September 2023

ClinicalTrials.gov

To Whom It May Concern,

Please see attached, the protocol 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:	Protocols v2.0 16Nov2021
Study ID:	**INN-005 EXT**
NCT No.	**NCT04333433**

Thank you,

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

INNFOCUS

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.

Clinical Investigation Plan

PRESERFLO® MicroShunt Extension Study

INN-005-EXT

Sponsored by:

InnFocus, Inc.

Version: 2.0

Date: 16NOV2021

Clinical Investigation Plan	
Study Name	**PRESERFLO® MicroShunt Extension Study**
Protocol Number	**INN-005-EXT**
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.**
Sponsor	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Principal Investigator Signature Page

The signature below constitutes the approval of this Clinical Investigation Plan and provides assurance that this trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as amended in 2013, according to all stipulations of the CIP, to local regulatory requirements, the applicable sections of and updates to the European Medical Device Regulation 2017/745, ICH/GCP, Title 21 CFR Part 812 (Investigator Responsibilities) and ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects- Good Clinical Practice). The clinical investigation shall not begin until the required approval or favorable opinion from the FDA, other relevant Regulatory Agency, and Institutional Review Board/Independent Ethics Committee, have been obtained.

Principal Investigator Signature: _____

Principal Investigator Name: _____

Print/Type

Date (DD-MMM-YYYY): _____

Confidentiality and Sponsor Compliance Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees, institutional review boards, and regulatory agencies. The contents of this document shall not be disclosed to others without written authorization from InnFocus, Inc.

InnFocus, Inc. ensures that this trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as amended in 2013, according to all stipulations of the CIP, to local regulatory requirements, the applicable sections of and updates to the European Medical Device Regulation 2017/745, ICH/GCP, Title 21 CFR Part 812 (Sponsor Responsibilities) and ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects- Good Clinical Practice). The clinical investigation shall not begin until the required approval or favorable opinion from the FDA, other relevant Regulatory Agency, and Institutional Review Board/Independent Ethics Committee, have been obtained.

Table of Contents

1. List of Abbreviations

Term	Definition
AE	Adverse Event
ALT	Argon Laser Trabeculoplasty
BCVA	Best Corrected Visual Acuity
CAI	Carbonic Anhydrase Inhibitor
CRO	Contract Research Organization
CFR	Code of Federal Regulations
CIP	Clinical Investigation Plan
CMP	Clinical Monitoring Plan
CRF	Case Report Form
DMP	Data Management Plan
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EXT	Extension
FDA	Food and Drug Administration
FE	Fellow Eye
5FU	5-Fluorouracil
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRT	Heidelberg Retinal Tomography
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IFU	Instructions for Use
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
LAR	Legally authorized representative
LASIK	Laser in situ keratomileusis
LOCS	Lens Opacity Classification System
LTF	Lost-to-Follow-up
MIGS	Minimally-Invasive Glaucoma Surgeries
MLT	MicroPulse Laser Trabeculoplasty
MMC	Mitomycin C
MR	Manifest Refraction
NRS	Numeric Rating Scale
OD	Oculus Dextrus (Right Eye)
OS	Oculus Sinister (Left Eye)

Term	Definition
OU	Oculus Uterque (Both Eyes)
PI	Principal Investigator
OAG	Open-Angle Glaucoma
OCT	Optical Coherence Tomography
POAG	Primary Open-Angle Glaucoma
RGCs	Retinal Ganglion Cells
RNFL	Retinal Nerve Fiber Layer
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SE	Study Eye
SITA	Swedish Interactive Thresholding Algorithm
SLE	Slit-lamp Examination
SLT	Selective Laser Trabeculoplasty
TA	Tonometry by applanation
UADE	Unanticipated Adverse Device Effect
VA	Visual Acuity
VF	Visual Field
YAG	Yttrium-aluminum-garnet laser used in posterior capsule opacity; also referred to as a neodymium (Nd): YAG laser

2. Synopsis

PROTOCOL SYNOPSIS	
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.
Sponsor	InnFocus, Inc.
Product Name	PRESERFLO® MicroShunt (previously InnFocus MicroShunt® Glaucoma Drainage System)
Product Status	The PRESERFLO® MicroShunt is investigational in the United States. The product is CE-marked.
Indication	Primary Open-Angle Glaucoma (POAG).
Indication for Use	The PRESERFLO® MicroShunt is indicated for the reduction of intraocular pressure (IOP) in eyes of patients with Primary Open-Angle Glaucoma where IOP is not controlled when using maximum tolerated glaucoma medications.

Study Purpose	The purpose of this study is to evaluate the long-term safety of the PRESERFLO® MicroShunt in subjects with Primary Open-Angle Glaucoma who have completed participation in the INN-005 clinical study, conducted under IDE G130028, by collecting safety data through 5 years post-operative follow-up.
Study Outcome Measures	**Primary Safety Outcome Measure:** • Incidence of sight-threatening adverse events.
	Secondary Outcome Measures – 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 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 examinations findings **Secondary Outcome Measures – Effectiveness:** • Proportion of study eyes with ≥ 20% 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 (total, complete, qualified). • Change in the number of glaucoma medications from INN-005 study screening.
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 the treatment and control arms of the INN-005 study.

Study Population	The study will attempt to include all subjects who have completed the Month 24 Follow-Up Visit of the INN-005 clinical study after randomization to either the PRESERFLO® MicroShunt treatment arm or the Trabeculectomy control arm. Therefore, the study population will include those subjects who are willing and able to extend their study participation and return for up to three (3) additional annual follow-up visits through post-operative Month 60. Subjects who have had the PRESERFLO® MicroShunt explanted, will also be included in the study.
Study Duration	Subjects enrolled in this study will be required to complete up to three (3) annual follow-up visits through post-operative Month 60 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 study.
Study Centers	Eligible subjects who consent to participate in this study will be evaluated at up to 24 sites located in the United States and at up to 5 sites located in Europe.
Sample Size	All 629 subjects who were randomized into both Phase I and II of the INN-005 study and have completed their 24-month follow-up 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.
Inclusion/Exclusion Criteria	**Inclusion Criteria** 1. Subject has completed their Month 24 Follow-Up Visit in the INN-005 clinical study conducted under IDE G130028. 2. Subject was randomized into the INN-005 study and received the PRESERFLO® MicroShunt device or trabeculectomy. (Subjects who have had the device explanted, or replaced with another device, may be included). 3. Subject is willing and able to comply with all study requirements, including signing an informed consent form. **Exclusion Criteria** 1. Subject has exceeded the timeframe for the Month 60 Follow-Up Visit prior to enrollment for participation in this long-term follow-up study.
Study Visits	Month 36 (± 90 days), Month 48 (± 90 days), and Month 60 (± 90 days) post-operative follow-up. Subjects who have passed the timepoints for the Month 36 and/or Month 48 Follow-Up Visits prior to re-enrolling for the PRESERFLO® MicroShunt Extension Study, may still be enrolled to complete the remaining Month 48 visit if the timepoint has not passed, and the Month 60 post-operative visit.

