September 2023

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To Whom It May Concern,

Please see attached, the Statistical Analysis Plan for the INN-005 EXT study

Official Title:

A Prospective, Concurrent Controlled, Open-Label, Multicenter Clinical Study to Assess the Long-Term Safety of the PRESERFLO® MicroShunt in Subjects with Primary Open-Angle Glaucoma Who Have Completed Participation in the INN-005 Randomized Controlled Study

Document:	Statistical Analysis Plan v1.0 July 13, 2021
Study ID:	**INN-005 EXT**
NCT No.	**NCT04333433**

Thank you,

Haydee Frost
Senior Clinical Research Associate
InnFocus, Inc. a Santen Company

STATISTICAL ANALYSIS PLAN

PRESERFLO® MICROSHUNT EXTENSION STUDY

Protocol Title:	A Prospective, Concurrent Controlled, Open-Label, Multicenter Clinical Study to Assess the Long-Term Safety of the PRESERFLO® MicroShunt in Subjects with Primary Open-Angle Glaucoma Who Have Completed Participation in the INN-005 Randomized Controlled Study
Product:	PRESERFLO® MicroShunt
Protocol Number:	INN-005-EXT
Sponsor:	InnFocus, Inc.
	[redacted]
Date:	July 13, 2021
Status:	Version 1.0

CONFIDENTIAL

APPROVAL SIGN-OFF SHEET

A Prospective, Concurrent Controlled, Open-Label, Multicenter Clinical Study to Assess the Long-Term Safety of the PRESERFLO® MicroShunt in Subjects with Primary Open-Angle Glaucoma Who Have Completed Participation in the INN-005 Randomized Controlled Study

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ABBREVIATIONS

Abbreviation	Explanation
AC	Anterior Chamber
AE	Adverse Event
ATC	Anatomical-Therapeutic-Chemical
BCVA	Best-Corrected Visual Acuity
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
CM	Concomitant Medications
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ETDRS	Early Treatment Diabetic Retinopathy Study
ECD	Endothelial Cell Density
EU	European Union
IOP	Intraocular Pressure
LogMAR	Logarithm of the Minimum Angle of Resolution
mmHg	Millimeter of Mercury
OCT	Optical Coherence Tomography
OD	Oculus Dexter (right eye)
OS	Oculus Sinister (left eye)
OU	Oculus Uterque (both eyes)
MD	Mean Deviation
MMC	Mitomycin C
POAG	Primary Open-Angle Glaucoma
PP	Per-Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
UADE	Unanticipated Adverse Device Effect
US	United States
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected from the INN-005-EXT study within the scope of InnFocus[ĀClinical Investigation Plan INN-005-EXT"ĀAXProspective, Concurrent Controlled, Open-Label, Multicenter Clinical Study to Assess the Long-Term Safety of the PRESERFLO® MicroShunt in Subjects with Primary Open-Angle Glaucoma Who Have Completed Participation in the INN-005 Randomized Controlled StudyY.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this study, to be compiled as a supplement to IDE G130028 under which the INN-005 study was conducted. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the Clinical Study Report (CSR).

2. OBJECTIVES AND OUTCOME MEASURES

2.1. Objectives

The objective of this study is to evaluate the long-term safety of the PRESERFLO® MicroShunt in subjects with Primary Open-Angle Glaucoma (POAG) who have completed their Month 24 Follow-Up Visit in the INN-005 clinical study, by collecting safety data through 5 years post-operative follow-up.

2.2. Outcome Measures

2.2.1. Primary Safety Outcome Measure

The primary safety outcome measure is the incidence of sight-threatening adverse events.

2.2.2. Secondary Safety Outcome Measures

The following secondary outcome measures will be assessed for safety:

- Incidence of ocular adverse events in the study eye.
- Incidence of needling and reoperations for glaucoma (e.g., trabeculectomy, repositioning or explantation of PRESERFLO® MicroShunt, bleb revision, glaucoma drainage device, or other incisional treatment to establish a new aqueous flow path from the anterior chamber in order to maintain acceptable IOP, iridectomy, re-suturing of scleral flap, glaucoma laser surgery).
- Change in Best Corrected Visual Acuity (BCVA) from INN-005 study Screening, as measured by ETDRS.
- Change in visual field mean deviation from INN-005 study Screening.
- Change in central corneal thickness from INN-005 study Screening as assessed by ultrasound pachymetry.
- Change in central corneal endothelial cell density (ECD) from INN-005 study Screening as assessed by specular microscopy.
- Change in lens opacity for phakic lens from INN-005 study Screening as assessed by LOCS III classification system.
- Ophthalmologic examination findings.

2.2.3. Secondary Effectiveness Outcome Measures

The following secondary outcome measures will be assessed for effectiveness:

- Proportion of study eyes with V20% decrease in intraocular pressure (IOP), from INN-005 study Screening, without increasing the number of glaucoma medications.
- Mean change in IOP from INN-005 study Screening.
- Proportion of study eyes with any qualifying glaucoma-related post-operative intervention.

