safety and effectiveness.

The sponsor will conduct this trial in accordance with all applicable regulations.

2.2 Risk and Benefit

Glaucoma is the second leading cause of visual impairment and blindness worldwide. It results in a substantial economic burden for patients, their families, and society due to sizeable costs of disease management, vision loss, and lost productivity. Current treatment modalities for ACG have significant limitations regarding IOP-lowering effectiveness, adjunctive medication use, requirement for concomitant cataract surgery, complications, and cost. XEN provides effective, minimally invasive, long-lasting, safe, and durable IOP-lowering method through subconjunctival drainage. Use of XEN in patients with ACG might be associated with complications related to narrow angle including aqueous misdirection, cataract formation/progression, choroidal effusion, choroidal hemorrhage, chronic iritis, corneal edema, endothelial touch, flat anterior chamber, hyphema (> 1 week), Gel Implant blockage, iris atrophy, shallow anterior chamber, and suprachoroidal hemorrhage. These risks can be mitigated with appropriate concomitant surgical procedures that widen the angle (eg, cataract extraction, goniosynechiaelysis, iridoplasty). Furthermore, retrospective/case series data available to date on narrow and closed angle patients suggest similar safety as in patients with OAG. Taken together, the benefits outweigh the risks of XEN use in ACG patients.

2.3 Clinical Rationale

Considering the ineffectiveness and complications of the available surgical treatments for controlling IOP in ACG, XEN might offer a safe and effective mode of IOP-lowering.

3. Study Objectives and Clinical Hypotheses

3.1 Study Objectives

The purpose of the trial is to evaluate the safety and IOP-lowering effectiveness of XEN in up to 65 patients with ACG.

3.2 Clinical Hypotheses

XEN will have an IOP-lowering effect and an acceptable safety profile in patients with ACG following implantation.

4. Study Design

4.1 Structure

This is a prospective, multicenter, single-arm, open-label clinical trial designed to demonstrate the safety and IOP-lowering effectiveness of XEN. Following completion of all required preoperative examinations, and if the patient meets the study criteria, XEN will be unilaterally implanted. Approximately 65 patients will be enrolled at up to approximately 15 clinical sites to be unilaterally implanted with XEN and followed for up to 12 months postoperatively.

4.2 Duration

The study will span a total of approximately 14 months including a maximum of 2 months between screening and baseline visits and for up to 12 months for follow-up.

4.3 Treatment Groups and Treatment Regimen

4.3.1 Study Treatment

XEN45 Glaucoma Treatment System, comprised of the XEN Gel Implant and XEN Injector.

4.3.2 Methods for Masking

Not applicable.

4.4 Permissible and Prohibited Medications/Treatments

4.4.1 Permissible Medications/Treatments

Use of concomitant medications other than the prohibited medications (Section 4.4.2) is allowed. The use of any concomitant medication or procedure, prescription or over-the-counter, is to be recorded on the patient's electronic case report form (eCRF) at each visit along with the reason the medication is taken. Prior medications will be recorded as part of the medical history on the participant's eCRF during the first study visit.

Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. If concurrent medications may have an effect on study outcomes, these medications must be administered in dosages that remain constant throughout the entire duration of the study. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

Treatment of the fellow (non-study) eye is not restricted, and fellow eyes will receive appropriate medical and/or surgical treatment, including IOP-lowering medications, per the investigator's discretion.

Use of ocular decongestants or antihistamines is allowed if not taken within 2 days prior to a scheduled visit. Ocular decongestants or antihistamines may be restarted 3 days after implantation per the investigator's discretion.

Systemic beta-blocker containing medications are permitted, provided that the dose/dosing regimen has remained stable for at least 2 months prior to screening and is not anticipated to change throughout the duration of the study.

The use of systemic nonsteroidal antiinflammatory drugs is also permitted.

Procedures to widen the iridocorneal angle in the target quadrant (eg, goniosynechialysis, lens extraction [clear lens extraction or cataract surgery/phacoemulsification], and intraocular lens [IOL] placement) are permitted on the operative day (Day 1) at the investigator's discretion; however, all procedures must be successful and uncomplicated for patients to receive XEN. If there are complications that would be significant enough to impact the study results, the patient will be exited from the study. Such complications include, but are not limited to, severe corneal burn, vitreous removal/vitrectomy required, severe anterior chamber injuries, or complications requiring the placement of an anterior chamber lens.

Medications and procedures required for pre-operative, operative, and postoperative management (See Protocol Procedure Manual), including the unlikely event that XEN requires removal for significant safety reasons, are permitted at the investigator's discretion.

4.4.1.1 IOP-lowering Medications

Systemic and topical (study eye only) IOP-lowering medications, will be suspended on the day of surgery (operative day [Day 1]); no washout period is required. They may be introduced postoperatively to manage elevated IOP. At least one of the following criteria must be met to introduce IOP-lowering medications postoperatively:

- Investigator determines IOP is not at target for the patient
- Progression of optic nerve cupping (vertical cup-to-disc ratio)
- Progression of visual field loss (confirmed with a second visual field test within one week).

It is recommended that the medications are prescribed in a step-wise fashion by introducing one drug class at a time. Prior to changing the first postoperative medication or adding subsequent medication(s), the medication must be maintained at a dosage and frequency recommended by the manufacturer's labeling for a reasonable trial period (eg, 1 week). Investigators will consider any contraindications the patient may have previously experienced (eg, allergic reaction or lack of efficacy) and/or the patient's current clinical situation. All changes to the IOP-lowering medication regimen, topical and systemic, will be recorded on the appropriate eCRF.

The investigator may consider discontinuing or lowering the dose or frequency of IOP-lowering medications whenever it is in the interest of patient safety, eg, cases of hypotony (IOP falls below 6 mm Hg).

4.4.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment is done with the safety of the study patient as the primary consideration. Therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. When possible, the sponsor is to be notified before the prohibited medication/treatment is administered.

Topical and systemic IOP-lowering medications must be suspended on the day of surgery (operative day [Day 1]); no washout period is required. If required, IOP-lowering medications may be introduced postoperatively to manage any elevated IOP (Section 4.4.1.1).

Use of contact lens in the study eye is prohibited during the study.

The following medications (or classes of medications) and treatment procedures are not permitted as concurrent therapy:

- Surgical procedures not related to XEN administration and postoperative management, including other incisional glaucoma treatments, such as trabeculectomy or glaucoma shunt implantation in the study eye, during the study period

- Laser glaucoma treatments, such as laser peripheral iridotomy and laser trabeculoplasty, in the study eye during the study period
- Subconjunctival, sub-Tenon's, intravitreal, or other ophthalmic injections of any medications in the study eye during the study period, with the exception of any medications required for bleb management (Section 6.1.3.2.2)
- Use of any nonstudy topical ophthalmic medications in the study eye, including use of IOP-lowering medications without meeting the criteria specified in Section 4.4.1.1, during the study period, with the exception of ocular decongestants or antihistamines (Section 4.4.1)
- Use of any ophthalmic (including topical, intravitreal, sub-Tenon's, subconjunctival) corticosteroids in either eye from 2 months prior to the baseline visit through study exit, except for use of preoperative, operative, and postoperative topical ocular corticosteroids related to surgery
- Initiation of or alterations in oral, intramuscular, or intravenous corticosteroids from 2 months prior to the baseline visit through the study exit
- Use of LATISSE® (bimatoprost for hypotrichosis) during the study period in the study eye

5. Study Population

5.1 Number of Patients

Approximately 65 patients unilaterally implanted with XEN either as a stand-alone procedure or in combination with lens extraction. A subset of this population will include a maximum of 10 phakic patients (ie, will not undergo lens extraction at time of XEN surgery) and 10 patients with a history of trabeculectomy or glaucoma shunt implantation, to allow for a representative ACG patient population in the study. Sixty-five patients will be implanted to ensure at least 50 evaluable patients with 12 months of follow-up. Patients will be enrolled at approximately 15 clinical sites in the Asia-Pacific and European regions.

