

# CLINICAL STUDY PROTOCOL

## *XEN-45 Gel Stent Versus Trabeculectomy in Glaucoma: Gold-standard Pathway Study (GPS)*

**Protocol Number:** CMO-US-EYE-0600

**EudraCT Number:** Not Applicable

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**Study Product:** XEN-45 Gel Stent (XEN)

**Phase:** Postmarketing study

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**Protocol Version:** Version 2.0

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Not applicable. Allergan uses an electronic approval system.

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### 3 SYNOPSIS

**Protocol Number:**

CMO-US-EYE-0600

**Title:**

XEN-45 Gel Stent Versus Trabeculectomy in Glaucoma: Gold-standard Pathway Study (GPS)

**Study Product:**

XEN-45 Gel Stent (XEN)

**Study Centers:**

Approximately 25 to 40 sites in the United States

**Phase:**

Postmarketing

**Objective:**

To compare the effectiveness and safety of XEN to trabeculectomy in subjects with glaucoma refractory to topical medical therapy defined as intraocular pressure (IOP) not at target on 1 or more topical medications.

**Study Design:**

Multicenter, randomized, parallel-group, prospective, open-label

**Number of Subjects:**

Eyes of approximately 285 subjects (1 eye per subject) will be randomized to have approximately 256 study eyes complete the study.

**Treatment:**

XEN or Trabeculectomy

**Study Duration:**

12 months per participating study eye

**Study Methodology:**

This study will include subjects with glaucoma poorly controlled on topical therapy who are candidates for a subconjunctival drainage procedure. Subjects will be screened for enrollment and eligible candidates will be approached to ascertain interest in study participation. Subjects will be randomized at a ratio of 2:1, resulting in approximately 190 eyes being implanted with XEN and approximately 95 eyes receiving trabeculectomy. A randomized study design was chosen because it prevents selection bias in treatment assignments and produces comparable groups.

**Study Population:**

***Inclusion Criteria***

To be eligible for study entry subjects must satisfy all the following criteria in the study eye (only 1 eye will be allowed in the study):

1. Male or female subjects ages  $\geq 18$  years
2. Able to provide signed written informed consent
3. Glaucoma in which the IOP is not controlled on current topical IOP-lowering glaucoma medication
4. Best-corrected baseline Snellen visual acuity of 20/100 or better

5. Visual field mean deviation no worse than -18.0 dB (with no dense paracentral scotomas, eg, >18 dB total deviation on 1 or more of the 4 paracentral points)
6. Medicated IOP  $\geq 15$  mm Hg and  $\leq 44$  mm Hg on at least 1 topical IOP-lowering medication
7. Subjects not anticipated to require any other ocular surgery (eg, cataract surgery) in either eye up to 3 months from the time of inclusion
8. Area of healthy, free, and mobile conjunctiva in the target area, ie, superior bulbar conjunctiva
9. Visible trabecular meshwork with Shaffer angle grade  $\geq 2$  in the target area or, in eyes with prior failed angle surgery, an open angle in the target area
10. Preoperative laser trabeculoplasty is allowed 3 or more months prior to randomization
11. Failed ab-interno canal or suprachoroidal microinvasive glaucoma surgery (MIGS) procedures (such as iStent<sup>®</sup>, gonioscopy-assisted transluminal trabeculotomy [GATT], ab-interno canaloplasty [ABiC<sup>™</sup>], Kahook Dual Blade goniotomy, etc) are allowed 3 or more months before enrollment, with the exception of CyPass<sup>®</sup> Micro-Stents, which are not allowed. Ab-interno ablative procedures (such as endoscopic cyclophotocoagulation [ECP]) are also allowed 3 or more months before enrollment.

#### **Exclusion Criteria**

Subjects will be excluded from the study if one or more of the following criteria are applicable in the study eye:

1. Subject has active neovascular, uveitic, or angle-recession glaucoma or any glaucoma associated with vascular disorders
  2. Subject has had prior ab-externo incisional glaucoma surgery (such as trabeculectomy, viscocanalostomy, canaloplasty, tube shunts of any type, collagen implants, etc.), conjunctival filtering surgery (such as XEN), transscleral cycloablative procedures (such as cyclophotocoagulation, micropulse cyclophotocoagulation, cryotherapy, ultrasonic circular cyclocoagulation [UC3], etc) or prior major conjunctival surgery (ie, scleral buckle)
  3. Clinically significant inflammation or infection within 30 days before the Preoperative Visit (eg, blepharitis, conjunctivitis, severe ocular surface disease, keratitis, uveitis, herpes simplex infection)
  4. Presence of conjunctival scarring or prior conjunctival surgery or other conjunctival pathologies (eg, pterygium) in the target area
  5. History of corneal surgery, corneal opacities, or corneal disease that could impact assessments/surgical outcomes in the study
  6. Central corneal thickness  $\leq 490$   $\mu\text{m}$  or  $\geq 620$   $\mu\text{m}$
  7. Subjects on systemic carbonic anhydrase inhibitors (eg, Diamox<sup>®</sup> [acetazolamide] and Neptazane<sup>®</sup> [methazolamide]) at Baseline Qualifying Visit
  8. Vitreous present in the anterior chamber
  9. Aphakia
  10. Subject has had prior intraocular surgery in either eye within  $\leq 3$  months before the Preoperative Visit (including phacoemulsification)
  11. History of complicated cataract surgery with visual impairment, vitreous loss, anterior chamber intraocular lens (ACIOL), sutured intraocular lens (IOL), scleral fixated IOL or cystoid macular edema (CME), dislocated IOL
  12. Presence of intraocular silicone oil
  13. **Active** diabetic retinopathy, proliferative retinopathy, choroidal neovascularization, branch retinal vein occlusion, central retinal vein occlusion, geographic atrophy, or other ophthalmic disease or
-

- disorder that could confound study results or impaired episcleral venous drainage (eg, Sturge-Weber or nanophthalmos, Axenfeld-Rieger, iridocorneal endothelial [ICE] syndrome, etc)
14. Known or suspected allergy or sensitivity to drugs required for the protocol (including anesthesia), or any of the device components (eg, bovine or porcine products, or glutaraldehyde)
  15. Pregnant or nursing women and those planning a pregnancy during the study period
  16. Participation in another drug or device clinical trial that concludes within 30 days before the Preoperative Visit or that starts at any time during this study

**Primary Effectiveness Endpoint:**

Percentage of subjects achieving  $\geq 20\%$  mean IOP reduction from baseline at Month 12 on the same or fewer number of topical IOP-lowering medications, without clinical hypotony, loss of vision to count fingers, or a secondary glaucoma surgical intervention.

**Secondary Endpoints:**

**Effectiveness:**

- Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time
- Change from baseline (medicated) in mean IOP and mean number of topical IOP-lowering medications at Month 12
- Proportion of eyes achieving specific IOP targets ( $\leq 18$  mm Hg,  $\leq 17$  mm Hg,  $\leq 16$  mm Hg,  $\leq 15$  mm Hg,  $\leq 14$  mm Hg,  $\leq 13$  mm Hg, and  $\leq 12$  mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline ( $\geq 25\%$  to 50% in 5% increments)
- Proportion of eyes achieving  $\geq 20\%$  IOP reductions and specific IOP targets detailed above on same or lower number of topical IOP-lowering medications at Month 12
- Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time in eyes with medicated baseline IOP  $\leq 18$  mm Hg
- Needling rates; number of needlings per eye; outcomes post needling, including mean IOP and number of medications measured by proportion of eyes achieving  $>20\%$  reduction at Month 12 on same or fewer topical IOP-lowering medications, and number of subjects not using any topical IOP-lowering medications; and antifibrotic use during needling

**Complete and qualified success:**

- Complete success (IOP  $\leq 18$  mm Hg, with 20% or greater IOP lowering from medicated baseline on no topical medications) at Month 12 (eyes with clinical hypotony will be excluded)
- Qualified success (IOP  $\leq 18$  mmHg with 20% or greater IOP lowering from medicated baseline with topical medications) at Month 12 (eyes with clinical hypotony will be excluded)
- Medication-free eyes, mean IOP in this cohort, and proportion of eyes at specific IOPs ( $\leq 18$  mm Hg,  $\leq 17$  mm Hg,  $\leq 16$  mm Hg,  $\leq 15$  mm Hg,  $\leq 14$  mm Hg,  $\leq 13$  mm Hg, and  $\leq 12$  mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline ( $\geq 25\%$  to 50% in 5% increments) with medication-free eyes.

**Intraoperative adjunctive antifibrotic therapy administered:**

- Compound/product, mode of administration, dose and concentration, timing of adjunctive agent (surgery day and pre- and postsurgical procedure/implantation)

**Visual parameters recovery post surgery:**

- Best corrected visual acuity (BCVA) with current glasses (preoperative and postoperative Day 1, Weeks 1 and 2, and Months 1, 3, 6, 9, and 12)
- Manifest refraction (baseline and postoperative Months 1, 3, 6, and 12)
- Surgically induced astigmatism (autorefractor reading [preoperative and postoperative Months 1, 6, and 12] and, at selected sites, topography [preoperative and postoperative Week 1 and Months 1 and 12])
- Optical biometry (anterior chamber depth and keratometric values [preoperative and postoperative Day 1 and Week 2]) at selected sites.

**Other:**

- Bleb morphology (anterior segment optical coherence tomography [AS-OCT] and slit lamp photography at selected sites).

**Safety:**

- Clinical hypotony defined as vision reduction (2 lines or more) related to macular changes consistent with hypotony maculopathy (macular folds), optic disc edema, and/or serous choroidal detachments because of low IOP
- Eyes with IOP 6 mm Hg or less at any time point and relevant clinical assessment (vision reduction [2 lines or more] related to macular changes consistent with hypotony maculopathy [macular folds], optic disc edema, anterior chamber status, and/or serous choroidal detachments because of low IOP) of these eyes at those time points
- Adverse events (AEs) including specific intraoperative and postoperative events of interest
- BCVA, pachymetry, visual field
- AE including serious AEs (SAEs)
- Adverse device effects (ADEs) including serious ADEs (SADEs)

**Patient-reported Outcomes:**

- Patient-reported Outcomes (PRO)

**Sample Size:**

The trial is intended to demonstrate that XEN is comparable to trabeculectomy in terms of treatment success rate. The sample size calculation is based on an equivalence test.

To control Type-I error rate at 5% and to attain 80% power for demonstrating that the difference is within the equivalence limit of 18%, about 256 study eyes will be needed for the study with a randomization ratio of 2:1 for the XEN arm: trabeculectomy arm. Allowing a 10% dropout rate for the first year, approximately 285 study eyes (190 for the XEN arm and 95 for the trabeculectomy arm) will need to be recruited for the study.