Statistics	This long-term safety study does not pre-specify any hypotheses to evaluate the study outcomes. Descriptive statistics will be used to summarize safety, effectiveness, and ancillary data.

3. Introduction

3.1. Background

This study is an extension of the randomized controlled trial conducted under IDE G130028, in which subjects were randomized to either the PRESERFLO® MicroShunt treatment arm or the trabeculectomy control arm and followed for 2 years post-surgery. The extension involves the addition of 3 follow-up visits through 5 years post-operative follow-up. The study does not require any new interventions, and aside from the exceptions outlined below, the same study assessments that were performed on the study eye during the Month 12 and 24 Follow-Up Visits in the INN-005 study, will be performed during the Month 36, 48, and 60 Follow-Up Visits in the Extension Study. A detailed overview of glaucoma, and its treatment options, is provided in Appendix A.

Study Assessment*	INN-005 Study[1] (Month 12 and 24)	INN-005-EXT Study[2] (Month 36, 48, and 60)	Comments
Ocular Medical History	X	X	
Ocular Medication Assessment	X	X	
Manifest Refraction	X	X	
BCVA (ETDRS)	X	X	
Visual Field	X	X	
Slit Lamp Exam	X	X	
Lens Status for Phakic Eyes	X	X	
IOP	X	X	INN-005: Diurnal IOP INN-005-EXT: Standard IOP
Pachymetry	X	X	
Endothelial Cell Density	X	X	
Dilated Fundus Exam	X	X	
Bleb and Seidel Test	X	X	
Diplopia	X	X	
Motility	X	X	
Anterior Segment OCT	Not performed	X	Added to INN-005-EXT as an optional assessment to further assess position of PRESERFLO® MicroShunt along with slit lamp examination; Only performed for subjects with device still implanted
Adverse Event Assessment	X	X	INN-005: All AEs collected INN-005-EXT: All ocular AEs in study & fellow eye and all SAEs will be collected. Non-serious, non-ocular AEs will not be collected.
Ocular QOL Questionnaire	X	---	Not included in INN-005-EXT
General Health Questionnaire	X	---	Not included in INN-005-EXT
Gonioscopy	X	X (Month 60)[3]	Added to INN-005-EXT to further assess position of PRESERFLO® MicroShunt; Only performed for subjects with device still implanted

[1]All assessments, except lens status for phakic eyes, performed in both study and fellow eye.

[2]Ocular Medical History, Ocular Medication Assessment, Adverse Event Assessment, and Endothelial Cell Density, performed in both study and fellow eye. All other assessments performed in study eye only.

[3]Only applies to MicroShunt subjects who agree to this assessment by signing the Informed Consent Addendum.

3.2. Study Rationale

The prospective, randomized, controlled, single-masked, multi-center INN-005 clinical study, conducted under IDE G130028 was designed to directly compare safety and effectiveness of trabeculectomy with Mitomycin C (MMC) to the PRESERFLO® MicroShunt with MMC, and to follow subjects through 2 years post-surgery.

This prospective, concurrent controlled, open-label, multicenter study is designed to collect additional safety data through 5 years of follow-up for subjects randomized to either the treatment arm (PRESERFLO® MicroShunt with MMC) or the control arm (Trabeculectomy with MMC) of the INN-005 clinical study.

3.3. Study Purpose

The purpose of this study is to evaluate the long-term safety of the PRESERFLO® MicroShunt in subjects with Primary Open-Angle Glaucoma who were randomized and have completed the Month 24 Follow-Up in the INN-005 clinical study, conducted under IDE G130028, by collecting safety data through 5 years post-operative follow-up.

4. Study Objective and Outcome Measures

4.1. Study Objective

The objective of this study is to evaluate the long-term safety of the PRESERFLO® MicroShunt in subjects with Primary Open-Angle Glaucoma 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.

4.2. Study Outcome Measures

The **Primary Safety Outcome Measure** for the study is the following:

- Incidence of sight-threatening adverse events.

Secondary Outcome Measures – 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 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.

Secondary Outcome Measures – Effectiveness:

- Proportion of study eyes with ≥ 20% 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 (total, complete, qualified).
- Change in the number of glaucoma medications from INN-005 study screening.

5. Study Design

5.1. Study Design Overview

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 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 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-up visit timepoints to be calculated from subjects' Operative Visit in the INN-005 study). 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.

5.2. Study Duration

Subjects enrolled in this study will be required to complete up to three (3) annual follow-up visits through post-operative Month 60 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.

5.3. Number of Centers

Investigative sites that participated in, and enrolled subjects in, the INN-005 clinical study will be participating in this long-term follow-up study. Eligible subjects who consent to participate in this study will be evaluated at up to 24 sites located in the United States and at up to 5 sites located in Europe.

5.4. Number of Subjects

All 629 subjects who were randomized into both Phase I and II of the INN-005 study will be assessed for eligibility to participate in this long-term follow-up study. The number of subjects participating in this

study will therefore be dependent upon the number who are willing to participate in, and who meet the eligibility criteria for, enrollment in this study.

6. Device Description

The device being evaluated in this study is the PRESERFLO® MicroShunt (previously InnFocus MicroShunt® Glaucoma Drainage System), previously implanted in the INN-005 study. In this long-term safety study, no new study devices will be implanted, and no study interventions will be required by the study protocol. Subjects may require reoperations, including treatment with other commercially available devices. A detailed description of the device is provided in Appendix B.

7. Description of the Study Population

7.1. Study Population

The study population includes all subjects who have completed the Month 24 Follow-Up Visit of the INN-005 clinical study after randomization to either the PRESERFLO® MicroShunt treatment arm or the Trabeculectomy control arm, and who are willing and able to extend their study participation and return for up to three (3) additional annual follow-up visits through post-operative Month 60. Up to 629 subjects may be enrolled at up to 24 sites located in the United States and at up to 5 sites located in Europe.

7.2. Inclusion Criteria

To qualify for enrollment in this study, subjects must meet ***all*** of the following inclusion criteria:

1. Subject has completed the Month 24 Follow-Up Visit in the INN-005 clinical study conducted under IDE G130028.
2. Subject was randomized into the INN-005 study and received the PRESERFLO® MicroShunt device or trabeculectomy. (Subjects who have had the device explanted, or replaced with another device, may be included).
3. Subject is willing and able to comply with all study requirements, including signing an informed consent form.

