1.0 TITLE PAGE

STATISTICAL ANALYSIS PLAN – Amendment 1

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

Amendment 1: 2022-04-14

Protocol Number:	1924-701-007
Development Phase:	Pivotal
Product Name:	XEN45 Glaucoma Treatment System
Study Statistician:	[redacted]
Sponsor:	Allergan, an AbbVie company 2525 Dupont Drive Irvine, California 92612 USA [redacted]

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3.0 LIST OF ABBREVIATIONS

AC	anterior chamber
ACG	angle closure glaucoma
AE	adverse event
BCVA	Best-corrected visual acuity
eCRF	electronic case report form
IEAE	implant emergent adverse event
IOP	Intraocular pressure
K-M	Kaplan-Meier
MMRM	mixed-effects model for repeated measures
MSP	medical safety physician
NA	not applicable
OD	right eye
OS	left eye
OU	both eyes
PID	patient identification
PT	preferred term
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SE	study eye
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
WOCF	worst observation carried forward

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study 1924-701-007 (version dated 04 OCT 2017). Specifications of tables, figures, and data listings are contained in a separate document.

4.1 STUDY DESIGN SUMMARY

4.1.1 Overall Design

This is a pivotal, prospective, multiregion, multicenter, single arm, open-label study in ≥ 18 years old adult patients who have been diagnosed with angle closure glaucoma (ACG) with uncontrolled intraocular pressure (IOP). To be eligible to enroll into the study, uncontrolled IOP (at Hour 0) in the study eye (SE) at screening and baseline must be ≥ 20 mm Hg and ≤ 35 mmHg as assessed by the Goldmann applanation tonometry. All patients enrolled into this study, in the opinion of the investigator, will have uncontrolled IOP after having failed previous medical and/or surgical treatments in the study eye (SE). The trial is designed to evaluate the safety and effectiveness of the XEN45 treatment system, henceforth referred to as XEN, in patients with ACG.

4.1.2 Number of Patients

Approximately 65 eligible patients in approximately 15 study sites globally will be unilaterally implanted with XEN either as a stand-alone procedure or in conjunction with lens extraction. A subset of these patients will include a maximum of 10 phakic patients (i.e., patients who will not undergo lens extraction at time of XEN surgery) and 10 patients with a history of trabeculectomy or glaucoma shunt implantation, to allow for a representative ACG patient population in the study. The schedule of evaluations for Study 1924-701-007 is presented in Table 4-1.

4.2 GENERAL STATISTICAL CONSIDERATIONS

In general, continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Description of the analysis of responses to Health Outcome Measures; i.e., Patient Ocular Symptoms Questionnaire, is not part of this SAP and will be described elsewhere by the group at Allergan that specializes in the analysis of health outcome measures.

Table 4-1 Schedule of Visits and Procedures

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

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

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

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

[c] Applicable to females of childbearing potential

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

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

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

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

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

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

5.0 OBJECTIVES

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

6.0 PATIENT POPULATION

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

7.0 PATIENT DISPOSITION

Number and percent of patients who entered and completed the screening phase and who failed during the screening phase further broken down by most important failed criterion collected on the screening disposition electronic case report form (eCRF) and timing of failure collected on the subject qualification eCRF will be tabulated for all screened patients. Failed criteria include 'Screen Failure', Adverse Event', 'Withdrawal by subject', 'Lost to Follow-Up', 'Pregnancy', 'Death', 'Physician decision', 'Protocol Deviation', 'Study Terminated by the Sponsor', 'Site Terminated by the Sponsor' and 'Other'. Under 'Screen Failure', timing of failure and inclusion/exclusion criterion not met will be presented.

