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Please see attached, the following document:

Official Title:	**A Randomized Study Comparing the Safety and Efficacy of the InnFocus MicroShunt® Glaucoma Drainage System to Standard Trabeculectomy In Subjects with Primary Open Angle Glaucoma**
Document:	Statistical Analysis Plan v1.11 (SAP)
Study ID:	**INN-005**
Dated:	**22Jul2019**
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Thank you,

DocuSigned by Haydee Frost
Haydee Frost
I am the author of this document
2022-Jul-11 | 11:40 EDT
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Haydee Frost
Clinical Research Associate
InnFocus, Inc. a Santen Company

A Randomized Study Comparing the Safety and Efficacy of the InnFocus MicroShunt® Glaucoma Drainage System to Standard Trabeculectomy In Subjects with Primary Open Angle Glaucoma

Protocol INN-005
Rev. 072117

Statistical Analysis Plan v1.11

InnFocus, Inc.

[redacted]

CONFIDENTIAL

APPROVAL SIGN-OFF SHEET

A Randomized Study Comparing the Safety and Efficacy of the InnFocus MicroShunt® Glaucoma Drainage System to Standard Trabeculectomy in Subjects with Primary Open Angle Glaucoma

DE-128 Study INN-005

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REVISION HISTORY AND CHANGES:

Summary of changes for Revision 1.11 (July 2019) as compared to Revision 1.10 (June 2018):

Section	Changes	Rationale for Change
Approval Sheet	Updated Santen signatories	To reflect most current study personnel
1. Introduction	Specified that analysis will be conducted following completed 12-month visits, and including some available 24-month visit data	Clarified to indicate intended timing of primary endpoint analysis
1. Introduction	Specified that analyses described in the SAP supersede those described in the protocol	Clarified to indicate that this SAP describes the final analysis approach
4.1 Primary Effectiveness Endpoint	Added details on reflecting medication washout in the analysis	Added based on FDA feedback
4.4. Exploratory Effectiveness Analyses	Changed hypotony definition in exploratory analysis to <6 mmHg	Fixed error to be consistent with hypotony definition throughout the SAP and protocol
11.2 Demographics and Pre-operative Characteristics	Changed age calculation based on day of screening visit instead of day of surgery	Consistent with all other pre-operative characteristics, which are summarized by the measurement at the screening visit.
11.4. Sensitivity Analyses	Revised language for the tipping-point approach, including best-case and worstcase scenario	Clarified to indicate the approach for the tipping-point analysis
11.4.2. Sensitivity Analyses for Secondary Effectiveness Endpoint #1	Added section to describe additional Sensitivity Analyses for the Secondary Effectiveness Endpoint #1	Added sensitivity analyses are intended to assess the robustness of the Secondary Effectiveness Endpoint #1.
11.7. Subgroup Analyses	Specified that subgroup analysis of the primary endpoint for the intervention type of 'laser suture lysis' is not required	Laser suture lysis is specific to trabeculectomy arm only, and comparison between study groups is not meaningful
11.9.4. Endothelial Cell Density	Added a second censored population for analysis of Endothelial Cell Density measures	Analysis was requested by the Data Safety and Monitoring Board.
APPENDIX 5: Washout Periods for Medications	Added appendix to specify washout periods for glaucoma medications	Washout periods are included in the primary analysis, based on FDA feedback
Multiple	Formatting and non-substantive changes	Clarification/ ease of reading

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LIST OF ABBREVIATIONS

AC	Anterior Chamber
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCVA	Best Corrected Visual Acuity
BOCF	Baseline Observation Carried Forward
DSMB	Data Safety Monitoring Board
ECD	Endothelial Cell Density
EQ-5D-5L	General Health Questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
ISO	International Organization for Standardization
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
LOCS	Lens Opacities Classification System
POAG	Primary Open-Angle Glaucoma
PP	Per-Protocol
MD	Mean Deviation
MMC	Mitomycin C
OUS	Out of the United States
PMA	Pre-Market Approval
POAG	Primary Open-Angle Glaucoma
PRO	Patient Reported Outcomes
QoL	Quality of Life
SAP	Statistical Analysis Plan
TVT	Tube Versus Trabeculectomy
US	United States
VAS	Visual Analogue Scale
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be implemented to analyze the Phase II data from Protocol INN-005 Revision 072117 after all patients complete the 12-month visit. The available 24-month visit data will also be included in the analyses.

Any changes to this plan will be reflected in revisions (to this plan) before the Phase II database lock or documented in the clinical study report. Analyses described in the SAP supersede those described in the protocol.

2. STUDY OBJECTIVE

The study objective is to demonstrate the safety and effectiveness of the InnFocus MicroShunt for lowering intraocular pressure (IOP) in subjects with primary open-angle glaucoma (POAG) where the IOP is not controlled when using maximum tolerated glaucoma medications.

3. STUDY DESIGN

This is a prospective, randomized, controlled, single-masked, multicenter trial. Two study groups will be included in the study. The treatment group consists of subjects who receive the InnFocus MicroShunt with Mitomycin C (MMC). The control group consists of subjects who receive trabeculectomy with MMC.

The study consists of two phases. In the initial phase (Phase I), **102** subjects (68 treatments and 34 controls, 2:1 randomization ratio) were randomized. After 75 Phase I subjects (approximately 50 InnFocus treatments and 25 controls) completed the 3-month follow-up examination, all data was submitted to the FDA to request approval for expansion (Phase II) to the full study population of an additional **412** randomized subjects (approximately 309 treatments and 103 controls, 3:1 randomization ratio). Subsequently an expansion of Phase II was granted for another 102 subjects with the same randomization schedule (3:1) for a total of 514 Phase II subjects. Data from Phase I and Phase II is collected and managed at separate databases. Phase I subjects will be analyzed as a feasibility cohort separately from Phase II.

With a drop-out rate of 6% per year, approximately **480** randomized subjects in Phase II (360 in treatment group and 120 in control) are expected to have the **12**-month examination and **448** randomized subjects (336 in treatment group and 112 control) are expected to have the **24**-month follow-up examination.

The randomization will be stratified by investigational site and within-site by lens type, with a target of at least 60 randomized phakic eyes in the treatment group and 20 randomized phakic eyes in the control group at 24 months. Additionally, no study investigator or study site will exceed 25% of the total number of randomized investigational device or control subjects. For study sites with more than one investigator, the total randomization will not exceed 33% of the total number of randomized investigational device or control subjects.