7.3. Exclusion Criteria

To qualify for enrollment in this study, subjects must ***not*** meet the following exclusion criterion:

1. Subject has exceeded the timeframe for the Month 60 Follow-Up Visit prior to enrollment for participation in this long-term follow-up study.

8. Subject Enrollment

8.1. Subject Consent

The Sponsor and IRB/IEC approved Informed Consent Form (ICF) will be presented and explained to each prospective subject by the Investigator, or a delegated site staff member, before any study-specific assessments and procedures are performed. The Investigator or delegated staff member will explain the elements of the informed consent form, including the risks or discomforts, and the fact that the study does not mandate any new treatment, and that he or she will continue to receive the same treatment recommended by the Investigator. If the subject is not yet aware, the Investigator or delegated staff member may inform the subject of the treatment he or she received upon initial randomization in the INN-005 study.

Once the subject has been informed of all aspects of the study, the potential subject will be given the opportunity to ask questions and will be allowed time to consider the information provided. The final approved informed consent document to be used in the consenting process must be presented to the subject in his or her native language. The subject's willingness and ability to meet follow-up visit requirements will be determined. The subject will be given a choice to voluntarily confirm his or her participation in the study as documented by completion of the Informed Consent. After signing and dating the Informed Consent, and any other applicable local or institutional documentation (e.g. the HIPAA (Health Insurance Portability and Accountability Act) authorization and the California Bill of Rights), the subject can then proceed with the enrollment evaluation. The subject has the right to withdraw from the study at any time without consequences, as indicated in the Informed Consent document.

If a potential study subject is illiterate, or visually impaired, and does not have a legally authorized representative, the Principal Investigator must provide an impartial witness to read the informed consent form to the subject, in their native language, and must allow time for questions. Thereafter, both the subject and the witness must sign the Informed Consent Form to attest that informed consent was freely given and understood.

The Investigator, or delegated site staff member, must retain the original, signed and dated Informed Consent Form. A copy of the signed and dated Informed Consent Form must be given to the subject. The acquisition of informed consent should be documented in the subject's medical records or study records, and the informed consent form should be signed and personally dated by the subject, or legally authorized representative, and by the Investigator or delegated site staff member, who conducted the informed consent discussion.

MicroShunt subjects who have not yet had their Month 60 Follow-Up Visit, and who still have the device implanted, will be required to sign an Addendum to the main Informed Consent Form, if they agree to have the additional assessment, gonioscopy, performed at this visit. If the subject is not willing to sign the Consent Addendum, only the assessments covered in the main Informed Consent Form will be performed at the Month 60 Follow-Up Visit.

8.2. Enrollment

All subjects who sign the Informed Consent Form will be considered enrolled in the study, even if they subsequently fail to meet the study eligibility criteria. All enrolled subjects will be entered onto the Screening and Enrollment Log and will continue to use the same subject identification (ID) number as originally enrolled under in the INN-005 study. Subjects who do not meet the eligibility criteria will be considered a screen failure and will be exited from the study. The reason(s) for screen failure will be recorded on the Screening and Enrollment Log.

8.3. Randomization and Treatment Assignment

This long-term follow-up study 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 trabeculectomy as part of the INN-005 clinical study. The study does not mandate any new treatment and subjects will continue to receive the same treatment recommended by the Investigator.

8.4. Subject Withdrawal or Discontinuation

All subjects have the right to withdraw at any point during the study without prejudice. The Investigator can discontinue any subject at any time if continued participation in the study would result in harm to the subject. All efforts should be made by the Investigator to retain the subject in the study. If a subject withdraws prematurely from the study, a genuine effort must be made to determine the reason(s) the subject discontinued the study. The reason must be recorded in the subject's file and on the End of Study Form. The site will then notify InnFocus, Inc.

8.5. Lost-to-Follow-up (LTF) Subjects

Subjects who do not present themselves for a follow-up must be contacted to encourage them to come for the follow-up visit. For those subjects who cannot be reached, at least three (3) telephone call attempts should be made and documented. If there is still no response, a registered letter shall be sent to the last known address on file for the subject in an attempt to make contact. If there is still no response, the subject will be considered Lost-to-Follow-up (LTF) unless there is subsequent communication by the subject.

9. Study Procedures and Schedule

9.1. Schedule of Events

Schedule of Events									
Activities	Enrollment[1]		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[4]
2. Eligibility Assessment	X								
3. Medical/Surgical History[2]	X	X							
4. Glaucoma Medications[3,5]	X	X	X	X	X	X	X	X	
5. Concomitant (ocular) Medications[3,5]	X	X	X	X	X	X	X	X	
6. Adverse Event Assessment[5]	X	X	X	X	X	X	X	X	
Study Procedures[6]									
1. Manifest Refraction			X		X		X		SOC[4]
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[7]			X		X		X		
8. Endothelial Cell Density			X	X	X	X	X	X	
9. Lens Status for Phakic Eyes[8]			X		X		X		
10. Dilated Fundus Exam *(incl. Vertical C/D Ratio)*			X		X		X		
11. Bleb and Seidel Test			X		X		X		
12. Diplopia			X		X		X		
13. Motility			X		X		X		
14. Gonioscopy[9]							X		

SE = Study Eye; FE = Fellow Eye

[1] 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.

[2] 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.

[3] 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.

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

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

[6] 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.