**Statistical Analysis:**

Four analysis populations will be used:

- Enrolled population: all study eyes for which the subject has signed the ICF

- Intent-to-treat (ITT) population: all enrolled eyes randomized to study glaucoma surgery (XEN or trabeculectomy)
- Modified Intent-to-treat (mITT) population: eyes in the ITT population that receive study glaucoma surgery and have no major protocol deviations
- Safety population: all enrolled eyes that undergo study glaucoma surgery, whether surgery is completed or aborted, and have follow-up visits or evaluations

The ITT population will be the primary effectiveness analysis population; some effectiveness analyses will also be run with the mITT population. All safety analyses will be run with the Safety population. Descriptive statistics (such as mean, SD, minimum, median, and maximum) will be presented for each continuous variable. Categorical variables will be displayed using frequency counts and percentages.

The number and proportion of subjects achieving  $\geq 20\%$  mean IOP reduction from baseline at Month 12 on the same or fewer number of topical IOP-lowering medications, without clinical hypotony, loss of vision to count fingers, or a secondary glaucoma surgical intervention will be tabulated with 95% CI calculated by using the normal approximation method. The difference of the proportions will be estimated and the 95% CI of the difference will also be calculated with the method of normal approximation. The 2 treatment arms will be claimed as equivalent if the 95% CI of the differences is within the -18% to 18% interval. The least squares mean change from baseline in IOP and the least squares mean difference between the 2 treatment groups will be estimated using the analysis of covariance (ANCOVA) model or the mixed-effect model repeat measurement (MMRM) model. The proportion and the 95% CI of complete success and qualified success will be calculated with normal approximation. All reported treatment-emergent AEs and all safety measures collected will be tabulated by counts and percentages.



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## 5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

### LIST OF ABBREVIATIONS

ABiC	ab-interno canaloplasty
ACIOL	anterior chamber intraocular lens
ADE	adverse device effect
AE	adverse event
ANCOVA	analysis of covariance
AS-OCT	anterior segment optical coherence tomography
BCVA	best corrected visual acuity
CAI	carbonic anhydrase inhibitors
CIGTS	Collaborative Initial Glaucoma Treatment Study
CME	cystoid macular edema
CRO	contract research organization
eCRF	electronic case report form
EDC	electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GATT	gonioscopy-assisted transluminal trabeculotomy
GCP	Good Clinical Practice
GPS	Gold-standard Pathway Study
HIPAA	Health Insurance Portability and Accountability Act
ICE	iridocorneal endothelial
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IOP	intraocular pressure
IOL	intraocular lens
IRB	institutional review board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MIGS	microinvasive glaucoma surgery
mITT	modified intent-to-treat
MMRM	mixed-effect model repeat measurement
MTMT	maximal tolerated medical therapy
n	number of subjects with an observation
N	number of subjects in the dataset or population
PACG	primary angle-closure glaucoma
POAG	primary open-angle glaucoma
PRO	patient-reported outcomes
RTSM	Randomization and Trial Supply Management
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SHPC-18	Symptom and Health Problem Checklist (18 items)
SLT	selective laser trabeculoplasty
SOP	standard operating procedure
UC3	ultrasonic circular cyclocoagulation
WHO	World Health Organization

WPAI            Work Productivity and Activity Impairment  
XEN            XEN-45 Gel Stent

## 6 INTRODUCTION

### 6.1 Overview of Glaucoma

Glaucoma is the leading cause of irreversible vision loss worldwide. Although several eye conditions are variants of glaucoma, the most common types of glaucoma are primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG). Asia accounts for a disproportionate number of PACG cases, whereas the prevalence of POAG is more evenly distributed throughout the world (Quigley 1996).

The goal in the treatment of glaucoma is to prevent further loss of functional vision during the remainder of a patient's life and to avoid an adverse impact on the patient's quality of life (AAO Glaucoma PPP Panel 2015).

There are many known risk factors for glaucoma including age, ethnicity, and family history. Intraocular pressure (IOP) is the only modifiable risk factor that is currently available to arrest visual field loss and reduction of IOP has been shown to reduce the risk of glaucomatous visual field loss in many landmark trials.

The prevention of glaucomatous loss of vision is mainly achieved by lowering the eye pressure to a threshold that is deemed to be safe for the ganglion cells given the current amount of damage in the optic nerve head (ie, target IOP).

There are many approaches to lower IOP including pharmacotherapy (topical and systemic), laser therapy, and surgery. Topical medications are often the first line of treatment, especially in early disease along with selective laser trabeculoplasty (SLT). Most patients require multiple medications to lower IOP to target (AAO Glaucoma PPP Panel 2015).

Traditional incisional glaucoma surgery results in robust IOP lowering; however, the accompanying side effects often preclude use earlier in the treatment paradigm. Trabeculectomy is the gold standard and currently the most commonly used drainage procedure, but complications are a major problem. Early and late complications include bleb leak, excessive drainage, flat anterior chamber, filtration failure, clinical hypotony, symptomatic blebs, bleb encapsulation, filtration failure, hyphema, choroidal effusion, suprachoroidal hemorrhage, and bleb infection (Gedde et al. 2007). Complications associated with drainage surgeries can have serious consequences and require careful management to prevent further problems. The bleb is currently the cornerstone of trabeculectomy drainage surgery, but the trabeculectomy bleb is also fragile and susceptible to scarring (Azura-Blanco and Katz 1998). Another subconjunctival surgical approach includes the Ex-PRESS<sup>®</sup> miniature glaucoma implant (Alcon Laboratories Inc., Fort Worth, TX), which is a biocompatible, nonvalved stainless steel tube. The Ex-PRESS is currently implanted using a procedure like standard trabeculectomy, and includes creation of a sclera flap and a conjunctival filtration bleb, but no peripheral iridectomy is required when implanting the Ex-PRESS (Moisseiev et al. 2015).

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Trabeculectomy and tube shunt surgeries have an important role in glaucoma management, offering the ability to achieve IOP lowering independent of patients' compliance in appropriate candidates. Tube shunts are being increasingly used in the surgical management of glaucoma. The Ahmed glaucoma valve and the Baerveldt implant represent the most commonly used tube shunts. The Ahmed valve has a valve mechanism to prevent postoperative hypotony and shallow anterior chambers, whereas the Baerveldt implants provide a greater surface area in the end plate for aqueous reabsorption, providing better IOP control and a reduced need for glaucoma medication over the long term (Gedde et al. 2010, Wang et al. 2016). All the above procedures, performed using an ab-externo approach, achieve lowering of IOP via drainage of aqueous from the anterior chamber to the subconjunctival space (Gedde et al. 2012). However, each of these procedures is associated with a lengthy and variable recuperation and prolonged time to visual recovery. In some instances, there is associated loss of best corrected visual acuity (BCVA) and significant risk of short- and long-term complications, including hypotony, choroidal effusion, cataract, and flat or shallow anterior chamber, as well as valve-related complications, such as tube blockage, erosion, and endothelial cell loss (Gedde et al. 2012, Shaarawy et al. 2004, Rulli et al. 2013, Vijaya et al. 2011).

An alternative option to the more invasive traditional surgeries described above, in the form of microinvasive glaucoma surgery (MIGS) devices, are now available that have an improved safety profile and recovery compared with trabeculectomy and tube shunts (Saheb and Ahmed 2012). There are several devices fitting the definition of MIGS including XEN-45 Gel Stent (XEN); they can be categorized by their intended mechanism of action, ie, they may improve outflow by targeting the trabecular meshwork or the supraciliary space (Caprioli et al. 2015). Unlike canal-based and supraciliary MIGS devices, XEN facilitates subconjunctival drainage like the gold-standard surgical option trabeculectomy to provide robust IOP lowering from a medicated baseline (Vera et al. 2018, Mansouri et al. 2018, Hengerer et al. 2017).

Topical therapy is often the first line intervention for IOP lowering in open-angle glaucoma. Although the standard practice is to prescribe a second IOP-lowering medication when the first drug has lowered a patient's IOP, but not to an optimal level, the efficacy seen with monotherapy may not translate into similar efficacy when a medication is used adjunctively. Additionally, the side effects of multiple medications need to be considered for patient quality of life (Fechtner and Singh 2001).

To quantify the IOP reduction after surgery in clinical trials versus topical IOP-lowering medications, a consistent definition of the baseline, or reference IOP is necessary. For practical purposes, the highest challenge for a trial is the maximal tolerated medical therapy (MTMT) of IOP-lowering medications because that level would be considered the best that those drugs can achieve (Shaarawy et al. 2004). To determine the MTMT for glaucoma and the amount of medication an eye can tolerate, patients may need to endure severe adverse effects before advancing to surgery. In contrast, in clinical practice, the goal is optimal medical therapy, in which the practitioner uses the least amount of medicine to achieve the desired goal with the least adverse effects. In

standard clinical practice, ophthalmologists prescribe at least 2 glaucoma medications before suggesting surgical intervention to a patient. After treatment failure with the second, and certainly after the third medication is added, it is unlikely that additional agents will improve the outcome (Fechtner and Singh 2001).

## **6.2 XEN Gel Stent**

### **6.2.1 Device Description**

A MIGS drainage device implanted via an ab-interno approach that facilitates drainage of aqueous from the anterior chamber to the subconjunctival space (XEN-45; Allergan, Irvine, CA) has recently been approved in the United States for use in the surgical management of glaucoma. This device, which can be used as a standalone procedure, offers the potential to achieve IOP lowering that is comparable to trabeculectomy, but with less tissue manipulation (Schlenker et al. 2017, Reitsamer 2016).

The device, which is implanted using a handheld disposable injector, is constructed from porcine-derived gelatin that is formed into a tube and cross-linked with glutaraldehyde, thus allowing it to expand and remain flexible when hydrated. The expansion of the tube's outer diameter, when in contact with fluid, also aids in retention of the gel stent in its intended location after surgical implantation, which helps minimize many of the issues associated with other materials, such as migration, erosion, and corneal endothelial damage (Aref and Varma 2012). The gel stent was designed using principles established by the Hagen–Poiseuille equation, whereby outflow resistance to the fluid increases linearly in proportion to the length of the tube, and decreases to the fourth power of the diameter of the tube lumen. In sum, a longer and thinner tube provides greater resistance than a shorter and wider tube (Sheybani et al. 2015).

The XEN Gel Stent, XEN-45, or XEN Gel Implant (XEN) is indicated for the management of refractory glaucomas, including cases in which previous surgical treatment has failed, cases of POAG, and cases of pseudoexfoliative or pigmentary glaucoma with open angles that are unresponsive to MTMT.

### **6.2.2 Clinical Experience**

XEN is the first ab-interno minimally invasive procedure that creates a new pathway for aqueous flow from the anterior chamber to the subconjunctival space. Clinical studies have shown XEN is effective at reducing IOP with fewer complications as compared with those published for trabeculectomy studies (Schlenker et al. 2017, Mansouri et al. 2018, Hengerer et al. 2017, DeGregorio et al. 2018, Grover et al. 2017).



## 7 STUDY OBJECTIVES

To compare the effectiveness and safety of XEN to trabeculectomy in subjects with glaucoma refractory to topical medical therapy defined as intraocular pressure (IOP) not at target on 1 or more topical medications.