Disposition summary tables for patients in the Implanted Population will be presented for study and study treatment. These tables will summarize the number and percent of patients who completed the study/study treatment and discontinued pre-maturely from study/study treatment further broken down by most appropriate reason for discontinuation as collected on the follow-up disposition and device complaint eCRF. Reasons for pre-mature discontinuation from the study include 'Adverse Event', 'Withdrawal by subject', 'Lost to Follow-Up', 'Pregnancy', 'Death', 'Physician decision', 'Protocol Deviation', 'Study Terminated by the Sponsor', 'Site Terminated by the Sponsor', 'Technical Problems', and 'Other'. Reasons for pre-mature discontinuation from the study treatment include 'Persistent hypotony that cannot be mitigated by other means', 'Uveitis, glaucoma and hyphema syndrome', 'Gross device malposition', 'Surgical procedure that requires explant (eg, trabeculectomy)', and 'Other'.

Study exit status will also be listed for all screened patients.

In addition, enrollment by region (Asia-Pacific, other) and study site will also be summarized in the Implanted Population.

8.0 DEMOGRAPHICS AND OTHER BASELINE DATA

8.1 DEMOGRAPHICS

Following demographic characteristics will be descriptively summarized for the patients in the Implanted Population.

- Age (years)
- Age group (<60, 60-<70, 70-<80, ≥ 80 years)
- Sex (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Native Pacific Islander, Multiple)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)

8.2 BASELINE AND DISEASE CHARACTERISTICS

Following baseline characteristics will be descriptively summarized for the patients in the Implanted Population (baseline is defined in Section 16.1):

- Study eye (SE) [right (OD), left (OS)]
- Lens status of study eye (phakic, pseudophakic, aphakic)
- Number of prior IOP-lowering medications (0, 1, 2, 3, 4, 5, >5), see Section 8.4.2 for IOP-lowering medication counts.
- Screening and baseline IOP [Hour 0] of SE (mmHg) category (<20, 20-25, >25-30, >30-35, and >35 mmHg) and descriptive summary at baseline
- Best corrected visual acuity (BCVA) of the SE (20/40 or better, <20/40 to 20/100, and worse than 20/100)
- Visual field result of SE (normal, abnormal). Abnormalities will be further broken down by abnormality condition (enlargement of blind spot, superior arcuate scotoma, inferior arcuate scotoma, paracentral scotoma, nasal step, central scotoma, generalized depression, temporal scotoma, other)
- Visual field mean deviation (dB) or mean defect of the SE (+, −)
- Ophthalmoscopy, cup to disc ratio of SE at baseline
- Contact Pachymetry at screening: central corneal thickness mean (μm) of the SE, and a categorical summary (<500, 500-<525, 525-<550, 550-<575, 575-<600 and ≥600 μm)

In addition, following medical history data collected on the 'Medical and Surgical History/Physical Findings' eCRF page will also be summarized.

- History of trabeculectomy or glaucoma shunt implantation (yes, no)
- History of trabeculectomy (yes, no)
- History of glaucoma shunt implantation (yes, no)
- Prior Cataract Surgery (yes, no)
- Prior Glaucoma Procedure (yes, no).
    - Yes, with incisional or cilioablative procedure
    - Yes, without incisional or cilioablative procedure

A look-up table of Medical Dictionary for Regulatory Activities (MedDRA) terms to identify the following procedures will be provided by the study medical safety physician (MSP):

- Trabeculectomy
- Glaucoma shunt implantation
- Cataract Surgery
- Glaucoma Procedure
    - Incisional or cilioablative procedure
    - Not incisional or cilioablative procedure

8.3 MEDICAL HISTORY

Medical and surgical histories will be coded using the MedDRA, version 24.0 or newer. The number and percentage of patients with non-ocular medical and surgical histories will be summarized by system organ class and preferred term in the Implanted Population. Ocular medical and surgical histories will be summarized by study and fellow eye, system organ class and preferred term in the Implanted Population.

Medical and surgical histories will also be listed for patients in the Implanted Population.

8.4 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded using the current version of World Health Organization (WHO) Drug Dictionary and anatomical therapeutic chemical classification system and patient incidences will be summarized by therapeutic class and preferred drug name for patients in the Implanted Population. If a patient took a specific medication multiple times or took multiple medications within a specific therapeutic class, that patient will be counted only once for the coded drug name or therapeutic class.

