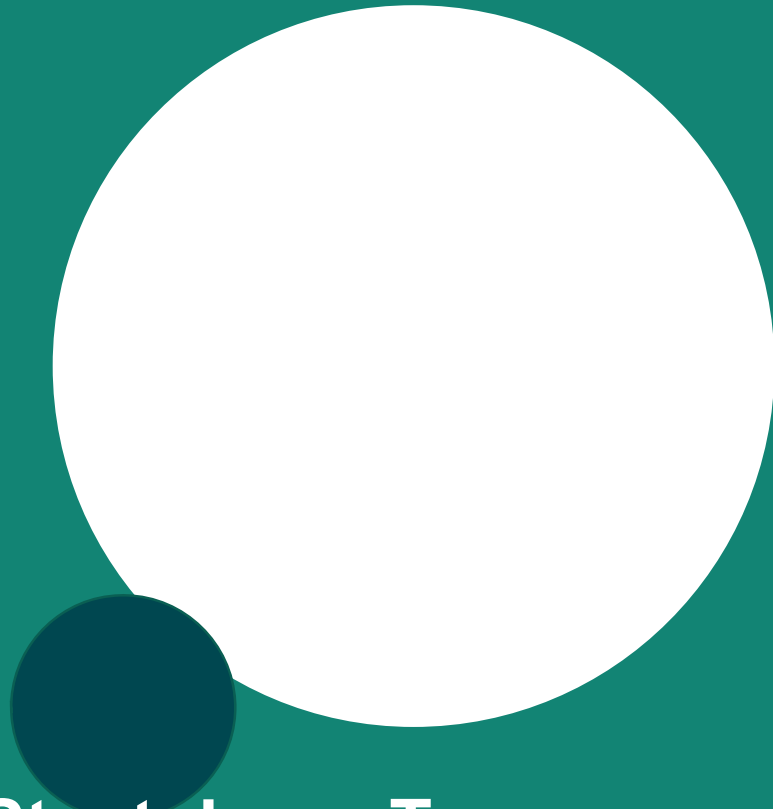


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**Study ID:** CMO-MA-EYE-0590