The schedule of follow-up examinations and clinical parameters is in Appendix 1. Specifically, IOP measurements will be taken at 9:00AM ± 1.5 hours, 12:00PM ± 1 hour, and 4:00PM ± 2 hours at screening, 12 months, and 24 months and will be averaged to determine the mean diurnal IOP at

these visits. For standard post-operative IOP measurements at 1 day, 1 week, 4 weeks, 3 months, 6 months, and 18 months, only one IOP measurement at each visit will be needed. Every attempt should be made to have standard IOP measurements taken at the same time interval across these post-operative visits. Detailed information on all follow-up examinations and clinical parameters is provided in Protocol INN-005 Revision 072117.

4. EFFECTIVENESS ENDPOINTS

4.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as achieving at least a 20% reduction in mean diurnal IOP from screening at 12 months without increasing the number of glaucoma medications compared to screening. 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)[1]. 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 12 months, then the number of glaucoma medications at 12 months will be counted as 2 (A and B) for this subject. The WHO-DDE 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 Santen Clinical Scientist based on a masked 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 12 month visit, a subject will still be considered "on" 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 Appendix 5.

The percentage of subjects achieving the primary effectiveness endpoint (12-month IOP response rate) will be compared between the treatment group and control group. The corresponding statistical hypotheses are as follows:

$$\mathbf{H_{0E1}}: p_t - p_c < -0.15$$

$$\mathbf{H_{1E1}}: p_t - p_c \geq -0.15$$

The p_t and p_c are the 12-month IOP response rates for the treatment group and control group, respectively. The non-inferiority margin of 0.15 was established based on different response rates reported in published articles (Appendix 2). The treatment group will be concluded to be noninferior to the control group in terms of primary effectiveness endpoint if $\mathbf{H_{0E1}}$ is rejected based on one-sided significance level of 0.025, i.e., the lower bound of the two-sided 95% confidence interval for the rate difference $(p_t - p_c) \geq -0.15$.

The following secondary surgical procedures or events will be considered as failures for the primary effectiveness endpoint:

1. No light perception vision confirmed at two consecutive visits

2. Intraocular pressure persistently below 6 mmHg (defined as an IOP below 6 mmHg that is present at two consecutive follow-up visits after the 3-month visit)
3. Requiring a reoperation in the study eye in an operating room consisting of:
    a. Trabeculectomy
    b. Placement of a drainage device
    c. Bleb revision (other than needling)
    d. Explantation or repositioning of the InnFocus MicroShunt
    e. Iridectomy
    f. Resuturing of the scleral flap
4. Glaucoma laser procedure (e.g., trabeculoplasty, iridotomy)
5. Other glaucoma surgery to reduce IOP
6. Post-operative introduction of an oral carbonic anhydrase inhibitor

The procedures shown below will be reported as complications but will not be considered as failures for the primary effectiveness endpoint:

1. Needling of the bleb with or without the use of an injected antifibrotic
2. Laser removal of blockage at the tip of the InnFocus MicroShunt or at the anterior chamber (AC) entry point for a trabeculectomy
3. Use of a viscoelastic to limit aqueous flow

The following procedures will not be considered as failures for the primary effectiveness endpoint or complications but will be documented:

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

4.2. Secondary Effectiveness Endpoint #1

The first secondary endpoint is the mean diurnal IOP change from screening at 12 months (i.e., mean diurnal IOP at 12 months – mean diurnal IOP at screening) between the treatment group and control group.

The corresponding statistical hypotheses are as follows:

$$\mathbf{H_{0E2a}}: \mu_t - \mu_c > 2.5 \text{ mmHg}$$

$$\mathbf{H_{1E2a}}: \mu_t - \mu_c \leq 2.5 \text{ mmHg}$$

The μ_t and μ_c are the mean diurnal IOP changes from screening at 12-months for the treatment group and control group, respectively. The non-inferiority margin of 2.5 mmHg was determined based on Gedde's tube versus trabeculectomy (TVT) study[2,3]. The treatment group will be concluded to be non-inferior to the control group in reducing the IOP if the null hypothesis ($\mathbf{H_{0E2a}}$) is rejected at a significance level adjusted based on a Hochberg step-up procedure specified in Section 11.5, i.e., the upper bound of the multiplicity-adjusted two-sided confidence interval for the mean difference ($\mu_t - \mu_c$) $\leq$ 2.5 mmHg.

4.3. Secondary Effectiveness Endpoint #2

The second secondary endpoint is having any post-operative intervention by 12 months (12-month post-operative intervention), where post-operative intervention is defined as occurrence of any of the following after the study surgery:

1. A reoperation in the study eye in an operating room consisting of:
    a. Trabeculectomy
    b. Placement of a drainage device
    c. Bleb revision (other than needling)
    d. Explantation or repositioning of the InnFocus MicroShunt
    e. Iridectomy
    f. Resuturing of the scleral flap
2. Glaucoma laser procedure (e.g., trabeculoplasty, iridotomy)
3. Other glaucoma surgery to reduce IOP
4. Needling of the bleb with or without the use of an injected antifibrotic
5. Laser removal of blockage at the tip of the InnFocus MicroShunt or at the AC entry point for a trabeculectomy
6. Use of a viscoelastic to limit aqueous flow
7. Laser suture lysis in a trabeculectomy
8. Medication intervention: Post-operative introduction of any glaucoma medication

The percentage of subjects receiving any post-operative intervention by 12 months (12-month intervention rate) will be compared between the treatment group and control group. The corresponding statistical hypotheses are as follows:

$$\mathbf{H_{0E2b}}: q_t - q_c > 0.15$$

$$\mathbf{H_{1E2b}}: q_t - q_c \leq 0.15$$

The q_t and q_c are the 12-month intervention rates for the treatment group and control group, respectively. The non-inferiority margin of 0.15 was established based on different intervention rates reported in published articles (Appendix 3). The treatment group will be concluded to be noninferior to the control group in terms of this secondary effectiveness endpoint if $\mathbf{H_{0E2b}}$ is rejected at a significance level adjusted based on a Hochberg step-up procedure specified in Section 11.5, i.e. the upper bound of the multiplicity-adjusted two-sided confidence interval for the rate difference $(q_t - q_c) \leq 0.15$.

4.4. Exploratory Effectiveness Analyses

For exploratory purposes, the following exploratory effectiveness analyses will be performed. No multiplicity adjustment is needed for these exploratory analyses.