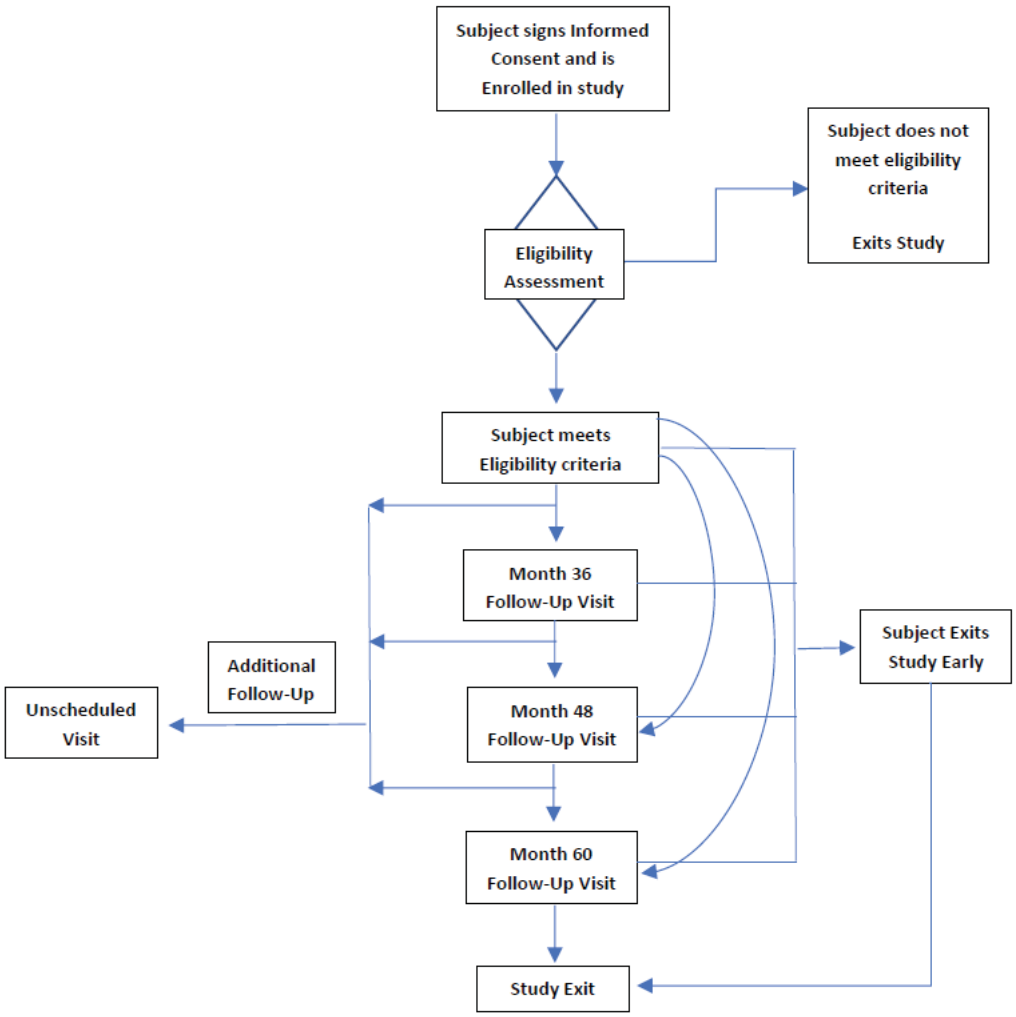
- Proportion of study eyes considered a treatment success (overall, complete, qualified).
- Change in the number of glaucoma medications from INN-005 study Screening.

3. STUDY DESIGN

3.1. General Study Design

The study is a prospective, concurrent controlled, open-label, multicenter study designed to collect safety data through 5 years of follow-up for subjects randomized to either the treatment arm (PRESERFLO® MicroShunt with Mitomycin C (MMC)) or the control arm (Trabeculectomy with MMC) of the INN-005 clinical study. All subjects who have completed the Month 24 Follow-Up Visit for the INN-005 study, will be assessed for their eligibility to be enrolled in this long-term follow-up study, and will be required, if enrolled in the INN-005-EXT study to return for up to three (3) follow-up visits through post-operative Month 60, i.e., at Month 36, Month 48, and Month 60 (follow-OJĀPDMDNĀNDG@JIDHNMĀNIĀ=@Ā><HNMĀ<N@?ĀALIG Operative Visit in the INN-005 study). As shown in the study schema in Figure 1, subjects will still be eligible to enroll if they have already passed any of the earlier follow-up visit windows. At a minimum, subjects enrolled in the PRESERFLO® MicroShunt Extension Study should be able to complete the Month 60 Follow-Up Visit.

Figure 1: INN-005-EXT Study Schema



3.2. Randomization and Masking

This long-term follow-up study is an open label study and does not involve randomization or treatment assignment. The subjects to be enrolled in this study were previously randomized to either receive the PRESERFLO® MicroShunt device or undergo trabeculectomy as part of the INN-005 clinical study. The study does not mandate any new treatment.

3.3. Sample Size Planning

All 629 subjects who were randomized into both Phase I and II of the INN-005 study, and have completed their Month 24 Follow-Up Visit, will be assessed for eligibility to participate in this long-term follow-up study. The sample size will therefore be dependent upon the number of subjects who are willing to participate in, and who meet the eligibility criteria for enrollment in this study.

3.4. Visits and Assessments

Subjects enrolled in this study will be required to complete up to three (3) annual follow-up visits through post-operative Month 60 Follow-Up Visit and may therefore be in the study for up to three (3) years following completion of their Month 24 Follow-Up Visit in the INN-005 clinical study. Assessments at each visit and the time/visit window for each follow-up assessment are specified in the Assessment Schedule (Table 1). Essentially, most of the study procedures are the same as those performed as part of the INN-005 study, the differences are listed as follows:

Study Assessment	INN-005 Study (Month 12 and 24)	INN-005-EXT Study (Month 36, 48, and 60)	Comments
IOP	Diurnal	Standard	INN-005: Diurnal IOP INN-005-EXT: Standard IOP
Anterior Segment OCT	Not performed	Performed	INN-005-EXT: An optional assessment only performed for subjects with device still implanted
Adverse Event Assessment	All AEs	All SAEs; Ocular AEs	INN-005: All AEs collected INN-005-EXT: All ocular AEs in study & fellow eye and all SAEs (ocular and non-ocular) will be collected. Non-serious, non-ocular AEs will not be collected.
Ocular QOL Questionnaire	Performed	Not performed	
General Health Questionnaire	Performed	Not performed	

