Title Page

Protocol Title:	**XEN-45 Gel Stent Versus Trabeculectomy in Glaucoma: Gold-Standard Pathway Study (GPS)**
Protocol Number:	**CMO-US-EYE-0600**
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Short Title:	**XEN-45 Gel Stent Versus Trabeculectomy in Glaucoma: Gold-Standard Pathway Study (GPS)**
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Table of Contents

List of Tables

No table of figures entries found.

SAP Version History

SAP Version History Summary			
SAP Version	**Approval Date**	**Change**	**Rationale**
1.0	01Apr2021	Not Applicable	Original version
2.0	13May2021	Enrolled and ITT populations descriptions updated	updated the SAP for the definitions of ITT and Enrolled Population due to the extraneous data that was included specific to the enrolled by terminated before treatment patients.

1. Introduction

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy, safety and patient reported outcome data as outlined and/or specified in the final protocol of Study CMO-US-EYE-0600 (version dated 21 Mar 2019). Specifications of tables, figures, and data listings are contained in a separate document.

This is a multi-center, randomized, parallel group, prospective, open-label clinical trial to evaluate the ability of XEN-45 Gel Stent (XEN) to reduce intraocular pressure (IOP) and reduce the amount of topical IOP-lowering medications in subjects poorly controlled on topical therapy.

Participants will be randomized in 2:1 ratio, resulting in approximately 68 eyes being implanted with XEN and approximately 34 eyes receiving trabeculectomy. Participants will be screened for enrollment, and eligible candidates will be approached to ascertain interest in study participation. Study duration will be approximately 12 months, and Table 1-1 shows the schedule of assessment.

If both eyes meet the inclusion criteria, the investigator will determine the study eye. And only the study eye will be treated with the randomized treatment.

Table 1-1 Schedule of assessment

Procedure / Data to be Recorded	Baseline Qualifying Visit[a]	Preoperative Visit 1[a]	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
Intraocular Pressure (IOP)	X[b]	X		X	X	X	X	X	X	X	X
Autorefractor		X					X		X		X
Visual Acuity (BCVA)[c]	X	X		X	X	X	X	X	X	X	X
Manifest Refraction	X						X	X	X		X
Biomicroscopy (slit lamp exam)	X	X		X	X	X	X	X	X	X	X
Gonioscopy Assessment (Schaffer's Scale)[d]	X			X[d]	X[d]						X[d]
Visual Field Exam	X[e]								X		X
Ophthalmoscopy		X		X	X						X
Pachymetry		X									X
Topography[f]		X			X		X				X
Biometry[f]		X		X		X					
AS-OCT[f]				X		X					
Bleb Photography[f]				X		X	X	X	X		X
PRO: SHPC-18[g]	X			X	X	X	X	X	X		
PRO: Postsurgical Question[g]						X	X	X			
PRO: WPAI[g]	X				X			X			X
Randomization		X									
Glaucoma Surgery			X								

Procedure / Data to be Recorded	Baseline Qualifying Visit[a]	Preoperative Visit 1[a]	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
Adverse Events Assessment		X	X[h]	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

[a] 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 ≥3 months since previous intraocular surgery in either eye.

[b] 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.

[c] BCVA should be performed using a Snellen chart with glasses.

[d] Performed at Baseline Qualifying Visit and then at other times at the investigator's discretion

[e] Can use valid results up to 3 months prior to screening

[f] At selected sites only

[g] Patient questionnaires should be self-administered prior to any clinical assessments.

[h] Refers to intraoperative events or surgical complications

1.1. Objectives and Endpoints

1.1.1. Objective

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

1.1.2. Primary Endpoint

Percentage of participants achieving ≥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.