5.2 Study Population Characteristics

Adult patients with ACG with uncontrolled IOP after having failed previous medical and/or surgical treatments will be included. If both eyes qualify for inclusion, then the eye with the

higher IOP at baseline will be the study eye. If both eyes qualify for inclusion and have the same baseline IOP, then the right eye will be the study eye. Qualified patients will be unilaterally implanted with the XEN either as a stand-alone procedure or in combination with lens extraction. A subset of this population will include a maximum of 10 phakic patients (ie, will not undergo lens extraction at time of XEN surgery) and 10 patients with a history of trabeculectomy or glaucoma shunt implantation, to allow for a representative ACG patient population in the study.

5.3 Inclusion Criteria

The following are requirements for enrollment into the study:

Non-ocular Criteria for Inclusion

1. Male or female, ≥ 18 years of age and of legal age of consent
2. Signed written informed consent has been obtained
3. Ability to understand and willingness to follow study instructions and is likely to complete all required visits and procedures

Ocular Criteria for Inclusion

4. Diagnosis of ACG defined as areas of ITC present in ≥ 2 quadrants and glaucomatous damage to optic disc and visual field, in the study eye.

   Note: Procedures to widen the iridocorneal angle in the target quadrant (eg, goniosynechialysis, lens extraction [clear lens extraction or cataract surgery/phacoemulsification], and IOL placement) are permitted on the operative day (Day 1) at the investigator's discretion; however, all procedures must be successful and uncomplicated for patients to receive XEN. A maximum of approximately 10 phakic patients (ie, will not undergo lens extraction at time of XEN surgery) is allowed in the study.

5. In the opinion of the investigator, the IOP is uncontrolled in the study eye after having failed previous medical and/or surgical treatment (eg, topical IOP-lowering medications, laser peripheral iridotomy, lens extraction, glaucoma shunt implantation, trabeculectomy)

6. IOP of ≥ 20 mm Hg and ≤ 35 mm Hg by Goldmann applanation tonometry in the study eye at screening and baseline (Hour 0)

7. Study eye has healthy, free, and mobile conjunctiva in the target quadrant

8. Glaucomatous visual field loss with a mean deviation score of at least -1 dB in the study eye that, in the opinion of the investigator, is not functionally significant (eg, split fixation, field defect within the central 10 degrees that is visually significant or likely to cause central visual impairment upon progression are excluded)

5.4 Exclusion Criteria

The following are criteria for exclusion from participating in the study:

Non-ocular Criteria for Exclusion

1. Uncontrolled systemic disease (eg, diabetes, hypertension)

2. Female patients who are pregnant, nursing, or planning a pregnancy during the study, or who are of childbearing potential and not using a reliable means of contraception during the study. For purposes of this study, females will be considered of childbearing potential unless they are naturally postmenopausal or permanently sterilized (ie, tubal occlusion, hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy). Natural menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhea without any other obvious pathological or physiological cause

3. Known or suspected allergy or sensitivity to any medications/diagnostic agents (eg, topical anesthetic, dilating drops, fluorescein) required for this protocol or any of the XEN components (eg, porcine products or glutaraldehyde)

4. Known history of bleeding disorder or prolonged bleeding after surgery (in the opinion of the investigator) or those on pharmacologic blood thinners other than aspirin (up to 100 mg/day)

5. Chemotherapy for cancer treatment within 6 months of screening

6. History of dermatologic keloid formation

7. Participation in another drug/device/observational clinical trial concurrently or concluding within 30 days of screening

8. Any condition that would preclude the patient's ability to comply with study requirements, including completion of the study

9. Any condition or a situation which, in the investigator's opinion, may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

Ocular Criteria for Exclusion

10. Open angle glaucoma, active acute angle closure attack, congenital glaucoma, juvenile glaucoma, secondary glaucomas (eg, anterior subluxation of the lens, iris or ciliary body cysts, active iris and angle neovascularization, iridocorneal endothelial syndrome, anterior uveitis, drug-induced) in the study eye

11. History of following surgeries in the study eye:

    a. incisional refractive surgery (eg, radial keratotomy), other than astigmatic keratotomy or limbal relaxing incisions

    b. corneal graft including partial grafts such as Descemet's stripping endothelial keratoplasty and Descemet's membrane endothelial keratoplasty

    c. previous laser or incisional intraocular surgery that might interfere with the outcome of this trial

    However, previous incisional and laser glaucoma surgeries (eg, trabeculectomy, glaucoma shunt implantation, laser trabeculoplasty, iridotomy, cilioablative procedures) or uncomplicated phacoemulsification with IOL, occurring more than 3 months prior to screening, are allowed in the study eye. A maximum of 10 patients with a history of trabeculectomy or glaucoma shunt implantation (away from the target quadrant), is allowed in this study.

12. Previous glaucoma shunt implantation in the target quadrant in the study eye

13. Anticipated need for ocular incisional and/or laser surgery in the study eye during the 12-month follow-up period

14. Anticipated use of other topical ocular medications in the study eye except as described in Permissible Medications/Treatments (Section 4.4.1)

15. Ocular (in the study eye) or systemic corticosteroid use within 30 days prior to screening (continuing chronic systemic corticosteroid use is allowed) or known corticosteroid responder

16. Clinically significant inflammation or infection in either eye within 30 days prior to screening (eg, blepharitis, conjunctivitis, keratitis, herpes simplex infection)

17. Active or history of chronic uveitis in the study eye

18. Corneal or other ocular abnormalities (eg, bullous keratopathy, keratoconus) in the study eye that would preclude accurate readings with an applanation tonometer and/or a contact pachymeter, or could confound study results

19. Nanophthalmos in either eye

20. Central corneal thickness $\leq$ 460 microns or $\geq$ 620 microns in the study eye

21. Unable to discontinue contact lens wear in the study eye during the study

22. Impaired episcleral venous drainage (eg, Sturge-Weber or other evidence of elevated venous pressure) in the study eye

23. Aphakia, anterior chamber intraocular lens, or previous complicated phacoemulsification surgery in the study eye

24. Vitreous present in the anterior chamber in the study eye

25. Presence of intraocular silicone oil in the study eye

26. Active diabetic retinopathy, choroidal neovascularization, branch retinal vein occlusion, central retinal vein occlusion, proliferative retinopathy, or other ophthalmic disease or disorder in the study eye that could confound study results

27. Visually significant cataract (ie, BCVA 20/40 Snellen equivalent using LogMar chart at screening and baseline) in the study eye that will not be removed at the time of XEN implantation

28. Study eye with best-corrected visual acuity (BCVA) worse than 20/100 (Snellen equivalent using LogMar chart) at screening and baseline; fellow (non-study) eye with BCVA worse than 20/200 at screening and baseline. A patient with a cataract in the study eye and BCVA worse than 20/100 in the study eye may be included if, in the opinion of the investigator, the patient is likely to have BCVA of 20/40 or better after cataract surgery that will be performed at the time of XEN implantation.

6. Procedures

6.1 Procedures to be Performed

Examination visits and visit windows are provided in Table 1-1. The examination requirements for each visit are provided in the following protocol sections and in Table 1-1. It is recommended that the examinations be completed in the order listed, unless otherwise specified.

Visits performed between reporting periods will be documented on an unscheduled visit eCRF. The investigator will report all findings obtained to the sponsor, including IOP measurements, biomicroscopic slit lamp and ophthalmoscopy examination findings, concomitant medications, and AEs.