Table 1: Assessment Schedule

Activities	Enrollment[a]		Follow-Up Evaluation						
			Month 36 Visit (Day 1080 +/-90 days)		Month 48 Visit (Day 1440 +/-90 days)		Month 60 Visit (Day 1800 +/-90 days)		Un-scheduled Visit
	SE	FE	SE	FE	SE	FE	SE	FE	
Study Assessments									
1. Informed Consent & Research Authorization	X								SOC[d]
2. Eligibility Assessment	X								
3. Medical/Surgical History[b]	X	X							
4. Glaucoma Medications[c,e]	X	X	X	X	X	X	X	X	
5. Concomitant (ocular) Medications[c,e]	X	X	X	X	X	X	X	X	
6. Adverse Event Assessment[e]	X	X	X	X	X	X	X	X	
Study Procedures[f]									
1. Manifest Refraction			X		X		X		SOC[d]
2. BCVA (ETDRS)			X		X		X		
3. Visual Field			X		X		X		
4. Slit Lamp Exam			X		X		X		
5. IOP			X		X		X		
6. Pachymetry			X		X		X		
7. Anterior Segment OCT[g]			X		X		X		
8. Endothelial Cell Density			X	X	X	X	X	X	
9. Lens Status for Phakic Eyes[h]			X		X		X		
10. Dilated Fundus Exam *(incl. Vertical C/D Ratio)*			X		X		X		

Table 1: Assessment Schedule (Continued)

Activities	Enrollment[a]		Follow-Up Evaluation						
			Month 36 Visit (Day 1080 +/-90 days)		Month 48 Visit (Day 1440 +/-90 days)		Month 60 Visit (Day 1800 +/-90 days)		Un-scheduled Visit
	SE	FE	SE	FE	SE	FE	SE	FE	
11. Bleb and Seidel Test			X		X		X		SOC[d]
12. Diplopia			X		X		X		
13. Motility			X		X		X		

SE = Study Eye; FE = Fellow Eye

[a] Enrollment may occur at any time prior to the close of the follow-up window for the post-operative Month 60 Visit. Subjects who have passed the timepoints for the Month 36 or Month 48 Follow-Up Visits, prior to enrolling in the PRESERFLO® MicroShunt Extension Study, may still be enrolled to complete the remaining post-operative visit(s). No study-specific assessments, procedures, or data collection shall be performed prior to obtaining informed consent.

[b] Medical/Surgical events occurring between completion of the INN-005 study i.e., the Month 24 Visit and enrollment in the Extension Study, are retrospectively collected. Events that are ongoing at the time of consent will be documented as AEs.

[c] The initial assessment at the time of enrollment includes only medications being taken at time of consent, and previously taken within 30 days of consent.

[d] No study assessments are required at unscheduled visits, and subjects should be assessed per the institutional standard of care (SOC).

[e] Adverse Events and medication changes occurring at any time throughout the duration of subject participation in the study shall be documented.

[f] It is recommended that Study Procedures be performed in the sequence listed in the Schedule of Events table. Visual field to be performed prior to dilation; Slit Lamp to be performed prior to IOP; IOP to be performed prior to Anterior Segment OCT and pupil dilation.

[g] Anterior Segment OCT is only required for subjects still implanted with a MicroShunt and is optional if the required equipment is not available.

[h] LOCS III (assessment of lens status) to be performed after dilation and before fundus exam.

4. TIME-RELATED TERMS

4.1. Baseline and Screening Visit

The *Baseline/Screening Visit* for this study is the same as the Screening Visit of the INN-005 study. The terms screening and baseline are used interchangeably in this SAP.

4.2. Study Day

The *study day* describes the post-operative day or the relative day of an observation starting with the surgery date of the INN-005 study designated as Study Day 0. Thus, the study day in this study will be consistent with that of the INN-005 study.

4.3. Analysis Visit and Analysis Window

Analysis visit is a timing variable to be used for analyses involving visits. Typically, for each analysis visit, an *analysis window* is set up to determine the analysis visit to which a measurement should be mapped. However, no study assessments are required at unscheduled visits; hence, the analysis visit of measurements is the same as the study visit at which the measurements were collected. The analysis window, specified in Table 2, will be used to categorize the timing of adverse events, serious adverse events and post-operative interventions that did not necessarily fall into the listed protocol visit windows.

Table 2: Analysis Visit and Visit Window

Analysis Visit Name (Target Day)	**Protocol Visit Window (for study measurements)**	**Analysis Window (for AEs, SAEs, interventions)**
Baseline (Screening)	[, -1]	[, -1]
Month 36 (Day 1080)	[990, 1170]	[781, 1170]
Month 48 (Day 1440)	[1350, 1530]	[1171, 1530]
Month 60 (Day 1800)	[1710, 1890]	[1531,]

5. GENERAL CONSIDERATIONS

There are two study groups in this study: treatment and control group. The treatment and the control group consist of all subjects who received PRESERFLO® MicroShunt device and trabeculectomy as part of the INN-005 study, respectively. All measures will be summarized by cohort and study group descriptively. Continuous variables will be summarized using descriptive statistics such as number of observations (n), mean, standard deviation, median, minimum, and maximum. Categorical variables will be tabulated using frequency (n) and percent (%).

Unless otherwise specified, the following conventions will be followed in reporting the decimal places.

Statistics	**How to report statistics**
Range (Low Value, High Value)	Recorded Decimal Places
Mean, Median	Recorded value + 1 Decimal Place
Confidence Interval, Standard Deviation, Standard Error	Recorded value + 1 Decimal Place
P-value	4 Decimal Places (ex. 0.0021)

Due to the nature of this study, there is no (confirmatory) label-claiming hypothesis testing foreseen in a strict statistical sense. Analyses are descriptive in nature and 95% (Wald) confidence intervals are used for exploratory purposes.

All data summary/analysis will be performed using SAS Version 9.4 or later. Individual data, including relevant derived variables, will be listed.

Additional analyses not specified in this SAP, including consistent cohort analysis, may be conducted if deemed necessary and will be documented in the CSR.

5.1. Adjustments for Covariates

The effectiveness and safety outcome measures will be summarized descriptively; hence no covariate adjustment will be necessary.