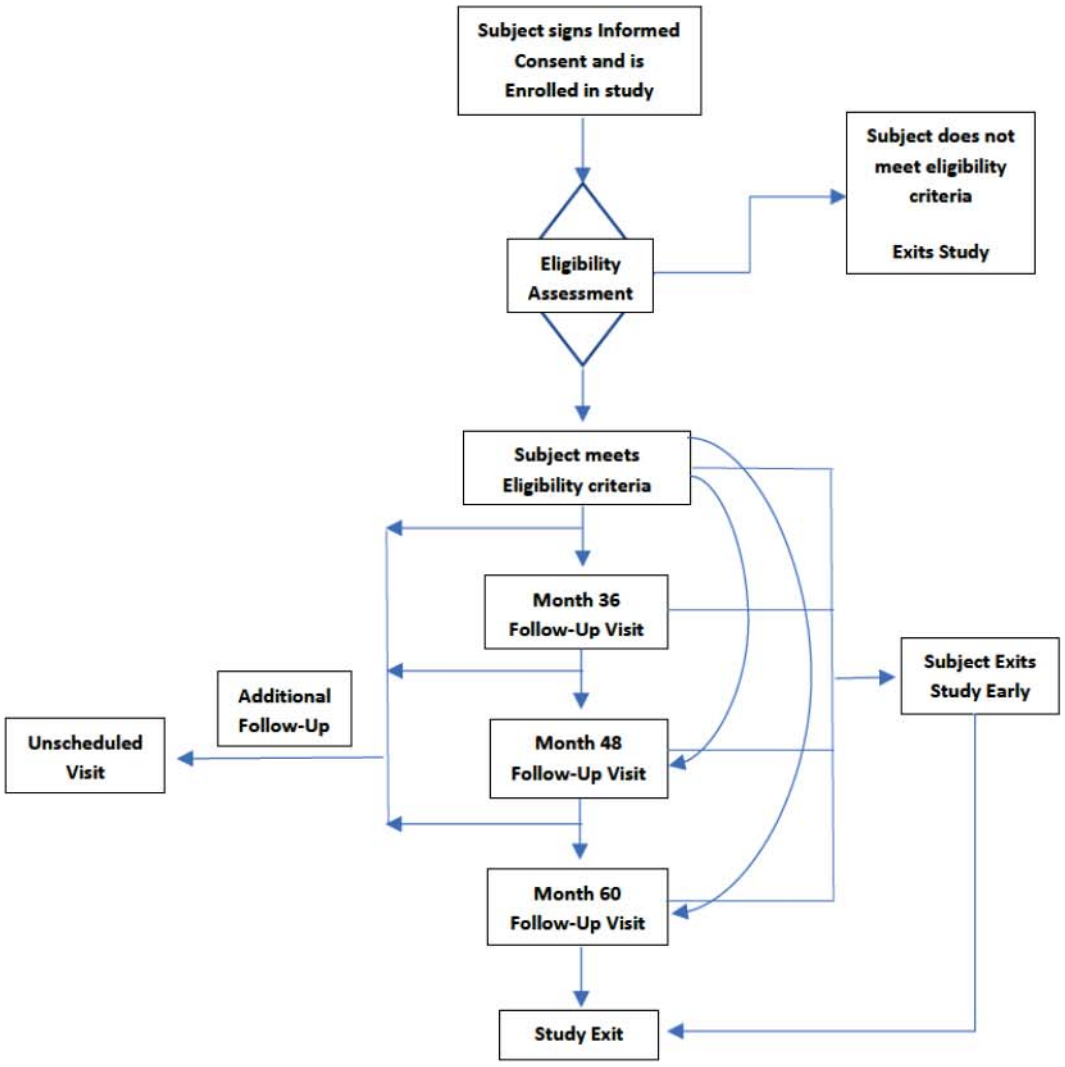
[7] Anterior Segment OCT is only required for subjects still implanted with a MicroShunt and is optional if the required equipment is not available.

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

[9] Gonioscopy is only required for MicroShunt subjects who have signed the Informed Consent Addendum and who still have the device implanted.

9.2. Study Schema

INN-005-EXT Study Schema



9.3. Study Assessments

9.3.1. Informed Consent & Research Authorization

A written informed consent (approved by InnFocus and the IRB/IEC) will be signed and dated by the subject (or the legally authorized representative, if appropriate), and the Investigator or delegated staff member prior to study enrollment. If required by local law, a HIPAA authorization form (approved by InnFocus and IRB/IEC) will be signed and dated by the subject (or legally authorized representative, if appropriate), and the Investigator prior to study enrollment. Subjects will be given a copy of the signed informed consent and HIPAA authorization form. The signed informed consent and HIPAA authorization forms will be retained with the study records at the site. It is the responsibility of the Investigator to ensure that informed consent and HIPAA authorization is obtained from each patient in accordance with GCP guidelines. Once the informed consent and HIPAA authorization is obtained, the subject will be entered into the subject Screening and Enrollment Log.

MicroShunt subjects who have not yet had their Month 60 Follow-Up Visit, and who still have the device implanted, will be required to sign an Addendum to the main Informed Consent Form, if they agree to have the additional assessment, gonioscopy, performed at this visit. If the subject is not willing to sign the Consent Addendum, only the assessments covered in the main Informed Consent Form will be performed at the Month 60 Follow-Up Visit.

9.3.2. Eligibility Assessment

After consent has been obtained, subjects will be screened for study eligibility according to the Inclusion and Exclusion criteria. Subjects deemed eligible for participation in the study, as well as screen failures, will be entered in the subject Screening and Enrollment Log. Subjects previously randomized to PRESERFLO® MicroShunt, and who had the device explanted or another device implanted, will be considered to be eligible for enrollment in this study and will not be a screen failure. For those subjects displaying mental confusion and/or signs of significant dementia, the Principal Investigator should make a determination as to whether or not the subject is able to comply with all study requirements per Inclusion criterion #3.

9.3.3. Medical/Surgical History

An assessment of the subject's medical and surgical history will be performed at the Enrollment Visit and documented on the appropriate Case Report Form (CRF). This history will include ocular medical treatments and surgeries for both the study and fellow eye. The assessment will document all ocular medical treatments and surgical events, including medication changes, occurring in the time period between the completion of the last INN-005 visit i.e. Month 24, and enrollment in this study. Adverse events (AEs) that occurred during this time period, that have ***resolved***, will be captured as part of the subject's medical/surgical history. Any AEs that are still ***ongoing*** at the time of consent will be documented as AEs and followed to resolution or study completion. Subjects with ongoing AEs at the time of study completion may exit the study if the Principal Investigator deems the subject to be stable. Any glaucoma reoperations occurring during this time period will be documented as part of the medical/surgical history and will also be captured by completing the Reoperation Form.

9.3.4. Glaucoma Medications

A glaucoma medications assessment will be performed at the Enrollment Visit and documented on the appropriate CRF for the duration of the study. This assessment will include medications for both the study and fellow eye. Only glaucoma medications taken at the time of consent, and those taken within 30 days of consent, are required to be collected. If the action taken to address an ongoing AE was to administer glaucoma medication more than 30 days prior to consent, the medication should be recorded on the appropriate CRF. Each ocular hypotensive medication will be recorded on the CRF.

9.3.5. Concomitant (Ocular) Medications

An ocular medication and supplements (including vitamins) assessment will be performed at the Enrollment Visit and documented on the appropriate CRF for the duration of the study. This assessment will include medications for both the study and fellow eye. Only medications taken at the time of consent, and those taken within 30 days of consent, are required to be collected. If the action taken to address an ongoing AE was to administer medication more than 30 days prior to consent, the concomitant medication should be recorded on the appropriate CRF.

9.3.6. Adverse Events Assessment

The Investigator or site staff will determine whether any AEs have occurred. Subjects should be encouraged during this assessment to report ocular AEs spontaneously or in response to general, non-directed questions. At any time during the study, the subject may volunteer information that resembles an AE. For subject-reported AEs, as much information as possible should be obtained, including all required treatments and outcomes of the AE.

An adverse event assessment will be performed as part of the Enrollment Visit, and at each of the Follow-Up Visits.