6.1.1 Screening Visit

The window for this visit is up to 60 days prior to surgery. After obtaining informed consent (Section 10.1.2), the following information will be obtained at this visit:

- Evaluation of inclusion/exclusion criteria
- Patient demographics
- Medical history, surgical history, ophthalmic history, and ophthalmic surgical history, including presence of ocular pathology and concomitant ocular medications (both eyes)
- Patient ocular symptom questionnaire

- Concomitant medications (systemic and ophthalmic) and procedures
- AEs
- Urine pregnancy test (for females of childbearing potential)
- Manifest refraction (both eyes)
- BCVA using LogMar chart (both eyes)
- Visual field testing (both eyes): Monocular visual field testing will be measured using the Humphrey 24-2 full threshold program or Swedish Interactive Thresholding Algorithm (SITA) Standard and a reliable, interpretable visual field will be obtained for patients with a preoperative BCVA of better than 20/100. This assessment is not required for patients with BCVA of 20/100 or worse. Visual field results must be reliable and interpretable, or if unreliable or uninterpretable, the visual field test must be repeated. An unreliable visual field is defined as visual field measurements with > 33% fixation losses, false positives, or false negatives. Visual field test performed up to 6 months prior to operative day (Day 1) is allowed.
- Biomicroscopic slit lamp examination (both eyes): includes determination of ophthalmic medical observations/complications, evaluation of the condition of the eyelids, conjunctiva, cornea, anterior chamber, iris/pupil, and lens (through a dilated pupil).
- IOP (Hour 0 = 8:00 am ± 1 hour) measurement using Goldmann applanation tonometry (both eyes) using the 2-person reading method (See Protocol Procedure Manual); IOP must be completed prior to pachymetry, gonioscopy, and ophthalmoscopy.
- Pachymetry measurement of central corneal thickness (both eyes) using an ultrasonic pachymeter
- Gonioscopy (both eyes): includes assessment of angle abnormalities, such as peripheral anterior synechiae, angle assessment of each quadrant by Shaffer Grade

- Ophthalmoscopy (both eyes): includes dilated fundus evaluation and vertical cup-to-disc ratio. Non-dilated ophthalmoscopy may be performed if the investigator believes that pupil dilation may put the patient at risk.

6.1.2 Baseline Visit

Baseline visit must be performed 5 to 7 days before the surgery. The following tests must be performed on the baseline visit prior to the initiation of preoperative corticosteroid treatment:

- Evaluation of inclusion/exclusion criteria
- Medical history, surgical history, ophthalmic history, and ophthalmic surgical history, including presence of ocular pathology and concomitant ocular medications (both eyes)
- Concomitant medications (systemic and ophthalmic [both eyes]) and procedures
- AEs
- Urine pregnancy test (for females of childbearing potential)
- Manifest refraction (both eyes)
- BCVA using LogMar chart (both eyes)
- Biomicroscopic slit lamp examination (both eyes)
- Diurnal IOP measurement (both eyes): Three IOP measurements taken over an 8-hour period on the same day approximately 4 hours apart, at Hour 0 (± 1 hour), Hour 4 = Hour 0 + 4 hours (± 30 minutes), and Hour 8 = Hour 0 + 8 hours (± 30 minutes). As scheduling permits, the patient must have approximately the same Hour 0 time of day throughout the study. IOP must be completed prior to ophthalmoscopy.
- Ophthalmoscopy (both eyes)

6.1.2.1 Preoperative Medications

At the baseline visit, patients will be prescribed and instructed to self-administer the following preoperative medications in Table 6–1 (See Protocol Procedure Manual). If

medications in Table 6–1 are not allowed as per local laws and/or regulations, investigator's standard practice may be substituted based on prior discussions with the sponsor. All preoperative medications will be recorded in the eCRF.

Table 6–1 Preoperative Medications

Medication	Dose	Duration
Topical broad spectrum ophthalmic antibiotic, recommended without preservative (See Protocol Procedure Manual)	QID	One day prior to surgery
Topical corticosteroid: difluprednate 0.05% or prednisolone acetate 1% or equivalent (See Protocol Procedure Manual)	QID	5 to 7 days prior to surgery, per investigator's discretion

QID = 4 times daily

Patients must be instructed to discontinue all topical and systemic IOP-lowering medications on the day of surgery.

6.1.3 Operative Visit (Day 1)

Patients must be scheduled for surgery within 60 days of screening. The following procedures must be performed prior to the implantation of study treatment:

- Evaluation of inclusion/exclusion criteria
- Medical history, surgical history, ophthalmic history, and ophthalmic surgical history, including presence of ocular pathology and concomitant ocular medications (both eyes)
- Concomitant medications (systemic and ophthalmic [both eyes]) and procedures
- AEs
- Urine pregnancy test (for females of childbearing potential)

The implantation procedure must be performed in an approved surgical suite or operating room using standard aseptic technique and standard ophthalmic surgical techniques to prepare the patient and the operative study eye. Preoperative and intraoperative surgical medications will be administered as customary for the investigator.

It is recommended that the target quadrant be the superior nasal quadrant, unless conjunctival scarring will inhibit bleb formation. If implantation is not possible in this quadrant, the order of preference for Gel Implant location is superior temporal, inferior nasal, and lastly inferior temporal.

A detailed description of the XEN surgical procedure is provided in the Protocol Procedure Manual. The general steps of the surgical procedure are as follows:

1. Standard ophthalmic surgery techniques must be used to prepare the patient and the eye. The target area must be pretreated with mitomycin C (see Protocol Procedure Manual for dosing and intraoperative application details).

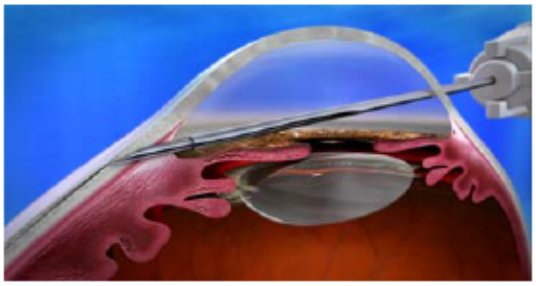
2. Surgeons may use their standard of care to obtain access to the surgical quadrant. The needle of the sterile XEN Injector preloaded with the XEN Gel Implant is advanced through the peripheral cornea and across the anterior chamber (ie, *ab interno*) toward the targeted quadrant. Corneal entry will be at least 1 to 2 mm anterior to the limbus (ie, not at the limbus or behind it) to ensure proper angulation on the Gel Implant up and away from the iris. The Gel Implant will be placed through the center of the angle.

3. Once the needle is aligned with the desired entry point in the anterior chamber angle, the surgeon advances the needle in the anterior chamber angle and sclera until the surgeon is able to visualize the needle bevel as it exits the sclera into the subconjunctival space.

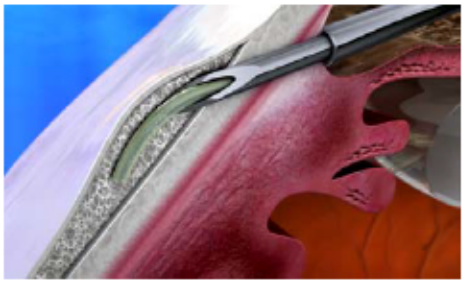
4. The surgeon initiates release of the XEN Gel Implant by moving the slider of the XEN Injector. To deploy the Gel Implant, a forward movement of the blue slider at the center of the Injector delivers the Gel Implant and retracts the needle. The slider will stop at the end of its travel indicating that the procedure is complete.

Figure 6–1 provides diagrams of the steps required to complete the implantation procedure.

Figure 6–1 XEN Implantation Procedure



a. The surgeon advances the needle through the trabecular meshwork and the sclera until the needle bevel can be visualized in the subconjunctival space.



b. Once the needle is properly positioned, the Gel Implant can be released from the needle by the surgeon.

Following surgery, a protective shield or glasses will be applied over the operative eye. The patient will be instructed to keep the shield or glasses over the operative eye until the first follow-up visit and then, at bedtime, for at least a week.