**Title:** XEN 45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT)

**Statistical Analysis Plan Date:** 18Oct2019

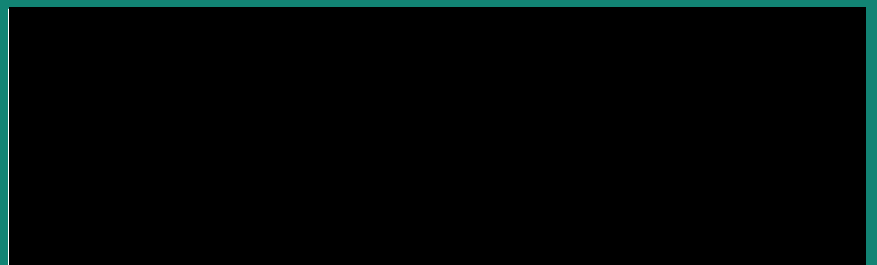


# **XEN 45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT) (CMO-MA-EYE-0590)**

## **Statistical Analysis Plan**

FINAL Version 1.0



October 18, 2019



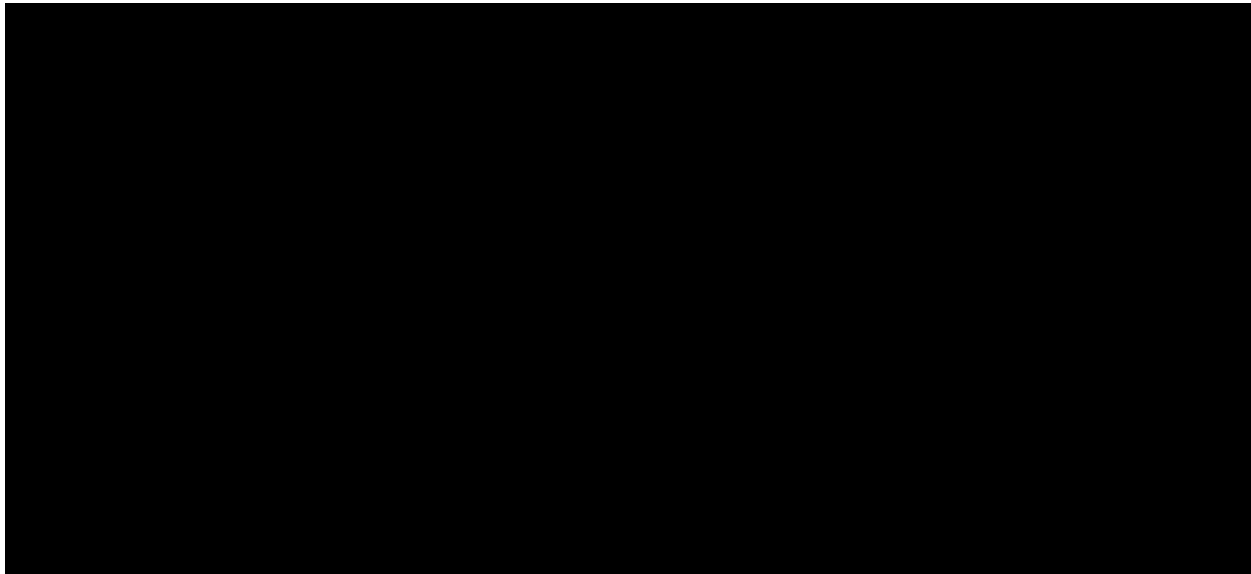


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**STATISTICAL ANALYSIS PLAN SPONSOR SIGN-OFF SHEET**




**Sponsor:** Allergan  
**Project Name:** XEN-45 Gel Stent: Long Term Performance and Safety Assessment (XEN LT)  
**Abbreviated Name:** NA  
**Protocol Number:** CMO-MA-EYE-0590  
   
**Date:** October 18, 2019  
**Version:** Final V1.0

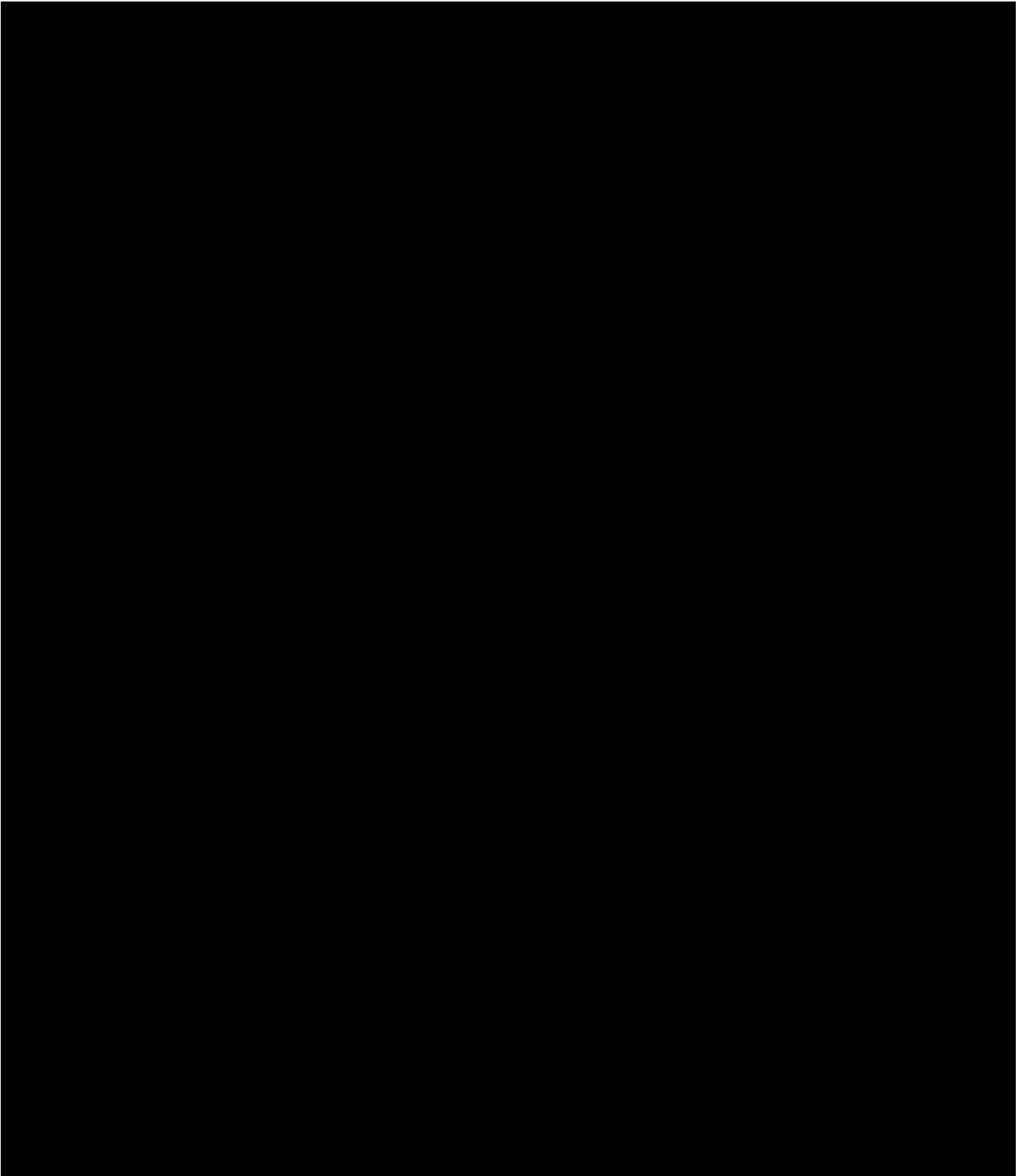
I approve the statistical analysis plan and authorize its implementation.