- IOP-related:
  - Mean diurnal IOP change from screening at 24 months;
  - 24-month IOP response: Achieving ≥ 20% reduction in mean diurnal IOP from screening at 24 months without increasing the number of glaucoma medications compared to screening;
  - Complete IOP response at 12 months (24 months): Achieving ≥ 20% reduction in mean diurnal IOP from screening with no glaucoma medication use at 12 months (24 months); ○ IOP 6-18 response at 12 months (24 months) for subjects with mean diurnal IOP

    > 21 mmHg at screening: Achieving mean diurnal IOP ≥ 6 mmHg and ≤ 18 mmHg at 12 months (24 months), without increasing the number of glaucoma medications compared to screening;
  - ○ IOP 6-15 response at 12 months (24 months) for subjects with mean diurnal IOP

    > 18 mmHg at screening: Achieving mean diurnal IOP ≥ 6 mmHg and ≤ 15 mmHg at 12 months (or 24 months), without increasing the number of glaucoma medications compared to screening;
- Glaucoma medication related:
  - Change from screening in the number of glaucoma medications in use at 12 months/18 months/24 months;
  - Having ≥ 50% reduction from screening in the number of glaucoma medications in use at 12 months/18 months/24 months;
  - Having no use of glaucoma medications at 12 months/18 months/24 months;
- Intervention related:
  - 18-month (24-month) post-operative intervention: Having any post-operative intervention by 18 months (24 months);
  - 12-month/18-month/24-month post-operative non-medication intervention: Having any post-operative intervention listed in Section 4.3 except the medication intervention (non-medication intervention) by 12 months/18 months/24 months;
  - Time to first post-operative intervention by 12 months/18 months/24 months; ○ Time to first post-operative non-medication intervention by 12 months/18 months/24 months;

- Others:
  - Time to recovery of visual acuity after study surgery by 12 months/18 months/24 months, where recovery is defined as the best-corrected visual acuity (BCVA) returned to screening BCVA;
  - Time to failure by 12 months/18 months/24 months: time from study surgery to glaucoma reoperation, loss of light perception vision, or the first of 2 consecutive scheduled visits after 3 months in which the subject showed persistent hypotony (i.e., IOP < 6 mmHg) or inadequately reduced IOP (i.e., IOP ≥ 21 mmHg or reduced < 20% from screening). The mean diurnal IOP at 12 months and 24 months and standard IOP measurements at other scheduled post-operative visits will be used as the IOP score for the time-to-failure endpoints.

5. SAFETY MEASURES

Safety measures include 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) as listed in Section 11.0 of Protocol INN-005 Revision 072117.

Within the descriptive summary of safety measures, the following will be calculated:

- Proportion of study eyes having a BCVA loss of 2 lines (i.e., 10 ETDRS letters) or more from screening at 12 months/18 months/24 months
- Proportion of study eyes having post-operative lens opacities or worsening of preexisting lens opacities (phakic lens only) as assessed by LOCS III classification system by 12 months/18 months/24 months
- Change and percent change in endothelial cell density (ECD) from screening at 3 months/6 months/12 months/24 months (mean and distribution analysis)
- Proportion of study eyes having a glaucoma re-operation due to complication (not due to high IOP) by 12 months/18 months/24 months

6. OTHER CLINICAL PARAMETERS

Other important clinical parameters are patient reported outcomes (PRO), which are assessed with the Ocular Quality-of-Life (QoL) Questionnaire and the General Health Questionnaire (EQ-5D-5L). Within the descriptive summary of PRO measures, the following will be calculated:

- Change from screening in Ocular QoL Visual Function subscale at each 12 months/18 months/24 months
- Change from screening in Ocular QoL Local Vision subscale at 12 months/18 months/24 months
- Change from screening in EQ Visual Analogue scale (VAS) at 12 months/18 months/24 months

7. GENERAL DESCRIPTION OF PLANNED ANALYSES

7.1. Interim Analysis in Support of Expansion to the Full Study Population

As described in Section 3, after the first 75 randomized subjects in Phase I reached the 3-month post-operative visit, an interim safety analysis was performed 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) were used to summarize the demographic data, screening characteristics, use of glaucoma medications, slit lamp examination findings, fundus examination findings, specular microscopy, complications, and AEs for each study group. No post-operative IOP data by study group was analyzed.

7.2. Periodic Data Analysis for Data Safety Monitoring Board

Safety data is being periodically reviewed and evaluated by a Data Safety and Monitoring Board (DSMB), which meets at specified intervals. The DSMB provides recommendations to the Sponsor regarding study continuation. It should be noted that the DSMB may request additional data analyses related to IOP. These IOP analyses, if requested, will be performed by an independent statistician and submitted to DSMB directly. The analyses outcomes will not be shared with the Sponsor, study investigators, or any person who is directly involved in the study (such as study coordinators and clinical research associates).

The DSMB also reviewed the 3-month safety data of the first 75 randomized subjects in Phase I and recommended expansion of the study population.

7.3. FDA Annual Report

Only safety data will be summarized for the FDA annual report. No post-operative IOP data will be analyzed.

7.4. Phase I Data Analysis

As indicated in Section 3, Phase I (i.e. feasibility) data are to be analyzed separately from the Phase II (i.e. pivotal) data. After all subjects in the feasibility cohort have reached the 2-year follow-up timepoint, a database lock and data analysis for this feasibility cohort will be performed. The effectiveness data for the Phase II cohort will remain masked and will not be part of this database lock and analysis.

7.5. Pre-Market Approval (PMA) Submission

After all randomized subjects in Phase II have either completed the 12-month follow-up examination or have discontinued from the study, a database lock and data analysis for this pivotal cohort including 514 Phase II subjects will be performed following this SAP for a PMA submission.

8. SAMPLE SIZE AND POWER CALCULATION

8.1. Sample Size Calculation for Primary Effectiveness Endpoint

The sample size calculation for the primary effectiveness endpoint is solely for Phase II of this study and the corresponding statistical hypotheses described in Section 4.1. Based on the following assumptions, the total sample size required is **514** subjects:

- The 12-month IOP response rates for the treatment group (p_t) and control group (p_c) are estimated to be 0.74 (Appendix 2).
- Significance level is 0.025 (one-sided) and statistical power is 90%.
- Z-test with normal distribution approximation will be used.
- A non-inferiority delta of -0.15.
- A yearly dropout rate of 6% is considered.
- Randomization ratio is 3:1 (treatment group to control group).

With such assumptions, we expect to have a total of 480 subjects (360 in treatment group and 120 in control) at 12 months and a total of 448 subjects (336 in treatment group and 112 in control) at 24 months.

8.2. Power Calculation for Secondary Effectiveness Endpoint #1

The given sample size of 514 subjects will provide 90% power to reject the null hypothesis of inferiority for the first secondary effectiveness endpoint, for the corresponding statistical hypotheses described in Section 4.2, based on the following assumptions:

- Based on the Dominican Republic InnFocus MicroShunt clinical study, the standard deviation of diurnal IOP change from screening at 12 months is assumed to be 6.7 mmHg.
- A non-inferiority margin of 2.5 mmHg.
- Adjusted significance level is 0.0125 (one-sided).
- Two-sample t-test will be used.
- Mean diurnal IOP change at 12 months is the same for both arms.
- A yearly dropout rate of 6% is considered.
- Randomization ratio is 3:1 (treatment group to control group).