1.1.3. 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 (≤18 mm Hg, ≤17 mm Hg, ≤16 mm Hg, ≤15 mm Hg, ≤14 mm Hg, ≤13 mm Hg, and ≤12 mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline (≥25% to 50% in 5% increments) over time
- Proportion of eyes achieving ≥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 ≤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 ≤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 ≤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 (≤18 mm Hg, ≤17 mm Hg, ≤16 mm Hg, ≤15 mm Hg, ≤14 mm Hg, ≤13 mm Hg, and ≤12 mm Hg at Month 12)
- Proportion of eyes achieving specific percentage IOP lower targets from baseline (≥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:

- Mean and mean change in 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)
- Mean and mean change in manifest refraction (baseline and postoperative Months 1, 3, 6, and 12)
- Mean and mean change in 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])
- Mean and mean change in 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 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)

1.1.4. Exploratory Endpoints

Effectiveness:

- Time to completed success (defined in Section 1.1.3)

Time to qualified success (defined in Section 1.1.3)

1.2. Study Design

This is a post-marketing, multi-center, randomized, parallel group, prospective, open-label clinical trial to evaluate the ability of XEN to reduce IOP and reduce the amount of topical IOP-lowering medications in participants poorly controlled on topical therapy.

Participants will be randomized at a ratio of 2:1, resulting in approximately 68 eyes being implanted with XEN and approximately 34 eyes will receive trabeculectomy. A randomized study design was chosen because it prevents selection bias in treatment assignments and it produces comparable groups. This study will include participants presenting with glaucoma poorly controlled on topical therapy who are candidates for a subconjunctival drainage procedure. Participants will be screened for enrollment and eligible candidates will be approached to ascertain interest in study participation.

Participants 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, and follow up exams will be identical for both groups.

At baseline, participants 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 participant is determined to be eligible for participation in the study and is enrolled, the physician may stop the previously prescribed medications 1-4 weeks before surgery and begin preoperative medications (e.g., steroids, antibiotics, artificial tears, oral 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).

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

2. Statistical Hypotheses

First, let the percentage of participants achieving ≥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 be denoted by P1 for XEN implanted group and by P2 for trabeculectomy group. By assuming the margin of non-inferiority at 24%, the null hypothesis for this non-inferiority testing is set up as $P1 - P2 \leq -0.24$ vs. the alternative hypothesis as $P1 - P2 > -0.24$.

Equivalently, non-inferiority of XEN to Trab can be declared if the lower limit of the 2-sided confidence interval (CI) of the difference of the above endpoint between the two treatment groups computed using normal approximation is greater than -24%.

3. Sample Size Determination

The initial sample size calculation in the protocol is provided in the following next two paragraphs.

Recent studies of XEN in treating primary open-angle glaucoma, patients 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, 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, 2018; Tan, 2018). However, it should be noted that the three studies are based on relatively small sample sizes in 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 XEN procedure and the standard of care therapy trabeculectomy are comparable in terms of treatment success (Schlenker, 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. 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 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.

In March 2020, COVID-19 significantly impacted clinical trials globally. The XEN GPS team evaluated the challenging situation facing enrollment of patients in the CMO-EYE-US-0600 XEN GPS study and decided to take a proactive approach to mitigate risk. A note-to-file document was filed on June 2, 2020 to reconsider the study sample size at a lower scale in order not to delay the study completion.

The recalculation still follows the initial sample size calculation by using a non-inferiority approach with an assumed proportion of Trab at 0.70. However, the margin of non-inferiority is changed to 24% from 15%.

SAS PROC POWER with the case of TWOSAMPLEFREQ is employed to yield a total sample size of 102 completors (68 in XEN and 34 in Trab). As a result, the study requires to enroll a minimum of 114 patients (76 in XEN and 38 in Trab) in order to achieve the study goal when 10% dropout rate is taken into account.

4. Populations for Analysis

The analysis populations will consist of participants as defined below:

- Enrolled population: For all study eyes for which subjects have signed ICF and met all inclusion/exclusion criteria.

- Intent-to-Treat (ITT) population: all enrolled eyes randomized to study glaucoma surgery (XEN or trabeculectomy), and received study glaucoma surgery (XEN or trabeculectomy).
  Note that analyses will be based on the randomized surgery.

- Safety Population : All enrolled eyes that have undergone study glaucoma surgery.
  Note that analyses will be based on the actual surgery treated.

Due to the nature of Phase 4 study, there will be no mIIT population to be implemented, unless there are significant protocol deviations or other reasons.