9.4. Study Procedures

Most of the study procedures are the same as those performed as part of the INN-005 study, as outlined in section 3.1. The only differences are the following:

Study Assessment*	INN-005 Study[1] (Month 12 and 24)	INN-005-EXT Study[2] (Month 36, 48, and 60)	Comments
IOP	Diurnal	Standard	INN-005: Diurnal IOP INN-005-EXT: Standard IOP
Anterior Segment OCT	Not performed	Performed	Added to INN-005-EXT as an optional assessment to further assess position of PRESERFLO® MicroShunt along with slit lamp examination; 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 will be

			collected. Non-serious, non-ocular AEs will not be collected.
Ocular QOL Questionnaire	X	---	Not included in INN-005-EXT
General Health Questionnaire	X	---	Not included in INN-005-EXT
Gonioscopy	X	X (Month 60) [3]	Added to INN-005-EXT to further assess position of PRESERFLO® MicroShunt; Only performed for subjects with device still implanted

[3]Only applies to MicroShunt subjects who agree to this assessment by signing the Informed Consent Addendum.

The following background information regarding the performance of some of the required study procedures is provided to assist with appropriate follow-up for all subjects in this study:

9.4.1. BCVA (ETDRS)

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 acuity testing should precede slit lamp examination, intraocular pressure measurement, the administration of topical anesthetic agents, or any examination requiring contact with the anterior segment.

The visual acuity chart must be retro-illuminated ("back-lit"). The standard chart requires a distance from subject to chart of 4 meters. Ideally, the subject should be seated. Sites should refer to the instructions on the commercial ETDRS charts and the Visual Acuity Testing Manual, provided as part of the INN-005 study.

The subject should attempt to read each letter, line by line, left to right, beginning with line 1 at the top of the chart (20/200 line). The subjects should be told that the chart has letters only, no numbers. If the subject reads a number, he or she should be reminded that the chart contains no numbers, and the examiner should then request a letter in lieu of the number. The subjects should be asked to read slowly, about one letter per second, so as to achieve the best identification of each letter. He/she is not to proceed to the next letter until he/she has given a definite response.

In order to provide standardized and well-controlled assessment of visual acuity during the study, all visual acuity assessments for a subject must be performed consistently (e.g., the same lighting conditions, viewing distance, etc.) during the entire study.

The following steps will be used for LogMAR scoring:

1. The examiner records each letter identified correctly by circling the corresponding letter on the Distance Visual Acuity Worksheet to be provided to the investigative sites.
2. Letters read incorrectly or not read at all are not marked on the form.
3. Each letter read correctly is scored as one point.
4. The total score for each eye is recorded on the worksheet after testing is completed.

9.4.2. Visual Field

Visual fields must be automated threshold visual fields, 24-2 Humphrey Stimulus III. The SITA Standard must be used for the visual field conducted at follow-up visit evaluations. If possible, follow-up visit measurements should be performed using the same instrument that acquired the INN-005 study screening measurements.

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., < 3mm). If dilation was performed at INN-005 study screening, it should be performed at all INN-005-EXT study follow-up visual field examinations. However, dilation should not be performed before the IOP measurement performed at follow-up visits.

9.4.3. Slit Lamp Exam

The study eye should include a measurement of aqueous cell and flare using the following grading system and then reported.

For anterior chamber cells, in a field size of 1x1-mm slit beam, the following grades are standardized as follows: 0 (< 1 cell), 0.5+ (1-5 cells), 1+ (6-15 cells), 2+ (16-25 cells), 3+ (26-50 cells), and 4+ (>50 cells). The presence of hypopyon is recorded separately.

The grading for anterior chamber flare is standardized as follows: 0 (none), 1+ (faint), 2+ (moderate, iris and lens details clear), 3+ (marked, iris and lens details hazy), and 4+ (intense, fibrin or plastic aqueous). The presence of corneal edema, pupillary irregularities, iris atrophy, pigment dispersion, and other slit lamp findings, should also be evaluated and noted.

9.4.4. Lens Status for Phakic Eyes

For subjects with a phakic study eye, the lens should be evaluated for presence of cataract. A LOCS III classification system is used and the outcome reported on the appropriate form. For anterior subcapsular cataracts, the LOCS III posterior subcapsular grading system is used to approximate the characteristics of the cataract and the number value reported. If no cataract is present, grade as a 0.0 in the respective categories. Use the visual LOCS III scale for grading each of the categories, i.e., nuclear (color and opalescence), cortical, posterior subcapsular, and anterior subcapsular.

9.4.5. Measurement of intraocular pressure

Each time IOP is measured, the physician or technician is to utilize a Goldmann tonometer. The individual operating the tonometer may view the dial during the measurement and may read and then record the measurement. At each visit, IOP will be measured prior to Anterior Segment OCT or dilation of the pupil.

Each time IOP is measured, two measurements should be taken, and the mean recorded on the case report form unless they differ by more than 2mmHg in which case a third measurement is taken, and the median value is recorded. All measurements must be recorded within the source documents. If possible, these values should be taken at approximately the same time of day for each visit.

9.4.6. Pachymetry

Pachymetry is performed to determine central corneal thickness. For each evaluation, three measurements are taken utilizing an electronic ultrasound pachymeter. The measurements and the mean value will be recorded in the source documents. If possible, follow-up visit measurements should be performed using the same instrument that acquired the INN-005 study screening measurements.

9.4.7. Anterior Segment OCT

In order to further assess the position of the PRESERFLO® MicroShunt tube in the eye along with slit lamp examination, Anterior Segment Optical Coherence Tomography (OCT) should be performed on subjects who still have the PRESERFLO® MicroShunt device implanted, if the required equipment is available at the investigative site.

9.4.8. Endothelial Cell Density

Endothelial cell densities may be taken before Anterior Segment OCT is completed. A Konan specular microscope is to be used for measurement of endothelial cell density at screening and at the defined follow-up periods. All readings will be conducted by the Corneal Image Analysis Reading Center (CIARC). CIARC will re-certify technicians who participated in the INN-005 study on an as-needed basis and will also re-approve specular microscopes for study participation, if required. Only instruments confirmed as calibrated by CIARC may be used. Only technicians certified by CIARC may conduct study imaging. Calibration of the specular microscope at each investigative site must be confirmed by CIARC prior to conducting the first readings. CIARC will provide sites with a detailed site manual.

All technicians at CIARC conducting endothelial cell reading will be masked to treatment group. Investigative site technicians are not required to be masked to treatment group for imaging.

For each subject, central images of the study eye and fellow eye will be collected at follow-up visits.