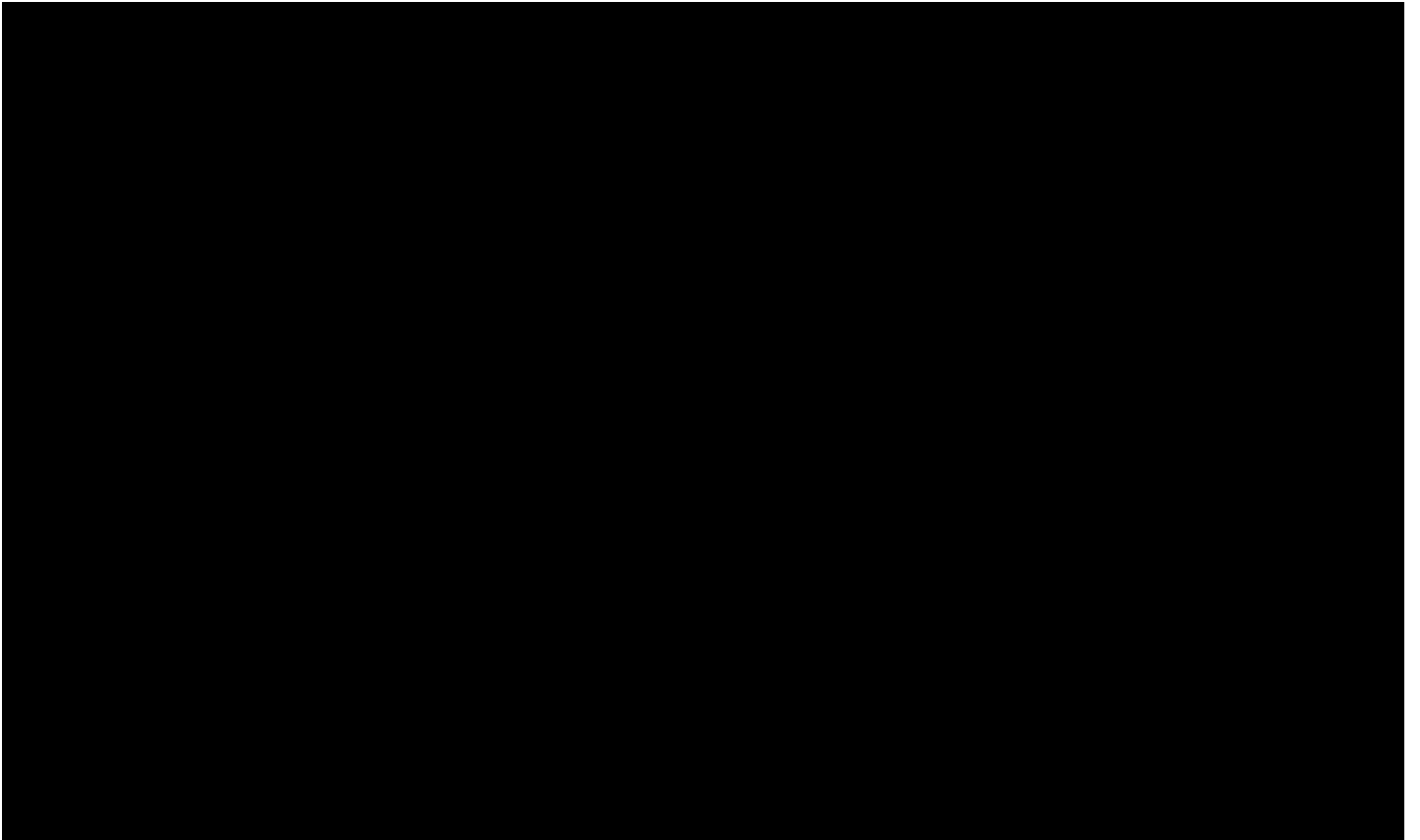


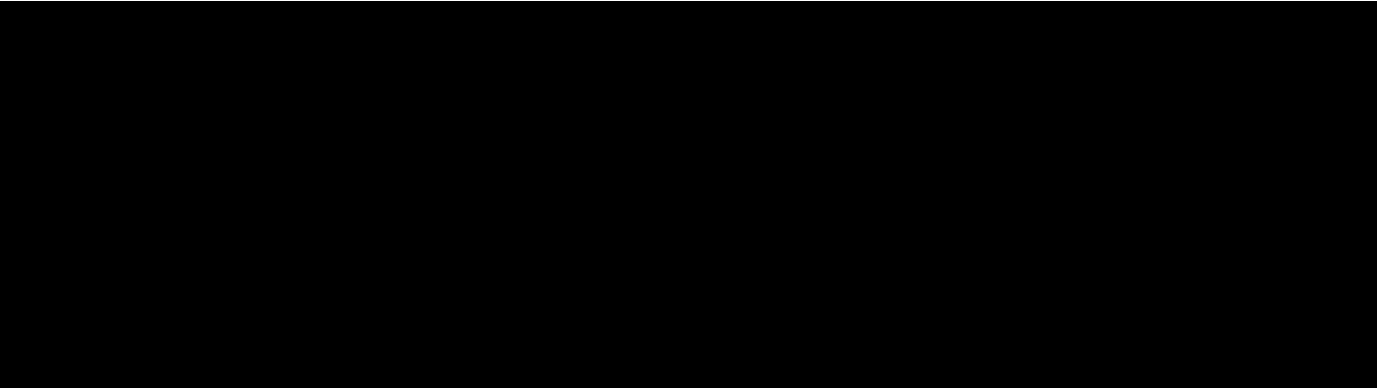


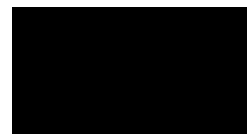
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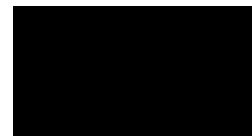




## Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event(s) of special interest
BCVA	Best corrected visual acuity
CI	Confidence interval
eCRF	Electronic case report form
EDC	Electronic data capture
EDTRS	Early Treatment Diabetic Retinopathy Study
IC	Inclusion criteria
IOP	Intra-ocular pressure
IQR	Interquartile range
LogMAR	Logarithm of the minimum angle of resolution
OD	Oculus dexter
OS	Oculus sinister
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SSI	Secondary surgical intervention
WHO	World Health Organisation





## 1. Overview

### 1.1. Background

The term “glaucoma” refers to a group of diseases that have in common a characteristic damage to the optic nerve with associated visual field loss. The goal in the treatment of glaucoma is to prevent further loss of functional vision and to avoid an adverse impact on the patient’s quality of life.<sup>1</sup> Currently, the only approach proven to be efficient in preserving visual function is lowering intra-ocular pressure (IOP)<sup>2</sup> as elevated IOP is recognised as the primary risk factor for glaucoma.