5.2. Handling of Missing Data

5.2.1. Safety Outcome Measures

For both descriptive summaries and exploratory analyses of ECD measures and ECD response status, subjects in whom the anterior chamber is entered for non-MicroShunt related indications (e.g., reoperation with trabeculectomy, implantation of other glaucoma drainage device, iridotomy/iridectomy, cataract extraction), and subjects who had the entire MicroShunt explanted, will be censored (i.e., treated as missing) from analysis after the qualifying event. No imputation will be performed on missing or censored ECD data.

Descriptive summaries of other safety measures will be based on observed data only. No imputation of missing scores will be implemented.

5.2.2. Effectiveness Outcome Measures

For subjects who received any qualified glaucoma reoperations, unless otherwise specified, their IOP data collected after the events will be censored (treated as missing) in effectiveness outcome measure analyses. The missing IOP response statuses due to the IOP being censored will be imputed using the Baseline-Observation-Carried-Forward (BOCF) approach (i.e., a non-responder imputation). Missing IOP measure and IOP response statuses due to other reasons will not be imputed as analyses will be based on only observed cases.

5.3. Multi-Center Studies

This is a multicenter study with approximately 25 centers, among which a maximum of 5 centers are planned to be outside of the United States (EU sites). Descriptive summaries of the demographics and baseline as well as effectiveness results may be provided for the United States (US) population and the EU population, respectively.

5.4. Multiple Comparisons / Multiplicity

For this study, there is no (confirmatory) label-claiming hypothesis testing foreseen. Analyses are descriptive in nature and 95% confidence intervals from statistical models are used for exploratory purposes. Hence, no multiplicity adjustment is needed.

5.5. Interim Analysis and Data Safety Monitoring Board

An annual interim analysis will be performed after the last subject completes his/her Month 36 and Month 48 Visit using all available data from these subjects. Descriptive statistics (mean, median, standard deviation, minimum, and maximum for continuous variables; counts and percentages for categorical variables) will be used to summarize the demographic data, screening characteristics, observed IOP, observed IOP response status, use of glaucoma medications, slit lamp examination findings, fundus examination findings, specular microscopy, ocular AEs, and SAEs for each study group.

A Data Safety Monitoring Board (DSMB) will meet at regularly scheduled intervals i.e., at least annually, to review the accumulated safety data for this trial. This board will share their observations and recommendations regarding safety trends based on safety data analysis reports provided at each meeting (with as much up-to-date information as possible). The meeting format, membership, and activities will be similar to that for the INN-005 study.

6. ANALYSIS POPULATION

Due to the timing gap between the INN-005 and the INN-005-EXT study, very few subjects who were randomized in Phase I of the INN-005 study are actually eligible for the INN-005-EXT study. Therefore, all analysis populations in the INN-005-EXT will be based on subjects who were randomized in Phase II of the INN-005 study.

6.1. Enrolled Population

The Enrolled population will include all subjects who were randomized in Phase II of the INN-005 study, completed the Month 24 Visit of the INN-005 study, signed the Informed Consent Form for the INN-005-EXT study, and enrolled in the study. This will be the primary analysis population; all effectiveness and safety outcome measure analyses will be based on the Enrolled population.

6.2. Per-Protocol Population (PP)

The Per-Protocol (PP) population will include enrolled subjects who were randomized in Phase II of the INN-005 study excluding those that had any protocol deviations that would impact the effectiveness outcome measures.

The PP population will be used to analyze the secondary effectiveness outcome measures. InnFocus[ĀMNSĀ?N@ĀQDFFĀL@PD@QĀ<FF@ĀDDNNDIIFMĀ<HSĀD?@@NMĀNIĀ>F@Ā?@ĀRĀ from the PP. The PP population analysis will be conducted once all Month 60 visit data is collected.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

Subject disposition will be summarized cumulatively for enrolled subjects by study group and overall. The summary will include the number and percentage (based on total number of subjects enrolled) of subjects in each of the following categories:

- Enrolled population
- Completed Month 36 Visit
- Discontinued prior to Month 36 Visit
- Completed Month 48 Visit
- Discontinued prior to Month 48 Visit
- Completed Month 60 Visit
- Discontinued prior to Month 60 Visit

A subject is considered to have discontinued the study if he/she withdraws participation or is withdrawn from the study by the Investigator, is deceased, or is Lost-to-Follow-up. The primary reason for exiting the study will also be provided.

7.2. Demographics and Screening Characteristics

Subject demographics and screening characteristics will be descriptively summarized for the Enrolled Population by study group and overall. Subject demographics and screening characteristics will also be summarized by countries (US or EU) separately. Specifically, for subject demographics, the following variables will be summarized:

- Age at INN-005 study Screening >IHNDHOIOMĀ<HBĀD>NĀ*Ā+SĀ@ĀMĀILĀVĀ('Ā years). Note: the continuous Age variable will be calculated for each subject by (Date of INN-005 study Screening Visit WDate of Birth + 1) ÷ 365.25 and rounded down to the nearest integer.
- Sex (categorical: Male or Female)
- Ethnicity (categorical: Hispanic/Latino or Not Hispanic/Latino)
- Race (categorical: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, or Other)
- Study eye (categorical: OD or OS)

For screening characteristics, the following variables will be summarized for the enrolled population in each cohort by study group and overall:

- The mean diurnal IOP at INN-005 study Screening (continuous and categorical: < 18 GG1B "ĀVĀ$)ĀGGand +Ā%$ĀGG1BLĀVĀ%$ĀGG1B!
- The number of glaucoma medications in use at INN-005 study Screening (continuous and categorical: 0-6)

- Lens type at INN-005 study Screening (categorical: phakic or pseudophakic/aphakic)
- BCVA ETDRS at INN-005 study Screening (categorical)
- Endothelial cell density (cells/mm^2) at the INN-005 study Screening (continuous)
- Glaucoma severity classification at the INN-005 study Screening based on visual field mean deviation (categorical: early: -6.00 dB to -3.00 dB, moderate: -12.00 dB to -6.01 dB, advanced: -20.00 dB to -12.01 dB, or severe: < -20.00 dB)

7.3. Ocular Medical and Surgical History

For this study, the history includes ocular medical treatments, medication changes, any glaucoma reoperations, and surgical events for both the study and fellow eye occurring in the period between the completion of the last INN-005 visit (i.e., Month 24 Visit) and enrollment in the study. The history also includes adverse events (AEs) that occurred and resolved during this period.