Prior medications are defined as medications taken before the date of XEN implantation. Concomitant medications are defined as those medications taken on or after the date of XEN implantation.

Prior and concomitant medications will also be listed for patients in the Implanted Population.

8.4.1 General Medications

Prior and concomitant medications discussed in this section do not include medications of interest collected on the 'IOP meds' and 'IOP meds other' eCRF pages.

Non-ocular medications will be summarized separately for:

- Prior medications
- Concomitant medication

Ocular medications will be summarized by study and fellow eye separately for:

- Prior medications
- Concomitant medications

8.4.2 IOP-lowering Medications

IOP-lowering medications collected on the 'IOP meds' and 'IOP meds other' eCRF pages will be summarized by study and fellow eye separately for:

- Prior medications
- Concomitant medications

In addition, the number of IOP-lowering medications is one of the secondary effectiveness endpoint (analysis is described in Section 10.2). Fixed-combination medications will be counted as multiple medications, including but not limited to Azarga, Combigan, Cosopt, Duotrav, Ganfort, Simbrinza, and Xalacom, which will be counted as 2 medications. A list of these medications will be confirmed by clinical team prior to database lock.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

XEN may be removed if the investigator believes that it is in the best interest of the patient. Time to XEN device explant will be summarized by Kaplan-Meier (K-M) analysis.

10.0 EFFECTIVENESS ANALYSES

The primary effectiveness measure is based on IOP measurements at post-baseline visits and number of IOP-lowering medications taken during post-baseline visits (see section 16.1 for more details). Any IOP measurements collected following non-study surgical procedures for IOP control or device explant (i.e., device failures) will be excluded from the analyses. Any medications taken following non-study surgical procedures for IOP

control will be excluded when determining the number of IOP-lowering medications. A look-up table of MedDRA terms to identify non-study surgical procedures for IOP control will be provided by the study MSP.
No formal statistical hypothesis will be tested.

10.1 PRIMARY EFFECTIVENESS ASSESSMENTS

10.1.1 Primary Analysis

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

100 x (Timepoint Hour 0 IOP – Baseline Hour 0 IOP) / Baseline Hour 0 IOP

First, a response variable will be derived from the effectiveness variables: Hour 0 IOP percent change from baseline and the number of concomitant IOP-lowering medications. If the percent change in Hour 0 IOP from baseline is less than or equal to −20% at an analysis timepoint of interest **and** the number of IOP-lowering medications taken at the that timepoint is same or fewer compared to that at baseline, the response variable will be coded to value 1 and 0 otherwise. Refer to Section 8.4.2 for a discussion on determining the number of IOP-lowing medications taken at a timepoint of interest. GENMOD procedure available in SAS software will be used to fit the repeated measures logistic regression model; see sample SAS code below:

```
proc genmod data=one(where=(visit gt 0)) descending;
    class visit pid;
    model resp=bliop visit/link=logit dist=bin;
    repeated subject=pid/type=un within=visit;
    lsmeans visit/cl alpha=0.05;
    ods output lsmeans=lsms(keep=visit estimate lower upper);
run;
```

The variable 'resp' denotes the derived response variable as described above; 'visit' denotes the analysis visit month with the value 0 representing baseline; 'pid' is the unique patient ID; 'bliop' is the baseline Hour 0 IOP. Required proportion and 95% CIs at each assessment visit will be obtained by respectively applying the inverse logit transformation, exp(·)/(1+exp(·)), to 'estimate', 'lower' and 'upper' values contained in output dataset 'lsms' created by the 'ods output' statement. The proportion estimates and 95% CIs for Month 1, 3, 6, 8, 10 and 12 will be tabulated. In fitting the above model, missing data will not be imputed.

For Baseline and Month 12/Exit visits, Hour 0 IOP data from Hour 0 IOP eCRF page will be used. For all other visits without diurnal IOP assessment, all IOP collected for efficacy will be used.