XEN 45 Gel Stent (Allergan Inc.) is an *ab interno* gelatin stent implanted via a clear corneal incision without conjunctival incision and is the only available filtering micro-invasive glaucoma surgery device that allows subconjunctival filtration. The XEN 45 Gel Stent is intended to reduce IOP in patients with primary open angle glaucoma where previous medical treatments have failed (XEN 45 Gel Stent directions for use). The performance and safety of XEN 45 Gel Stent has been previously demonstrated in a few clinical trials but the follow-up time has only been up to two years.

### 1.2. Study Rationale

XEN 45 Gel Stent performance and safety have been previously demonstrated in clinical trials designed for regulatory approval, and these studies only provide data for up to 2 years. This study will allow an assessment of the long-term performance and safety of the XEN 45 Gel Stent surgeries performed in Europe in typical clinical settings.

### 1.3. Study Objectives

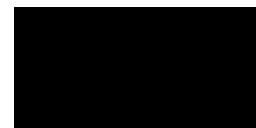
#### 1.3.1. Primary objective

The primary objective of this study is to assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in IOP compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 3 years after implantation.

#### 1.3.2. Secondary objective

The secondary objectives of this study are to:

- Assess the performance of XEN 45 Gel Stent over the long term as assessed by the change in IOP compared to medicated IOP at baseline and the change in the number of topical IOP-lowering medications compared to baseline, 4 years after implantation.
- Assess success over the long term following implantation of the XEN 45 Gel Stent as defined in Section 1.4.
- Assess safety over the long term following implantation of the XEN 45 Gel Stent.