General instructions are as follows:

1. Place chin forward on chin rest until it touches the chin stop. Ask the subject to close teeth together and relax their head, which depresses the chin rest.
2. Forehead should touch forehead bar. Lower table enough for subject to lean in comfortably.
3. The axis of head should be perpendicular to the forehead bar.
4. Ask the subject to focus on the green indicator light.
5. Ensure the subject's pupil is within the target circle on the monitor in upper right of screen.
6. Once adjusted, tell the subject you are going to record and let them know they can blink until told to hold the eye open.
7. Press the record button.
8. Allow subject to blink until just before the "rec" sign in upper left of monitor starts flashing. This can be predicted because the beam begins to move toward dead center.
9. Tell subject to open wide and hold as soon as "rec" starts flashing.

Notes:
a. Use saline drops to moisten the eye if it is dry, photograph is black, or photograph resembles the moon's surface.
b. If a shadow prevents analysis, straighten the head left or right to center in camera. Auto may need to be turned off and camera adjusted manually + 5 increments to start to photograph in Manual Mode.
c. If subject's eyelid interferes with photograph, hold the lid for subject while keeping the forehead against the forehead bar, or lightly tape the eyelid up still allowing the subject to be able to blink.
d. IOLs can reflect multiple beams of light into the camera interfering with the photograph. If so, have subject look slightly off (right/left/up/down) from indicator light until white reflections coalesce into one or two reflection spots and then take picture.

9.4.9. Dilated Fundus Exam

A mydriatic should be used to dilate the pupil so that an examination of the fundus can be conducted with an indirect ophthalmoscope and slit lamp biomicroscopy (with contact lens, Hruby lens or 60-, 66-, 78-, or 90 diopter lens). The appearance of the optic disc, macula, vessels, and periphery should be evaluated and reported on the follow-up visit form. A measurement of the vertical cup-to-disc ratio should be made and reported. All methods used to assess nerve abnormalities at INN-005 study screening must also be used at all required INN-005-EXT study follow-up visits.

The examination will be conducted at the prescribed intervals in the schedule of events and may be used for further investigation at other follow-up periods in cases of hypotony to assure there are no choroidal effusions, choroidal detachments, or related concerns.

9.4.10. Bleb and Seidel Test

A Seidel test will be used to detect ocular perforation or a wound leak by applying a moistened fluorescein strip directly over the suspected site of perforation while observing the site through a biomicroscope using the cobalt-blue light (35).

9.4.11. Gonioscopy

Gonioscopy will be performed to assess the location of the PRESERFLO™ MicroShunt in the eye, on eligible subjects who still have the PRESERFLO® MicroShunt device implanted and who have signed the Informed Consent Addendum. A Zeiss, Sussman, or similar lens should be used and gonioscopy is to be conducted in a dark room with a narrow, short slit beam that does not pass through the pupil and without a fixation light being used. The Shaffer method will be used as follows: grade 4, wide open (35º-45º): grade 3, moderately open (25º-34º); grade 2, moderately narrow (20º); grade 1, very narrow (10º); grade 0, closed (0º). The grade number will be reported for each quadrant of the eye in the appropriate location on the form.

The position of the PRESERFLO™ MicroShunt in the anterior chamber angle, will be reported as one of the following locations: Schwalbe's line or anterior to Schwalbe's line, Trabecular meshwork, Scleral spur, or Iris root.

9.5. Equipment Requirements

The following equipment are required to be available at the investigative site in order to perform the study assessments and procedures:

1. Goldmann Applanation Tonometer
2. Humphrey Visual Field Analyzer
3. Ultrasound Pachymeter
4. Slit Lamp and Fundus contact lens, Hruby lens, or 90 diopter lens
5. Indirect Ophthalmoscope
6. ETDRS Visual Acuity System/Snellen Visual Acuity System
7. Specular Microscope (Konan XL)
8. LOCS Light Box
9. Fundus Camera
10. Light Meter
11. Goniolens (Zeiss, Sussman, or similar – not Goldmann

NOTE:

- OCT is an optional piece of equipment within this extension study. Slit lamp examination remains the primary method of assessing implant location.
- The Goldmann tonometer should be calibrated at each investigative site in accordance with the manufacturer's instructions.
- Each site is also to follow their own standard procedures for equipment maintenance and calibration by outside vendors.
- Calibration values should be recorded, and the documents maintained accordingly.

9.6. Study Visits

9.6.1. Enrollment

The following **study assessments** are to be performed at the Enrollment Visit:

1. Informed Consent & Research Authorization
2. Eligibility Assessment
3. Medical/Surgical History
4. Glaucoma Medications
5. Concomitant (ocular) Medications
6. Adverse Event Assessment

9.6.2. Month 36, 48, and 60 Follow-Up Visit

All Follow-Up Visit Assessments are identical for the Month 36, Month 48, and Month 60 Visits.

The Month 36, 48, and 60 Follow-Up Visits shall be conducted per the following windows, calculated from the subject's date of surgery in the INN-005 study:

Follow-Up Visit	Visit Window
Month 36	Day 1080 ± 90 days
Month 48	Day 1440 ± 90 days
Month 60	Day 1800 ± 90 days

The following **study assessments** are to be performed at all 3 Follow-Up Visits:

1. Glaucoma Medications
2. Concomitant (ocular) Medications
3. Adverse Event Assessment

The following **study procedures** are to be performed at all 3 Follow-Up Visits:

1. Manifest Refraction
2. BCVA (ETDRS)
3. Visual Field
4. Slit Lamp Exam
5. IOP
6. Pachymetry
7. Anterior Segment OCT
8. Endothelial Cell Density
9. Lens Status for Phakic Eyes
10. Dilated Fundus Exam *(including Vertical C/D Ratio)*
11. Bleb and Seidel Test
12. Diplopia
13. Motility

The following **additional study procedure** is to be performed at the Month 60 Follow-Up Visit, if subject has signed the Consent Addendum:

1. Gonioscopy (for MicroShunt subjects who still have device implanted)

9.6.3. Subject Follow-Up

All subjects will complete up to three (3) follow-up visits through post-operative Month 60, i.e., at Month 36, Month 48, and Month 60 (follow-up visit timepoints to be calculated from subjects' Operative Visit in the INN-005 study). 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 visit. A Follow-Up Visit Case Report Form shall be completed from source data gathered at the time the subject is examined. For any surgery or interventions not directly related to the subject's glaucoma that occur during the study, e.g., cataract surgery, the standard of care for the particular type of intervention will be followed until the subject has recovered.

Unscheduled or interim visits should also be recorded using the appropriate forms. The Schedule of Events provides an overview of all activities to be conducted during the clinical study. All attempts should be made to conduct each follow-up evaluation within the time intervals specified. Evaluations conducted outside the prescribed time period will be considered protocol deviations.