### 7.1 Primary Endpoint

Percentage of subjects achieving  $\geq 20\%$  mean IOP reduction from baseline at Month 12 on the same or fewer number of topical IOP-lowering medications, without clinical hypotony, loss of vision to count fingers, or secondary glaucoma surgical intervention.

### 7.2 Secondary Endpoints

Effectiveness:

- Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time
- Change from baseline (medicated) in mean IOP and mean number of topical IOP-lowering medications at Month 12
- Proportion of eyes achieving specific IOP targets ( $\leq 18$  mm Hg,  $\leq 17$  mm Hg,  $\leq 16$  mm Hg,  $\leq 15$  mm Hg,  $\leq 14$  mm Hg,  $\leq 13$  mm Hg, and  $\leq 12$  mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline ( $\geq 25\%$  to  $50\%$  in  $5\%$  increments)
- Proportion of eyes achieving  $\geq 20\%$  IOP reductions and specific IOP targets detailed above on same or lower number of topical IOP-lowering medications at Month 12
- Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time in eyes with medicated baseline IOP  $\leq 18$  mm Hg
- Needling rates; number of needlings per eye; outcomes post needling, including mean IOP and number of medications measured by proportion of eyes achieving  $>20\%$  reduction at Month 12 on same or fewer topical IOP-lowering medications, and number of subjects not using any topical IOP-lowering medications; and antifibrotic use during needling.

Complete and qualified success:

- Complete success (IOP  $\leq 18$  mm Hg, with  $20\%$  or greater IOP lowering from medicated baseline on no topical medications) at Month 12 (eyes with clinical hypotony will be excluded)
- Qualified success (IOP  $\leq 18$  mm Hg with  $20\%$  or greater IOP lowering from medicated baseline with topical medications) at Month 12 (eyes with clinical hypotony will be excluded)

- Medication-free eyes, mean IOP in this cohort, and proportion of eyes at specific IOPs ( $\leq 18$  mm Hg,  $\leq 17$  mm Hg,  $\leq 16$  mm Hg,  $\leq 15$  mm Hg,  $\leq 14$  mm Hg,  $\leq 13$  mm Hg, and  $\leq 12$  mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline ( $\geq 25\%$  to  $50\%$  in  $5\%$  increments) with medication-free eyes.

Intraoperative adjunctive antifibrotic therapy administered:

- Compound/product, mode of administration, dose and concentration, timing of adjunctive agent (surgery day and pre- and postsurgical procedure/implantation).

Visual parameters recovery post surgery:

- BCVA with current glasses (preoperative and postoperative Day 1; Weeks 1 and 2; and Months 1, 3, 6, 9, and 12)
- Manifest refraction (baseline and postoperative Months 1, 3, 6, and 12)
- Surgically induced astigmatism (autorefractor reading [preoperative and postoperative Months 1, 6, and 12] and, at selected sites, topography [preoperative and postoperative Week 1, and Months 1 and 12])
- Optical biometry (anterior chamber depth and keratometric values) at preoperative and postoperative Day 1 and Week 2 at selected sites.

Other:

- Bleb morphology (anterior segment optical coherence tomography [AS-OCT] and slit lamp photography at selected sites).

Safety:

- Clinical hypotony defined as vision reduction (2 lines or more) related to macular changes consistent with hypotony maculopathy (macular folds), optic disc edema, and/or serous choroidal detachments because of low IOP
- Eyes with IOP 6 mm Hg or less at any time point and relevant clinical assessment (vision reduction [2 lines or more] related to macular changes consistent with hypotony maculopathy [macular folds], optic disc edema, anterior chamber status, and/or serous choroidal detachments because of low IOP) of these eyes at those time points
- Adverse events (AEs) including specific intraoperative and postoperative events of interest
- BCVA, pachymetry, visual field
- AEs including serious AEs (SAEs)
- Adverse device effects (ADEs) including serious ADEs (SADEs)

Patient-reported Outcomes:

- Patient-reported Outcomes (PRO)

### **7.3 Exploratory Objective**

Not applicable.

## 8 INVESTIGATIONAL PLAN

### 8.1 Overall Study Design and Plan: Description

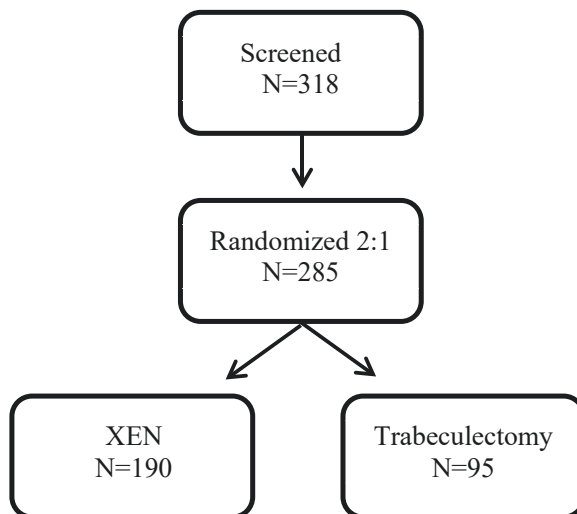
This is a multicenter, randomized, parallel-group, prospective, open-label clinical trial to compare the ability of XEN and trabeculectomy to reduce IOP and reduce the number of topical IOP-lowering medications in subjects with IOP that is poorly controlled on topical therapy.

Subjects will be randomized 2:1, resulting in approximately 190 eyes being implanted with XEN and approximately 95 eyes receiving trabeculectomy. Subjects will be screened for enrollment, and eligible candidates will be approached to ascertain interest in study participation. Duration of participation in the study will be approximately 12 months. The study design is depicted in [Figure 8-1](#).

If both eyes of a subject meet the study entry criteria, the study eye will be selected by the investigator.

#### 8.1.1 Study Design

**Figure 8-1 Flow Chart of the Study**



Note: These numbers are approximate.

#### 8.1.2 Schedule of Assessments

The schedule of planned study assessments is shown in [Table 8.1](#).

**Table 8.1 Schedule of Assessments**

Procedure / Data to be Recorded	Baseline Qualifying Visit <sup>a</sup>	Preoperative Visit 1 <sup>a</sup>	Operative		Postoperative Visits (visit window; time since Day 0)														
			Visit 2 Day 0	Visit 3 Day 1 (6-48 h)	Visit 4 Week 1 (3-10 d)	Visit 5 Week 2 (11-20 d)	Visit 6 Month 1 (3-8 wk)	Visit 7 Month 3 (9-17 wk)	Visit 8 Month 6 (18-32 wk)	Visit 9 Month 9 (33-47 wk)	Visit 10 Month 12 (48-60 wk)								
Demographics	X																		
Medical and Ophthalmic History	X																		
Subject Eligibility	X																		
Informed Consent/HIPAA	X																		
Concomitant Medications and/or Procedures Review	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular Pressure (IOP)	X <sup>b</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Autorefractor		X								X									
Visual Acuity (BCVA) <sup>c</sup>	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Manifest Refraction	X									X	X	X	X	X	X	X	X	X	X
Biomicroscopy (slit lamp exam)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Gonioscopy Assessment (Schaffer's Scale) <sup>d</sup>	X			X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>
Visual Field Exam	X <sup>e</sup>																		
Ophthalmoscopy		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pachymetry		X																	
Topography <sup>f</sup>		X								X									
Biometry <sup>f</sup>		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AS-OCT <sup>f</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bleb Photography <sup>f</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO: SHPC-18 <sup>g</sup>				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PRO: Postsurgical Question <sup>g</sup>																			
PRO: WPAI <sup>g</sup>	X							X											X
Randomization																			
Glaucoma Surgery																			X

Procedure / Data to be Recorded	Baseline Qualifying Visit <sup>a</sup>	Preoperative Visit 1 <sup>a</sup>	Operative		Postoperative Visits (visit window; time since Day 0)										
			Visit 2 Day 0	Visit 3 Day 1 (6-48 h)	Visit 4 Week 1 (3-10 d)	Visit 5 Week 2 (11-20 d)	Visit 6 Month 1 (3-8 wk)	Visit 7 Month 3 (9-17 wk)	Visit 8 Month 6 (18-32 wk)	Visit 9 Month 9 (33-47 wk)	Visit 10 Month 12 (48-60 wk)				
Record Needling and Laser Suture Lysis, and Antifibrotic Treatments			X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events Assessment		X	X <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X

AS-OCT = anterior segment optical coherence tomography; BCVA = Best corrected visual acuity; d = day; h = hour; HIPAA = Health Insurance Portability and Accountability Act; IOP = intraocular pressure; PRO = patient reported outcome; SHPC-18 = Symptom and Health Problem Checklist; wk = week; WPAI = Work Productivity and Activity Impairment

<sup>a</sup> The Baseline Qualifying Visit and the Preoperative Visit may be done on the same day if there are no changes in preoperative IOP medications. The Preoperative Visit may be repeated to complete all procedures, if needed. The visit window for Preoperative Visit 1 (including any repeated visits) is up to 4 weeks before study glaucoma surgery in the study eye and  $\geq 3$  months since previous intraocular surgery in either eye.

<sup>b</sup> This is the medicated baseline IOP value. This should be performed at approximately the same time at each visit whenever possible. Subject has taken IOP medication.

<sup>c</sup> BCVA should be performed using a Snellen chart with glasses.

<sup>d</sup> Performed at Baseline Qualifying Visit and then at other times at the investigator's discretion

<sup>e</sup> Can use valid results up to 3 months prior to screening

<sup>f</sup> At selected sites only

<sup>g</sup> Patient questionnaires should be self-administered prior to any clinical assessments.

<sup>h</sup> Refers to intraoperative events or surgical complications

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## 8.2 Discussion of Study Design

### 8.2.1 Study Design

Subjects will be randomized at a ratio of 2:1, resulting in approximately 190 eyes being implanted with XEN and approximately 95 eyes receiving trabeculectomy. A randomized study design was chosen because it prevents selection bias in treatment assignments and produces comparable groups. This study will include subjects presenting with glaucoma poorly controlled on topical therapy who are candidates for a subconjunctival drainage procedure. Subjects will be screened for enrollment and eligible candidates will be approached to ascertain interest in study participation. Subjects can be enrolled into one of the following groups:

Group 1: XEN implanted (XEN group)

Group 2: Trabeculectomy (Trab group).

All inclusion/exclusion criteria, effectiveness endpoints, success rate determinations, and follow-up examinations will be identical for both groups.