5. Statistical Analyses

5.1. General Considerations

- The analysis will be performed after the database is locked and randomization schedule is released.
- All efficacy analyses will be performed using the ITT population. Safety analyses will be performed using the Safety population.
- Efficacy analyses will be performed for the study eye, unless stated otherwise.
- Baseline is defined as the last non-missing value prior to the start of study intervention unless specified in some cases. In general it is preoperative visit (Visit 1). However, there is another medicated baseline for IOP, which is defined at baseline qualifying visit. Please note the term "baseline" refers to pre-operative baseline throughout the document unless it is specified as "medicated" baseline.
- Descriptive statistics for continuous variables include the sample size (N), mean (Mean), standard deviation(SD), median(Median), Q1, Q3, minimum (Min), and maximum (Max).
- Summary statistics for categorical variables include the sample size (N), frequency count and percent.
- No imputation of missing values will be performed, unless otherwise specified.
- The level of significance used for all statistical tests will be 0.05, 2-sided, unless stated otherwise.
- The change from baseline values will be computed as the value for the post baseline visit minus the baseline value, unless otherwise indicated.
- All statistical analysis will be performed using SAS version 9.2 or higher. MedDRA will be used to code adverse events and medical and ophthalmic history. WHODRUG will be used to code medications.

5.2. Participant Dispositions

Number of participants screened for the study will be provided. Summary of study disposition will be provided by study intervention for the following:

- Number of participants enrolled/randomized
- Number of participants treated
- Number of participants completed the study
- Number of participants discontinued the study
- Reasons for discontinuation

5.3. Primary Endpoint Analysis

It is essential to note that when IOP measure at a visit is referred, it usually stands for the mean of 3 IOP readings for a patient performed within 24 hours at a given visit.

5.3.1. Definition of Primary Endpoint

The primary effectiveness endpoint is the proportion of responders meeting all criteria below:

- Achieving ≥20% mean IOP reduction from baseline at Month 12
- No increase in number of topical IOP-lowering medications at Month 12 compared to the baseline
- No clinical hypotony
- No loss of vision to count fingers or worse
- No secondary glaucoma surgical intervention.

The IOP will be assessed at all study visits by standard Goldmann Applanation Tonometry. For each IOP assessment, two consecutive measurements will be taken for each eye. If these 2 measurements differ by > 1 mm Hg, a third measurement will be performed for the given eye. The IOP value for a given eye will be the average of all measurements, which will be obtained from the eCRF, and the percent change from baseline at Month 12 will be computed as

$$Percent\ change = \frac{Month\ 12\ IOP - Baseline\ IOP}{Baseline\ IOP} x\ 100$$

The subject having the computed value of ≤ -20 will be considered achieving ≥20% mean IOP reduction from baseline at Month 12.

The usage of topical IOP-lowering medication will be collected in the concomitant medication page. The IOP-lowering medication that were started before the Month 12 visit and stopped on or after the Month 12 visit or recorded as ongoing will be considered as the medication taken at Month 12. The partial start and stop dates of the medication will be imputed based on missing dates imputation rules specified in Appendix 3.

The clinical hypotony is 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. The following steps provide the identification of a patient with clinical hypotony. A patient at any time point with the following conditions:

1- filter any eyes with IOP of 6 mmHg or less, from this list...

2- Filter any eyes with VA reduction 2 lines or more compare to baseline, from the eyes left (and this is where it becomes more clinical and difficult, but the n should not be too high at this point)...

3- Filter any eyes that reported on the "OPHTHALMOSCOPY CRF" abnormal macula or periphery; AND any eyes that reported any of these AE:

- Anterior chamber shallow with peripheral irido-corneal touch
- Anterior chamber flat with irido-corneal touch

- BCVA loss of ≥2 lines (≥10 ETDRS letters)
  - ≤ 30 days
  - > 30 days
  - At 12 months (persistent loss)

- 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
- Hypotony maculopathy
- Macular edema

The Best Corrected Visual Acuity (BCVA) should be performed using a Snellen Chart with glasses at all study visits. For participants with vision lose that Snellen Chart cannot be used, the vision acuity will be collected as Count Fingers, Hand Movement, Light Perception, or No Light Perception. Patients with vision loss to count fingers will be counted as not meeting the criteria.