For this study, medical and surgical history and adverse events will be mapped into a coded term by a Santen Clinical Scientist based on a review of all AE description records before the database lock.

The medical and surgical history will be summarized for the Enrolled Population. Subjects reporting any medical and surgical history at the Enrollment Visit will be tabulated by coded terms for each study group and overall.

7.4. Protocol Deviations

In this study, protocol deviations are categorized as follows:

- Assessment Not Performed Per Protocol
- Inclusion or Exclusion Criteria
- Informed Consent
- Missed Assessment
- Missed Visit
- Out of Window Visit
- Other

A protocol deviation is considered *major* if it adversely affects the risk/benefit ratio of the study, the rights, safety, or welfare of the participants or others, or the integrity of the study. A protocol deviation that is not major is a *minor* protocol deviation. A *fellow eye protocol deviation* is one that only impacts the fellow eye.

InnFocus[ĀMNSĀNG@ĀQDFFĀL@PĀDQNĀ=HĀPD<NDIHMĀ<GDĀ?@ĀGDMNĀJaĀ major protocol deviations prior to database lock. All enrolled subjects with any major protocol deviation(s) will be tabulated by deviation category for each study group and overall. In addition, the following listings will be provided: (1) all major protocol deviations, (2) subjects excluded from the per

protocol population (at Month 60 analysis), (3) all minor protocol deviations, and (4) fellow eye protocol deviations.

7.5. Concomitant Medications

For this study, a concomitant medication is defined as any non-glaucoma medication, like ocular medicine and supplements (including vitamins), taken during the study, at the time of consent, or within 30 days of consent. Medications that were administered more than 30 days prior to the consent to address an ongoing AE will also be considered as concomitant medication. Glaucoma medications in this study will not be considered as concomitant medications and will be analyzed separately. Concomitant medications will be mapped to preferred names in a similar manner as it was done in the INN-005 study.

Concomitant medications will be summarized for the Enrolled population. Subjects taking any concomitant medications will be tabulated by preferred drug name for each study group and overall. A subject will be counted at most once for each concomitant medication, even if the subject took the same concomitant medication on multiple occasions. In addition, concomitant medications will also be listed, separately.

8. EFFECTIVENESS ANALYSES

8.1. Effectiveness-Related Definitions

8.1.1. Study Eye and Fellow Eye

The study eye of a subject is the eye that received either the PRESERFLO® MicroShunt with MMC or underwent trabeculectomy with MMC in the INN-005 study. Hence, the study eye in this study is the same as the study eye in the INN-005 study. The other eye is the non-study eye, or the fellow eye.

8.1.2. Screening Score

For any measure, the screening values are those that were obtained at the Screening Visit of the INN-005 clinical study. The terms screening and baseline are used interchangeably in the SAP.

8.1.3. Change (and Percent Change) from Screening

The change and the percent change from screening in a measure at a post-operative follow-up visit will be derived as:

- Change = (Score at the follow-up Visit) W(Screening Score)
- Percent Change from Screening = 100 × Change / (Screening Score)

8.1.4. Post-operative Interventions

At post-operative follow-up visits, interventions can be performed to assure a diffuse bleb and lower IOP. Interventions can be classified as either glaucoma medications or non-medication physical interventions.

8.1.4.1. Glaucoma Medications

This study collects data on glaucoma medications for both study eye and fellow eye at the Enrollment Visit and all the follow-up visits for the duration of the study. The number of glaucoma medications at a visit will be derived as the number of glaucoma medication classes a subject was receiving at that visit per Guidelines on Design and Reporting of Glaucoma Surgical Trials by World Glaucoma Association (2008). For example, if a subject was receiving a glaucoma medication of class A, a glaucoma medication of class B, together with a glaucoma combination therapy of classes A+B at 36 months, then the number of glaucoma medications at 36 months will be counted as 2 (A and B) for this subject. The WHODrug ATC Level 4 will be used to determine the primary glaucoma medication class (e.g., Beta blocking agents, Carbonic anhydrase inhibitors, Parasympathomimetics, Prostaglandin analogues, or Sympathomimetics in glaucoma therapy). For a glaucoma combination therapy that consists of two glaucoma medications of different classes, the secondary glaucoma medication class(es) will be determined by a Santen Clinical Scientist based on a review of all coded glaucoma medication records before the database lock. The washout time for each medication is to be incorporated; in the case where a subject discontinued a medication shortly before the screening or a post-operative follow-up visit (i.e., Month 36, Month 48, or Month 60)"Ā<ĀMO=E@>NĀQDIHĀMQ@DĀXĀHY@ĀA> the medication if the time from discontinuation to the corresponding study visit is less than the

washout period for that medication. The washout period for each medication is documented in the Appendix 1.

8.1.4.2. Physical Interventions

8.1.4.2.1. Glaucoma Reoperations

Secondary surgical procedures which will be considered as failures of the INN-005 study original procedure include:

1. Trabeculectomy
2. Placement of a drainage device
3. Bleb revision (other than needling)
4. Explantation or repositioning of the PRESERFLO® MicroShunt
5. Iridectomy
6. Resuturing of the scleral flap
7. Glaucoma laser procedure (e.g., trabeculoplasty, iridotomy)
8. Other glaucoma surgery to reduce IOP

8.1.4.2.2. Other Glaucoma Procedures

Physical interventions will be performed to reduce the IOP, but will not be considered as failures of the INN-005 study original procedure, as follows:

1. XNeedling the blebYĀNPĀQILG@Ā3LND<FĀKGLĀ@N@ĀMOL@AĀNC@Ā=F@=
2. Needling with an injected antifibrotic
3. Laser removal of the blockage at the tip of the PRESERFLO® MicroShunt or at the Anterior Chamber entry point for a trabeculectomy

8.1.4.2.3. Other Post-Operative Intervention Procedures

Other post-operative intervention procedures that can be performed by the Investigator include:

1. Eye massage
2. Laser suture lysis in a trabeculectomy

8.1.4.3. Classification of Post-Operative Interventions

Qualifying glaucoma-related post-operative intervention includes glaucoma reoperations listed in Section 8.1.4.2.1, needling procedure and laser treatment listed in Section 8.1.4.2.2, use of a viscoelastic to limit aqueous flow, laser suture lysis in a trabeculectomy, and the introduction of any glaucoma medication. Eye massage will not be considered as a qualifying glaucoma-related post-operative intervention.