At baseline, subjects with glaucoma not at target IOP when using at least 1 topical IOP-lowering medication will be screened for eligibility to participate in the study. After the subject is determined to be eligible for participation in the study and is enrolled, the physician may stop the previously prescribed medications 1 to 4 weeks before surgery and begin preoperative medications (eg, steroids, antibiotics, artificial tears, oral carbonic anhydrase inhibitors [CAIs]) to prepare the ocular surface before surgery. The detection and treatment of comorbid conditions, particularly diseases of the ocular surface disease (dry eye) and blepharitis, can help reduce eye inflammation ([Baudouin 2012](#)). Stopping or reducing IOP-lowering medications and replacing them, if necessary, with oral acetazolamide prior to surgery may be considered along with use of topical steroids and preservative-free lubricants to reduce ocular surface inflammation and improve the likelihood of successful implantation ([Vera et al. 2018](#)).

Subjects will undergo at least 1 preoperative visit (and more as needed), and then be scheduled for XEN gel stent implantation or trabeculectomy. Subjects will be examined postoperatively at the following timepoints: Day 1; Weeks 1 and 2; and Months 1, Month 3, Month 6, Month 9, and Month 12.

### 8.2.2 Quality Management and Risk Evaluation

As noted in XEN's Directions for Use the complications that may occur in conjunction with the use of XEN include, but are not limited to, the following: choroidal effusion, hyphema, hypotony, implant migration, implant exposure, wound leak, need for secondary surgical intervention and other known complications of intraocular surgery (eg, flat or shallow chamber, corneal edema, endophthalmitis).

The risk profile for XEN has been established based on the review of all applicable safety data. These complications include adverse reaction to implant material, infection, implant failure, device malfunction, hypotony, flat anterior chamber (central lens, corneal touch), endophthalmitis, and ocular injury (inadvertent perforation of the sclera, hyphema, inadvertent loss of vitreous, choroidal hemorrhage or effusion, bleeding, device wound dehiscence). Risks involved in the procedure include persistent inflammation, corneal complications, retinal complications, choroidal complications, visual acuity loss (loss of 2 Snellen lines or more), chronic pain, unplanned secondary surgical intervention, loss of eye, and infection.

XEN is currently contraindicated under the following circumstances or conditions: angle-closure glaucoma, previous glaucoma shunt/valve in the target quadrant, presence of conjunctival scarring, prior conjunctival surgery or other conjunctival pathologies (eg, pterygium) in the target quadrant, active inflammation (eg, blepharitis, conjunctivitis, keratitis, uveitis), active iris neovascularization or neovascularization of the iris within 6 months of the surgical date, anterior chamber intraocular lens (ACIOL), presence of intraocular silicone oil, vitreous present in the anterior chamber. The exclusion criteria of this trial are in accordance with the contraindications for the device (see [Section 8.3.3](#)).

The risks associated with the use of XEN are considered reasonable in comparison with the anticipated benefits to subjects. XEN poses an acceptable level of risk for its intended use.

The risks associated with the gold-standard subconjunctival filtering procedure trabeculectomy have been well studied and include choroidal effusion, shallow/flat anterior chamber, wound leak, hyphema, dysesthesia, encapsulated bleb, and persistent corneal edema ([Gedde et al. 2007](#)).

### **8.3 Selection of Study Population**

#### **8.3.1 Number of Planned Subjects**

This study will include subjects with glaucoma poorly controlled on topical therapy including those who may have had prior SLT or MIGS surgeries who meet the inclusion and exclusion criteria. Any questions regarding a subject's eligibility should be discussed with the sponsor prior to enrollment.

This study plans to enroll subjects at approximately 25 to 40 sites in the United States. A total of approximately 285 subjects will be included in the study: approximately 190 subjects in the XEN arm and 95 subjects in trabeculectomy arm. One eye per subject will be enrolled into the study. This includes an estimated 10% dropout rate after screening (see [Section 11.2](#) for the calculation of sample size).



### 8.3.2 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria in the study eye (only 1 eye will be allowed in the study):

1. Male or female subjects ages  $\geq 18$  years
2. Able to provide signed written informed consent
3. Glaucoma in which the IOP is not controlled on current topical IOP-lowering glaucoma medication
4. Best-corrected baseline Snellen visual acuity of 20/100 or better
5. Visual field mean deviation no worse than -18.0 dB (with no dense paracentral scotomas, eg,  $>18$  dB total deviation on 1 or more of the 4 paracentral points)
6. Medicated IOP  $\geq 15$  mm Hg and  $\leq 44$  mm Hg on at least 1 topical IOP-lowering medication
7. Subjects not anticipated to require any other ocular surgery (eg, cataract surgery) in either eye up to 3 months from the time of inclusion
8. Area of healthy, free, and mobile conjunctiva in the target area, ie, superior bulbar conjunctiva
9. Visible trabecular meshwork with Shaffer angle grade  $\geq 2$  in the target area or, in eyes with prior failed angle surgery, an open angle in the target area
10. Preoperative laser trabeculoplasty is allowed 3 or more months prior to randomization
11. Failed ab-interno canal or suprachoroidal MIGS procedures (such as i-Stent<sup>®</sup>, gonioscopy-assisted transluminal trabeculotomy [GATT], ab-interno canaloplasty [ABiC<sup>™</sup>], Kahook Dual Blade goniotomy, etc) are allowed 3 or more months before enrollment, with the exception of CyPass<sup>®</sup> Micro-Stents, which are not allowed. Ab-interno ablative procedures (such as endoscopic cyclophotocoagulation [ECP]) are also allowed 3 or more months before enrollment.

### 8.3.3 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable in the study eye:

1. Subject has active neovascular, uveitic or angle-recession glaucoma or any glaucoma associated with vascular disorders
2. Subject has had prior ab-externo incisional glaucoma surgery (such as trabeculectomy, viscocanalostomy, canaloplasty, tube shunts of any type, collagen implants, etc), conjunctival filtering surgery (such as XEN), transscleral

- cycloablative procedures (such as cyclophotocoagulation, micropulse cyclophotocoagulation, cryotherapy, ultrasonic circular cyclocoagulation [UC3], etc) or prior major conjunctival surgery (ie, scleral buckle)
3. Clinically significant inflammation or infection within 30 days before the Preoperative Visit (eg, blepharitis, conjunctivitis, severe ocular surface disease, keratitis, uveitis, herpes simplex infection)
  4. Presence of conjunctival scarring or prior conjunctival surgery or other conjunctival pathologies (eg, pterygium) in the target area
  5. History of corneal surgery, corneal opacities, or corneal disease that could impact assessments/surgical outcomes in the study
  6. Central corneal thickness  $\leq 490$   $\mu\text{m}$  or  $\geq 620$   $\mu\text{m}$
  7. Subjects on systemic CAIs (eg, Diamox<sup>®</sup> [acetazolamide] and Neptazane<sup>®</sup> [methazolamide]) at Baseline Qualifying Visit
  8. Vitreous present in the anterior chamber
  9. Aphakia
  10. Subject has had prior intraocular surgery in either eye within  $\leq 3$  months before the Preoperative Visit (including phacoemulsification)
  11. History of complicated cataract surgery with: visual impairment, vitreous loss, ACIOL, sutured intraocular lens (IOL), scleral fixated IOL or cystoid macular edema (CME), dislocated IOL
  12. Presence of intraocular silicone oil
  13. **Active** diabetic retinopathy, proliferative retinopathy, choroidal neovascularization, branch retinal vein occlusion, central retinal vein occlusion, geographic atrophy, or other ophthalmic disease or disorder that could confound study results or impaired episcleral venous drainage (eg, Sturge-Weber or nanophthalmos, Axenfeld-Rieger, iridocorneal endothelial [ICE] syndrome, etc)
  14. Known or suspected allergy or sensitivity to drugs required for the protocol (including anesthesia), or any of the device components (eg, bovine or porcine products, or glutaraldehyde)
  15. Pregnant or nursing women and those planning a pregnancy during the study period
  16. Participation in another drug or device clinical trial that concludes within 30 days before the Preoperative Visit or that starts at any time during this study.

### **8.3.4 Removal of Subjects from Therapy or Assessments**

Every attempt must be made to gather complete follow-up data for all subjects enrolled. Subjects who would be traveling, relocating or otherwise unavailable for the postoperative follow-up schedule should not be chosen for the study.

Subjects should be discontinued from the study only if irretrievably lost to follow-up for unavoidable reasons such as inability to locate, subject uncooperativeness, subject illness, or subject death. A subject may also be discontinued from the study if complications occur during surgery and the subject does not receive XEN or undergo trabeculectomy. If a subject does receive XEN or undergo trabeculectomy following complications, then the subject should be followed up per the study protocol. Also, if the eye undergoes additional glaucoma surgery after the study intervention due to poor IOP control, it will be discontinued from the study as a failure.

In the event that a subject is discontinued from the study, the investigator shall complete a Subject Exit Form in the electronic data capture (EDC) system, indicating the early termination reason.

Subjects may withdraw their consent to continue in the study at any time. Subjects withdrawing from the study after receiving XEN or undergoing trabeculectomy will be encouraged to complete the same final evaluations as subjects completing the study according to this protocol, particularly safety evaluations. The aim is to record data in the same way as for subjects who completed the study. Subjects who discontinue before undergoing a study surgery will not be required to return for study follow-up visits.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time, in case of SAEs, or if special circumstances concerning the study product or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) will be informed of the reason for study termination.

## **8.4 Investigated in Protocol**

### **8.4.1 Study Product and Procedures**

#### **8.4.1.1 XEN**

XEN is manufactured by Allergan, Plc (Ireland). XEN is composed of a gelatin derived from porcine dermis, formed into a tube, and cross-linked with glutaraldehyde. It is intended to be inserted in the angle and through the sclera, connecting the anterior chamber to the subconjunctival space. XEN is preloaded in the XEN Injector, a single-use mechanical delivery system. XEN is packaged with directions for use and the procedure to insert XEN should be carried out in line with surgical training provided by the manufacturer and following the standard of care at each investigative center.

#### **8.4.1.2 Comparator – Trabeculectomy**

Trabeculectomy will be performed in accordance with the standard of care at each investigative center with adjunctive antifibrotic therapy and including essential steps: conjunctival flap, scleral flap, and sclerostomy. Note: Peripheral iridectomy is not mandated and is left to the standard practice of the surgeon.

### **8.4.2 Packaging and Labeling**

XEN used will be commercial supply of XEN-45 Gel Stent in the United States.

### **8.4.3 Device Complaint Reporting**

Device complaints and malfunctions should be reported per the package insert or directions for use.

### **8.4.4 Method of Assigning Subjects to Treatment Groups**

Subjects will be randomized by investigational site to a 2:1 (XEN:trabeculectomy) randomization schedule by the Medidata Rave RTSM (Randomization and Trial Supply Management) application. The randomization list will be generated by the sponsor's independent Randomization Services Group using a customized validated system composed of a series of SAS<sup>®</sup> Macros (version 1.4). This list will be provided to the contract research organization's (CRO's) independent randomization team, who will upload the list into the Medidata Rave RTSM application and validate it. Upon completion of a randomization electronic case report form (eCRF), indicating that a study eye meets all entry criteria, the data will be sent to the RTSM system for randomization. The RTSM system will then provide the surgery group assignment for the study eye and integrate it back into the randomization eCRF. The sponsor's and CRO's study team members, investigational site staff, and subjects will not have access to the randomization list.