## 1.4. Key Variable Definitions

**Qualified success** of implantation of the XEN 45 Gel Stent will be defined as  $\geq 20\%$  reduction from medicated baseline with no Secondary Surgical Intervention (SSI) for glaucoma and no clinical hypotony while staying on the same number or fewer topical IOP-lowering medications than at baseline.

**Complete success** of implantation of the XEN 45 Gel Stent will be defined as  $\geq 20\%$  reduction from medicated baseline with no SSI for glaucoma and no clinical hypotony while taking no topical IOP-lowering medications.

## 1.5. Outcome Variables

### Performance outcomes:

- Change in IOP from medicated baseline to 3 years after XEN 45 Gel Stent implantation
- Change in IOP from medicated baseline to 4 years after XEN 45 Gel Stent implantation
- Study pre-defined IOP outcomes achieved while staying on the same number or fewer topical IOP-lowering medications and without clinical hypotony: 20% reduction from medicated baseline, as well as IOP below 12 mmHg and through to IOP below 18 mmHg
- Change in the number of topical IOP-lowering medications from medicated baseline to 3 years after XEN 45 Gel Stent implantation
- Change in the number of topical IOP-lowering medications from medicated baseline to 4 years after XEN 45 Gel Stent implantation
- Qualified or complete success 3 years after XEN 45 Gel Stent implantation
- Qualified or complete success 4 years after XEN 45 Gel Stent implantation

### Safety outcomes:

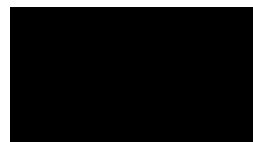
- Adverse events of special interest (AESIs), as defined in Section 1.8 below.

## 1.6. Study Design

This is a retrospective, non-interventional, observational, multi-centre, chart review study conducted in patients who underwent placement of the XEN 45 Gel Stent as a standalone procedure or in combination with phacoemulsification from 1 January 2014 to 1 October 2015.

For each eligible eye, all retrospective data available from baseline (i.e. day when decision was made to implant XEN 45 Gel Stent) until Last Visit (i.e. date of the last follow-up visit available prior to 1 October 2018 or date on which the patient had a SSI for glaucoma, whichever occurs first) are extracted from existing medical records into the electronic CRF (eCRF) in Dacima.

If both eyes from the same patient meet eligibility criteria, each eye is included in the study database with a unique identifier and eyes are paired in the electronic data capture system (EDC). See section 4 for how bilateral eyes included in the study are handled in the analyses.



## 1.7. Study Population

The study population includes patients with one or both eyes with open angle glaucoma that underwent XEN 45 Gel Stent implantation.

Patients meeting the following criteria are eligible for participation in the study:

1. Eye treated with XEN 45 Gel Stent for open angle glaucoma as a standalone procedure or in combination with phacoemulsification
2. XEN 45 Gel Stent was implanted between 1 January 2014 and 1 October 2015
3. Charts contain minimum required data (age, gender, IOP at baseline until last visit, number of topical IOP-lowering medications prescribed for the study eye from baseline until last visit, date of the SSI for glaucoma if applicable)

## 1.8. Data Collection

Data are being collected from patients' medical records using an eCRF on the Dacima platform. The eCRF includes edit and range checks to minimize the amount of missing or invalid data.

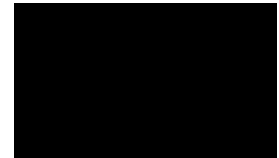
The schedule for data collection is presented below:

Data Collected	Baseline[a]	XEN 45 Gel Stent Implantation	Study Period[b]
<b>Eligibility Assessment</b>	X		
<b>Demography</b>	X		
<b>Ocular and Glaucoma Medical History</b>	X		
<b>Surgery-related data</b>		X	
<b>Number of IOP-lowering medications</b>	X		X
<b>Visual field exam</b>	X		X
<b>Intraocular pressure</b>	X		X
<b>Best corrected visual acuity</b>	X		X
<b>Needling procedures</b>			X
<b>Secondary surgical intervention for glaucoma</b>			X
<b>Adverse events of special interest</b>			X

IOP=intra-ocular pressure.

[a] Baseline is defined as the day when the decision was made to implant XEN 45 Gel Stent.

[b] The study period is defined as the period between XEN 45 Gel Stent implantation and 1 October 2018. For each eye selected, all retrospective data available from baseline until 1 October 2018 or until the date on which the patient received a SSI for glaucoma, whichever occurs first, are from existing medical records.