8.1.5. Treatment Success and Failure

Total treatment success is defined as a subject with 20% or more reduction in IOP from the INN-005 study Screening to 60 months of post-operative follow-up without increasing the number of glaucoma medications.

Complete treatment success is defined as a subject with 20% or more reduction in IOP from the INN-005 study Screening without any glaucoma medication.

Qualified treatment success is defined as a subject with 20% or more reduction in IOP from the INN-005 study Screening with glaucoma medication supplement. The number of glaucoma medications should not exceed that at the INN-005 study Screening.

For this study, a *failure* is defined as a subject with one or more of the following:

1. No light perception vision confirmed on two consecutive study follow-up visits (i.e., two consecutive annual scheduled visits).
2. IOP persistently below 6mmHg (defined as an intraocular pressure below 6mm that is present on two consecutive scheduled/unscheduled visits).
3. Glaucoma Reoperations listed in Section 8.1.4.2.1.
4. Introduction of an oral carbonic anhydrase inhibitor.

The glaucoma needling procedures, listed in Section 8.1.4.2.2, and use of a viscoelastic to limit aqueous flow will be reported as *complications* but will not be considered failures, while other procedures, listed in Section 8.1.4.2.3, will not be considered as failures or complications.

8.2. Analyses of Primary Effectiveness Outcome Measure

There is no primary effectiveness outcome measure in this study.

8.3. Analysis of Secondary Effectiveness Outcome Measures

Unless specified otherwise, effectiveness analyses will be performed on the study eye, based on the Enrolled population, and summarized by study group. The analysis of the IOP secondary outcome measure will also be performed on IOP data, any of which will be censored (i.e., treated as missing) after a procedure or an event described in the definition of a failure in Section 8.1.4.3. Details on how to handle missing values are described in Section 5.2.1.

At each interim analysis, all effectiveness outcome measures will be summarized with descriptive statistics based only on observed cases.

8.3.1. Total Treatment Success Rate

The total treatment success rate is ?@ADH@M?ĀNC@IĀNDIHĀIAĀSMS@?ĀQCĀVĀ%#ĀĀreduction in IOP from the INN-005 study Screening Visit to 60 months of post-operative follow-up without increasing the number of glaucoma medications.

The analysis of the treatment success rate will be performed on both the Enrolled and PP population at 60 months, separately. For each analysis population, the number and percentage of 60-month IOP responders and the 95% confidence intervals will be calculated for each study group. Subjects with secondary surgical procedures or events by 60 months that fall into the

failure category in Section 8.1.4.3 will be considered as non-responders. Additionally, the rate difference and the 95% confidence interval of the rate difference will also be provided for the exploratory purpose.

Since the comparison between treatment group and control group at each follow-up visit will be exploratory, no multiplicity adjustment will be made. Missing IOP values and IOP response status at each visit will not be imputed.

For the exploratory purpose, all treatment failures will be tabulated by categories of failure (i.e., having less than 20% reduction in IOP or failure categories of the original device/procedure as defined in Section 8.1.4.3) for each study group. The number and percentage of subjects who experienced each category of failure will be calculated. Subjects can be listed in multiple categories if they experienced more than one failure category concurrently.

8.3.2. Intraocular Pressure (IOP)

IOP data collected in both the INN-005 study and INN-005-EXT study on the Enrolled Population will be summarized descriptively by visits (INN-005 study Screening Visit and all postoperative follow-up visits). Subjects with any glaucoma reoperations will have their IOP data censored (i.e., treated as missing) and no imputation will be implemented. Change and percent change from the INN-005 study Screening in IOP will also be summarized for each study visit. In addition, the difference in mean percent change from Screening in IOP between study group and the corresponding 95% confidence intervals will be provided.

8.3.3. Qualifying Glaucoma-related Post-operative Interventions

The number and percentage of subjects with any qualifying glaucoma-related post-operative intervention by 36 months/48 months/60 months and the corresponding 95% confidence interval for such intervention rate will be calculated for each study group. Additionally, the rate difference and the corresponding 95% confidence interval of the rate difference will also be provided.

8.3.4. Glaucoma Medications

Glaucoma medications will be summarized descriptively by study group and study visits (Month 36, Month 48, and Month 60 visit). Number and percentage of subjects who are taking a given glaucoma medication will be provided for each study group at each study visit.

Number of glaucoma medication in use, change and percent change in number of glaucoma medications from the INN-005 study Screening will be summarized descriptively for each study group.

In addition to the glaucoma medication outcome measure, the following responder rates will also be summarized descriptively by study group and by study follow-up visits:

- Taking no glaucoma medications
- Having a V50% reduction in number of glaucoma medications from the INN-005 study Screening

The number, percentage of responders and the 95% confidence interval for the responder rates will be calculated for each study group. Additionally, the rate differences and their corresponding 95% confidence intervals will also be provided.

8.3.5. Treatment Success

Proportion of study eyes considered a treatment success (total, complete, and qualified) will be summarized descriptively by study group and study visit. The number and percentage of subjects whose study eyes meet the treatment success criteria and the corresponding 95% confidence interval will be calculated for each study group. Additionally, the rate difference and the 95% confidence interval of the rate difference will also be provided.