6.1.3.1 Postoperative Medications

The investigator will prescribe and instruct the patient to self-administer the postoperative medications listed in Table 6–2 (See Protocol Procedure Manual). Investigator discretion may be used to adjust the below postoperative medication regimen, if required. All changes in the postoperative regimen will be documented on the appropriate eCRF.

Table 6–2 Postoperative Medications

Medication	Dose	Duration
Topical broad spectrum ophthalmic antibiotic, recommended without preservative (See Protocol Procedure Manual)	QID	Week 1 following surgery
Topical corticosteroid: difluprednate 0.05% or prednisolone acetate 1% or equivalent (See Protocol Procedure Manual)	QID TID BID QD	Weeks 1-4 following surgery Week 5 following surgery Week 6 following surgery Weeks 7-12 following surgery

QID = 4 times daily; TID = 3 times daily; BID = twice daily; QD = once daily

6.1.3.2 Postoperative Management

6.1.3.2.1 Hypotony

Investigators must monitor patients for clinically significant findings related to hypotony, such as shallow anterior chamber, persistent choroidal effusions, hypotony maculopathy, and

vision loss. Investigators will use their best medical judgment to manage hypotony, including reformation of the anterior chamber. Cycloplegic medications may be used for patients, as needed, during the initial healing phase or in phakic eyes. If used, medications must be recorded on the eCRF.

6.1.3.2.2 Bleb Management

A fibrotic response may occur in study patients as a function of previous surgeries and medication use. Investigators will monitor patients for maintenance of a functional bleb. Investigators will use standard of care customary for bleb needling. Anti-fibrotic agents (eg, mitomycin C) can be used during needling as per investigator's discretion.

To allow XEN to continue to provide a conduit for aqueous flow into the subconjunctival space, needling may be performed to mechanically remove tissue adhesions between the sclera and the conjunctiva.

In addition to having IOP above target level, at least one of the following criteria must be met prior to performing a needling procedure:

- Flat bleb where filtration area is fibrotic or blocked
- Patient has a high risk of bleb failure, based on assessment by the investigator

The investigator will consider the patient's current clinical situation as the basis for performing a needling procedure. A small gauge needle (eg, 27G or less) is recommended, with entry into conjunctiva a few millimeters away from the bleb/implant exit area. Advance the needle carefully towards the implant exit and break any tissue adhesions and fibrotic tissue around the implant exit site. See Protocol Procedure Manual for further details.

6.1.3.2.3 Device Explant

XEN may be removed if the investigator believes that it is in the best interest of the patient. Device removal may be considered in the following situations:

- Persistent hypotony that cannot be mitigated by other means (see Section 6.1.3.2.1)
- Uveitis, glaucoma and hyphema syndrome
- Gross device malposition

- Surgical procedure that requires explant (eg, trabeculectomy)

Investigators will make all efforts to notify the sponsor prior to explantation of the device.

For explantation of XEN, the following will be considered:

- Implant removal through the conjunctiva:

  A small (1 to 2 mm) conjunctival incision is made near the distal end of the implant. Using forceps, slowly remove the implant out of the eye. Investigator's discretion will be used to close the conjunctival wound.

- Implant removal from the anterior chamber:

  A small (1 to 2 mm) incision is created to enter the anterior chamber. After using appropriate methods to maintain the anterior chamber shape (eg, injection of viscoelastic), forceps can be used to remove the implant from the eye. Investigator's discretion will be used in the method for closure of the corneal incision.

All device explants will be considered device failures. Patients who have their devices removed will be withdrawn from the study. These patients will be followed until the patient is deemed stable by the investigator. Examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study period.

6.1.4 Follow-up Examinations and Clinical Parameters

The postoperative follow-up duration will be 12 months.

Patients will undergo postoperative visits according to the visit schedule in Table 1-1.

The following information will be obtained for the study eye at the postoperative visits, although not all are required at each visit:

- Patient ocular symptom questionnaire
- Concomitant medications (ophthalmic and systemic) and procedures
- Changes in health that may influence the study outcomes

- AEs
- Manifest refraction, obtained for BCVA testing: to be completed at scheduled visits. In addition, manifest refraction will be performed during any visit if best-corrected visual acuity (BCVA) reduction of ≥ 2 lines is observed since the last BCVA examination.
- BCVA using LogMar chart
- Biomicroscopic slit lamp examination, including assessment for Gel Implant placement and bleb characteristics
- IOP measurement (Hour 0 ± 1 hour) using Goldmann applanation tonometry; IOP must be completed prior to pachymetry, gonioscopy, and ophthalmoscopy.
- Pachymetry measurements of central corneal thickness using an ultrasonic pachymeter
- Gonioscopy
- Ophthalmoscopy

6.1.5 12-Month Postoperative Visit/Early Exit Visit

Patients will be exited from the study once they have completed the 12-month visit.

The following information will be obtained for the study eye:

- Patient ocular symptom questionnaire
- Concomitant medications (ophthalmic and systemic) and procedures
- AEs
- Urine pregnancy test (for females of childbearing potential)
- Manifest refraction
- BCVA using LogMar chart

- Visual field testing: If the visual field assessment at this visit shows progression of visual field loss from baseline (defined as a worsening of at least 3 dB in mean deviation score), a second visual field test must be performed within one week to confirm the progression. If the second visual field test is not confirmatory or is equivocal, a third test must be performed within a week to confirm results.
- Biomicroscopic slit lamp examination, including assessment for Gel Implant placement and bleb characteristics
- Diurnal IOP using Goldmann Applanation Tonometry; IOP must be completed prior to pachymetry, gonioscopy, and ophthalmoscopy.
- Pachymetry measurements of central corneal thickness using an ultrasonic pachymeter
- Gonioscopy
- Ophthalmoscopy

6.2 Instructions for the Patients

Patients will be instructed to strictly follow the study visit schedule, adhere to pre- and post-operative medication instructions (Sections 6.1.2.1 and 6.1.3.1), and to report all changes in their condition to the investigative site.

Instructions will be given to the patient to maintain a stable dose of any concomitant medication used chronically, or any new medications initiated during the study whenever possible. Patients will be instructed to communicate any changes to their medication at their next study visit. Patients will also be reminded to contact the study site if they are experiencing any difficulties during their study participation.

6.3 Unscheduled Visits

Additional examinations may be performed as necessary to ensure the safety and wellbeing of patients during the study period. Unscheduled visit eCRFs must be completed for each unscheduled visit. An assessment of any AE must be completed.

6.4 Early Discontinuation of Patients

Each patient reserves the right to withdraw from the study at any time without jeopardy to his/her future medical care. In addition, patients meeting withdrawal criteria (Section 6.5) will be discontinued from the study. All follow-up assessments and procedures are to be performed at the final study visit. Patients may also be administratively withdrawn if they do not return for follow-up visits.

For any patient who withdraws from the study, the date and reason for withdrawal will be recorded on the eCRF. If an AE is ongoing at the time of withdrawal, the investigator will attempt to follow the patient until the AE has been resolved or follow-up is no longer possible. The investigator shall ask for the patient's permission to follow his/her status/condition outside the study.

If a patient fails to return for one or more scheduled study visits, the investigator will attempt to contact the patient to determine and document the reason the patient has failed to return and to encourage compliance with the study visit schedule.

Notification of early patient discontinuation from the study and the reason for discontinuation will be made to the sponsor and clearly documented on the appropriate eCRF.

When a patient discontinues or withdraws from the study before 12 months, every effort should be made to have these patients return to the clinical center to complete the procedures for the early exit visit.

6.5 Withdrawal Criteria

Patients may voluntarily withdraw from the study at any time.

Patients who have their devices removed or have a suture placed to close the scleral channel, will be withdrawn from the study.

Patients who are not implanted with XEN during surgery will be withdrawn from the study and considered a screen failure. Investigators are recommended to follow the patient until they are stable.