10.1.2 Sensitivity Analyses

A sensitivity analysis will be performed using descriptive summary statistics for the primary effectiveness endpoint but based on the observed data in the Implanted Population.

Another sensitivity analysis will be performed to assess the impact of missing data on the primary effectiveness analysis. Multiple imputation (van Buuren 2007) will be used for missing IOP data for patients lost to follow-up prior to Month 12 (see sample SAS code below). The worst observation carried forward (WOCF) method will be used to impute missing IOP data following non-study surgical procedures for IOP control or device explant and missing concomitant IOP-lowering medication counts.

```
proc mi data=eff out=mi seed=123456 nimpute=20;
    where eos='lost to follow-up';
    class sex race;
    fcs nbiter = 100 reg(/details);
    var iop12 iop10 iop08 iop06 iop03 iop01 iopb medcntb age sex race;
run;
```

The imputed IOP and/or medication counts will be used to derive the missing binary outcomes for the primary effectiveness analysis. The estimation of proportion and the standard error of the estimation will be calculated for each imputation based on primary analysis model:

```
proc genmod data=mi(where=(visit gt 0)) descending;
    by _impuation_;
    class visit pid;
    model resp=bliop visit/link=logit dist=bin;
    repeated subject=pid/type=un within=visit;
    lsmeans visit/cl alpha=0.05;
    ods output lsmeans=lsms(keep=visit estimate lower upper);
run;
```

PROC MIANALYZE procedure available in SAS software will be used to combine results and generate the overall estimate and corresponding 2-sided 95% CI; see sample SAS code below:

```
proc mianalyze data=lsms;
    modeleffects prop;
    stderr prop_se;
    ods output parameterestimates=miresult;
run;
```

10.1.3 Subgroup Analyses

Descriptive summary statistics of the primary effectiveness outcome will be provided in the following subgroups:

- Race (Asian, other)
- Lens status of study eye (phakic, pseudophakic)
- History of trabeculectomy (yes, no)
- Prior glaucoma procedures (with incisional or cilioablative procedure, without incisional or cilioablative procedure, no)
- Baseline IOP ≥ 20 mm Hg and ≤ 35 mm

A forest plot will be provided to summarize all subgroup analyses results.

10.2 SECONDARY EFFECTIVENESS ASSESSMENTS

The mean and 2-sided 95% CI for raw Hour 0 IOP and the corresponding change from baseline Hour 0 IOP will be estimated using mixed-effects model for repeat measures (MMRM) at Month 1, 3, 6, 8, 10, and 12 with visit as a fixed effect and baseline Hour 0 IOP as a covariate. An unstructured covariance matrix will be used for repeated measures on the same patient; if the model with unstructured covariance fails to converge, an alternative covariance structure will be chosen. MIXED procedure available in SAS software will be used to fit the MMRM model; see sample SAS code below:

```
proc mixed data=one(where=(visit gt 0)) method=reml;
  class visit pid;
  model respvar=bliop visit/ddfm=kr;
  repeated visit/subject=pid type=un;
  lsmeans visit/cl alpha=0.05;
  ods output lsmeans=lsms(keep=visit estimate lower upper);
run;
```

The variable ‘respvar’ represents the Hour 0 IOP or corresponding change from baseline as applicable. Other variables are same as those described in Section 10.1. The least squares means and 95% CIs for Months 1, 3, 6, 8, 10 and 12 will be tabulated. In fitting the above model, missing data will not be imputed.

The number of IOP-lowering medications taken and corresponding change from baseline will be summarized by visit with descriptive statistics and 2-sided 95% CI for the mean. The change from baseline in the number of IOP-lowering medications taken will also be summarized by visit and the following categories: ≥ 3 medications reductions, 2 medications reductions, 1 medication reduction, no change, 1 medication increase, 2 medications increase, and ≥ 3 medications increase.

Mean (SE) Hour 0 IOP will be plotted overtime without missing data imputation and mean number of IOP-lowering medications taken will be displayed by visit in the plot.