Data collected includes:

- Demographics
- Selected eye characteristics (oculus dexter vs. oculus sinister), along with information about whether patient's other eye was also selected.
- Ocular and Glaucoma Medical History
- Surgery-Related Data
  - Use of anti-metabolite and/or anti-fibrotic
  - Procedure performed (i.e., XEN 45 Gel Stent implantation alone or phacoemulsification + XEN 45 Gel Stent implantation)
  - XEN 45 Gel Stent and cataract-related complications
- Intraocular Pressure Data
  - IOP-related data, i.e. IOP and number of topical IOP-lowering medications
- Visual Field Exam
- Best Corrected Visual Acuity (BCVA), including method used
- Needling Procedures
- Secondary Surgical Intervention (nature and date, if applicable)
- Adverse events of special interest (AESI):
  - Anterior chamber defects:
    - Shallow with peripheral iridocorneal touch
    - Flat with irido-corneal touch extending to the pupil
  - Bleb leak
  - Blebitis
  - Choroidal effusion, hemorrhage or mixed effusion hemorrhage recorded as follows:
    - Extending posterior to the equator
    - Obscuring disc or macula
    - With choroids touching in the centre of the eye
    - Persistent choroidal effusion, hemorrhage or mixed effusion hemorrhage occurring > 30 days post-operation
  - Corneal oedema:
    - Transient corneal decompensation / edema (<30 days)
    - Persistent corneal decompensation / edema (>30 days)
    - Mild corneal decompensation / edema



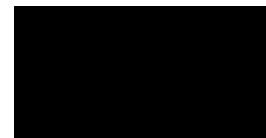
- Moderate corneal decompensation / edema
- Severe corneal decompensation / edema
- Cyclodialysis
- Endophthalmitis
- Hyphema
  - $\geq 2$  mm in height (layered) at any time; present or arising > 30 days postoperatively
- Persistent hypotony: IOP < 6 mmHg, present at two consecutive visits postoperatively > 30 days apart
- Clinical hypotony: 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
- Implant blockage in the anterior chamber
- Implant exposure or extrusion
- Implant fracture
- Implant migration
- Implant repositioning requiring surgical intervention
- Implant touching iris
- Implant touching cornea
- Iridodialysis
- Iritis (requiring treatment after the postoperative medication taper)
- Macular edema
- Ptosis
- Retinal detachment
- Suture abscess or other local infection
- Vitreous hemorrhage
- Any other adverse event that leads to permanent visual impairment or requires surgical or medical intervention to prevent permanent visual impairment



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## 2. Sample Size

A sample size of 150 patient eyes was selected, as it is anticipated that this will allow for the inclusion of a minimum of 60 independent study eyes have at least 3 years of follow-up data without a SSI for glaucoma after the initial implant with XEN 45 Gel Stent. Based on the Allergan study MS-001, for month 36 the 95% confidence interval (CI) of the projected mean IOP reduction afforded by a sample of 60 study eyes is -7.2 to -4.0 mmHg. That is, the half-length of the interval is 1.6 mmHg, which provides a reasonable precision for the estimate of the projected mean reduction in IOP.



## 3. Data Handling

### 3.1. Raw Datasets

The raw database generated in Dacima, containing all completed eCRFs will be exported directly into SAS.

### 3.2. Derived Datasets

Analysis will be conducted on derived datasets. These datasets will include raw variables, and variables created from the raw variables as required for the analysis. Derived datasets will be created in SAS; all codes used to create derived datasets will be saved and validated. No ADaM or SDTM datasets will be produced.

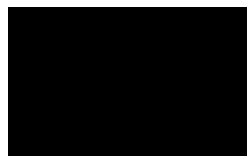
### 3.3. Data Dictionary

A data dictionary is automatically generated within the Electronic Data Capture (EDC) based on the electronic Case Report Form (eCRF). The data dictionary has been exported from the EDC into a Microsoft® Excel worksheet. Any derived variables will be added to the data dictionary. The data dictionary will provide the following information: 1) raw data set variable name; 2) derived variable name; 3) description of the variable; 4) variable type/permissible entries; 4) allowance of not applicable entries; and 5) notes.

### 3.4. Missing Data

The eCRF is designed to ensure that no questions are left unanswered. If 'unknown' is selected, this will be included as such in the results and tabulated for all variables. Central tendencies will not be measured for continuous unknown data, only counts and percentages will be recorded.