The secondary glaucoma surgical intervention will be recorded in the glaucoma surgery eCRF page.

5.3.2. Main Analytical Approach

The primary effectiveness hypothesis described in section 2 will be tested on the ITT population. The 95% CI for the difference in proportion of responders (P1-P2) between treatment groups will be constructed using normal approximation, and the non-inferiority of XEN to Trab will be claimed if lower limit of the 95% CI for P1-P2 is greater than 24%.

There will be no missing data imputation.

5.4. Secondary Endpoints Analysis

The analysis will be performed for the study eye using ITT population for efficacy and PRO.

5.4.1. Key/Confirmatory secondary endpoints

As there is no key secondary endpoint that is selected for label update and multiple testing adjustment, this section is not applicable.

5.4.2. Secondary endpoints

All secondary endpoints will be analyzed using ITT population for efficacy and PROs.

Effectiveness:

- Mean and changes in mean IOP from preoperative baseline over time
- Number of topical IOP-lowering medications from preoperative baseline over time
- Mean and changes in mean IOP and number of topical IOP-lowering medications from preoperative baseline over time in eyes with medicated baseline IOP ≤18 mm Hg
- Change in mean IOP from medicated baseline at Month 12
- Change in mean number of topical IOP-lowering medications from medicated baseline, at Month 12
- Proportion of participants with IOP value of ≤18 mmHg at Month 12
- Proportion of participants with IOP value of ≤17 mmHg at Month 12
- Proportion of participants with IOP value of ≤16 mmHg at Month 12
- Proportion of participants with IOP value of ≤15 mmHg at Month 12
- Proportion of participants with IOP value of ≤14 mmHg at Month 12
- Proportion of participants with IOP value of ≤13 mmHg at Month 12
- Proportion of participants with IOP value of ≤12 mmHg at Month 12
- Proportion of participants achieving ≥25% IOP reduction from baseline at Month 12
- Proportion of participants achieving ≥30% IOP reduction from baseline at Month 12
- Proportion of participants achieving ≥35% IOP reduction from baseline at Month 12
- Proportion of participants achieving ≥40% IOP reduction from baseline at Month 12
- Proportion of participants achieving ≥45% IOP reduction from baseline at Month 12
- Proportion of participants achieving ≥50% IOP reduction from baseline at Month 12
- Proportion of participants meeting all following criteria:
    - ≥20% IOP reductions at Month 12
    - IOP value of ≤18 mmHg at Month 12
    - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:
    - ≥20% IOP reductions at Month 12
    - IOP value of ≤17 mmHg at Month 12
    - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:
    - ≥20% IOP reductions at Month 12
    - IOP value of ≤16 mmHg at Month 12
    - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:
    - ≥20% IOP reductions at Month 12
    - IOP value of ≤15 mmHg at Month 12
    - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:

  - ≥20% IOP reductions at Month 12
  - IOP value of ≤14 mmHg at Month 12
  - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:
  - ≥20% IOP reductions at Month 12
  - IOP value of ≤13 mmHg at Month 12
  - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- Proportion of participants meeting all following criteria:
  - ≥20% IOP reductions at Month 12
  - IOP value of ≤12 mmHg at Month 12
  - Same or lower in number of topical IOP-lowering medications at Month 12 compared to the baseline
- 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 12 months on same or fewer topical IOP-lowering medications, and number of patients not using any topical IOP-lowering medications, antifibrotic use during needling

Complete and qualified success:

- Proportion of participants with complete success at Month 12 which is defined as meeting all following criteria in the study eye
  - IOP ≤18 mmHg at Month 12
  - ≥20% reduction in IOP from medicated baseline, which is the IOP value at Baseline Qualifying Visit, at Month 12
  - No topical medications at Baseline Qualifying Visit
  - No clinical hypotony

  The topical medication includes any topical ophthalmic medication used on the study eye regardless of the indication and dosage.

  This endpoint will be analyzed among the participants without topical medication at Baseline Qualifying Visit.