#### **8.4.5 Prior and Concomitant Therapy**

Topical IOP-lowering medication may be stopped 1 to 4 weeks before surgery and re-started according to the investigator's recommendation. At baseline, subjects are to be using at least 1 topical IOP-lowering medication and, when using that medication at the maximum tolerated dose, their IOP is not controlled. After the subject is determined to be eligible for participation in the study and is enrolled, the physician may stop the previously prescribed medications 1 to 4 weeks before surgery and begin preoperative medications (eg, steroids, antibiotics, artificial tears) to prepare the ocular surface before surgery. The detection and treatment of comorbid conditions, particularly diseases of the ocular surface disease (dry eye) and blepharitis, can help reduce eye inflammation (Baudouin 2012). Stopping or reducing IOP-lowering medications and replacing them, if necessary, with oral acetazolamide prior to surgery may be considered along with use of topical steroids and preservative-free lubricants to reduce ocular surface inflammation and improve the likelihood of successful implantation (Vera et al. 2018).

Subjects who have had prior ab-externo incisional glaucoma surgery (such as trabeculectomy, viscocanalostomy, canaloplasty, tube shunts of any type, collagen implants, etc), conjunctival filtering surgery (such as XEN), transscleral cycloablative procedures (such as cyclophotocoagulation, micropulse cyclophotocoagulation, cryotherapy, UC3, etc) or prior major conjunctival surgery (ie, scleral buckle) are not eligible for the study (see Section 8.3.3).

Perioperative adjunctive antifibrotic therapy should be used according to physician training and practice.

## **9 TIMING OF STUDY PROCEDURES**

The planned study assessments are in [Section 8.1.2](#).

Every attempt should be made to schedule the visits (specifically measurement of IOP) at approximately the same time of day to avoid the influence of diurnal fluctuations. Assess IOP using Goldmann applanation tonometry. Take 2 measurements. If the first 2 measurements differ by more than 3 mm Hg, take a third measurement. Use the average if 2 measurements are taken (or the median if 3 measurements are taken) to determine each day's IOP.

### **9.1 Pretreatment Visits**

#### **9.1.1 Baseline Qualifying Visit**

During the study Baseline Qualifying Visit, the procedures will be performed following the Schedule of Assessments ([Table 8.1](#)).

When these procedures have been performed, the next visit will be scheduled. The Baseline Qualifying Visit and Preoperative Visit may occur on the same day if there are no changes to the IOP-lowering medications prior to surgery.

#### **9.1.2 Preoperative Visit (Visit 1)**

During the study Preoperative Visit, the procedures will be performed as shown on the Schedule of Assessments ([Table 8.1](#)).

This visit may be repeated as necessary to complete required examinations. The visit window for Preoperative Visit 1 (including any repeated visits) is up to 4 weeks before study glaucoma surgery in the study eye and  $\geq 3$  months since previous intraocular surgery in either eye. When all Visit 1 procedures have been performed, if all entry criteria are met, the study eye will be randomized to glaucoma surgery procedure, and the next visit will be scheduled.

#### **9.1.3 Operative Visit (Visit 2)**

The Operative Visit (Visit 2) will be Day 0 of the study. At this visit, glaucoma surgery (XEN or trabeculectomy) will be performed. Record any intraoperative complications.

### **9.2 Postoperative Visits**

#### **9.2.1 Day 1 (Visit 3)**

The first postoperative visit will take place on study Day 1 (6-48 hours) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments ([Table 8.1](#)).

#### **9.2.2 Week 1 (Visit 4)**

Visit 4 will take place 1 week (3-10 days) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.3 Week 2 (Visit 5)**

Visit 5 will take place 2 weeks (11-20 days) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.4 Month 1 (Visit 6)**

Visit 6 will take place 1 month (3-8 weeks) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.5 Month 3 (Visit 7)**

Visit 7 will take place 3 months (9-17 weeks) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.6 Month 6 (Visit 8)**

Visit 8 will take place 6 months (18-32 weeks) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.7 Month 9 (Visit 9)**

Visit 9 will take place 9 months (33-47 weeks) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.8 Month 12 (Visit 10)**

Visit 10 will take place 12 months (48-60 weeks) after the Operative Visit. During this visit the procedures will be performed following the Schedule of Assessments (Table 8.1).

#### **9.2.9 Early Withdrawal Visit**

In the case of an early withdrawal, an Early Withdrawal Visit should be scheduled for subjects who underwent a study surgery, if possible. Procedures should be performed as for the Month 12, Visit 10.

### **9.3 Duration of Study**

The duration of study participation will be approximately 12 months.

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#### **9.4 Pregnancy**

If a female XEN subject 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 +1-877-605-4524 or +1-714-796-9567. Best practices are to be followed to ensure the welfare of the subject 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 subject will continue to be followed up as part of the implanted population. Pregnancy by itself will not be considered an AE or 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.



## **10 EFFECTIVENESS AND SAFETY VARIABLES**

### **10.1 Effectiveness and Safety Measurements Assessed**

#### **10.1.1 Effectiveness Variables**

##### **10.1.1.1 Intraocular Pressure**

Every attempt should be made to schedule the visits at approximately the same time of day to avoid the influence of diurnal fluctuations on study procedures, specifically measurement of IOP.

Except at the Operative Visit (Visit 2), IOP will be measured at all study visits by standard Goldmann applanation tonometry. The readings will be recorded on the appropriate eCRF. The tonometer should be checked for proper calibration monthly and the date of calibration checking should be recorded. The eye cannot have received pupil-dilating medications.

##### **10.1.1.2 Topical IOP-lowering Medication**

For endpoints evaluating the number of topical IOP-lowering medications taken by the subject, the following are examples of the classes of medications to be recorded: prostaglandin analogues, beta-adrenergic antagonists, CAIs, alpha-adrenergic agonists, pilocarpine, and combinations of these treatments.

##### **10.1.1.3 Patient-reported Outcomes**

The following 3 questionnaires will be completed to assess subject status. Questionnaires will be administered to subjects on an electronic tablet at the visits designated in [Table 8.1](#). Data from completed questionnaires will be imported into the eCRF using a validated process.

1. Collaborative Initial Glaucoma Treatment Study (CIGTS) Symptom and Health Problem Checklist (SHPC-18)
2. Postsurgical question on resumption of activities and daily routine
3. Work Productivity and Activity Impairment (WPAI): Productivity outcomes.

The SHPC-18 is an 18-item questionnaire that asks subjects being treated for glaucoma questions about eye symptoms or problems they may experience. The questionnaire includes 2 domains: local eye symptoms (7 items) and visual function problems (11 items). The development of the SHPC-18 and validation of its 2 domains have been published. Each question first asks the subject if they have experienced the symptom or problem in the last 7 days. If the subject responds “Yes”, they are then asked how

burdensome the symptom or problem was, with Likert-type response options ranging from “Not at all” to “A lot” (Musch et al. 2017).

The WPAI is included because overall work productivity is significantly related to general health perceptions and the global measures of interference with regular activity (Reilly et al. 1993).

Additionally, responses to the Postsurgical Question will be collected to better understand differences, if any, in postoperative recovery between the 2 procedures.

These measures can be found in [Appendix 17](#).

### **10.1.2 Safety Analysis**

Safety analysis will be performed in both the XEN population and the population randomized to trabeculectomy. The numbers and percentage of subjects reporting AEs will be tabulated regardless of causality. AEs, ADEs, and all safety measures will be summarized by frequencies at each visit.

#### **10.1.2.1 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 participants. Needling and laser suture lysis will be captured as procedures but will not be considered AEs.

All AEs and device deficiencies that occur between visits are to be recorded on the date of the next postoperative examination on the subject’s eCRF.

##### **10.1.2.1.1 Definitions**

The investigators will classify the AEs based on the following definitions according to ISO 14155 (2011).

##### **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 subjects, users or other persons, if 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. Disease signs and symptoms that existed prior to the study treatment are not considered AEs unless the condition recurs after the participant 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 the Preoperative Visit. At each postbaseline visit, the investigator will begin querying for AEs by asking each participant a general, nondirected 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.

#### **Adverse Device Effect (ADE)**

An 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.

#### **Device Deficiency or Complaints**

A device deficiency is defined in accordance with ISO 14155 as inadequacy of a medical device including issues 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 eCRF. Device deficiencies shall be documented throughout the study and appropriately managed by Allergan. The Clinical Trial Site will enter all the information regarding device deficiency into the appropriate eCRFs. Allergan shall review all device deficiencies and determine and document in writing whether they could have led to the SADE. These shall be reported to the regulatory authorities and independent ethics committees/institutional review boards (IECs/IRBs) as required by Federal regulations.

#### **10.1.2.1.2 Possible Adverse Events**

The following is a list of AEs that can occur intraoperatively during implantation of XEN and/or trabeculectomy surgery. These and any other AEs that occur should be reported in the AE eCRF:

- Detached Descemet’s membrane
- Iris damage
- Lens contact
- Vitreous bulge or loss
- Anterior chamber bleeding
- Retrobulbar hemorrhage
- Conjunctival perforation

- Conjunctival or scleral flap tearing
- Shallow anterior chamber with peripheral iridocorneal touch
- Flat anterior chamber with iridocorneal touch extending to the pupil
- Device malfunction identified prior to implantation
- Choroidal hemorrhage or effusion

The following is a list of AEs that can occur postoperatively for XEN and/or trabeculectomy surgery. These and any other AEs that occur should be reported in the AE eCRF:

- Angle recession
  - Anterior chamber shallow with peripheral iridocorneal touch
  - Anterior chamber flat with iridocorneal touch
  - BCVA loss of  $\geq 2$  lines ( $\geq 10$  Early Treatment Diabetic Retinopathy Study [ETDRS] letters)
    - $\leq 30$  days
    - $>30$  days
    - At 12 months (persistent loss)
  - Bleb leak (without operative room or slit lamp revision)
  - Bleb leak (with operative room or slit lamp revision)
  - Blebitis (with or without anterior chamber reaction or hypopyon)
  - Cataract formation
  - Clinically significant progression of cataract, based on an assessment by the investigator
  - Choroidal effusion (extending posterior to equator, without blood)
  - Choroidal effusion (obscuring disc or macula, without blood)
  - Choroidal effusion (with choroids touching in the center of the eye, without blood)
  - Choroidal effusion (extending posterior to equator, with blood)
  - Choroidal effusion (obscuring disc or macula, with blood)
  - Choroidal effusion (with choroids touching in the center of the eye, with blood)
  - Choroidal effusion and/or hemorrhage occurring  $>30$  days (persistent)
  - Chronic pain (present greater than 3 months)
  - Corneal edema grade 3 or grade 4 ( $>30$  days postoperatively)
  - Cyclodialysis
  - Dellen
  - Device malfunction
  - Endophthalmitis
  - Fixed dilated pupil
  - Hyphema ( $\geq 2$  mm in height [layered] at any time)
  - Hyphema (present or arising  $>30$  days)
  - Hypotony (IOP  $<6$  mm Hg at any time)
-