8.3. Power Calculation for Secondary Effectiveness Endpoint #2

The given sample size of 514 subjects will provide 84% power to reject the null hypothesis of inferiority for the second secondary effectiveness endpoint, for the corresponding statistical hypotheses described in Section 4.3, based on the following assumptions:

- The post-operative intervention rates by 12 months for the treatment group (qt) and control group (qc) are estimated to be 0.70 (Appendix 3).

- A non-inferiority delta of 0.15 (Appendix 3).
- Adjusted significance level is 0.0125 (one-sided).
- Z-test with normal distribution approximation will be used.
- A yearly dropout rate of 6% is considered.
- Randomization ratio is 3:1 (treatment group to control group).

9. ANALYSIS POPULATIONS

9.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all subjects who were randomized in Phase II. Subjects will be grouped according to their randomization assignment (as randomized) regardless if they actually receive the assigned procedure.

This is the primary analysis population and all effectiveness endpoint analyses will be based on the ITT population.

9.2. Safety Population

The Safety population will include all ITT subjects who underwent the study surgery (i.e. InnFocus MicroShunt or trabeculectomy).

9.3. Per-Protocol Population

The Per-Protocol (PP) population will include ITT subjects excluding those who did not undergo the study surgery, were allocated to the wrong treatment group, or had any other protocol deviation that would impact the primary effectiveness outcome (e.g., unmasking to IOP assessor before 12 months), or did not meet any of the following eligibility criteria as specified in Protocol INN-005 Revision 072117:

Inclusion criterion:

9.2.1.5 Patient must have signed and dated the Informed Consent form.

Exclusion criteria:

9.2.2.13 A history of corneal surgery (including Lasik or PRK), corneal opacities or disease/pathology if accurate IOP measurement may be affected. (Active corneal infection or Fuch's dystrophy are examples.)

9.2.2.17 Prior clear corneal cataract, angle or trabecular meshwork surgery conducted within the past 6 months (e.g., iStent, Trabectome, gonioscopy-assisted transluminal trabeculotomy)

The PP population will be used to analyze principal effectiveness measures including but not limited to the primary and secondary effectiveness endpoints.

9.4. Feasibility Cohort

The Feasibility cohort includes all subjects who were randomized in Phase I. A separate SAP will be finalized before the Phase I database lock.

10. DATA HANDLING

10.1. General Procedure for Data Summary

Descriptive statistics on continuous variables will include number of observations (n), mean, standard deviation, median, and range. Confidence intervals will be included for selected endpoints. Categorical variables will be summarized using frequency counts and percentages. Statistical testing for the primary effectiveness endpoint will be one-sided with a significance level of 0.025. Data listings of individual subject data may be provided.

10.2. Baseline Definition

The baseline values are those that are obtained at the scheduled Screening visit. The terms screening and baseline are used interchangeably in the SAP.

11. STATISTICAL METHODS

11.1. Subject Enrollment and Disposition

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

- ITT population
- PP population
- Safety population
- Completed examination at 12 months
- Discontinued prior to the 12 months examination
- Completed examination at 18 months
- Discontinued prior to the 18 months examination
- Completed examination at 24 months
- Discontinued prior to the 24 months examination

The primary reason for exiting the study before 12 months, 18 months, and 24 months will also be provided.

11.2. Demographics and Pre-operative Characteristics

Subject demographics (age, race/ethnicity and gender) will be summarized by study group and overall using descriptive statistics. Age will be calculated for each subject by (Date of Screening Visit – Date of Birth + 1) ÷ 365.25 and rounded down to the nearest integer. Age will be summarized as a continuous variable and categorized into the following groups: < 65 years and ≥ 65 years.

The mean diurnal IOP at screening will be summarized by study group as continuous variables and categorized into the following groups: < 18 mmHg, ≥ 18 and < 21 mmHg, and ≥ 21 mmHg.

The number of glaucoma medications in use at screening will be summarized by study group and overall as a continuous variable and a categorical variable.

Medical and ocular history will be summarized by study group and overall descriptively.

Other pre-operative characteristics for the study eye including lens type, glaucoma severity classification, BCVA, and visual field mean deviation (MD) will also be summarized descriptively by study group and overall.

11.3. Primary Analyses for Primary and Secondary Effectiveness Endpoints

11.3.1. Primary Analyses for Primary Effectiveness Endpoint

The analyses of the primary effectiveness endpoint will be performed on both the ITT and PP populations. For each analysis population, the number and percentage of 12-month IOP responders and the 95% confidence interval for the 12-month IOP response rate will be calculated for each study group. Additionally, the rate difference, the 95% confidence interval of the rate difference from the Farrington and Manning score test, and the corresponding p-value will also be provided. Subjects with any secondary surgical procedure or event by 12 months that fall into the failure category as described in Section 4.1 will be considered as non-responders at 12 months.

For missing IOP response statuses at 12 months related to procedure or device (i.e., subjects prematurely discontinued the study before 12 months or skipped the 12-month IOP assessment due to a procedure- or device-related AE, excluding those who experienced any failure by 12 months), the Baseline-Observation-Carried-Forward (BOCF) approach (i.e., a non-responder imputation) will be applied to impute the missing data. For missing IOP response statuses at 12 months not related to procedure or device (i.e., subjects prematurely discontinued the study or skipped the 12month IOP assessment due to other reasons, excluding those who experienced any failure by 12 months), multiple imputation will be used to impute missing mean diurnal IOP scores at 12 months. The multiple imputation model will include study group, lens type, number of glaucoma medications in use at screening, mean diurnal IOP at screening, and IOP at all scheduled postoperative visits prior to 12 months as covariates. The imputed mean diurnal IOP score at 12 months will then be used to determine whether the subject achieved ≥ 20% reduction from screening in mean diurnal IOP at 12 months.

Non-inferiority will be claimed if $\mathbf{H_{0E1}}$ is rejected based on one-sided significance level of 0.025. Or equivalently, the lower bound of the two-sided 95% confidence interval for the rate difference $(p_t - p_c) \geq -0.15$.

Furthermore, if the lower bound of the two-sided 95% confidence interval of the rate difference ≥ 0, then superiority is claimed in terms of the primary effectiveness endpoint.

Study success will be achieved if the null hypothesis for the primary effectiveness endpoint is rejected for both the ITT and PP populations. Therefore, no multiplicity adjustment is needed.