8.4. Subgroup Analyses

Due to the small number of subjects who will enrolled in the INN-005-EXT study, no subgroup analysis is planned for this study.

9. SAFETY ANALYSES

9.1. Safety-Related Definitions

9.1.1. Adverse Event

Under Protocol INN-005-EXT Section 12, an adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or procedure. Any ocular AE that occurred prior to but is still ongoing at the time of consent or occur at any time after the date of informed consent through the last study visit will be collected for the INN-005-EXT study. Non-ocular serious adverse events (SAEs), whose definition is listed below, will also be collected; however, non-ocular non-serious adverse events will not be collected.

The severity of each AE will be graded by the Principal Investigator as Mild, Moderate, or Severe. AEs will also be rated by the Investigator as to their causality/relationship to the study procedure and to the study device.

Each AE will be mapped into a coded term by a Santen Clinical Scientist based on a review of all AE description records before the database lock.

9.1.1.1. Anticipated Adverse Event

Anticipated adverse events include those that might reasonably be expected to occur in this study because they are associated with glaucoma, glaucoma surgery, and/or prior cataract surgical procedures. A list of post-operative anticipated adverse events are available in section 13.1 and section 13.2 of the Clinical Investigation Plan (CIP) INN-005-EXT.

9.1.1.2. Serious Adverse Event

An AE will be counted as a *serious adverse event* (SAE) if the Principal Investigator selected X8@ŌYĀNIĀNC@@MĀKOHĀZ[ĀIHĀNC@electronic Case Report Form (eCFR). Any AE is considered a SAE if it fulfills one or more of the following criteria:

a. Led to death
b. Led to serious deterioration in the health of the subject, that either resulted in
    1. A life-threatening illness or injury
    2. A permanent impairment of a body structure or a body function
    3. In-patient or prolonged hospitalization
    4. Medical or surgical intervention to prevent left-threatening illness or injury or permanent impairment to a body structure or a body function
a. Led to fetal distress, fetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP (Clinical Investigational Plan, i.e., the study protocol), without serious deterioration in health, is not considered a serious adverse event.

A Sight-Threatening Adverse Event (see definition below) may be considered to be a sub-category of SAEs due to the potential to lead to irreversible blindness if left untreated.

9.1.1.2.1. Sight-Threatening Serious Adverse Event

An AE will be counted as a *sight-threatening AE* if the Principal 2HP@[illegible] Threat@H[illegible]ption as the reason for the serious adverse event on the AE eCRF. Sight-threatening AEs include but are not limited to events such as endophthalmitis, corneal decompensation, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment, and aqueous misdirection.

9.1.1.3. Unanticipated Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on the health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. An AE will be counted as an *unanticipated adverse device effect* if the Principal Investigator answered Z8@M[ĀNIĀNC@Ā-0Ā eCRF.

9.1.2. Safety Measures

Table 3 lists the measures to be evaluated for this study.

Table 3: Safety Assessments

Safety Measures	Note
Slit Lamp Exam	Slit-lamp examinations will be performed with anterior chamber cells, anterior chamber flare being graded on a standardized scaling as listed in Section 9.4.3 of the CIP INN-005-EXT. The presence of corneal edema, encapsulated bleb, hyphema, hypopyon, iris atrophy, pigment dispersion, pupillary irregularities, tube exposure and other slit lamp findings will be evaluated and noted.
Best Corrected Visual Acuity	Best Corrected Visual Acuity (BCVA) should be measured using Early Treatment of Diabetic Retinopathy Study (ETDRS) charts at 4 meters (13 feet and 1.5 inches, or 157.5 inches) in both eyes and reported in LogMAR units.
Visual Field	Visual fields are to be performed with a non-dilated pupil unless, in the opinion of the Investigator, the pupil is so miotic that dilation is required (e.g., < 3 mm). If possible, measurements should be performed using the same instrument that acquired the INN-005 study Screening measurements.

Table 3: Safety Assessments (Continued)

Safety Measures	Note
Lens Status for Phakic Eyes	LOCS III classification system should be used to evaluate the lens for the presence of cataract for subjects with a phakic study eye.
Pachymetry	Three measurements are taken utilizing an electronic ultrasound pachymeter to determine central corneal thickness. If possible, measurements should be performed using the same instrument that acquired the INN-005 study Screening measurements.
Anterior Segment OCT	Anterior Segment Optical Coherence Tomography (OCT) should be performed on subjects who still have the PRESERFLO® MicroShunt device implanted, if equipment available.
Endothelial Cell Density	Central enthothelial cell density (ECD) images will be collected for study and fellow eyes. ECD can be taken before Anterior Segment OCT is completed. All readings will be conducted by the Corneal Image Analysis Reading Center.
Dilated Fundus Exam	The appearance of the optic disc, macula, vessels, and periphery should be evaluated. A measurement of vertical cup-to-disc ratio should be made.
Bleb and Seidel Test	A Seidel test will be used to detect ocular perforation or a wound leak.
Manifest Refraction	Manifest refraction will be performed.
Diplopia	Subjects will be assessed for diplopia.
Ocular Motility Test	Ocular motility will be evaluated.

The safety-related measures collected in this study include ocular AEs, SAEs, Best Corrected Visual Acuity (BCVA), visual field, results of slit lamp, fundus examination, specular microscopy (endothelial cell density), lens evaluation classification system (LOCS III), and the incidence of surgical complications and adverse events (AEs), Anterior Segment OCT, Bleb and Seidel test, manifest refraction, diplopia, and ocular motility. All safety-related measures are collected only on the study eye, except AEs, SAEs and Endothelial Cell Density, which will be collected for both eyes.

9.2. Analysis of Safety Outcomes

All the safety-related outcome measures will be summarized descriptively for each cohort of the Enrolled population by study group.