- Persistent hypotony (IOP <6 mm Hg at 2 visits >30 days apart)
- Hypotony maculopathy
- Implant exposure
- Implant fracture
- Implant migration
- Implant obstruction (complete or partial)
- Implant repositioning requiring surgical intervention
- Increase in cup/disc ratio of  $\geq 0.3$  units on slit lamp examination
- Increase in corneal thickness of  $\geq 10\%$  in the presence of corneal edema
- IOP increase  $\geq 10$  mm Hg from baseline
- Iridodialysis
- Iritis (requiring treatment after the postoperative medication taper)
- Loss of eye
- Macular edema
- Macular puckering
- Posterior capsule opacification
- Ptosis
- Retinal complications
- Secondary surgical intervention
  - Explant
  - Secondary glaucoma procedure with explant
  - Secondary glaucoma procedure
- Significant (2-grade) worsening or a grade of moderate or severe, for any slit lamp observation for which a standard grading scale is not available (>30 days postoperatively)
  - Anterior chamber cells
  - Blepharitis
  - Chalazion
  - Dysesthetic bleb
  - Hyperemia
- Significant iris injury or atrophy
- Strabismus
- Suture abscess or other local infection
- Vitreous hemorrhage
- Vitreous loss
- Wound leak/dehiscence

### **Assessment of Severity**

Severity is a clinical determination of the intensity of an AE. The severity assessment for a clinical AE will be assigned a category by the investigator as follows:

- Mild: An AE that is easily tolerated by the subject, causes minimal discomfort, may require only minimal treatment and does not interfere with everyday activities.
- Moderate: An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed, but poses no significant or permanent risk of harm.
- Severe: An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

### **Assessment of Causality**

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.

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the device and/or study procedure. Causality should be assessed using the categories presented in the following table:

- Not related: Clinical event of which the relationship to the device and/or procedure can be excluded, such as if the event is incompatible time relationship to study procedure and/or use of the device, involves a body part or organ not expected to be affected by the device or procedure, could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study device, and is not due to use error.
- Unlikely: Clinical event whose time relationship to use of the device and/or study procedure makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
- Possible: Clinical event with a reasonable time relationship to the use of the device and/or study procedure, but that could also be explained by concurrent disease or other drugs or chemicals. Cases in which relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable:	Clinical event with a reasonable time relationship to the use of the device and/or study procedure, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Causal relationship:	Clinical event with plausible time relationship to the use of the device and/or study procedure, is a known side effect of the product category the device belongs to or of similar devices and procedures; follows a known response pattern to the medical device; involves a body-site or organ that the device or procedures are applied to and/or influence; harm is due to error in use, and that cannot be explained by concurrent disease or other drugs or chemicals.

### **Follow-up of Adverse Events**

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF.

#### **10.1.2.1.3 Serious Adverse Events**

##### **Serious Adverse Event Definition**

An AE is considered an SAE if it:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient or prolonged hospitalization, or
  - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) 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.

##### **Serious Adverse Device Effect (SADE)**

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

##### **Reporting of Serious Adverse Events**

All device- or surgery-related SAEs must be entered into the EDC system within 24 hours of being notified of the event. The sponsor will be notified by EDC system once the SAE electronic form has been submitted.

The relationship of the clinical event to the devices and procedure should be reported on the Serious Adverse Event Form for Devices and will be determined by the investigator.

Following evaluation of each SAE, the responsible IEC/IRB will be notified as appropriate based on national regulations.

All SAEs that occur from the time the informed consent form (ICF) is signed through to their final study visit must be reported to the sponsor. In addition to entering the information into the EDC system, the investigator must:

- Notify the sponsor immediately (within 24 hours) by fax using the Serious Adverse Event Form for Devices. The form should be sent directly to the sponsor at [LC-Medical\\_Safety@allergan.com](mailto:LC-Medical_Safety@allergan.com) or fax to +1-877-605-4524 or +1-714-796-9567. The SAE report should be completed regardless of the amount of information available although the investigator is expected to provide as much information as possible.
- 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 subject.
- Provide the sponsor with a complete, written case history (AE report form) which includes a statement as to whether the event was or was not related to the use of the investigational device or procedure.

The sponsor (or its representative) will report all SAEs associated with the use of the study device to the regulatory agencies (IEC/IRB, Competent Authorities) as appropriate according to relevant SOPs and to the national laws of the country where the trial is performed.

For every SAE, appropriate measures should be taken to treat/resolve and monitor the subject. The investigator should keep Allergan closely informed of the progress as related to the SAE. Any subjects who are withdrawn from the study due to an AE shall still be followed up until the outcome is resolved.

## **10.2 Data Safety Monitoring Board**

Not applicable

### **10.2.1 Appropriateness of Measurements**

The effectiveness and safety assessments planned for this study are widely used and generally recognized as reliable, accurate and relevant to the disease condition.



## **11 STATISTICAL METHODS**

Prior to database lock a statistical analysis plan (SAP) defining all details of analysis will be prepared and finalized.

### **11.1.1 Datasets or Populations Analyzed**

The Enrolled population consists of all study eyes for which the subject has signed the ICF. The Enrolled population will be used to summarize disposition data.

The Intent-to-treat (ITT) population consists of all enrolled eyes randomized to study glaucoma surgery (XEN or trabeculectomy). The ITT population will be the primary analysis population for effectiveness data. Subject demographics, baseline characteristics, and PRO data will be analyzed using the ITT population. Subjects will be grouped and analyzed according to the actual surgery received.

The Modified Intent-to-treat (mITT) population consists of eyes in the ITT population that receive study glaucoma surgery and have no major protocol deviations, which will be defined in the SAP and identified prior to database lock. The mITT population will be used for selected effectiveness endpoints (as specified in the SAP), and will be used for the analyses of PRO data also.

The Safety population consists of all enrolled eyes that undergo study glaucoma surgery, whether surgery is completed or aborted, and have follow-up visits or evaluations. The Safety population will be used to analyze AEs, medical and ophthalmic history, and concomitant medications (ocular and systemic). Subjects will be grouped and analyzed according to the surgery they received.

### **11.1.2 Demographic and Other Baseline Characteristics**

Demographic and baseline subject characteristics will be summarized. Descriptive statistics (such as mean, SD, minimum, median, and maximum) will be presented for each continuous variable. Categorical variables will be displayed using frequency counts and percentages.

### **11.1.3 Effectiveness Variables and Statistical Analyses**

#### **Definition of Primary Effectiveness Endpoint**

The primary endpoint for the study will be the percentage of subjects achieving  $\geq 20\%$  mean IOP reduction from baseline at Month 12 on the same or fewer number of topical IOP-lowering medications, without clinical hypotony, loss of vision to count fingers, or secondary glaucoma surgical intervention.

## **Definition of Secondary Effectiveness Endpoints**

Effectiveness will be determined by comparing the medicated preoperative IOP with the postoperative IOP at Month 12, and the number of topical IOP-lowering medications at screening with number of topical IOP-lowering medications at Month 12. Individual secondary effectiveness endpoints are defined in [Section 7.2](#).

## **Definition of Performance Endpoints (Device Studies)**

The IOP change at all visit windows will be summarized by mean, SD, median, maximum, and minimum. The percentage change in IOP from baseline to Month 12 will also be summarized descriptively. When necessary, appropriate parametric or nonparametric analyses will be used to determine statistically significant differences.

## **Methods of Statistical Analysis**

The number and proportion of subjects achieving  $\geq 20\%$  mean IOP reduction from baseline at Month 12 on the same or fewer number of topical IOP-lowering medications, without clinical hypotony, loss of vision to count fingers, or secondary glaucoma surgical intervention will be tabulated with 95% CI calculated by using the normal approximation method. The difference of the proportions will be estimated and the 95% CI of the difference will also be calculated with the method of the normal approximation. The 2 treatment groups will be claimed as equivalent if the 95% CI of the differences is within the -18% to 18% interval. The least squares mean change from baseline in IOP and the least squares mean difference between the 2 treatment groups will be estimated using the analysis of covariance (ANCOVA) model or the mixed-effect model repeat measurement (MMRM) model. The proportion and 95% CI of complete success and qualified success will be calculated with normal approximation.

### **11.1.4 Safety Variables**

All reported treatment-emergent AEs (TEAEs), treatment-related TEAEs, SAEs, and all safety measures collected will be tabulated by counts and percentages. Adverse events will be summarized by presenting the number and percentage of subjects having any AE. Any other information collected (such as AE severity) will be tabulated and listed as appropriate. Pregnancy of female subjects should also be tabulated. Analyses of AEs and other safety variables will be described in the SAP.

### **11.1.5 Interim Analyses**

An interim analysis may be performed.

### **11.1.6 Handling of Missing Data**

No imputation will be performed for any missing IOP. IOP, change in IOP from

baseline, percentage change in IOP from baseline, number of topical IOP-lowering medications used, and change in number of topical IOP-lowering medications used will be summarized descriptively at each scheduled visit.

### **11.2 Determination of Sample Size**

Recent studies of XEN in treating patients with POAG have reported significantly high treatment success rates. Grover et al. reported 75.4% of the treated patients having achieved success, as defined by a >20% reduction from baseline in IOP at Month 12 on the same or fewer medications (Grover et al. 2017). Mansouri et al. reported 81% success rate at Month 12, and Tan et al. (2018) reported success rates of 87% and 92% at Month 12 depending on if patients were using medications (Mansouri et al. 2018, Tan et al. 2018). However, it should be noted that the 3 studies are based on relatively small sample sizes in the XEN alone arm, ranging from 21 to 61 evaluable study eyes, and a more conservative estimate of the success rate is about 70%. A previous study supported that the XEN procedure and the standard of care therapy trabeculectomy are comparable in terms of treatment success (Schlenker et al. 2017). Moreover, it is assumed that neither treatment is better or worse than the other by more than 20% in terms of treatment success rate. This trial is intended to demonstrate that XEN is comparable to trabeculectomy in terms of treatment success rate. The sample size calculation is based on an equivalence test.

To control Type-I error rate at 5% and to attain 80% power for demonstrating that the difference is within the equivalence limit of 18%, about 256 study eyes will be needed for the study with a randomization ratio of 2:1 for the XEN arm: trabeculectomy arm. Allowing a 10% dropout rate for the first year, approximately 285 study eyes (190 for the XEN arm and 95 for the trabeculectomy arm) will need to be recruited for the study.

### **11.3 Protocol Deviations**

Should a protocol deviation occur, the sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable regulatory authority mandates is an investigator's responsibility.