The investigator will consider withdrawing a patient from the study early if any of the following criteria are met:

- Patient develops (or has an exacerbation of) a medical condition that, in the opinion of the investigator, compromises the patient's ability to participate in the study
- Patient is unwilling or unable to continue to comply with study procedures
- Patient is unwilling or unable to continue in the study

Whenever possible, the decision to withdraw a patient from the study or study treatment will be discussed with the sponsor.

7. Response Measures and Summary of Data Collection Methods

Detailed information on equipment and methodology to be used is provided in the Protocol Procedure Manual.

7.1 Effectiveness Measures

Primary effectiveness measures will be assessed at all visits according to the schedule in Table 1-1.

The primary effectiveness measure, IOP, will be measured using a Goldmann applanation tonometer. Examiners must perform all effectiveness IOP measurements at approximately the same time of day for a given patient throughout the study whenever possible. IOP must be completed prior to pachymetry, gonioscopy, and ophthalmoscopy.

The number of concomitant IOP-lowering medications following implantation will also be recorded.

7.2 Safety Measures

The following will be collected and recorded on the appropriate eCRF page(s):

- AEs: All AEs, from the moment the patient signs the Informed Consent Form, will be monitored and recorded in the patient's source documents. All events will be reported to the sponsor on an AE eCRF, including seriousness, severity, action taken and relationship to study treatment. If AEs occur, the first concern will be the safety of the study patient.

- Females of childbearing potential will have pregnancy tests performed. Pregnancy test kits will be provided by the site and will be administered according to the instructions provided with the tests.

Measures of ocular safety include:

Visual acuity: Visual acuity tests will be performed at all scheduled visits, as described in Table 1-1. Manifest refraction using Snellen equivalent with a logMar chart (see Protocol Procedure Manual) will be performed at Screening, Baseline, Month 3, and Month 12/Exit. At all other visits, the visual acuity technician will use the last manifest refraction performed and determine the Snellen equivalent visual acuity using the logMar chart. If there is a 2-line or more reduction in visual acuity from the last BCVA performed, a repeat manifest refraction in both eyes and BCVA will be performed.

Pachymetry: Corneal thickness using ultrasound (contact) pachymetry will be performed on the central cornea. The same instrument will be used throughout the study for a given patient. Contact pachymetry will be performed after IOP measurement.

Visual field test: Visual field will be assessed using automated perimetry (using either Humphrey 24-2 full threshold program or SITA Standard). The same test methodology must be used throughout the entire study for a given patient.

Biomicroscopic slit lamp examination: Biomicroscopic examinations will be performed using a slit lamp. The examinations will include evaluation of the condition of the eyelids, conjunctiva (including assessment of bleb characteristics), cornea (including assessment for corneal stromal edema at the XEN Gel Implant location), anterior chamber, iris/pupil, and lens, and assessment of Gel Implant placement.

Gonioscopy: Iridocorneal angle assessments will include Shaffer grade; postoperative gonioscopy will include device displacement, malposition, movement, device contact with cornea and/or iris, and device tip occlusion.

Ophthalmoscopy: The stereoscopic fundus assessments will be conducted through a dilated pupil. Non-dilated ophthalmoscopy may be performed if the investigator believes that pupil dilation may put the patient at risk. The examinations will include evaluation of the macula, vitreous, and retina. The cup/disc ratio and presence of optic disc pathology will be determined using stereoscopic evaluation. When dilation is used, ophthalmoscopy should be the last examination.

7.3 Health Outcome Measures

The frequency of symptoms will be assessed using a modified version of the ocular symptom questionnaire designed for the collaborative initial glaucoma treatment study (CIGTS), which is referred to as the patient ocular symptoms questionnaire within this protocol.

All patients will be asked to complete the Patient Ocular Symptoms Questionnaire at screening and then again at Months 3, 6, and 12.

7.4 Summary of Methods of Data Collection

Electronic data capture using a validated electronic data capture system (EDC) will be used to collect study-specific information, such as patient and investigator assessments. The data will be entered on the eCRF in a timely manner on an ongoing basis. The investigator is responsible for ensuring that data are properly recorded on each patient's eCRF and related documents. An investigator who has signed the protocol signature page must review and personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the findings are recorded on the eCRFs correctly and completely. The designated monitor will source-verify the data. Investigators will provide access to hospital files, medical records, and other source documents containing patient clinical/medical information.

8. Statistical Procedures

A separate statistical analysis plan will be prepared to provide specifications for all analyses. The plan will be finalized and approved prior to clinical database lock.

8.1 Analysis Populations

An analysis will be performed after all implanted patients have completed the 12-month visit or exited the study and the database has been locked.

Implanted population: The implanted population will include all patients implanted with XEN. This population will be used for all primary and secondary effectiveness analyses and all safety analyses.

8.2 Collection/Derivation of Primary and Secondary Effectiveness Assessments

The primary effectiveness measure, IOP, will be measured using a Goldmann applanation tonometer. The measurements will be collected using the masked examiner method described in the Protocol Procedure Manual. Additionally, the number of concomitant IOP-lowering medications following implantation will be recorded. To determine the number of concomitant IOP-lowering medications, fixed-combination medications will be counted as multiple medications. For example, Combigan will be counted as 2 medications. Any IOP measurements or medication counts collected following non-study surgical procedures for IOP control or device explant (ie, device failures) will be excluded from the analyses.

8.2.1 Primary Effectiveness Variable

The primary effectiveness endpoint is the proportion of patients achieving at least a 20% reduction from baseline Hour 0 IOP while on the same number or fewer IOP-lowering medications at Month 12 and is derived from the effectiveness variables: Hour 0 IOP percent change from baseline and the number of concomitant IOP-lowering medications. The Hour 0 IOP percent change from baseline is calculated as 100 * (Hour 0 IOP change from baseline) / baseline Hour 0 IOP.

The number of concomitant IOP-lowering medications following implantation will be compared with the number prior to implantation.

8.2.2 Secondary Effectiveness Variables

The secondary effectiveness variables are Hour 0 IOP, the associated change from baseline, and the number of concomitant IOP-lowering medications.

8.2.3 Other Effectiveness Variables

Other effectiveness variables include diurnal IOP fluctuation, the associated change from baseline, the reason for device failure (such as non-study surgical procedures for IOP control or device explant), and the change in the number of concomitant IOP-lowering medications compared to baseline. Additional details regarding the definition of device failure will be included in the analysis plan.

8.3 Hypothesis and Methods of Analysis

Unless otherwise specified, continuous variables will be summarized by descriptive statistics including sample size, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency and percentage. Statistical analyses will use 2-sided 95% CIs unless otherwise specified.

8.3.1 Primary Effectiveness Analyses

The primary effectiveness analysis will estimate the proportion of patients, with corresponding 2-sided 95% CI, that achieve at least a 20% reduction from baseline Hour 0 IOP while on the same number or fewer IOP-lowering medications at Month 12 compared with baseline using a repeated measures logistic regression model. The model will include visit and baseline IOP as fixed effects with data from Months 1, 3, 6, 8, 10, and 12. An unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance fails to converge, an alternative covariance structure will be chosen. The primary effectiveness analysis will be performed using the implanted population.

8.3.2 Secondary Effectiveness Analyses

The mean and 2-sided 95% CI for raw IOP with the corresponding change from baseline will be estimated using mixed effect model repeat measurement including all post-baseline visits with visit and baseline IOP as fixed effects with data from Months 1, 3, 6, 8, 10, and 12. An unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance fails to converge, an alternative covariance structure will be chosen. Additionally, the number of IOP-lowering medications will be summarized by visit with descriptive statistics (mean, standard deviation, minimum, maximum) and 2-sided 95% CI for the mean. The secondary effectiveness analyses will be performed using the implanted population.