- Proportion of participants with qualified success at Month 12 which is defined as meeting all following criteria in the study eye
  - IOP ≤18 mmHg at Month 12
  - ≥20% reduction in IOP from medicated baseline, which is the IOP value at Baseline Qualifying Visit, at Month 12
  - Taking topical medications at Baseline Qualifying Visit
  - No clinical hypotony

The topical medication includes any topical ophthalmic medication used on the study eye regardless of the indication and dosage.

This endpoint will be analyzed among the participants with topical medication at Baseline Qualifying Visit.

- Proportion of participants with IOP value of ≤18 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤17 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤16 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤15 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤14 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤13 mmHg at Month 12 in medication-free eye
- Proportion of participants with IOP value of ≤12 mmHg at Month 12 in medication-free eye

- Proportion of eyes achieving specific percentage IOP lower targets from baseline ((≥25-50% in 5% increments) with medication-free eyes

  Note: medication-free eye at Month 12 is defined as no IOP-lowering medication was used to the study eye at Month 12.

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)

Note: The data will be presented only if they are collected on CRF.

Visual parameters recovery post surgery:

- Mean and mean change in 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)
- Mean and mean change in manifest refraction (baseline and postoperative Months 1, 3, 6, and 12)
- Mean and mean change in 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])
- Mean and mean change in optical biometry (anterior chamber depth and keratometric values [preoperative and postoperative Day 1 and Week 2]) at selected sites.

Other:

- Bleb photograpy (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)

5.4.2.1. Main Analytical Approach

All secondary endpoints will be analyzed using ITT population except for safety endpoints and PRO, which will be done using safety population.

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All secondary endpoints in Section 5.4.2. will be summarized with descriptive statistics except for the endpoints referring to effectivenss and success (complete and qualified) .

These endpoints regarding complete/qualified success will be analyzed as follows:

For categorical secondary endpoints, the proportion of each treatment group will be computed and the 95% CI of difference between treatment groups will be computed using normal approximation.

For continuous secondary endpoints that is defined for one timepoint, the least squares mean change from baseline and the least squares mean difference between the treatment groups will be estimated using the analysis of covariance model with treatment as the factor, and baseline as a covariate variable. For continuous secondary endpoints that is defined for over time, the least squares mean change from baseline and the least squares mean difference between the treatment groups will be estimated using or mixed effects model repeated measure with treatment, time as the factor, treatment by time interaction and baseline as a covariate variable.

5.4.3. Multiplicity Adjustment

Not applicable.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

The time to complete success and the time to qualified success were added to furthere explore the timing of achieving compelte success or qualified success with the treated eyes. If the patients haven't achieve the 'event' (complete success or qualified success) prior to study completion or study withdrawal, the last known date in the study will be used and the situation will treated as censored in the statistical analysis.

Kaplan-Meier (KM) analysis will be performed on the time to complete success and the time to qualified success. The median, 25% percentile and 75% percentile will be reported.

5.6. Safety Analyses

Safety analyses will be employed using Safety population.

For ocular safety assessment, analyses will be performed by treatment group including both eyes if both eyes are qualified.

5.6.1. Patients with the Procedure

The procedure that patients are applied will be summarized for the Safety population by treatment group and overall.

The study duration will be calculated as the number of days between the randomization and study exit, inclusively (study exit day – randomization date + 1). The study duration will be summarized using descriptive statistics by treatment group and overall.

5.6.1.1. Treatment Compliance

Not applicable

5.6.2. Adverse Events

Adverse events will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version #21.0 or newer.

Adverse events will be classified to either ocular AEs or nonocular AEs. An ocular AE will be determined as indicated on the AE form of eCRF, and thus are not limited to AEs with primary SOCs of eyes. The adverse events will be also classified to either AE or adverse device effect (ADE). The summary of AEs will be separately done for nonocular AEs, ocular AEs and ADEs. Ocular AEs and ADEs will be tabulated by treatment group for the study , and nonocular AEs will be summarized by treatment group for participants.eye

An AE will be considered a treatment emergent adverse event (TEAE) if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the surgery.

An TEAE and ADE will be considered a TESAE or SADE if it meets any SAE criterion.

Overall summary of TEAEs will be provided for categories of all TEAEs, treatment-related TEAEs/TEADEs, TESAEs/TESADE, deaths, TEAEs/TEADEs leading to study discontinuation,. TEAEs/TEADEs, treatment-related TEAEs/TEADEs, TESAEs/TESADEs and TEAEs/TEADEs leading to study discontinuation will be further classified into ocular and nonocular subcategories.