## **12 QUALITY ASSURANCE AND QUALITY CONTROL**

### **12.1 Audit and Inspection**

Study centers and study documentation may be subject to Quality Assurance audit during the study or after the study has been completed by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

### **12.2 Monitoring**

Subject data will be monitored remotely. Monitoring visits may be scheduled throughout the study, if needed. Monitoring visits will be scheduled in advance, to ensure that the investigator has sufficient time to meet with the monitor and discuss all relevant findings. Subject data will be reviewed and/or audited, and all deficiencies corrected on site, if possible. A complete report will be made of all monitoring visits. If the study is terminated, a study close-out visit may be scheduled with the site if needed to retrieve all remaining study records.

The monitor will review the study conduct to determine compliance with the study protocol and GCP guidelines. The monitor will review and/or audit the electronic forms and source documents to ensure the accuracy and completeness of the data captured for the study. The monitor will review the subject ICFs to ensure that no forms were signed prior to the date of IEC/IRB approval of the study. The system for record-keeping will be reviewed.

### **12.3 Data Management and Coding**

The CRO will be responsible for activities associated with the data management of this study. This will include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of Syneos Health.

Study centers will enter data directly into an EDC system by completing the eCRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified and the eCRF will be considered the source document. Any changes to the data entered into the EDC system will be recorded in the audit trail and will be compliant with FDA CFR 21 Part 11. PRO data will not require source documentation.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs, and World Health Organization (WHO) Drug Dictionary for medications. Secondary surgical procedures and intra- and postoperative complications will be captured by their specific nomenclature (not upper-level terms).

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

#### **12.4 Quality Management and Risk Evaluation**

Details are provided in Section [8.2.2](#).

## **13 RECORDS AND SUPPLIES**

### **13.1 Device Accountability**

If devices are not supplied to the site, this section does not apply.

If devices are supplied to the site, on receipt of the study device, the investigator (or deputy) will conduct an inventory of the supplies and verify that study device supplies are received intact and in the correct amounts before completing a supplies receipt. The investigator will retain a copy of this receipt at the study center. The monitor may check the study supplies at each study center at any time during the study.

### **13.2 Financing and Insurance**

Financing and insurance of this study will be outlined in a separate agreement between Syneos Health and the sponsor. The fully executed Clinical Trial Agreement covers the agreement between the study site and Allergan.

## **14 ETHICS**

### **14.1 Independent Ethics Committee or Institutional Review Board**

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other requested study documentation will be submitted to the appropriate IEC/IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

### **14.2 Regulatory Authorities**

If required, relevant study documentation may be submitted to regulatory authorities. If required on completion of the study, the regulatory authorities may be provided the clinical study report.

### **14.3 Ethical Conduct of the Study**

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, ISO 14155:2011, and the applicable national and local laws and regulatory requirements.

### **14.4 Informed Consent**

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits, and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points s/he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived

by the investigator in the investigator's study file. A signed and dated copy of the subject's ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IEC(s)/IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re consent will be obtained.

#### **14.5 Subject Confidentiality**

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IEC(s)/IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.



## **15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING**

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the study is closed. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

Data from individual study centers in this multicenter study may not be published separately.

## 16 REFERENCES

- American Academy of Ophthalmology (AAO) Glaucoma Preferred Practice Pattern® (PPP) Panel. Primary open-angle glaucoma Preferred Practice Pattern. San Francisco: American Academy of Ophthalmology; 2006. Available from: <https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp-2015>. Accessed 07 Mar 2019.
- Aref AA, Varma R. Advanced glaucoma surgery, essentials in ophthalmology. Switzerland: Springer; 2012
- Azuara-Blanco A, Katz LJ. Dysfunctional filtering blebs. *Surv Ophthalmol*. 1998;43:93-126.
- Baudouin C. Ocular surface and external filtration surgery: mutual relationships. *Dev Ophthalmol*. 2012;50:64-78.
- Caprioli J, Kim JH, Friedman DS, Kiang T, Moster MR, Parrish RK 2<sup>nd</sup>, et al. Special commentary: supporting innovation for safe and effective minimally invasive glaucoma surgery: summary of a joint meeting of the American Glaucoma Society and the Food and Drug Administration, Washington, DC, February 26, 2014. *Ophthalmology*. 2015;122:1795-1801.
- De Gregorio A, Pedrotti E, Russo L, Morselli S. Minimally invasive combined glaucoma and cataract surgery: clinical results of the smallest ab interno gel stent. *Int Ophthalmol*. 2018 Jun;38:1129-1134.
- Fechtner RD, Singh K. Maximal glaucoma therapy. *J Glaucoma*. 2001 Oct;10(5 Suppl 1):S73-S75.
- Gedde SJ, Herndon LW, Brandt JD, Budenz DL, Feuer WJ, Schiffman JC. Surgical complications in the Tube Versus Trabeculectomy Study during the first year of follow-up. *Am J Ophthalmol*. 2007 Jan;143:23-31.
- Gedde SJ, Heuer DK, Parrish RK 2<sup>nd</sup>; Tube Versus Trabeculectomy Study Group. Review of results from the Tube Versus Trabeculectomy Study. *Curr Opin Ophthalmol*. 2010 Mar;21:123-128.
- Gedde SJ, Schiffman JC, Feuer WJ, Herndon LW, Brandt JD, Budenz DL, et al. Treatment outcomes in the Tube Versus Trabeculectomy (TVT) study after five years of follow-up. *Am J Ophthalmol*. 2012 May;153:789-803.
-

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.

Hengerer FH, Kohnen T, Mueller M, Conrad-Hengerer I. Ab interno gel implant for the treatment of glaucoma patients with or without prior glaucoma surgery: 1-year results. *J Glaucoma*. 2017 Dec;26:1130-1136.

Mansouri K, Guidotti J, Rao HL, Ouabas A, D'Alessandro E, Roy S, Mermoud A. Prospective evaluation of standalone XEN Gel Implant and combined phacoemulsification-XEN Gel Implant surgery: 1-year results. *J Glaucoma*. 2018 Feb;27:140-147.

Moisseiev E, Zunz E, Tzur R, Kurtz S, Shemesh G. Standard trabeculectomy and EXPRESS Miniature Glaucoma Shunt: a comparative study and literature review. *J Glaucoma*. 2015 Aug;24:410-416.

Musch DC, Tarver ME, Goren MJ, Janz NK. Development of an 18-Item measure of symptom burden in patients with glaucoma from the Collaborative Initial Glaucoma Treatment Study's Symptom and Health Problem Checklist. *JAMA Ophthalmol*. 2017 Dec 1;135:1345-1351.

Quigley HA. Number of people with glaucoma worldwide. *Br J Ophthalmol*. 1996;80:389-393.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993;4:363-365.

Reitsamer HA. Translimbal collagen implant. Aquesys XEN Gel Stent. In: Francis BA, Sarkisian SR, Tad JC (eds): *Minimally invasive glaucoma surgery*. Stuttgart: Thieme; 2016.

Rulli E, Biagioli E, Riva I, Gambirasio G, De Simone I, Floriani I, et al. Efficacy and safety of trabeculectomy vs nonpenetrating surgical procedures: a systematic review and meta-analysis. *JAMA Ophthalmol*. 2013 Dec;131:1573-1582.

Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. *Curr Opin Ophthalmol*. 2012;23:96-104.

Schlenker MB, Gulamhusein H, Conrad-Hengerer I, Somers A, Lenzhofer M, Stalmans I, et al. Efficacy, safety, and risk factors for failure of standalone ab interno gelatin microstent implantation versus standalone trabeculectomy. *Ophthalmology*. 2017 Nov;124:1579-1588.

Shaarawy T, Flammer J, Haefliger IO. Reducing intraocular pressure: is surgery better than drugs? *Eye (Lond)*. 2004;18:1215-1224.

Sheybani A, Reitsamer H, Ahmed II. Fluid dynamics of a novel micro-fistula implant for the surgical treatment of glaucoma. *Invest Ophthalmol Vis Sci*. 2015;56:4789-4795.

Tan SZ, Walkden A, Au L. One-year result of XEN45 implant for glaucoma: efficacy, safety, and postoperative management. *Eye (Lond)*. 2018 Feb;32:324-332.

Vera V, Ahmed IIK, Stalmans I, Retisamer H. Gel stent implantation-recommendations for preoperative assessment, surgical technique, and postoperative management. *US Ophthalmic Rev*. 2018;11:38-46.

Vijaya L, Manish P, Ronnie G, Shantha B. Management of complications in glaucoma surgery. *Indian J Ophthalmol*. 2011 Jan;59 Suppl:S131-140.

Wang S, Gao X, Quan N. The Ahmed shunt versus the Baerveldt shunt for refractory glaucoma: a meta-analysis. *BMC Ophthalmol*. 2016 Jun 8;16:83.

**17 APPENDICES**

**17.1 The SHPC-18 Questionnaire**

Protocol Title: XEN-45 Gel Stent Versus Trabeculectomy in Glaucoma:  
Gold-Standard Pathway Study (GPS)

Site Number XX Subject Number XXX Date (DD-MMM-YYYY): - -

VISIT:  Screening  1 Day  1 Week  2 Week  1 Month  3 Month  6 Month

Below are questions about eye symptoms and vision-related problems you may be experiencing. Some of these questions may not apply to you, but please indicate now if you have had any of the following symptoms or problems during the past 7 days. If you answer “Yes” to any of these symptoms or problems, please also answer a follow-up question about how much these symptoms or problems bother you.

Local Eye Symptoms	Have you had this symptom in the past 7 days?	If Yes, please rate how much you feel the symptom is due to your glaucoma or its treatment	If “Yes”, how much has this problem bothered you?
1. Eye irritation or burning	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
2. Feeling like something is in your eye(s)	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
3. Droopy eyelids	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot

Local Eye Symptoms	Have you had this symptom in the past 7 days?	If Yes, please rate how much you feel the symptom is due to your glaucoma or its treatment	If "Yes", how much has this problem bothered you?
4. Excessive tearing	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
5. Skin sensitivity around your eye(s)	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
6. Eye pain	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
7. Red eyes	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot

Visual Function Problems	Have you had this symptom in the past 7 days?	If Yes, please rate how much you feel the symptom is due to your glaucoma or its treatment	If "Yes", how much has this problem bothered you?
1. Difficulty with distant vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot

Visual Function Problems	<b>Have you had this symptom in the past 7 days?</b>	If Yes, please rate how much you feel the symptom is due to your glaucoma or its treatment	If "Yes", how much has this problem bothered you?
2. Difficulty with near vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
3. Changes in depth perception	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
4. Distortion in vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
5. Dimming of vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
6. Trouble with color vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot

Visual Function Problems	<b>Have you had this symptom in the past 7 days?</b>	If Yes, please rate how much you feel the symptom is due to your glaucoma or its treatment	If "Yes", how much has this problem bothered you?
7. Blurry vision	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
8. Difficulty with light transition (e.g., from bright to dark)	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
9. Difficulty seeing in dark places	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
10. Difficulty with bright lights	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot
11. Difficulty seeing when stepping down	<input type="checkbox"/> No <input type="checkbox"/> Yes: which eye(s) is/are affected? <input type="checkbox"/> Surgery eye <input type="checkbox"/> Other eye <input type="checkbox"/> Both eyes	<input type="checkbox"/> Entirely due <input type="checkbox"/> Partially due <input type="checkbox"/> Not due	<input type="checkbox"/> Not at All <input type="checkbox"/> A Little <input type="checkbox"/> Somewhat <input type="checkbox"/> A Moderate Amount <input type="checkbox"/> A Lot



**17.2 Postsurgical Question on Resumption of Activities and Daily Routine**

Since your glaucoma surgery, would you consider that you have resumed your usual activities and daily routine?