9.6.4. Unscheduled Visits

Any additional visits performed to evaluate the subject outside of the scheduled follow-up visit timeframes as set forth in the protocol, will be considered "Unscheduled Visits". An Unscheduled Visit Form will be completed to document the visit. Only assessment forms relating to actual assessments performed, are to be completed.

Unscheduled Visits are not required by this protocol. The Investigator may perform whatever assessments deemed necessary and per standard of care. Emergent Unscheduled Visits may be conducted by non-study staff, if study staff members are not available. Every attempt should be made to conduct the visit at the main study site, but treatment of emergent situations may be conducted at a non-study site (i.e. non IRB/IEC approved). Unscheduled visits performed by non-study staff, and the conduct of these visits at a non-study site, will not be considered to be protocol deviations.

Any adverse events and/or medication changes identified during an unscheduled visit should be documented in the appropriate CRF. The requirements outlined above will be the same for any unscheduled visits occurring between the time of consent for this study and the Month 36 Follow-Up Visit.

9.6.5. Subject Study Completion

Subjects complete and exit the study when they have completed the Month 60 Follow-Up Visit. Subjects will then continue to be followed by their primary health care provider as required. A subject will also be exited from the study in the following instances:

- Subject is Lost-to-Follow-Up. Multiple attempts must be made to contact the subject before withdrawing them from the study. These attempts must be documented in the appropriate CRF. For those subjects who cannot be reached, at least three (3) telephone call attempts should be made. If there is still no response, a registered letter shall be sent to the last known address on file for the subject in an attempt to make contact. If there is still no response, the subject will be considered Lost-to-Follow-up unless there is subsequent communication by the subject.
- Subject withdraws participation from the study or is withdrawn from the study by the Investigator
- Subject expiration

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or who are Lost-to-Follow-Up) will be accounted for and documented. If a subject withdraws from the clinical study, the reason(s) for withdrawal shall be reported on the appropriate CRF. If such withdrawal is due to problems related to the PRESERFLO® MicroShunt, the Investigator will ask for the subject's permission to follow his or her status/condition outside of the clinical study.

Subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. The Investigator may withdraw a subject if, in his/her clinical judgement, it is in the best interest of the subject or if the subject cannot comply with the protocol. The Sponsor must be notified of all withdrawals.

If a subject withdraws their consent to participate, or the Investigator decides to withdraw the subject, it will be documented in the appropriate CRF. No additional data may be collected after the point at which a subject has been withdrawn from the study or withdraws consent. Withdrawn subjects will not be replaced. All open Adverse Events should be closed or documented as ongoing. Data collected up to the point of subject withdrawal may still be used.

10. Risks and Benefits

InnFocus has reviewed the potential risks and benefits associated with the PRESERFLO® MicroShunt device. The risks have been evaluated, and design and procedure recommendations implemented, to mitigate these risks where applicable.

10.1. Potential Risks

This protocol extends the study participation period for subjects who were previously randomized and treated with either a PRESERFLO® MicroShunt or a trabeculectomy procedure in the INN-005 clinical study. The risks originating from participation in the original INN-005 study persist regardless of a subject's participation in this Extension Study. Subjects who consent for this Extension Study will return for up to three (3) additional annual follow-up visits through post-operative Month 60, and have their data collected. No medical or surgical intervention is required by this protocol, and subjects may receive treatment as recommended by their clinician, if needed. Participation in this Extension Study, therefore, does not result in any additional risk to subjects.

10.2. Potential Benefits

There are no specific benefits to participating in this extension study, other than contributing to the furtherance of research that could potentially benefit other patients with Primary Open-Angle Glaucoma.

10.3. Risk-Benefit Rationale

The additional clinical assessments required as part of participation within this extension study pose negligible risk as all assessments are performed using FDA cleared devices.

10.3.1. Risk Minimization Actions

Additional risks may exist. Measures which have been taken to minimize risks include:

- Specific Investigator training on the management of the device
- A well-defined clinical protocol, including specific inclusion/exclusion criteria to enroll appropriate subjects in the study
- Ongoing monitoring of study data and results by the study Sponsor or designee

Risks can be minimized at the investigative site through:

- Compliance with this protocol
- Performing assessments and procedures in the appropriate clinical or hospital environment
- Adherence to subject inclusion/exclusion criteria
- Close monitoring of the subject's physiologic status during follow-ups

11. Interventions

11.1. Physical Interventions

At follow-up visits relatively routine practices may need to be performed by the Investigator, at his/her discretion, to assure a diffuse bleb and lower IOP. These interventions **are not considered to be Adverse Events** in the study. Examples of such interventions are the following:

a) Eye massage done by the Investigator. Eye massage will be documented on the appropriate Follow-Up Visit Form. **Eye massage should only be done by Investigators and not by subjects.**
b) Laser suture lysis. Laser suture lysis is commonly used to lyse one or more sutures after surgery to bring the IOP down. Tensioning of the sutures used to close the scleral flap may set the pressure higher than desired, but tight suturing is done purposely in many cases to limit acute hypotony. Suture lysis is to be documented on the appropriate Follow-Up Visit Form.
c) Use of temporary glaucoma medications. Depending on the surgeon's method of tightening the scleral flap during trabeculectomy procedures, the surgeon may choose to temporarily use glaucoma medications rather than lyse a suture too early and cause hypotony. Therefore, the use of temporary glaucoma medications for post trabeculectomy subjects may be employed and will be documented on the appropriate CRF as needed. The use of a topical Carbonic Anhydrase Inhibitor (CAI) or alpha-2 adrenergic agonist is typically used for this purpose because of the short washout periods (5 days for CAI and 14 days for alpha-2 adrenergic agonist), and if any other glaucoma medication is used, a rationale should be provided on the appropriate Follow-Up Visit Form.

Interventional techniques may be employed at the discretion of the Investigator to control any increase or decrease in a subject's IOP. For any intervention, the reason for the decision will be noted on the case report form as one or more of the following: IOP increase, IOP decrease, visual field change, optic nerve change, or temporary glaucoma medication use pending suture lysis. A field for "Other" will be used to document any other reason for the intervention.

Additional **Physical Intervention** may be considered prior to employing glaucoma medications to bring the IOP down. The reasons for the IOP increase are multiple but there are two commonly observed methods for reducing the IOP:

1. **"Needling the bleb"** to overcome partial or complete closure of the bleb. In these cases, the PRESERFLO® MicroShunt or trabeculectomy path to the anterior chamber is open and can allow flow, but the lack of an adequate subconjunctival drainage field is preventing this. To improve the flow, a needle is inserted into the sub-Tenons/conjunctival area, any fibrous attachment separated, and the pocket re-established (this is not a failure criterion but an event requiring needling is to be **documented on the Adverse Event form**). ("Failure" is as defined in section 21.3).
2. **Needling with an injected antifibrotic** may be preferred. Both MMC and 5FU are used to accomplish this. If either antifibrotic is injected subconjunctivally, the type of antifibrotic, dosage, and method of introduction by the Investigator, should remain consistent throughout the study. Dosages of MMC and 5FU vary by Investigator and are in the 10-100 microgram range for MMC and 5-10 milligram range for 5FU. The dosage may be delivered as a mixture with an anesthetic, e.g., Lidocaine. The total dosage volume is in the 0.1-0.3ml

range. The name of the antifibrotic, injection volume, dosage, and mixed anesthetic or other agents, are to be documented in the Concomitant Medications Log and needling is to be indicated on the **Adverse Event Form** as the action taken to address the event.