10.3 OTHER EFFECTIVENESS ASSESSMENTS

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Implanted Population. Safety assessments include adverse events (AEs), XEN procedure and assessments, pregnancy test, and ocular parameters as determined through assessments of visual acuity, visual field, pachymetry, biomicroscopic slit lamp, gonioscopy, and ophthalmoscopic examinations.

11.1 ADVERSE EVENTS

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

An AE will be considered treatment-emergent adverse event (TEAE) if it started after the initiation of XEN implant related procedures.

An overall summary of subject incidences of TEAEs will be presented and will include experiencing the following:

- TEAE (ocular, non-ocular)
- Treatment emergent serious adverse event (TESAE) (ocular, non-ocular)
- TEAE with outcome of death (ocular, non-ocular)
- Study treatment (XEN) related TEAE (procedure related, device related)
- TEAE leading to study treatment discontinuation (XEN device removal)
- TEAE leading to study discontinuation

In general, the number and percent of patients in the Implanted Population reporting TEAEs will be tabulated by system organ class (SOC) in alphabetical order and by preferred term (PT) in descending order of incidence within the SOC, and further categorized by severity and causal relationship to the implant procedure or the device. If

more than 1 AE is coded to the same PT for the same patient, the patient will be counted only once for that PT using the greatest severity and strictest relatedness for the summarization by severity and relationship. These summaries will include:

- Non-ocular TEAEs by SOC, PT and severity grade
- Ocular TEAEs by SOC, PT and severity grade (SE, fellow eye)
- Non-ocular TEAEs by SOC and PT
- Ocular TEAEs by SOC and PT (SE, fellow eye)
- XEN procedure related TEAEs by SOC and PT
- XEN device related TEAEs by SOC and PT
- Incidence of common (≥ 5% of patients) TEAEs by PT
- XEN procedure or device related adverse events occurring in ≥2% of the patients by PT
- Serious non-ocular TEAEs by SOC and PT
- Serious ocular TEAEs by SOC and PT (SE, fellow eye)
- TEAEs leading to XEN device removal by SOC and PT
- TEAEs leading to XEN device replacement by SOC and PT
- TEAEs leading to the study discontinuation by SOC and PT

Subject data listings will also be provided to support each summary table.

11.2 XEN PROCEDURE AND ASSESSMENTS

Following data related to XEN procedure and assessments will be summarized for patients in the Implanted Population.

11.2.1 XEN Surgical Assessment

- XEN procedure (XEN implant only, XEN and other procedures). Further breakdown the other procedures (Cataract extraction/phacoemulsification, Clear lens extraction, Goniosynechialysis, Iridoplasty, other)
- Target Quadrant location (Superior, Nasal, Inferior, Temporal)
- Antifibrotic used (Mitomycin, Other)
- Number of sclera channels (1, 2, …, 6)
- XEN freely mobile under the conjunctiva (yes, no)
- Additional surgical maneuvers (yes, no)
- Post-implantation bleeding (yes, no)
- Bleb formation (yes, no)
- Surgical complications (yes, no). If yes, further breakdown by complication (Detached Descemet's membrane, Iris damage, Lens contact, Vitreous bulge or loss, Significant AC bleeding, Retrobulbar hemorrhage, Conjunctival perforation, Shallow anterior chamber with peripheral iridocorneal touch, Flat anterior chamber with peripheral iridocorneal touch extending to the pupil, Other)

11.2.2 XEN Bleb Assessment

- A bleb present (yes, no). If yes:
  - Bleb location (superior, nasal, inferior, temporal)
  - Bleb height (flat, low, medium, high)
  - Horizontal extent (0 to <1 clock hour, 1 to 2 clock hours, >2 to <4 clock hours, 4 or more clock hours)
  - Vascularity (avascular-white, avascular-cystic, mild, moderate, extensive)
  - If leak suspected, Seidel Test result (no leak, multiple pinpoint leaks, streaming leak)

11.2.3 XEN Implant Assessment

- Implant visible in the anterior chamber (yes, no, not evaluable). If yes:
  - Implant location (superior, nasal, inferior, temporal)
  - Implant length (mm)
- Implant visible in the sub-conjunctival space (yes, no). If yes:
  - Implant location (superior, nasal, inferior, temporal)
  - Implant length (mm)
- Implant contact (cornea, iris, other)
- Implant appear to be occluded (yes, no, not evaluable)

11.3 OTHER SAFETY PARAMETERS

Pregnancy: Pregnancy test results for females of childbearing potential will be listed.