In some cases, imputation of unknown variables may be conducted if the variable is to be used in calculations for another variable or analysis. For example, the eCRF allows some dates to be incomplete (i.e. day is unknown) if it is not available in the medical chart. This may impact accurate calculation of durations, resulting in an imputation needing to be made. If the day is missing, the date will be imputed as the 15<sup>th</sup> of the month, except in cases where this would lead to a negative duration, in which case the 1<sup>st</sup> or last day of the month will be used (whichever addresses the negative duration). No imputation will be made for missing month/year; these are classified as date unknown within the eCRF. All imputed values will be documented and presented as footnotes in the result tables.



## 4. Planned Analyses

The analyses detailed below will be performed to meet the project objectives. There will be two analysis populations specified for the analyses to be conducted:

- The **Effectiveness Population** consists of all eligible study eyes in the population except in instances when a patient has contributed both eligible eyes in the study, then only the eye that received the Xen-45 implant first will be selected; this eye will be presented in tables as the 'primary eye'. All results tables in the Effectiveness Population will include stratified results presenting data for the primary eye, as well as data on all included patient eyes (even if both eyes from a single patient are included).
- The **Safety Population** consists of all eligible study eyes in the population.

All results tables will be stratified by Xen-45 implant only, implant plus phacoemulsification, and total population. Sensitivity analyses will be conducted to assess study results in the 'second eye' (i.e. not the primary eye as described above), for patients where both eyes were included. The sensitivity analyses will focus on the tables conducted using the Effectiveness Population.

Categorical variables will be summarised by number and percentage of each response and will include number of unknown responses. Continuous variables will be summarised by mean, standard deviation, median, upper and lower quartiles, minimum and maximum values and proportion with unknown data.

### 4.1. Time Windows for Follow-up Period

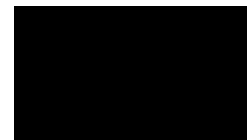
For IOP and number of IOP-lowering medications only, data from the latest clinic visit recorded within the following time windows will be used in the analysis:

- Month 12: data between Month 9 and Month 15 after XEN 45 Gel Stent implantation
- Month 24: data between Month 21 and Month 27 after XEN 45 Gel Stent implantation
- Month 36: data between Month 33 and Month 39 after XEN 45 Gel Stent implantation
- Month 48: data between Month 45 and Month 51 after XEN 45 Gel Stent implantation
- >Month 51 after XEN 45 Gel Stent implantation

Unless otherwise specified, all other retrospective data (See Section 1.8) collected from baseline until the last visit will be categorised into the following groups for the follow-up period analyses, based on latest available data within the time window:

- $\leq 12$  months: data  $\leq 12$  months after XEN 45 Gel Stent implantation
- $> 12$  to  $\leq 24$  months: data  $> 12$  to  $\leq 24$  months after XEN 45 Gel Stent implantation
- $> 24$  to  $\leq 36$  months: data  $> 24$  to  $\leq 36$  months after XEN 45 Gel Stent implantation
- $> 36$  to  $\leq 48$  months: data  $> 36$  to  $\leq 48$  months after XEN 45 Gel Stent implantation
- $> 48$  months: data from  $> 48$  months after XEN 45 Gel Stent implantation to end of study period





Needling procedures will be summarised descriptively within the following time-windows:

- < 3 months: data < 3 months after XEN 45 Gel Stent implantation
- > 6 to ≤ 12 months: data > 6 to ≤ 12 months after XEN 45 Gel Stent implantation
- > 12 to ≤ 24 months: data > 12 to ≤ 24 months after XEN 45 Gel Stent implantation
- > 24 to ≤ 36 months: data > 24 to ≤ 36 months after XEN 45 Gel Stent implantation
- > 36 to ≤ 48 months: data > 36 to ≤ 48 months after XEN 45 Gel Stent implantation
- > 48 months: data > 48 months after XEN 45 Gel Stent implantation

## 4.2. Disposition and patients' characteristics

Number and percentage of eyes in both the Effectiveness and Safety Analysis Populations will be described. Demographic characteristics will be summarised descriptively for all included patients in the study.