After the primary analyses of the primary effectiveness endpoint on the ITT and PP population, the same analysis will be performed on ITT subjects with mean diurnal IOP ≥ 18 mmHg at screening. This subgroup analysis is pre-specified as a key subgroup analysis because both univariate and multivariate risk factor analyses performed by Gedde et al. on the 1-year primary TVT data[4,5] suggest that higher pre-operative IOP is significantly associated with a decreased cumulative failure rate by 12 months (p-values = 0.006) as shown in the table in Appendix 4. In addition, the primary TVT[4,5] and Ab interno gelatin microstent vs trabeculectomy studies[6] suggest that the performance of trabeculectomy relative to tube shunt surgery improves at lower levels of pre-operative IOP, while the performance of tube shunt surgery relative to trabeculectomy improves at higher levels of preoperative IOP. This subgroup analysis is planned to mitigate the impact of potential treatment effect heterogeneity with respect to pre-operative IOP levels on the primary analysis results.

11.3.2. Primary Analyses for Secondary Effectiveness Endpoints

The analyses for the secondary effectiveness endpoints will be performed only if the null hypothesis for the primary effectiveness endpoint is rejected for both the ITT and PP populations. The analyses for the secondary effectiveness endpoints will be performed on the ITT population as primary analyses and will also be performed on the PP population and ITT subjects with mean diurnal IOP at screening ≥ 18 mmHg as sensitivity analyses.

The family-wise Type I error rate for the two secondary effectiveness endpoints will be controlled with a Hochberg step-up procedure specified in Section 11.5.

11.3.2.1. Primary Analysis for Secondary Effectiveness Endpoint #1

The mean diurnal IOP change from screening at 12 months will be analyzed using a mixed-effects model for repeated measures (MMRM) on observed cases up to 24 months. The MMRM model will include study group, post-operative visit (12 months and 24 months only), and study group-byvisit as fixed effects, number of glaucoma medications in use at screening, screening score, and screening score-by-visit as covariates, and subject as a random effect. The denominator degrees of freedom for fixed effects will be estimated using the Kenward-Roger approximation. An UN covariance matrix will be used to model the within-subject errors. Subjects who had any glaucoma re-operation defined as failure in Section 4.1 will be censored from analysis after glaucoma reoperation.

The least squares mean change from screening at 12 months in each study group with its standard error will be reported. The multiplicity-adjusted two-sided confidence interval of the least squares mean difference at 12 months between study groups will also be provided. Non-inferiority of this secondary effectiveness endpoint will be claimed once $\mathbf{H_{0E2a}}$ is rejected at a significance level adjusted based on a Hochberg step-up procedure specified in Section 11.5, i.e., the upper bound of the multiplicity-adjusted two-sided confidence interval for the mean difference $(\mu_t - \mu_c) \leq 2.5$ mmHg.

11.3.2.2. Primary Analysis for Secondary Effectiveness Endpoint #2

The analysis of the post-operative intervention by 12 months will be based on the Farrington and Manning score test. The number and percentage of subjects with any post-operative intervention by 12 months and the 95% confidence interval for the 12-month post-operative intervention rate will be calculated for each study group. Additionally, the rate difference, the multiplicity-adjusted twosided confidence interval of the rate difference from the Farrington and Manning score test, and the corresponding adjusted p-value will also be provided. Non-inferiority of this secondary endpoint will be claimed once $\mathbf{H_{0E2b}}$ is rejected at a significance level adjusted based on a Hochberg step-up procedure specified in Section 11.5, i.e., the upper bound of the multiplicity-adjusted two-sided confidence interval for the rate difference $(q_t - q_c) \leq 0.15$.

11.4. Sensitivity Analyses

11.4.1. Sensitivity Analyses for Primary Effectiveness Endpoint

To assess the robustness of the primary analysis results, the following sensitivity analyses will be performed:

- Farrington and Manning test on observed cases (i.e., ITT subjects with observed IOP data at 12 months)
- Unpooled Z test on the ITT population

To assess the impact of missing data on the primary analysis results, sensitivity analyses with the following imputation approaches will be performed on the ITT population:

- BOCF approach (i.e., a non-responder imputation): impute missing IOP data at 12 months by screening IOP
- Tipping-point approach. This will examine every possible combination of successes/failures for the treatment and control groups for subjects with missing IOP data at 12 months. In particular the tipping point approach will include both as bestcase and worst-case scenario as defined below:
    - Best case: all subjects with missing IOP data at 12 months in the treatment group are assumed to be successes; while all subjects with missing IOP data at 12 months in the control group are assumed to be failures.
    - Worst case: all subjects with missing IOP data at 12 months in the treatment group are assumed to be failures; while all subjects with missing IOP data at 12 months in the control group are assumed to be successes.

In the primary analysis of the primary effectiveness endpoint, subjects with secondary surgical procedures or events by 12 months that fall into the failure category in Section 4.1 will be considered as non-responders.

11.4.2. Sensitivity Analyses for Secondary Effectiveness Endpoint #1

To assess the robustness of the primary analysis results of the secondary effectiveness endpoint #1, the following sensitivity analyses will be performed:

- Only subjects who completed both 12 months and 24 months' visits will be included in the MMRM model
- Any IOP data at 12 months and 24 months' visits that is below 6 mmHg will be excluded from the MMRM model
- Any IOP data that was collected after secondary surgical procedures or events that fall into the failure category in Section 4.1 will be excluded from the MMRM model.

11.5. Multiplicity

The multiplicity adjustment is not needed for the two sets of statistical hypotheses for the primary efficacy endpoint on the ITT and PP populations since study success will be based on the all-ornone-win criterion, i.e., study success is achieved only if the null hypothesis for the primary effectiveness endpoint is rejected for both the ITT and PP populations.

The analyses for the secondary effectiveness endpoints will be performed only if the study success is achieved. For the secondary effectiveness endpoint hypothesis tests, a Hochberg step-up procedure will be used to control the family-wise Type I error rate at the 0.025 level (one-sided) and adjust the significance level and confidence interval as follows:

- Let p_a and p_b denote unadjusted p-values of one-sided tests for H0E2a and H0E2b, respectively. Order p_a and p_b and let [1] and [2] denote the random indices such that $p_{[1]} \leq p_{[2]}$.

  Step 1: If $p_{[2]} < 0.025$, set the adjusted significance level at 0.025 (one-sided), report the two-sided 95% confidence interval for each endpoint, and reject $H_{0[1]}$ and $H_{0[2]}$; otherwise go to Step 2.