8.3.3 Other Effectiveness Analyses

[redacted]

8.3.4 Safety Analyses

Safety analyses will be performed using the implanted population. The number and percentage of patients reporting AEs will be tabulated regardless of causality. AEs, adverse device effects (ADEs), BCVA, line change in BCVA from baseline, biomicroscopic slit lamp, and ophthalmoscopy findings will be summarized by frequencies at each visit.

8.4 Subgroup Analyses

No subgroup analyses are planned.

8.5 Sample Size Calculation

Fifty patients will provide a precision of at least ±0.145 to estimate the proportion of patients achieving an IOP reduction ≥ 20% at 12 months on the same number or fewer IOP-lowering medications compared with baseline based on a 95% exact Clopper-Pearson CI. Sixty-five patients will be implanted to ensure at least 50 evaluable patients with 12 months of follow-up.

8.6 Interim Analyses

No interim analyses or reports are planned.

9. Materials

9.1 Study Treatment

9.1.1 Product Description

The XEN45 Glaucoma Treatment System is comprised of the XEN Gel Implant (also referred to as the Gel Implant) and the XEN Injector (also referred to as the Injector). The XEN Glaucoma Gel Implant is intended to create a channel through the sclera allowing flow of aqueous humor from the anterior chamber into the subconjunctival space to reduce IOP. The XEN Gel Implant is inserted using the XEN Injector via an *ab interno* approach, through a small corneal incision.

The XEN Glaucoma Treatment System is a sterile, single-use component. The XEN Injector is for single use only and is not reusable. Reuse may result in contamination, loss of function, and other undesirable side effects. The package must be examined to verify the appropriate model has been selected and product has not expired prior to implantation.

The inside diameter of the tube is approximately 45 µm, its outside diameter is approximately 150 µm, and it has a length of approximately 6 mm.

The XEN Gel Implant is composed of a gelatin derived from porcine dermis, formed into a tube, and then cross-linked with glutaraldehyde. The gelatin is designed to expand and become flexible when hydrated. The expansion of the tube's outer diameter also aids in retention of the Gel Implant in its intended location after surgical implantation.

The XEN Injector is a single use mechanical delivery system for the XEN Gel Implant. The Gel Implant is preloaded in the XEN Injector which houses the Gel Implant during insertion and delivery into the eye. The XEN Injector allows the surgeon to advance and deliver the Gel Implant to the desired location

9.1.2 Instructions for Use and Administration

An investigational directions for use (IDFU) brochure will be provided for the XEN45 Glaucoma Treatment System.

Surgical training will be required and provided by an Allergan representative.

Protocol specific details on administration will be provided in the Protocol Procedure Manual.

9.2 Other Study Supplies

The following supplies will be provided by Allergan or designated suppliers:

- Surgical instruments specific to the surgery for implantation of XEN, including the durable surgical instruments, two sizes of sterile, single use blades and the operative gonio lenses

Sites that are not able to receive supplies from Allergan due to country regulations will need to provide their own supplies.

10. Study Administration Procedures

The clinical study shall not begin until the required approvals from the appropriate regulatory authorities and ECs have been obtained.

10.1 Patient Entry Procedures

10.1.1 Overview of Entry Procedures

Prospective patients, as defined by the criteria in Sections 5.3 and 5.4 (inclusion/exclusion criteria), will be considered for entry into this study. A patient is considered to have enrolled in the study upon signing the informed consent, which occurs prior to any screening procedures. Screening procedures include:

- Collection of demographic information
- Collection of medical/surgical history, including ophthalmic and ophthalmic surgical history.
- Completion of Patient Ocular Symptoms Questionnaire
- Collection of concurrent medications (systemic and ophthalmic) and procedures
- Evaluation of inclusion/exclusion criteria
- Urine pregnancy test (for females of childbearing potential)
- AEs

- Ophthalmic evaluation, which includes the following:
  - IOP
  - Manifest refraction
  - BCVA using LogMar chart
  - Pachymetry
  - Visual field test
  - Biomicroscopic slit lamp examination
  - Gonioscopy
  - Ophthalmoscopy

Note: Photography (or video recordings) are not required by the protocol, but may be taken as part of the investigators' standard practice, and therefore may be collected by Allergan for general research, education, and/or informational purposes. Patients choosing not to allow Allergan permission to use these photography or video recordings taken of them will not be excluded from the study.

10.1.2 Informed Consent and Patient Privacy

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential patient. The patient must also give Data Protection Consent and other written documentation in accordance with the relevant country and local privacy requirements (where applicable) prior to any study-related procedures or change in treatment.

The investigator or his/her authorized designee conducts the informed consent discussion and will document in the patient's medical records the acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician about the study. The informed consent shall include all aspects of the study that are relevant to the patient's decision to participate throughout the study. The informed consent process is to avoid any coercion or undue influence on, or inducement of, the patient to participate. The patient is to personally sign and date the informed consent. The investigator will retain the original copy of the signed form, and the patient will receive a copy. Upon signing the informed consent form, the patient is considered to be enrolled in the study and receives a patient number that

will be used on all documentation for the patient throughout the study. Patient numbers will be assigned in ascending order, and numbers will not be omitted or reused. The patient number is coupled with the site identification number for unique identification of each patient. The investigator is to ensure important new information is provided to new or existing patients throughout the study.

10.1.3 Method for Assignment to Treatment Groups

All eligible patients will be assigned to treatment with XEN. Investigational product will be labeled with kit numbers that will be recorded on the eCRF.

10.2 Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of Allergan will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review patient and device accountability records for compliance with the protocol. Any protocol deviations will be discussed with the investigator upon identification. All protocol deviations will be reported to the EC according to the EC's reporting requirements.

10.3 Pregnancy

If a female becomes pregnant during the study, the investigator will notify Allergan immediately by completing the Pregnancy Surveillance Form after the pregnancy is confirmed and faxing it to the appropriate number on the front page of this protocol. The investigator shall (1) instruct the patient to notify her physician that they are being treated with an investigational device (ie, XEN) and (2) follow the pregnancy to term. Best practices are to be followed in order to ensure the welfare of the patient and the fetus. Once the pregnancy has reached term, the second page of the Pregnancy Surveillance Form concerning outcome is to be completed. The medical safety physician will contact the investigator to obtain information about the pregnancy outcome. The patient will continue to be followed as part of the implanted population but the pregnancy will be documented as a protocol deviation. Pregnancy by itself will not be considered an AE or serious adverse event (SAE). Hospitalization for a normal delivery or elective abortion of a normal fetus does not constitute an SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these are to be reported as described in Sections 11.3 to 11.4.

10.4 Study Termination

If conditions arise during the study that indicate that the study or an investigational site needs to be terminated, the sponsor, investigator, monitor, EC, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to patients enrolled in the study
- The decision on the part of Allergan to suspend or discontinue testing, evaluation, or development of the study device
- Failure of the investigator to comply with pertinent national or state regulations, EC-imposed conditions, or protocol requirements
- Investigator submission of knowingly false information to the sponsor, monitor, EC, or any regulatory agency

Per International Organization for Standardization (ISO) 14155, if a study is prematurely terminated or suspended due to safety issues, Allergan shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The EC is also to be informed promptly and provided the reason(s) for the termination or suspension by Allergan or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, Allergan shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of patients enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled patients, if applicable.

11. Adverse Events

Throughout the course of the study, all AEs will be monitored and reported on an AE eCRF, including seriousness, severity, action taken and relationship to study treatment. If AEs occur, the first concern will be the safety of the study patients.

Although the risk of developing a serious complication is small, the investigator and the research staff will monitor each patient closely, and, if a complication occurs, they will use their medical judgment to do whatever is necessary to treat the problem. Additional information is available in the IDFU.

The following may occur in conjunction with the use of the XEN Gel Implant: Gel Implant migration, Gel Implant exposure or extrusion, Gel Implant blockage, choroidal effusion or hemorrhage, hypotony maculopathy, bleb related complications, or endophthalmitis and other known complications of intraocular surgery (eg, flat or shallow chamber, hyphema, corneal edema, macular edema, retinal detachment, vitreous hemorrhage, uveitis).