The number and percentage of participants reporting TEAEs/TEADEs in each treatment group will be tabulated by SOC in descdending frequency order of XEN first, then by preferred term in descdending frequency order of XEN, and further categorized by severity. If more than 1 AE/ADE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the greatest severity and strictest causality for the summarization by severity and causal relationship.

The number and percentage of participants with treatment-related TEAEs/TEADEs will be tabulated by SOC and preferred term.

Summary tables will be provided for participants with TESAEs and participants with TEAEs/TEADEs leading to discontinuation. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The same analysis will be repeated for ocular TEAEs/TEADEs, ocular TESAEs/TESADEs.

5.6.2.1. Adverse Events of Special Interest

Intraoperative AEs

- 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 of effusion

Postoperative AEs

The following is a list of AEs that can occur postoperatively for XEN and/or trabeculectomy surgery.

- Angle recession
- Anterior chamber shallow with peripheral iridocorneal touch
- Anterior chamber flat with iridocorneal touch
- BCVA loss of ≥2 lines (≥10 Early Treatment Diabetic Retinopathy Study [ETDRS] letters)
- ≤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 (≥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 ≥0.3 units on slit lamp examination
- Increase in corneal thickness of ≥10% in the presence of corneal edema
- IOP increase ≥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

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Hypotony

Clinical hypotony is defined as vision reduction (2 lines or more) related to macular changes consistent with hypotony maculopathy (macular folds), optic disc edema, and/or serious choroidal detachments because of low IOP.

5.6.3.2. Biomicroscopy and ophthalmoscopy

Findings from slit-lamp biomicroscopy and ophthalmoscopy will be recorded.

The number and percentage of participants with biomicroscopy and ophthalmoscopy findings with more than 1 severity grade increase from baseline for items with severity grade and status change from absence at baseline to presence at post-baseline visits for items without severity grade will be tabulated by preferred term in descending order of incidence rate. The number and percentage of participants with any clinically significant findings will be presented (as "Overall") by treatment group for study eye.

The data will be presented in the subject listing if the findings are not coded in MedDRA. In addition, some information, like severity grade may not be collected, then the data will not be presented.

5.6.3.3. Best Corrected Vision Acuity (BCVA)

BCVA will be performed using a Snellen chart with glasses, and the BCVA data collected in the visual acuity eCRF page will be analyzed. The line change from baseline at each follow-up evaluation will be calculated using the following formula:

$$\text{Line change} = 10 \times [\log10\ (20/d_{\text{follow-up}}) - \log10\ (20/d_{\text{baseline}})]$$

Where d_{baseline} = denominator of the Snellen equivalent unit at baseline

$d_{\text{follow-up}}$ = denominator of the Snellen equivalent unit at follow-up

The logarithmic values are to be rounded to the nearest tenth before calculation of the line change. A positive value indicates an improvement and a negative value indicates a worsening.

The data for the worst line change from baseline across follow-up will be summarized by treatment group for the study eye. The worst line change is defined as the greatest decrease from baseline in the number of lines read. Summary statistics of the worst line change will be presented in each of the following categories: worsening (< -2), no change (≥ -2 and ≤ 2) and improving (>2). The number and percentage of participants with study eye meeting criteria of each category will be presented.

5.6.3.4. Visual field

Visual field examinations will be reported as mean deviation (Humphrey) or mean sensitivity (Octopus) and PSD (Humphrey) or LV (Octopus) in decibels (dB). Visual field mean change from baseline in the study eye will be summarized using descriptive statistics by machine type (Humphrey and Octopus).

5.6.3.5. Pachymetry

The central corneal thickness in microns will be collected. The mean change from baseline in the study eye will be summarized using descriptive statistics.

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5.7. Other Analyses

5.7.1. Patient Reported Outcomes

Patient Reported Outcomes (PRO) data will be analyzed using ITT population.