Device problems/malfunctions: Number and percent of patients with device problems/malfunctions anytime during the study will be presented by reporting period the problem/malfunction occurred.

Manifest Refraction: The data associated with Sphere (+/-, measurement in Diopter), Cylinder (+/-, measurement in Diopter) and Axis (measurement in degrees) are collected at screening, baseline, Month 3 and Month 12/Early exit visit. Manifest refraction will be performed during any visit if BCVA reduction of ≥ 2 lines is observed since the last BCVA examination. These data will be summarized by visit.

Best corrected visual acuity (BCVA): Visual acuity exams will be performed at screening, baseline, and Months 1, 3, 6, 8 ,10 and 12/Early exit. BCVA will be recorded in Snellen equivalent units. Number and percent of patients with BCVA of the SE falling in each level will be summarized by visit. In addition, BCVA will be categorized into 3 groups: 20/40 or better, <20/40 to 20/100, and worse than 20/100. Number and percent of patients falling into each group will be summarized by visit.

Line change in BCVA 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 value in the formula above needs to be rounded to the nearest tenth before proceeding to the calculation of the line change. A positive value indicates an improvement, a negative value indicates a worsening, and a zero indicates no change. Ling changes in BCVA from baseline will be summarized using the following categories: decrease of > 2 lines, decrease of 2 lines, decrease of 1 line, no change, increase of 1 line, increase of 2 lines, and increase of > 2 lines.

Visual Field Test: Visual field tests will be performed at baseline and at Month 12/Early Exit visits. Number and percent of patients with an abnormal visual field in SE will be presented by visit and abnormality condition (Enlargement of blind plot, Superior arcuate scotoma, Inferior arcuate scotoma, Paracentral scotoma, Nasal step, Central scotoma, Generalized depression, Temporal scotoma, or Other). Note that a patient may have more than one abnormality condition. Further, visual field mean deviation and change from baseline to Month 12/Early Term will also be descriptively summarized. A change (Month 12/Early Term – Baseline) in visual field mean deviation measured using the same program of > 3.0 dB will be categorized as 'Better', a change of -3.0 dB to +3.0 dB will be categorized as 'no change' and a change of <-3.0 dB will be categorized as 'Worse'. Number and percent of patients belonging to each the three categories will also be presented.

Pachymetry: Contact pachymetry will be performed at screening and Month 12/Early exist. Three measurements of central corneal thickness and their average are recorded. These average values will be summarized by visit. Changes from screening to Month 12/Early exit visit will also be summarized.

Gonioscopy: Gonioscopy exams will be performed at screening, month 1, 6 and 12/Early Exit. The findings will be summarized by visit.

Ocular Biomicroscopic Exam: These exams will be performed at screening, baseline, Day 2, Day 8, Week 2, Months 1, 3, 6, 8, 10 and 12/Early Exit. At each of these exams, any findings related to Eyelids/Eyelid Margins/Lashes, Conjunctiva (Bulbar of

Palpebral), Cornea, Anterior Chamber, or Iris/Pupil are noted (yes, no, not evaluable) will be recorded. Number and percent of patients showing findings in each of the above areas will be summarized by visit. Further, associated with each eye, symptom severity data except for 'Iris/Pupil' will also be collected for the sub-categories described below:

- Eyelids/Eyelid Margins/Lashes:
  - Erythema
  - Edema
  - Other
- Conjunctiva:
  - Hyperemia
  - Edema
  - Subconjunctival Hemorrhage
  - Pterygium, encroaching on visual axis
  - Pterygium, not encroaching on visual axis
  - Other
- Cornea (Central, Peripheral, or Central and Peripheral):
  - Filaments
  - Infiltrates
  - Edema
  - Corneal Guttata
  - Endothelial Pigment
  - Keratic Precipitates
  - Neovascularization
  - Opacity
  - Stromal Haze
  - Other
- Anterior Chamber:
  - Cells
  - Flare
  - Anterior Synechiae
  - Hypopyon
  - Hyphema
  - Other

Number and percent of patients in each of the above sub-categories will be presented using the worst severity observed in the SE by visit.