  Step 2: If $p_{[1]} < 0.0125$, set the adjusted significance level at 0.0125 (one-sided), report the two-sided 97.5% confidence interval for the corresponding endpoint, reject $H_{0[1]}$ and stop. Testing for superiority on the primary effectiveness endpoint will be performed if the null hypothesis for the primary effectiveness non-inferiority tests is rejected.

As only the safety measurements will be reviewed or descriptively summarized during the interim analysis for the expansion request, DSMB meetings, and FDA annual reports, no multiplicity adjustment is needed for these interim analyses. Any other calculated p-values will not be adjusted for multiplicity.

11.6. Multi-Center Studies

This is a multicenter study with approximately 30 centers, among which a maximum of 6 centers are planned to be outside of the United States (OUS). Descriptive summaries of the demographics and baseline as well as effectiveness results will be provided for the United States (US) population and the OUS population, respectively. In addition, a Breslow-Day test will be conducted on the primary effectiveness endpoint to assess the homogeneity of treatment differences between the US population and OUS population.

If the p-value from the Breslow-Day test is less than 0.15, a logistic regression will be performed with independent variables including study group, region (US vs OUS) and the interaction term of the two.

A similar analysis will be performed to examine the heterogeneity of treatment effects across study centers. If heterogeneity of treatment effects across centers is found, baseline characteristics and demographics will be examined to attempt to explain such heterogeneity. If baseline characteristics and demographics do not explain the heterogeneity in treatment effect across centers, a mixedeffects model, treating center as a random effect, will be used to estimate the variability of treatment effects across centers.

Centers with five or fewer subjects will be combined into one "super-center" for analysis examining heterogeneity of treatment effects across study centers in order to avoid difficulties with estimates at small centers.

11.7. Subgroup Analyses

The following subgroups will be examined for their prognostic value to the primary effectiveness and secondary endpoints for the ITT population:

- Age group (<65 vs. ≥65 years)
- Gender (male vs. female)
- Race (white vs. non-white)
- Ethnicity (Hispanic or Latino vs. not Hispanic or Latino)
- Country (US vs. OUS)
- Number of glaucoma medications in use at screening (< 3, 3, or ≥ 4)
- Lens type at screening (phakic vs. pseudophakic)
- Pre-operative IOP group (mean diurnal IOP at screening < 18, 18 to < 21, or ≥ 21 mmHg). The subgroup analysis on subjects with mean diurnal IOP ≥ 18 mmHg at screening is specified as a key subgroup analysis in Section 11.3.1.
- Glaucoma severity classification at screening based on visual field MD (early: -3.00 to -6.00, moderate: -6.01 to -12.00, advanced: -12.01 to -20.00, or severe: < -20.00 dB)

In addition, the primary effectiveness endpoint will be summarized for subjects who were on the same or a fewer number of glaucoma medications at 12 months compared to screening. It will also be summarized for subjects requiring any of the following interventions by 12 months by intervention type and the number of interventions (1, 2, or ≥ 3):

- Needling of the bleb with or without the use of an injected antifibrotic
- Laser removal of blockage at the tip of the InnFocus MicroShunt or at the AC entry point for a trabeculectomy
- Use of a viscoelastic to limit aqueous flow

- Laser suture lysis in a trabeculectomy (separate summarization by intervention type is not required for laser suture lysis, as this intervention is specific to trabeculectomy)

Forest plots will be provided to visualize treatment differences across subgroups.

11.8. Exploratory Analyses

11.8.1. Analyses for Exploratory Purposes

The following inferential analyses will be performed for the exploratory outcomes listed in Section 4.4.

Analyses of binary IOP outcomes and binary glaucoma medication outcomes at 12 months will follow the primary analysis of the primary effectiveness endpoint specified in Section 11.3.1. For binary IOP at 24 months and glaucoma medication outcomes at 18 months and 24 months, the analyses will be similar to the primary analysis of the primary effectiveness endpoint, except that the handling of missing data and failure category will be expanded to 18 months or 24 months.

The mean diurnal IOP change from screening at 24 months will be compared between study groups using the same MMRM model for the mean diurnal IOP change from screening at 12 months as specified in Section 11.3.2. The change from screening in the number of glaucoma medications in use at 12 months, 18 months, and 24 months will also be compared between study groups using an MMRM model on observed cases up to Month 24. The MMRM model will include study group, post-operative visit (all post-operative visits), and study group-by-visit as fixed effects, the number of glaucoma medications in use at screening, and screening-by-visit as covariates, and subject as a random effect. The denominator degrees of freedom for fixed effects will be estimated using the Kenward-Roger approximation. An UN covariance matrix will be used to model the within-subject errors. Subjects who had any glaucoma re-operation defined as failure in Section 4.1 will be censored from analysis after glaucoma re-operation.

Analyses of binary intervention outcomes will follow the primary analysis of the second secondary effectiveness endpoint specified in Section 11.3.3.

Analyses of time-to-event outcomes will be based on a log-rank test. Reverse Kaplan-Meier (1 minus the freedom from event probability) curves will be generated to depict the cumulative event rate over time.

No multiplicity adjustment is needed for these exploratory analyses.

11.8.2. Other Exploratory Analyses

For the ITT population, the following outcomes will be summarized descriptively with observed cases for each study group at each scheduled visit unless specified otherwise. For these descriptive summaries, subjects who had any glaucoma re-operation defined as failure in Section 4.1 will be censored from analysis after glaucoma re-operation:

- Mean diurnal IOP, change and percent change in mean diurnal IOP from screening summarized at applicable visits (screening, 12 months, and 24 months) with n, mean, median, standard deviation, minimum, and maximum. The percent mean diurnal IOP

reduction will also be categorized at 12 months and 24 months as < 10%, 10% to < 20%, 20% to < 30%, 30% to < 40%, or ≥ 40%.

- The analysis will be stratified by mean diurnal IOP at screening categorized as < 18 mmHg, 18 to < 21 mmHg, or ≥ 21 mmHg; o The analysis will be stratified by post-operative glaucoma medication status: on no medications, on medications but same with or fewer than screening, or on more medications than screening. If data suggests, analysis will also be stratified by route of glaucoma medication administration (systemic or non-systemic).