5.7.1.1. The SHPC-18 Questionnaire

There will be 7 items on the local eye symptoms and 11 items on the visual function problems as following;

Local Eye Symptoms

- Eye irritation or burning
- Feeling like something is in your eye
- Droopy eyelids
- Excessive tearing
- Skin sensitivity around your eye(s)
- Eye pain
- Red eyes

Visual Function Problems

- Difficulty with distant vision
- Difficulty with near vision
- Changes in depth perception
- Distortion in vision
- Dimming of vision
- Trouble with color vision
- Blurry vision
- Difficulty with light transition
- Difficulty seeing in dark places
- Difficulty with bright lights
- Difficulty seeing when stepping down

Each item will have questions for presence of the symptom, location of the symptom, relativity to glaucoma or its treatment and the severity of the symptoms. A subject listing will be provided for all of the individual items.

The summary of the total bothersome score (sum of all items divided by 18), the summary of the local eye symptom domain bothersome score (sum of all 7 items divided by 7), and visual function problem domain bothersome score (sum of all 11 items divided by 11) will be presented.

Note that a total score or a domain score will be treated as missing if more than 50% of the corresponding items are missing. In addition, if not all items are answered, then the score will be obtained by taking the average of available items.

See 6.4.1 for detailed analysis instructions.

5.7.1.2. Postsurgical question on resumption of activities and daily routine

The participants will be asked to answer on the question of "Since your glaucoma surgery, would you consider that you have resumed your usual activities and daily routine?", and the answer choices are "Not at all", "Somewhat", "Moderately so", Mostly" and "Completely".

The number and percentage of participants in each category will be presented by treatment group.

5.7.1.3. Work Productivity and Activity Impairment Questionnaire

The following questions will be asked about the ability to work and perform regular activities.

Table 5.7-1 Work Productivity and Activity Impairment Questionnaire

Questions	Answers
Are you currently employed	Yes/No
During the past seven days, how many hours did you miss from work because of your health problems	Number of hours
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?	Number of hours
During the past seven days, how many hours did you actually work?	Number of hours
During the past seven days, how much did your health problems affect your productivity while you were working?	Scale of 0 to 10
During past seven days, how much did your health problems affect your ability to do your regular daily activities, other than work at a job?	Scale of 0 to 10

The summary of WPAI:GH in 2 components: percent overall work impairment due to health, and percent activity impairment due to health will be presented for subjects who are currently employed.

A subject listing of all individual elements will be presented.

See 6.4.2 for detailed analysis instructions.

5.7.2. Subgroup analyses

There is no subgroup analysis planned in the protocol.

5.8. Interim Analyses

Even the protocol states that there may be an interim analysis during the study, it is decided that no interim analysis will be conducted for the reason that the study reduced the sample size to 114 from 285 due to the impact of COVID-19 on patient enrollment.

6. Supporting Documentation

Demographics and baseline characteristics, protocol deviation, and data derivation rules can be found in Appendix 3.

6.1. Appendix 1 List of Abbreviations

ADE	adverse device effects
AE	adverse event
BCVA	best corrected visual acuity
CI	confidence interval
eCRF	electronic case report form
IOP	intraocular pressure
ITT	intent to treat
LV	
MD	mean deviation
MedDRA	medical dictionary for regulatory activities
mITT	modified intent to treat
PSD	
SADE	serious adverse device effects
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
XEN	XEN-45 gel stent

6.2. Appendix 2: Changes to Protocol-Planned Analyses

A Note-To-File is in place to address the concern of sample size reduction.

Appendix 3: Supporting Study Information

6.3.1. Demographics

Demographic parameters (age; sex; race) and baseline IOP will be summarized descriptively by treatment group and overall for the ITT population and safety population.

6.3.2. Baseline and Disease Characteristics

The following baseline disease characteristics will be summarized if available:

- Diagnosis: POAG, PXE, Pigment dispersion syndrome, Mixed mechanism glaucoma, uveitic glaucoma, steroid-induced glaucoma, neovascular glaucoma
- Lens status – phakic, pseudophakic, visually significant cataract
- Based on baseline visual field MD, stratification to mild, mod, severe (we can use a published paper as guideline)- see attached
- Medical history: Diabetes, hypertension
- Prior glaucoma procedures – SLT, i-stent, GATT, Kahook Dual Blade (KDB), Endo cyclophotocoagulation (see full list in protocol)

Note that the data were not collected, so there is no corresponding summary table.