Standard of care should be implemented whenever an AE occurs to treat and/or resolve the AE and to monitor the patient. The investigator should ensure the sponsor is kept informed of all details related to the resolution and/or progression of the AE. Any patient who is withdrawn from the study due to an AE shall be followed until the outcome is resolved or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

11.1 Definitions

11.1.1 Adverse Event

An AE is defined in accordance with ISO 14155 as "any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users, or other persons, whether or not related to the investigational medical device." This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational medical devices.

Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the patient has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

AEs will be monitored throughout the study beginning with signing of informed consent. At each post-baseline visit, the investigator will begin querying for AEs by asking each patient a general, non-directed question such as "Have you had any changes to your condition since your last visit?" Previous AEs and changes in therapy/concomitant medications are to be updated. Directed questioning and examination will then be done as appropriate. All reportable AEs and clinically significant abnormal laboratory findings will be documented on the appropriate eCRF.

11.1.2 Serious Adverse Event

An SAE is defined in accordance with ISO 14155 as an AE that:

1. Led to death
2. Led to serious deterioration in the health of the patient, that either resulted in:
    a. a life-threatening illness or injury, or
    b. a permanent impairment of a body structure or a body function, or
    c. inpatient or prolonged hospitalization, or
    d. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    e. led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.

See Section 11.4 for procedures for reporting an SAE.

11.1.3 Adverse Device Effect

An adverse device effect (ADE) is defined in accordance with ISO 14155 as "an adverse event related to the use of an investigational medical device." This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error (per ISO 62366) or from intentional misuse of the investigational medical device.

See Section 11.3 for procedures for reporting an ADE.

11.1.4 Serious Adverse Device Effect

A serious adverse device effect (SADE) is defined in accordance with ISO 14155 as "an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event."

See Section 11.4 for procedures for reporting a SADE.

11.1.5 Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is defined in accordance with ISO 14155 as "any serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report." The investigator is to consult the IDFU for anticipated risks or anticipated AEs.

11.1.6 Device Deficiency

A device deficiency is defined in accordance with ISO 14155 as "inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance." Device deficiencies include malfunctions, use errors, and inadequate labeling.

If a device deficiency occurs, the investigator will notify Allergan using the fax number or email on the front page of the protocol. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to an SADE. These shall be reported to the regulatory authorities and ECs as required by national regulations.

11.1.7 Severity

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE is to be completed using the following definitions as guidelines:

Mild	Awareness of sign or symptom, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity
Severe	Incapacitating with inability to work or do usual activity

11.1.8 Relationship to Device or Procedure

Relationship to a device refers to a determination of the relationship (if any) between an AE and the device. A causal relationship is present if the investigator determines that there is a reasonable possibility that the AE may have been caused by the device.

An AE could be considered procedure-related when, in the judgment of the investigator, it is reasonable to believe that the event is associated with the procedure, regardless of the relationship to the study device. Procedure-related causes that contribute to the occurrence of the event can be attributed to other products, surgical techniques, or medications required specifically for the procedure.

Relationship to the device or procedure must be determined by the investigator and cannot be delegated to other study staff.

11.2 Timelines for Reporting

The investigator is to adhere to the following schedule in reporting different types of AEs.

Adverse Event Type	Reporting to Allergan	Start of Collection	End of Collection
AEs, ADEs	Record on AE eCRF upon awareness for review by the Clinical Monitor	After signing of IC	Last patient visit
SAEs, SADEs	Record on SAE Form and fax to Allergan within 24 hours of awareness	After signing of IC	Last patient visit

AE = adverse event; ADE = adverse device effect; eCRF = electronic case report form; IC = informed consent; SADE = serious adverse device effect; SAE = serious adverse event

11.3 Procedures for Reporting an AE or ADE

All AEs or ADEs occurring during the study period (beginning with the signing of informed consent) are to be recorded on the appropriate eCRF. Any AE or ADE that is ongoing at the exit visit must be followed up as appropriate.

Both the investigator and Allergan will comply with all Medical Device Reporting requirements.

11.4 Procedures for Reporting an SAE or SADE

All SAEs and SADEs occurring during the study period (beginning with the signing of informed consent) or for at least 30 days after the last study visit are to be immediately reported to an Allergan representative at a phone number/email address listed on the cover page and recorded on the appropriate eCRFs. All patients with an SAE/SADE must be followed up and the outcomes reported. The investigator is to supply Allergan and the EC with any additional requested information (eg, hospital discharge summary, autopsy reports, and terminal medical reports). Allergan shall evaluate all SADEs and determine and document in writing whether they meet the definition of USADE. These shall be reported to

all participating investigators, the regulatory authorities, and ECs as required by national regulations.

In the event of an SAE/SADE, the investigator must:

1. Notify Allergan immediately by fax using the SAE/SADE reporting forms. For the SAE/SADE fax number, see the front page of the protocol. An emergency phone number is also on the front page of the protocol.
2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the patient.
3. Provide Allergan with a complete, written case history that includes a statement as to whether the event was or was not related to the use of the investigational device.
4. Promptly inform the governing EC of the event, if it is device-related. For other SAEs, notify the governing EC as required by the EC, local regulations, and the governing health authorities.

12. Administrative Issues

12.1 Protection of Human Patients

12.1.1 Compliance with Informed Consent Regulations

Written informed consent is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative.

12.1.2 Compliance with EC Regulations

This study is to be conducted in accordance with applicable EC regulations. The investigator must obtain approval from a properly constituted EC prior to initiating the study and reapproval or review at least annually. Allergan is to be notified immediately if the responsible EC has been disqualified or if proceedings leading to disqualification have begun. Copies of all EC correspondence with the investigator are to be provided to Allergan.

12.1.3 Compliance with Good Clinical Practice

This protocol is to be conducted in compliance with GCP guidelines, and with ethical principles for clinical research that have their origin in the Declaration of Helsinki.

12.1.4 Compliance with Electronic Records and Signature Regulations

This study is to be conducted in compliance with the regulations on electronic records and electronic signature.

12.2 Changes to the Protocol

The investigator is not to implement any deviation from or changes to the protocol without approval by Allergan and prior review and documented approval/favorable opinion from the EC of a protocol amendment, except where necessary to eliminate immediate hazards to study patients, or when the changes involve only logistical or administrative aspects of the study (eg, change in monitors, change of telephone numbers). Allergan may amend the protocol during the course of the study. The amended protocol shall be distributed to the investigators and ECs upon approval by regulatory authorities.

12.3 Patient Confidentiality and Privacy

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study device may ultimately be marketed, but the patient's name will not be disclosed in these documents. The patient's name may be disclosed to Allergan, the governing health authorities, or the FDA, if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Data Protection Consent, and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, European Union [EU] Data Protection Directive 95/46/EC [EU Directive]).

12.4 Documentation

12.4.1 Source Documents

Source documents may include a patient's medical records, hospital/clinic charts, laboratory notes, device accountability records, patient questionnaires and diaries, photographic negatives or digital images, video recordings, radiographs, clinic charts, the investigator's patient study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and magnetic resonance imaging. The SAE Form and Pregnancy Surveillance Form are also considered source documents. The investigator's copies of the eCRFs serve as part of the investigator's record of a patient's study-related data.