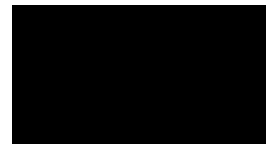
## 4.3. Disease progression

Ocular medical history will be summarised descriptively in the Safety Population overall and not by the time windows specified. Needling procedures will be summarized in the Safety Population by the time windows indicated in Section 4.1. Anti-metabolite/anti-fibrotic use will be described during the stent implantation, during conjunctiva bleb revision (if applicable), during needling procedures (if applicable), and also when used alone. Anti-metabolite/anti-fibrotic use during needling procedures will be determined based on the date of each anti-metabolite/anti-fibrotic use and date of the needling procedure; the same date assumes that the anti-metabolite/anti-fibrotic was used in conjunction with the needling procedure. IOP lowering medications (oral) will be described at baseline and post-implantation in the Effectiveness Population by class of medication (carbonic anhydrase inhibitors or alpha-agonist hypotensive agent). Visual field exam will be summarised descriptively at baseline and for all time points of interest (as described in Section 4.1) in the Safety Population. All BCVA values will be converted to logarithm of the minimum angle of resolution (logMAR) units.<sup>3</sup> To do this, Snellen values will be converted by taking the negative base 10 logarithm of the decimal. ETDRS letters will be converted to approximate Snellen scores by the following formula.

$$\text{Snellen} \cong \exp \left\{ \frac{1}{50} (\text{ETDRS} - 85) \right\}.$$

This will then be converted into logMAR units using the negative base 10 logarithm of the decimal as above. Any non-numerical BCVA values (i.e. including count fingers, hand movement, light perception and non-light perception) will also be converted to logMAR units as described below:<sup>4</sup>

Non-numerical BCVA value	LogMAR
Count fingers (CF)	1.8
Hand movement (HM)	2.3



Light perception (LP)	2.8
No light perception (NLP)	3.0

#### 4.4. Change in IOP and number of topical IOP-lowering medications after XEN 45 gel stent implantation

Change in IOP from medicated baseline and change in the number of topical IOP-lowering medications will be summarised. Change in number of IOP-lowering medications will be made by examining the class of the medication as follows:

- Beta Blocking Agents
- Carbonic Anhydrase Inhibitors
- Parasympathomimetics
- Prostaglandin Analogues
- Sympathomimetics In Glaucoma Therapy

These will be compared to baseline and will be summarised descriptively at months 12, 24, 36 and 48 after XEN 45 Gel Stent implantation in eyes from the Effectiveness Population. Analyses will only include those with available data at each of the time points of interest and those who were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.

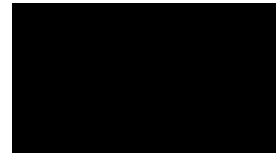
A paired t-test will be applied for statistical analysis in comparing the difference between post baseline to baseline values. The assumptions of the test are as follows:

- No significant outliers in the differences between time points (which can be tested by a scatter plot of the data)
- The distribution of the differences in the dependent variable between the two time points should approximately follow a normal distribution (which can be tested through the Shapiro-Wilk test)
- The dependent variable is measured on a continuous scale

If the assumptions of the t-test are heavily violated then the non-parametric analogue (Wilcoxon Signed-Rank test) should be used to test the difference between time points.

##### 4.4.1. Success over the long term of following implantation of the XEN 45 Gel Stent

Number and proportion of eyes achieving a 20% reduction in IOP from medicated baseline, and number and proportion of eyes with an IOP between 6 and 18 mmHg, IOP between 6 and 17 mmHg, ..., down to IOP between 6 and 12 mmHg will be described by the time-windows described in Section 4.1 in eyes from the Effectiveness Population that did not undergo SSI for glaucoma, and were not treated with Diamox on the day when decision was taken to implant XEN 45 Gel Stent.



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The number and proportion of eyes achieving qualified or complete success at each time point of interest (i.e. 12, 24, 36, 48 and >51 months) after XEN 45 Gel Stent implantation will be summarised descriptively. Analyses will be conducted in the Effectiveness Population.

The time from XEN 45 Gel Stent implantation to SSI for glaucoma will be described using Kaplan Meier curves.

#### 4.5. Safety over the long term following implantation of the XEN 45 Gel Stent

Surgical complications and post-operative AESIs will be summarised descriptively using frequencies and percentages.

#### 4.6. Secondary surgical intervention

The median time for a patient in the Safety Population to have an SSI will be described by Kaplan-Meier curves. A summary of patients with SSI will be recorded by the time windows described in Section 4.1.



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## 7. References

1. Glaucoma Panel. *Preferred practice pattern for primary open-angle glaucoma*. San Francisco 2006.
2. Heijl A, Leske M, Bengtsson B, al. e. Reduction of Intraocular Pressure and Glaucoma Progression: Results from the Early Manifest Glaucoma Trial. *Arch Ophthalmology*. 2002;120:1268-1279.
3. Gregori N, Feuer W, Rosenfeld P. Novel method for analyzing Snellen visual acuity measurements. *Retina*. 2010;30:1046-1050.