6.3.3. Protocol Deviations

Participants reporting major protocol deviations will be summarized in total and by treatment group for the ITT population.

The major protocol deviations that are thought to potentially affect the analysis will be reviewed and finalized in a blinded manner prior to the data base lock. The major deviations are following:

- Prior XEN/trab/tube in study eye
- Prior transscleral ablative procedures in study eye
- No baseline IOP /IOP-lowering medication count recorded
- Wrong study procedure performed
- XEN not implanted (surgery aborted)

6.3.4. Medical and Ophthalmic History

Abnormalities in participants' medical and ophthalmic histories will be coded using the MedDRA.

The number and percentage of participants with abnormalities in medical/ophthalmic history in each SOC and preferred term will be summarized by treatment group and overall for patients in the safety population.

6.3.5. Prior/Concomitant/Follow-up medications (including dictionary)

Medication data will be coded using World Health Organization Drug Dictionary.

Prior medications include all medications taken prior to day 1 (randomization/treatment visit), whether or not the medication is continuing beyond day 1. Concomitant medications encompass all medicinal products that the participant was taking prior to the day 1 visit that are ongoing at the visit, in addition to all medications that have a start date on or after the day 1 visit date.

Prior and concomitant medication will be tabulated separately for the Safety population. The frequency (number and percentages) of participants who have taken each medication will be tabulated for each treatment group and for overall.

6.4. Appendix 4: PRO Analysis Instructions

6.4.1. Glaucoma Symptom and Health Problem Checklist (SHPC-18) Scoring recommendations:

Scoring of the Glaucoma Symptom a

6.4.2. Work Productivity and Activity Impairment Questionnaire Scoring

WPAI Scoring.pdf

6.5. Data handling convention

6.5.1. Analysis Window

Table 6-1 below presents the visits assigned for analyses and the corresponding range of treatment days during which an actual visit may occur.

Table 6-1 Analysis Window

Scheduled Visit	Target Day of the Visit	Analysis Visit Window
Baseline qualifying visit[a]	N/A	N/A
Preoperative Visit 1[a]	N/A	Up to 28 days before the operation
Visit 2	Day 0	Day of operation
Visit 3	Day 1	6 hours after operation to Day 2
Visit 4	Week 1	Day 3 to Day 10
Visit 5	Week 2	Day 11 to Day 20
Visit 6	Month 1	Day 21 to Day 56
Visit 7	Month 3	Day 57 to Day 119
Visit 8	Month 6	Day 120 to Day 224
Visit 9	Month 9	Day 225 to Day 329

Visit 10	Month 12	≥ Day 330

[a] Participants may have the baseline qualifying visit and preoperative visit on the same day.

If there are two or more values fall within the same analysis window, the one closest to the target date will be used.

6.5.2. Missing Date Imputation

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6–2 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[1]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	No[1]

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6–3 Initial Imputed Date Algorithm

Available Year (YYYY)	Available Month (MM)			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—		
< Target Year	YYYY-12-31	YYYY-MM-LD		
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	YYYY-MM-01		

LD = last day of the month; MM = available start date month; YYYY = available start date year.

6.5.2.1. Missing/Incomplete AE and Medication Start Date

Imputation of dates with missing day and/or month is required for the start date of an AE and medication. If adequate information is available, no imputation is needed. AE and medication start dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the operation date if they have the same year, whichever is later

- If day is missing but the month and year are available, then the imputed day will be the first day of the month or the randomized operation date if they have the same month and year, whichever is later.

6.5.2.2. Missing/Incomplete AE and Medication End Date

Imputation of dates with missing day and/or month is required for the end date of an AE and medication. If adequate information is available, no imputation is needed. AE and medication end dates with missing day or month will be imputed as following:

- If day and month are missing but year is available, then the imputed day and month will be the study exit date if they have the same year

If day is missing but the month and year are available, then the imputed day will be the last day of the month or the study exit date if they have the same month and year, whichever is earlier. If the imputed end date is before the start date, the imputed end date will be set to the start date.

7. References