- Box-plots of mean diurnal IOP, change and percent change in mean diurnal IOP from screening at applicable visits (screening, 12 months, and 24 months);
- Scatter plots of post-operative IOP (12 months and 24 months) as a function of mean diurnal IOP at screening, distinguished by post-operative medication status: IOP with any medication vs. IOP without medications.
- For each subject, plot the IOP score (mean diurnal or standard IOP) versus scheduled visit (including screening and all scheduled post-operative visits). The number of glaucoma medications the subject was taking at each scheduled visit and the reoperation date if any will also be indicated on the plot.
- The number and percentage of subjects adding or not adding glaucoma medications from screening at or after 6 weeks post-surgery at 12 months and 24 months.
  - The number and percentage of subjects adding glaucoma medications from screening at or after 6 weeks post-surgery stratified by the number of added glaucoma medications.
- Change from screening in the number of glaucoma medications in use, subjects on the same or fewer number of glaucoma medications than screening, and subjects adding glaucoma medications from screening at or after 6 weeks post-surgery will be summarized descriptively for each subgroup defined in Section 11.7.

11.9. Safety Analysis

All safety analyses will be performed on the Safety population based on observed cases unless specified otherwise.

11.9.1. Adverse Event

Adverse events will be classified as intra-operative or post-operative. The number and percentage of subjects reporting at least one AE of a given type will be summarized by study group. Summaries will also be provided for AEs judged to be device- or procedure-related. In addition, AEs will also be stratified by subjects on whom a 23-gauge cannula was used versus those who did not require use of a 23-gauge cannula.

11.9.2. Best Corrected Visual Acuity

Best corrected visual acuity (BCVA) and change in BCVA from screening will be summarized descriptively by study group and by visit. Numbers and percentages of subjects with a BCVA loss

of 2 lines (i.e., 10 ETDRS letters) or more from screening will also be provided for each of the two study groups at each post-operative visit.

For exploratory purposes, percentages of subjects with a BCVA loss of 2 lines or more from screening at 12 months, 18 months, and 24 months will be compared between study groups with the Farrington and Manning score test. Missing BCVA data at 12 months, 18 months, and 24 months will be imputed by the last-observation-carried-forward (LOCF) approach. Rate differences at 12 months, 18 months, and 24 months, the 95% confidence interval of each rate difference, and the corresponding p-values will be provided.

The data listing of subjects who experienced a BCVA loss of 2 lines or more from screening including the reason for vision loss will be provided.

11.9.3. Post-Operative Lens Opacities

For exploratory purposes, percentage of subjects who developed post-operative lens opacities or experienced worsening of pre-existing lens opacities (phakic lens only) as assessed by LOCS III classification system by 12 months, 18 months, and 24 months will be compared between study groups with the Farrington and Manning score test. Rate differences at 12 months, 18 months, and 24 months, the 95% confidence interval of each rate difference, and the corresponding p-values will be provided.

The data listing of these subjects will be provided.

11.9.4. Endothelial Cell Density

The endothelial cell density (ECD), change and percent change in ECD from screening will be descriptively summarized by study group and by visit. In addition, for exploratory purposes, the change and percent change in ECD from screening at 3 months, 6 months, 12 months, and 24 months will be compared between study groups using an MMRM model on observed cases up to 24 months. Each MMRM model will include study group, post-operative visit, and study group-byvisit as fixed effects, screening ECD, and screening ECD-by-visit as covariates, and subject as a random effect. The denominator degrees of freedom for fixed effects will be estimated using the Kenward-Roger approximation. An UN covariance matrix will be used to model the within-subject errors.

Additionally, the change and percent change in ECD between two consecutive post-operative visits will be summarized descriptively by study group.

For both descriptive summaries and inferential analyses of ECD measures, subjects who had any glaucoma re-operation defined as failure in Section 4.1 will be censored from analysis after glaucoma re-operation.

Separately, for both descriptive summaries and inferential analyses of ECD measures, 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); or the entire MicroShunt is explanted, will be censored from analysis after the qualifying event.

11.9.5. Glaucoma Re-operation Due to Complication

For exploratory purposes, percentages of subjects with any glaucoma re-operation due to complication (not due to high IOP) by 12 months, 18 months, and 24 months will be compared between study groups with the Farrington and Manning score test. Rate differences at 12 months, 18 months, and 24 months, the 95% exact confidence interval of each rate difference, and the corresponding p-values will be provided.

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

11.9.6. Other Safety Analyses

Slit lamp, fundus examination, and gonioscopy results at screening and at post-operative 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 visit. The visual field MD and change from screening will be presented descriptively by study group and by visit. Pachymetry and change from screening will be summarized descriptively by study group and by visit.

11.10. Analyses for Patient Reported Outcomes

11.10.1. Ocular Quality-of-Life Questionnaire

The Visual Function subscale and the Local Eye subscale of the Ocular QoL Questionnaire will be calculated and summarized descriptively by study group and by visit.

For exploratory purposes, the mean change from screening in each subscale of the Ocular QoL Questionnaire at 12 months, 18 months, and 24 months will be compared between study groups using MMRM models on observed cases up to 24 months. Each MMRM model will include study group, post-operative visit, and study group-by-visit as fixed effects, screening score, and screening-by-visit as covariates, and subject as a random effect. The denominator degrees of freedom for fixed effects will be estimated using the Kenward-Roger approximation. An UN covariance matrix will be used to model the within-subject errors.

For both descriptive summaries and inferential analyses of the Ocular QoL Questionnaire data, subjects who had any glaucoma re-operation defined as failure in Section 4.1 will be censored from analysis after glaucoma re-operation.

11.10.2. General Health Questionnaire (EQ-5D-5L)

The EQ-5D-5L data will be summarized into 5 categories of general health (Mobility, Self-Care, Usual Activities, Pain/Discomfort and Anxiety/Depression) and a separate Visual Analog scale (VAS). In each of the 5 categories, a value from 1-5 assigned based on the selection from the 5 choices will be reported. The VAS is used to give a self-rated health score with 100 as the best health and 0 as the worst health.

For the 5 EQ-5D-5L categories and the VAS, data will be summarized descriptively by study group and by visit.

For exploratory purposes, the mean change from screening in VAS at 12 months, 18 months, and

24 months will be compared between study groups using MMRM models on observed cases up to 24 months. Each MMRM model will include study group, post-operative visit, and study group-byvisit as fixed effects, screening score, and screening-by-visit as covariates, and subject as a random effect. The denominator degrees of freedom for fixed effects will be estimated using the KenwardRoger approximation. An UN covariance matrix will be used to model the within-subject errors.