The following information is to be entered into the patient's medical record:

- Patient's name
- Patient's contact information
- Date that the patient entered the study and patient number
- Study title and/or the protocol number and study sponsor
- A statement that informed consent was obtained, including the date and a statement that Data Protection Consent, or other country and local patient privacy required documentation for this study has been obtained, including the date
- Details of the implantation procedure
- Dates of all patient visits
- All concurrent medications (List all prescription and non-prescription medications being taken at the time of enrollment. At each subsequent visit, changes to the list of medications are to be recorded.)
- All concurrent medical procedures
- Occurrence and status of any AEs

- Date the patient exited the study, and a notation as to whether the patient completed the study or reason for discontinuation
- Results of laboratory tests performed by the site (eg, results of urine pregnancy tests)

12.4.2 Case Report Form Completion

The investigator is responsible for ensuring that data are properly recorded on each patient's eCRFs and related documents. An investigator who has signed the protocol signature page or his/her authorized designee is to personally sign the eCRFs (as indicated on the eCRF) to validate that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed and explained, if necessary, and shall not obscure the original entry (ie, an audit trail shall be maintained); this applies to both written and electronic changes or corrections.

12.4.3 Investigator Reports

In accordance with ICH E6 4.10 and 4.13, the investigator is to submit written summaries of study status to the EC annually (or more frequently if requested by the EC) and promptly provide written reports to Allergan, the EC, and, where required by applicable regulatory requirements, the institution regarding any changes significantly affecting the conduct of the study and/or increasing the risk to patients. Upon completion of the study and where required by the applicable regulatory requirements, the investigator is to inform the institution of the completion of the study. The investigator/institution is to provide Allergan with all required reports, the EC with a summary of the study outcome, and the regulatory authorities with any reports they require of the investigator/institution.

12.4.4 Retention of Documentation

All study-related correspondence, patient records, consent forms, patient privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs are to be maintained on file.

Allergan-specific essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

Allergan requires notification in writing if the investigator wishes to store study documents off-site or to relinquish the study data records so that mutually agreed-upon arrangements can be made for transfer of the data records to a suitably qualified, responsible person. Notification is to go to Allergan Medical, Attn: Clinical Research Dept., 71 South Los Carneros Road, Goleta, CA 93117, USA.

12.5 Labeling, Packaging, Storage, and Return of Study Devices

12.5.1 Labeling/Packaging

All investigational devices will be clearly labeled "For Investigational Use Only."

12.5.2 Storage of Study Devices

All devices will be stored and maintained in accordance with the corresponding IDFU.

The study device must be stored in a secure area accessible to delegated study personnel only and administered only to patients entered into the clinical study, at no cost to the patient, in accordance with the conditions specified in this protocol.

12.5.3 Study Device Accountability

The investigator must keep an accurate accounting of the number of study devices received from Allergan, dispensed to patients, and returned unused to Allergan during and at the completion of the study. A detailed inventory must be completed for the study devices dispensed to patients, including patient initials, device serial/lot number, date of implantation, and date of explantation if applicable. The study product must be dispensed to study patients by an appropriately qualified person and is to be used in accordance with the protocol under the direct supervision of a study investigator.

12.5.4 Return of Study Devices

Upon completion of the study, all unused XEN will be returned to Allergan unless other arrangements for disposition are agreed upon in writing with Allergan.

In the event of XEN Gel Implant explantation, contact the Allergan study manager for instructions.

12.6 Monitoring by Allergan

Appropriately trained representatives of Allergan will monitor the conduct of the trial at each investigational site, including visits to the site to review, audit, and retrieve copies of study-related documents. It is the responsibility of the principal investigator to be present or available for consultation and to assure that Allergan has access to all study-related records during scheduled monitoring visits.

Allergan will review device accountability records and completed eCRFs to ensure completeness and consistency with the source records and compliance with the protocol requirements.

Allergan representatives will meet with the investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

12.7 Publications

This study will be registered and results posted on www.clinicaltrials.gov. Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

12.8 Coordinating Investigator

A signatory coordinating investigator will be designated prior to the writing of the Clinical Study Report.

13. References

American Association of Ophthalmology. Clinical Education: Angle Closure Glaucoma. [updated 2013 Dec 13]. Available from: https://www.aao.org/munnerlyn-laser-surgery-center/angleclosure-glaucoma-19. Accessed 26 Jul 2017.

Azuara-Blanco A, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): a randomised controlled trial. Lancet. 2016;388:1389-1397.

Azuara-Blanco A, Burr JM, Cochran C, Ramsay C, Vale L, Foster P, et al. The effectiveness of early lens extraction with intraocular lens implantation for the treatment of primary angle-closure glaucoma (EAGLE): study protocol for a randomized controlled trial. Trials. 2011;12:133.

Chen DZ, Koh V, Sng C, Aquino MC, Chew P. Complications and outcomes of primary phacotrabeculectomy with mitomycin C in a multi-ethnic asian population. PLoS One. 2015;10:e0118852.

Chen YH, Lu DW, Cheng JH, Chen JT, Chen CL. Trabeculectomy in patients with primary angle-closure glaucoma. J Glaucoma. 2009;18:679-683.

European Glaucoma Society. Terminology and guidelines for glaucoma. 4th edition. Savona, Italy: Publicomm; 2014.

Fang AW, Yang XJ, Nie L, Qu J. Endoscopically controlled goniosynechialysis in managing synechial angle-closure glaucoma. J Glaucoma. 2010;19:19-23.

Foster PJ. The epidemiology of primary angle closure and associated glaucomatous optic neuropathy. Semin Ophthalmol. 2002;17:50-58.

Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC, et al. Postoperative complications in the Tube Versus Trabeculectomy (TVT) study during five years of follow-up. Am J Ophthalmol. 2012;153:804-814.e1.

Grover D, Flynn W, Bashford K, Lewis R, Duh YJ, Nangia RS, et al. Performance and safety of a new ab interno gelatin stent in refractory glaucoma at 12 months. Am J Ophthalmol. 2017;183:25-36.

Marchini G, Chemello F, Berzaghi D, Zampieri A. New findings in the diagnosis and treatment of primary angle-closure glaucoma. Prog Brain Res. 2015;221:191-212.

Millan F, Reveron M, Gonzalez L, Siso M, Suescum C, Novack G, et al. Evaluation of the XEN45 gel stent in patients with primary angle closure glaucoma. Poster presentation at the Association for Research in Vision and Ophthalmology Annual Conference. Baltimore, United States 2017.

Murthy SK, Damji KF, Pan Y, Hodge WG. Trabeculectomy and phacotrabeculectomy, with mitomycin-C, show similar two-year target IOP outcomes. Can J Ophthalmol. 2006;41:51-59.

Qing G, Wang N, Mu D. Efficacy of goniosynechialysis for advanced chronic angle-closure glaucoma. Clin Ophthalmol. 2012;6:1723-1729.

Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006;90:262-267.

Rosman M, Aung T, Ang LP, Chew PT, Liebmann JM, Ritch R. Chronic angle-closure with glaucomatous damage: long-term clinical course in a North American population and comparison with an Asian population. Ophthalmology. 2002;109:2227-2231.

Saheb H, Gedde SJ, Schiffman JC, Feuer WJ. Tube Versus Trabeculectomy Study Group. Outcomes of glaucoma reoperations in the Tube Versus Trabeculectomy (TVT) Study. Am J Ophthalmol. 2014;157:1179-1189.e2.

Sun X, Dai Y, Chen Y, Yu DY, Cringle SJ, Chen J, et al. Primary angle closure glaucoma: What we know and what we don't know. Prog Retin Eye Res. 2017;57:26-45.

Wang M, Fang M, Bai YJ, Zhang WZ, Lin MK, Liu BQ, et al. Comparison of combined phacotrabeculectomy with trabeculectomy only in the treatment of primary angle-closure glaucoma. Chin Med J (Engl). 2012;125:1429-1433.

Weinreb RN, Friedman DS, editors. Angle closure and angle closure glaucoma. Reports and consensus statements of the 3rd global Association of International Glaucoma Societies (AIGS) consensus meeting on angle closure glaucoma. The Hague, Netherlands: Kugler Publications; The Netherlands 2006. p. 112.

14. Attachments

Not applicable.

ALLERGAN

Protocol 1924-701-007

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
04-Oct-2017 18:56 GMT-070	[redacted]	Clinical Development Approval