\_\_\_\_ Not at all    \_\_\_\_ Somewhat    \_\_\_\_ Moderately so    \_\_\_\_ Mostly    \_\_\_\_ Completely

### 17.3 Work Productivity and Activity Impairment Questionnaire

#### Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH)

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_ NO \_\_\_\_ YES  
*If NO, check "NO" and skip to question 6.*

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*

\_\_\_\_ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

\_\_\_\_ HOURS

4. During the past seven days, how many hours did you actually work?

\_\_\_\_ HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your health problems affect your productivity while you were working?

*Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.*

Consider only how much health problems affected productivity while you were working.

Health problems had no effect on my work	_____	Health problems completely prevented me from working
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?

*By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.*

Consider only how much health problems affected your ability to do your regular daily activities, other than work at a job.

Health problems had no effect on my daily activities	_____	Health problems completely prevented me from doing my daily activities
	0 1 2 3 4 5 6 7 8 9 10	

CIRCLE A NUMBER

## 17.4 Protocol Revision History

Key changes are listed below. Other changes may have included editorial revisions, updates to the list of abbreviations and table of contents, reformatting and restyling of text (including the reference list and appendices), and changes in study team staff. Specific revisions in verbatim text are shown in **bold font** in the changes listed below.

Version	Date	Description of Change (location)	Rationale
1.3	30 Jun 2018	Not applicable	Original protocol
2.0	21 Mar 2019	Added NCT number (title page)	Trial was registered on ClinicalTrials.gov on 31 Aug 2018
		Updated name of CRO (title page, Section 12.3, and Section 13.2)	INC Research merged with inVentive Health and is now doing business as Syneos Health
		Added description of statistical analyses in the <a href="#">Synopsis</a>	Corrected an omission in the synopsis
		Added objectives statement to Section 7)	Added a missing objectives statement that matches the one in the synopsis
		Added a secondary effectiveness objective: “Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time in eyes with medicated baseline IOP $\leq$ 18 mm Hg” (Section 7.2 and <a href="#">Synopsis</a> )	Adds a subgroup analysis for study eyes with IOP in the lower part of the allowed IOP range (15 to 18 mm Hg) at preoperative baseline
		Corrected timing of autorefractor measurements and biometry (Section 7.2 and <a href="#">Synopsis</a> )	Corrected mistakes in the text of the protocol to match the timing of these procedures in <a href="#">Table 8.1</a>
		Clarified study duration is per study eye (Section 8.1 and <a href="#">Synopsis</a> )	Distinguishes duration for a study eye versus overall study duration (ie, all study eyes)
		Investigator will select the study eye if both eyes meet entry criteria (Section 8.1)	Allows the investigator to make the decision
		Clarified that 1 study eye per subject will be enrolled (Section 8.3.1 and <a href="#">Synopsis</a> )	Clarifies that only 1 of a subject’s eyes will be enrolled, even if both eyes meet entry criteria
		Added visit windows to <a href="#">Table 8.1</a> ; revised postoperative visit windows in Sections 9.1.2 and 9.2	Provides a visit range for each postoperative study visit
		Added randomization to <a href="#">Table 8.1</a> and the description of the Preoperative Visit (Section 9.1.2)	Specifies at which visit randomization occurred
Gonioscopy is required at the Baseline Qualifying Visit and is optional at	Allows investigators to follow their standard of care for timing of		

Version	Date	Description of Change (location)	Rationale
		postoperative Visits 3, 4 and 10 (Table 8.1)	postoperative gonioscopy
		Removed AS-OCT at Visit 1 (Table 8.1)	Preoperative AS-OCT is not required.
		Changed one of the listed risks of the XEN implantation procedure to be “unplanned <b>secondary surgical intervention</b> ” (Section 8.2.2)	Corrected an error in the protocol (previously was “unplanned surgical <b>re-invention</b> ”)
		Increased the number of study sites to “approximately 25 <b>to 40 sites</b> ” (Section 8.3.1 and Synopsis)	Increase enrollment rate into the study to complete enrollment in a timely manner
		Inclusion criterion 4. “Best-corrected baseline Snellen visual acuity of 20/ <b>100</b> or better” (Section 8.3.2 and Synopsis)	Allows inclusion of study eyes with poorer vision in order to improve enrollment rate based on investigator feedback
		Inclusion criterion 5. “Visual field mean deviation no worse than <b>-18.0 dB</b> (with no dense paracentral scotomas, eg, <b>&gt;18 dB</b> total deviation on 1 or more of the 4 paracentral points)” (Section 8.3.2 and Synopsis)	Allows inclusion of study eyes with slightly more advanced visual field damage in order to improve enrollment rate based on investigator feedback
		Inclusion criterion 6. “Medicated IOP $\geq$ <b>15 mm Hg</b> and $\leq$ <b>44 mm Hg on at least 1</b> topical IOP-lowering medication” (Section 8.3.2 and Synopsis)	Allows study eyes with lower medicated IOP at baseline to improve enrollment rate based on investigator feedback. Clarifies that more than 1 IOP-lowering medication will be allowed.
		Inclusion criterion 7. “Subjects not anticipated to require any other ocular surgery (eg, cataract surgery) in either eye up to <b>3</b> months from the time of inclusion” (Section 8.3.2 and Synopsis)	Allows inclusion of study eyes that may require ocular surgery during the 12-month study, provided the surgery occurs at least 3 months after enrollment
		Inclusion criterion 9. “Visible trabecular meshwork with Shaffer angle grade $\geq$ <b>2</b> in the target area <b>or, in eyes with prior failed angle surgery, an open angle in the target area</b> ” (Section 8.3.2 and Synopsis)	Clarification that the angle is open in eyes that have had angle surgery, such as GATT
		Inclusion criterion 10. “Preoperative laser trabeculoplasty is allowed <b>3 or more months</b> prior to randomization” (Section 8.3.2 and Synopsis)	Corrects an error in the allowed period for laser trabeculoplasty

Version	Date	Description of Change (location)	Rationale
		Inclusion criterion 11. “Failed ab-interno canal or suprachoroidal <b>microinvasive glaucoma surgery (MIGS)</b> procedures (such as iStent <sup>®</sup> , <b>gonioscopy-assisted transluminal trabeculotomy [GATT]</b> , <b>ab-interno canaloplasty [ABiC™]</b> , Kahook <b>Dual Blade</b> goniotomy, etc) are allowed 3 or more months before enrollment, <b>with the exception of CyPass<sup>®</sup> Micro-Stents, which are not allowed. Ab-interno ablative procedures (such as endoscopic cyclophotocoagulation [ECP]) are also allowed 3 or more months before enrollment.</b> ” (Section 8.3.2 and Synopsis)	Excludes CyPass Micro-Stents, which have been withdrawn from the market  Distinguishes ab-interno ablative procedures, such as ECP which is allowed, from transscleral cycloablative procedures that are excluded per exclusion criterion 2
		Exclusion criterion 16. “Participation in another drug or device clinical trial <b>that concludes</b> within 30 days before the Preoperative Visit <b>or that starts at any time during this study</b> ” (Section 8.3.3 and Synopsis)	Prohibits concurrent participation in another drug or device clinical trial
		Added “Subjects may withdraw their consent to continue in the study at any time.” (Section 8.3.4)	Clarifies that subjects will be free to withdraw consent at any time
		Added “Subjects who discontinue before undergoing a study surgery will not be required to return for study follow-up visits” (Section 8.3.4) and updated Section 9.2.9 accordingly	Allows subjects who discontinue before glaucoma surgery to not return, as they will not be included in the safety population and no effectiveness data will be available
		Added marketed product name (XEN-45 Gel Stent) (Section 8.4.2)	Clarified XEN implant lumen size
		Added a description of the randomization process (Section 8.4.4)	Adds information that was missing from the protocol
		Clarified that IOP will not be measured at Visit 2 (Section 10.1.1.1)	Corrected the text to match Table 8.1
		Added that the PRO questionnaires will be administered using an electronic tablet, from which data will be imported into the eCRF (Section 10.1.1.3)	Clarifies that PRO data will be entered externally in an electronic tablet and then imported into the eCRF electronically (ie, data will not be entered manually into the PRO eCRFs)
		Added “ <b>These and any other AEs that occur should be reported in the AE eCRF.</b> ” to Section 10.1.2.1.2)	Clarifies that all AEs, in addition to the listed possible intraoperative and postoperative AEs are to be reported in the AE eCRF

Version	Date	Description of Change (location)	Rationale
		Revised the worsening cataract AE to <b>“Clinically significant progression of cataract, based on an assessment by the investigator”</b> (Section 10.1.2.1.2)	Removed mention of Lens Opacities Classification System scoring because it will not be used in this study
		Added Enrolled and mITT populations as analysis populations; updated definitions of ITT and Safety populations (Section 11.1.1)	Adds an Enrolled population to fully describe disposition of study eyes. Adds an analysis population (mITT) that excludes study eyes that do not undergo glaucoma surgery or have predefined major protocol deviations. Adds detail on which populations are used for study analyses.
		Removed statement that all available IOP data will be used for calculations of changes from baseline, and added some statistical methodology (Section 11.1.3, latter in Synopsis, too)	Selection of IOP values for change from baseline calculations will be described in the SAP, as it will be based on timing of IOP measurements relative to the visits. Briefly describes statistical testing that was missing.
		Clarified that treatment-emergent AEs will be summarized and added details on some types of tabulations that are planned (Section 11.1.4 and Synopsis)	Clarifies that any AEs that occur before study surgery will not be included in AE summary tables. Cross-references the SAP for more details on safety analyses.
		Revised “IOP, change in IOP from baseline, percentage change in IOP from baseline, number of <b>topical IOP-lowering</b> medications used, and change in number of <b>topical IOP-lowering</b> medications used will be summarized descriptively at each scheduled visit.” (Section 11.1.6)	Clarified that the analysis will be of number of topical IOP-lowering medications
		Deleted from the reference list those references not cited in the text (Section 16)	Corrected an error in the protocol
		Increased row height in SHPC-18 questionnaire (Appendix 17.1)	Makes “Both eyes” checkboxes visible in all rows
		Added protocol revision history (Appendix 17.4)	Adds a section to describe changes made in the protocol since the original version was approved
		Added expansion of abbreviations and acronyms on first use in the synopsis and main text; used abbreviation/acronym thereafter	Standardizes use of abbreviations and acronyms