12. REFERENCES

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APPENDIX 1: SCHEDULE OF VISITS

Study Visits and Parameters for Treatment Eyes

Activities	Screening	Op	Follow-up Evaluation							
			1 D	1W	4W	3 M	6 M	12M	18M	24M
Informed Consent	X									
Randomization		X								
Ocular Medical History	X	X								
Ocular Medication Assessment	X	X	X	X	X	X	X	X	X	X
History/Demographics	X									
Manifest Refraction	X				X	X	X	X	X	X
BCVA (Snellen)			X	X						
BCVA (ETDRS)	X				X	X	X	X	X	X
Visual Field	X					X	X	X		X
Slit Lamp Exam	X		X	X	X	X	X	X	X	X
Lens Status for Phakic Eyes	X					X	X	X	X	X
IOP	X[1]		X	X	X	X	X	X[1]	X	X*
Pachymetry	X							X		X
Endothelial Cell Density	X					X	X	X		X
Gonioscopy	X									
Dilated fundus exam	X									
Vertical C:D Ratio	X				X	X	X	X		X
Optic Disc Photo	X				X	X	X	X		X
Diplopia	X					X	X	X		X
Motility	X					X	X	X		X
Pregnancy Test (as applicable)	X									
Surgical Procedure		X								
Observations Recorded	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
Patient Questionnaire (PRO)	X			X	X	X	X	X	X	X
General Health Questionnaire	X				X	X	X	X	X	X

*Diurnal IOP

APPENDIX 2: NON-INFERIORITY MARGIN OF 0.15 FOR 12-MONTH IOP RESPONSE

Regarding the primary effectiveness endpoint (12-month IOP response), the expected IOP response rate of the trabeculectomy with MMC group is 74% at 12 months when taking into consideration the additional failure categories included in this study that have not been considered as failures in historical studies. This response rate was determined by an analysis of historical studies involving POAG patients who received trabeculectomy with MMC. The analysis looked at several sources of trabeculectomy with MMC data involving POAG patients as follows: 1) the patients treated with 0.2-0.4 mg/mL MMC in the 1997 Robin study, 2) the patients treated with 0.2 mg/mL MMC in the 1997 Costa study, 3) the patients treated with 0.4 mg/mL MMC for 1-2 minutes in the 2007 Maris study (50 patients), and 4) the cohort of patients with prior cataract extraction only who were treated with 0.4 mg/mL MMC for 4 minutes in the Gedde study (TVT). The table below summarizes the data. After adjusting the success rates for additional failure modes requested by FDA in this study, the mean value was 74% with a standard deviation of 12.5% at 12 months of follow-up. For a categorical outcome in a clinical study as outlined above with the inherent patient and treatment variability as can be observed with the standard deviation shown, a 15% margin for non-inferiority is considered acceptable.

Study	Patient Population	Reported Success Rate by 1 Year	Added Failure Rate Based on Complications	Overall Success Rate at 12 Months	Projected 2 Year Success Rate*
Costa[7]	Primary, all phakic	71% (10/14)	0%	71% (based on ≤ 15 mmHg)	
Robin[8]	Primary, all phakic	83% (137/166)	0%	83%	
Maris[9]	Primary, 86% phakic	91% (32/35)	6% (2/35) Hypotony Maculopathy	85%	
Gedde[3]	Pseudophakic only (46)	80%* (projected based on reported 60% at 3 year)	22% 5 FU injection	58%	
	Overall	**82%**		**74% (SD = 12.5%)**	**64% (SD = 12.5%)**

* 10% per year failure is expected per S. Gedde and his literature.

APPENDIX 3: NON-INFERIORITY MARGIN OF 0.15 FOR POST-OPERATIVE INTERVENTION BY 12 MONTHS

Regarding the second secondary effectiveness endpoint (post-operative intervention by 12 months), the expected 12-month post-operative intervention rate of the trabeculectomy group is about 70% when taking into consideration additional interventions (e.g., glaucoma re-operation, medication intervention) in this study that have not been considered as intervention in historical studies. This intervention rate was determined by an analysis of historical studies involving POAG patients who received trabeculectomy with MMC.

The analysis looked at several sources of trabeculectomy with MMC data involving POAG patients as follows: 1) the patients treated with 0.4 mg/mL MMC for 4 minutes in the 2007 Gedde study (TVT), 2) the patients treated with 0.2 mg/mL MMC in the 2017 Schlenker study, and 3) the patients treated with 0.4 mg/mL MMC for 2 minutes in the 2018 Gedde study (primary TVT). The table below summarizes the data. After adjusting the intervention rate for additional interventions considered in this study, the estimated intervention rate by 12 months for the trabeculectomy group for the 391 patients was about 70%, with a 95% confidence interval of [65%, 75%]. As it is legitimate to assume that a "placebo" group would have a 100% intervention rate, the effect of trabeculectomy is considered to be 30% and maintaining half (50%) of that effect yields a non-inferiority margin of 15%.

Study	Patient Population	Reported Surgical Intervention Rate	Reported Glaucoma Re-operation Rate	Overall Intervention Rate by 12 Months
Gedde[10]	80% POAG; 20% phakic (N=105)	Suture lysis: 49%; 5-FU injection: 22%; Needling: 8%; Injection of intracameral tPA (2%); Suture wound leak (1%)	5% with reoperation due to complication	49%-86%
Schlenker[6]	7% POAG, including phakic and pseudophakia (N=169)	30 Months: 98% Most frequent: Suture lysis: 50%	6%	< 98%
Gedde[5]	93% POAG, all phakic (N=117)	1 Year: 63% Most frequent: Suture lysis: 49%	5%	≥ 63%
Overall [95% CI]				**70% [65%, 75%]**

APPENDIX 4: DATA FROM THE GEDDE ET AL PTVT STUDY AFTER ONE YEAR OF FOLLOW-UP*

Risk Factor Analysis

Risk Factor	P-value	
	Univariate	Multivariate
Stratum	0.52	0.51
Age	0.57	0.33
Gender	0.26	0.25
Race	0.080	0.087
Hypertension	0.88	0.94
Diabetes	0.072	0.084
Previous ocular laser treatment	0.70	0.39
Preoperative IOP	0.006	0.006
Preoperative number of glaucoma medications	0.43	0.54
Preoperative Snellen VA	0.072	0.067
Preoperative HVF MD	0.74	0.91
Clinical center	0.47	0.41
Randomized treatment	0.013	0.011

* Gedde SJ et al. Treatment Outcomes in the Primary Tube Versus Trabeculectomy (PTVT) Study After One Year of Follow-up. Proceedings of the AGS 28th Annual Meeting, Symposium 4: Application of Glaucoma Multicenter Randomized Clinical Trials in Clinical Practice; 2018 March 1-4; New York City, New York.

Note:

1. A risk factor analysis was performed to identify baseline demographic and clinical factors that would predict failure.
2. Only pre-operative IOP and randomized treatment were significantly associated with failure in univariate and multivariate analyses.
3. And a significant interaction was observed between these two factors.

APPENDIX 5: 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 [Travatan®], bimatoprost [Lumigan®], tafluprost [Ziptan™])	4 weeks