Ophthalmoscopy Exam: These exams will be performed at Screening, Baseline, Months 1, 3, 6 and 12/Early Exit. At each of these exams, any findings noted (yes, no, not

evaluable) in the 'Vitreous', 'Optic Nerve Exam', 'Fundus Exam', 'Macula', and 'Retina Periphery' will be recorded.

Number and percent of patients with findings noted in the above areas in the SE will be summarized by visit. Further, following data will also be collected associated with each of the above categories.

Vitreous: Severity (+0.5, +1, +2, +3, +4, not evaluable) associated with each finding: 'Cells', 'Vitreous Haze', Vitreous Hemorrhage', 'Posterior Vitreous Detachment' and 'Other'. These data associated with the SE will be summarized in number and percent of patients format by visit.

Optic Nerve: 'Disc Hemorrhage' and 'Other Disc Pathology'. Number and percent of patients with findings in each of these two areas in the SE will be summarized by visit.

In addition, Optic Nerve-Cup/Disc ratio data (numerical) of the SE will also be summarized by visit.

Lens Status and Opacification: Lens status findings questionnaire will be administered at screening, baseline, Months 1, 3, 6 and 12/Early Exit. Lens status at each assessment will be recorded as 'Phakic', 'Pseudophakic' or 'Aphakic'. Lens status of the SE will be summarized by visit.

12.0 HEALTH OUTCOME MEASURES

Patient ocular symptom questionnaire that assessed 7 symptoms related right, left or both eyes will be administered at screening, Months 3, 6, 12 or Study Exit visit. Seven symptoms assessed are:

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

Responses will be recorded as whether a symptom occurred or not.

Number and percent of patients with each of the above symptoms occurring in the SE will be presented by visit.

Further detailed analysis of the above symptoms is not part of this SAP and will be described elsewhere by the group at Allergan that specializes in the analyzing of health outcome measures.

13.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

14.0 DETERMINATION OF SAMPLE SIZE

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

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS software.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16.1–1 presents the analysis visits assigned for efficacy and safety analyses and the corresponding range in Study days (window) during which an actual visit may occur.

Table 16.1–1. Visit Time Windows

Analysis Visit	Target Visit Day[a]	Window
Baseline	Day 1	Days ≤ 1
Day 2	Day 2	Days [2, 4]
Day 8	Day 8	Days [5, 11]
Week 2	Day 15	Days [12, 22]
Month 1	Day 31	Days [23, 61]
Month 3	Day 92	Days [62, 137]

Month 6	Day 183	Days [138, 213]
Month 8	Day 244	Days [214, 274]
Month 10	Day 305	Days [275, 335]
Month 12	Day 366	Days ≥ 336

a Relative to the date of the XEN implant. Day 1 = the date of the XEN implant. There is no Day 0 or Week 0.

If an assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of XEN implant, the study day is calculated using (Assessment date – date of the XEN implant + 1). If the assessment date is before the date of the XEN implant, the study day is calculated using (Assessment date – date of XEN implant). Therefore, a negative day indicates a day prior to XEN implant date.

For multiple scheduled or unscheduled visits falling within the same analysis visit window, the assessment closest to the target visit day will be used for by visit summaries. If two visits are equally close to the target visit day, the later visit will be used as analysis visit.

For by visit and severity summaries, the results with maximum severity for the visit should be chosen if multiple scheduled or unscheduled visits falling within the same analysis visit window.