9.2.1. Analysis of Primary Safety Outcome Measure

The analysis of the primary safety outcome measure, the incidence of sight-threatening AEs, will be performed on the Enrolled population. The number and percentage of subjects who experienced any sight-threatening AEs, and the 95% exact (Clopper-Pearson) confidence intervals of the incidence rate will be computed for each study group at each study follow-up visit. Additionally, the rate differences and their corresponding 95% exact (Chan-Zhang) confidence interval of the rate differences will also be provided.

The data listing of subjects who experienced at least one sight-threatening AE will be provided.

9.2.2. Analysis of Secondary Safety Outcome Measures

9.2.2.1. Adverse Events

Subjects with any ocular AEs, SAEs, and UADEs will be tabulated and summarized by type of AEs for each study group. Ocular AE summaries (i.e., the number and percentage of subjects reporting to at least one AE) will also be provided for ocular AEs judged to be device- or procedure-related.

AEs, SAEs, and UADEs, if any, will be listed separately.

9.2.2.2. Best-Corrected Visual Acuity (BCVA)

Best corrected visual acuity (BCVA), changes and percent changes in BCVA from the INN-005 study Screening, collected in both INN-005 and INN-005-EXT study, will be summarized descriptively by study group and study follow-up visit. Number and percentages of subjects with a BCVA AE, (a BCVA loss of 2 lines, i.e., 10 ETDRS letters, or more from the INN-005 study Screening on 2 consecutive standard follow-ups 90 days or more after the original procedure will be provided for each study group at each study follow-up visit. However, a loss of BCVA in conjunction with posterior capsule opacification, followed by Nd:YAG capsulotomy and improvement of BCVA will not be considered as an adverse event.

9.2.2.3. Endothelial Cell Density

The endothelial cell density (ECD), change, and percent change in ECD from INN-005 study Screening will be descriptively summarized by study group and by study follow-up visits for study eyes and fellow eyes, separately.

In addition to ECD measures, the following ECD-related responder rates will also be summarized descriptively by study group and by study follow-up visits:

- 1<PDHĀBV&#ĀL2@>NDIHĀDHĀ0./ĀG@ĀMGĀLNĀ4 -005 study Screening
- Having ECD measure less than 1000 cells per square millimeter

The number, percentage of responders and the 95% confidence interval for the responder rates will be calculated for each study group. Additionally, the rate differences at 36 months, 48 months, and 60 months and their corresponding 95% confidence intervals will also be provided.

To further assess the ECD data, descriptive summaries and analyses of ECD measures and ECD response status will also be conducted on the censored population where subjects whose anterior chamber is entered for non-MicroShunt related indications (e.g., reoperation with trabeculectomy, implantation of other glaucoma drainage device, iridotomy/iridectomy, cataract extraction) and subjects who have their entire MicroShunt explanted will have their ECD data censored (i.e., treated as missing) from analysis after the qualifying event.

9.2.2.4. Post-Operative Lens Opacities

Number and percentage of subjects who developed post-operative lens opacities or experienced worsening (i.e., 0.7 units increase from INN-005 study Screening) of pre-existing lens opacities

(phakic lens only) as assessed by LOCS III classification system by study follow-up visit will be compared between study groups. Rate differences at each study follow-up visit and their corresponding 95% confidence interval will be provided.

The data listing of these subjects will be provided.

9.2.2.5. Glaucoma Reoperation Due to Complication

For exploratory purposes, number and percentage of subjects with any glaucoma re-operation due to complication (not due to high IOP) by 36 months, 48 months and 60 months will be compared between study groups. Rate differences at those visits and their corresponding 95% confidence interval will be provided.

The data listing of subjects who experienced any glaucoma reoperation including the reason for glaucoma reoperation will be provided.

9.2.2.6. Other Safety Analyses

Slit lamp, fundus examination, and other ophthalmic examination results at Screening and at study follow-up visits if applicable will be tabulated such that the number and percentage of subjects in each category will be summarized by study group and by study follow-up visit. The visual field mean deviation and change from the INN-005 study Screening will be presented descriptively by study group and by visit. Pachymetry and change from the INN-005 study Screening will be summarized descriptively by study group and by visit.

APPENDIX 1. WASHOUT PERIODS FOR MEDICATIONS

Medication Class	Minimum Washout Period
Parasympathomimetics (e.g., pilocarpine [Isopto® Carpine], carbachol [Isopto® Carbachol])	4 days
Carbonic Anhydrase Inhibitors (e.g., acetazolamide [Diamox®], dorzolamide hydrochloride [Trusopt®], brinzolamide [Azopt®])	4 days
Sympathomimetics (e.g., dipivefrin [Propine®], epinephrine [Epifrin®])	2 weeks
Alpha-agonists (e.g., apraclonidine [Iopidine®], brimonidine tartrate [Alphagan®, Alphagan P®], brominidine tartrate and brinzolamide [Simbrinza®])	2 weeks
Beta-adrenergic blocking agents (e.g., timolol [Timoptic®, Betimol®, Timoptic XE®, Istalol®], timolol maleate and dorzolamide (Cosopt®], timolol maleate and brimonidine tartrate [Combigan®], levobunolol [Akbeta®, Betagan®], betaxolol [Betoptic®, Betoptic-S®], metipranolol [Opti-Pranolol®], carteolol [Ocupress®])	4 weeks
Prostaglandin analogs (e.g., latanoprost [Xalatan®], travoprost :6L<P<N<H;T Ā=DN J LMN Ā:OG DBHT;"ĀN<AIMNĀ 9N<U;!Ā	4 weeks

APPENDIX 2. SAS CODE FOR ANALYSIS OF THE PRIMARY SAFETY OUTCOME MEASURE

```
/* Sample code for the primary analysis of sight-threatening
incidence */


PROC FREQ data=DataP2 order=data
   TABLES treatment*AE_SighTreaten/ riskdiff (cl=exact);
   EXACT riskdiff(method=score);
   ODS output   RiskDiffCol1 = RiskDiffs
                PdiffCLs=exact_cz;
run;
```

This is a representation of an electronic record that was signed electronically
and this page is the manifestation of the electronic signature.

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