For number of IOP-lowering medications taken during post-baseline visits, analysis visits for IOP measurements will be derived first. Post-baseline analysis visit days of IOP measurements will then be compared to start and stop date of each concomitant IOP-lowering medication record to determine number of IOP-lowering medications taken during post-baseline visits.

16.2 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

Following unscheduled assessments are allowed: Pregnancy test, IOP assessment, Manifest refraction, Gonioscopy, Pachymetry, BCVA and Visual field exam.

IOP assessment done at unscheduled visits for safety purpose will not be included in efficacy analysis of IOP.

16.3 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of XEN implant, severity of mild will be assigned. If severity is missing for an AE that started on or after the date of

XEN implant, severity of 'severe' will be assigned. The imputed values for severity assessment will be used for the incidence summaries; the values will be shown as missing in the data listings.

16.4 MISSING CAUSAL RELATIONSHIP TO XEN IMPLANT FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of XEN implant, a causality of 'yes' will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summaries; the values will be shown as missing in the data listings.

16.5 MISSING DATE INFORMATION FOR ADVERSE EVENTS

Per database design, only the day part of an AE start or stop date could be set to 'unknown', month and year cannot be set to 'unknown'. If the day part is missing, it will be set to the day part of XEN implant date. However, after the imputation if the stop date appears to be before the start date, start date will be set to stop date if the stop date was complete (non-missing) and stop date will be set to start date if the start date was complete (non-missing).

16.6 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including medications of interest, incomplete (i.e., partly missing) start dates and/or stop dates will be imputed. Per database design, year part of a medication start or stop date cannot be set to 'unknown'. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

16.6.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the XEN implant date, the month and day of the XEN implant will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the XEN implant date, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the XEN implant, *January 1* will be assigned to the missing fields.

Missing month only
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to rules described above.

Missing day only
- If the month and year of the incomplete start date are the same as the month and year of the XEN implant date, the day of the XEN implant date will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the XEN implant or if both years are the same, but the month of the incomplete start date is before the month of the XEN implant date, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the XEN implant or if both years are the same, but the month of the incomplete start date is after the month of the XEN implant date, the first day of the month will be assigned to the missing day

16.6.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the imputed stop date is before the start date (imputed or non-imputed start date), the imputed stop date will be set equal to the start date.

Missing month and day
- If the year of the incomplete stop date is the same as the year of the XEN implant date, the month and day of the XEN implant will be assigned to the missing fields.

- If the year of the incomplete stop date is before the year of XEN implant date, *December 31* will be assigned to the missing fields.

- If the year of the incomplete stop date is after the year of the XEN implant date, *January 1* will be assigned to the missing fields.

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the rules described above.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the XEN implant date, the day of the XEN implant will be assigned to the missing day.

- If either the year of the incomplete stop date is before the year of the date of XEN implant or if both years are the same, but the month of the incomplete stop date is before the month of the date of the XEN implant, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the XEN implant or if both years are the same, but the month of the incomplete stop date is after the month of the date of the XEN implant, the first day of the month will be assigned to the missing day

17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Sensitivity analyses for secondary effectiveness endpoints will not be conducted.

18.0 REFERENCES

van Buuren, S. (2007), "Multiple Imputation of Discrete and Continuous Data by Fully Conditional Specification," *Statistical Methods in Medical Research*, 16, 219–242.

19.0 AMENDMENTS

19.1 AMENDMENT 1

1. In Section 10.1.1, clarification added about CRF source for Hour 0 IOP for Baseline and Month 12/Exit visits.

2. In Section 10.1.2, clarification added for SAS code for sensitivity analysis.

3. In Section 10.1.3, added subgroup analysis for Baseline IOP ≥ 20 mm Hg and ≤ 35 mm.

4. In Section 10.3, clarification added for diurnal IOP analysis.

5. In Section 11.3, clarification added for BCVA analysis.

6. In Section 16.1, added analysis window for Month 8.

7. In Section 16.2, specified that IOP for safety will not be used for efficacy analysis.

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