3. **Laser removal of blockage** at the tip of the PRESERFLO® MicroShunt, or at the anterior chamber entry point for a trabeculectomy, is another possibility and is to be documented on the **Adverse Event Form** as the action taken to address the event.

A **Secondary Procedure** that is performed including a trabeculectomy, repositioning of a PRESERFLO® MicroShunt, Tenon's resection, glaucoma laser (other than to remove a blockage), glaucoma drainage device, or other incisional treatment to establish a new aqueous flow path from the anterior chamber in order to maintain acceptable IOPs, will be **considered a failure of the original procedure**.

If the PRESERFLO® MicroShunt is repositioned, removed, and/or replaced with another type of device based on the device performance, the conjunctiva should be cut at the limbus in a similar manner to the original procedure. The device should be exposed, and the repositioning or removal conducted. If the device is removed, verify that there is no aqueous leakage from the track. If there is, use a Vicryl or Nylon suture to seal the track. The limbus should then be resutured in a similar manner as the original surgery. The removed PRESERFLO® MicroShunt should be returned to InnFocus, Inc. for analysis in accordance with the Device Return Procedure.

If the PRESERFLO® MicroShunt is removed, an alternate procedure/treatment should be used. If repositioning, removal, replacement, or removal with another glaucoma procedure occurs, the event will result in the subject being followed according to standard of care until the adverse event resolves, and the follow-up visits per the protocol schedule will be part of the safety analyses.

11.2. Glaucoma medications

The Investigator may also reinitiate glaucoma medication at his/her discretion.

NOTE: It is no longer required that medical therapy only be reintroduced if the predesignated intervention pressure is reached. Glaucoma medications may be added if common physical interventional techniques have been employed, but do not decrease the IOP for any subject, or if physical intervention is not attempted at all to reduce the IOP.

If glaucoma medications need to be re-introduced, the Investigator has the discretion to defer glaucoma medications to which the subject is naïve until after previously used medications have been introduced. Barring interfering factors regarding the method of re-introduction of glaucoma medications, the Investigator may decide to first add a beta blocker, then a prostaglandin, and either an alpha adrenergic agonist or a carbonic anhydrase inhibitor as a third medication. In keeping with routine practice, the Investigator may also elect to add medications one at a time in order to determine the IOP lowering effect, before introducing the next medication. Based on the IOP level, the physician should decide on which medications, dosage, and order of re-introduction to choose. The rationale for the re-introduction or discontinuation should be documented in the appropriate Follow-Up Visit Form field identified as

"Investigator rationale for medication re-introduction or discontinuation". New categories of topical glaucoma medical therapies introduced into medical practice after the initiation of this study may be added at the discretion of the Principal Investigator (PI), but it is encouraged to begin with the four categories mentioned above that were available at the beginning of the INN-005 study.

Based on the sequence of drug re-introduction chosen by the Principal Investigator, if an oral carbonic anhydrase inhibitor is required, it will be counted as a failure. This is unlikely to occur if oral carbonic anhydrase inhibitors are the last drug added.

Medications which have been re-started by the Investigator may be discontinued if in the Investigator's judgment the target IOP has been reached and the continued use of some or all of the therapy may not be required. Discontinuation of medications after re-introduction is recommended to be in the reverse order of re-introduction. The rationale for discontinuation will also be documented on the appropriate Follow-Up Visit Form by the Investigator. For medication discontinuation, the reason for the decision will be noted on the case report form such as IOP controlled, allergy to medication, or subject has undergone additional glaucoma surgery. A field for "Other" will be used to document any other reason for glaucoma medication discontinuation.

Another potential reason for intervention is an IOP below 6mmHg (hypotony). Interventions such as those indicated below should only be considered if the hypotony has caused or is likely to cause sequelae such as a flat chamber. No intervention is indicated when the vision is unchanged from the previous visit, there is no persistent choroidal detachment, the anterior chamber is not flat with lens-corneal touch, or the subject is asymptomatic. No intervention should be undertaken for hypotony which is not causing, or threatening to cause, a reduction in vision, as the intervention might cause procedure failure. These interventions should be documented as Adverse Events. Otherwise, the hypotony should be monitored with additional follow-ups as necessary.

1) Too loose or not enough sutures can result in hypotony that may be treated by adding more sutures in a separate surgical intervention (this action will be **considered a failure**).

2) Introduction of viscoelastic into the Anterior Chamber for the purpose of slowing aqueous flow and eliminating hypotony that is causing a reduction of best corrected visual acuity (two or more lines) or causing the presence of persistent choroidal detachment (3 or more months if peripheral, up to one month if kissing), or causing hypotony maculopathy (also **documented on the Adverse Event Form as the action taken for an event**.)

12. Adverse Events

An adverse event is any symptom, sign, illness, or experience, which develops or worsens during the course of the study, and which may or may not be considered device and/or procedure related.

Terms and definitions for the assessment of safety are in accordance with FDA Code of Federal Regulations Title 21 Part 812 and the ISO 14155:2011 standard, entitled "Clinical investigation of medical devices for human subjects- Good clinical practice".

Adverse Event (AE)

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.

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.

Serious Adverse Event (SAE)

A Serious Adverse Event is an adverse event that:

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, or
    2) a permanent impairment of a body structure or a body function, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: 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.

NOTE: 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.

Sight-threatening Adverse Event

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.

Unanticipated Adverse Device Effect (UADE)

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.

13. Assessment of Safety

Adverse Events will be collected for all enrolled subjects beginning at the Enrollment (Screening) Visit until the subject completes the study. The Principal Investigator is responsible for ensuring that all adverse events observed by the Investigator or site staff, or reported by subjects, are properly captured and recorded on the Adverse Event Form.

ENROLLMENT:

All SAEs that occurred between the Month 24 Visit of the INN-005 study and the time of consent for the INN-005-EXT study, are still ***ongoing*** at the time of consent, and for which surgery, physical intervention, or medication changes was required, whether they are considered to be device- or procedure-related or not, will be documented as AEs at the Enrollment Visit.

All ocular AEs, for both the study and fellow eye, that occurred between the Month 24 Visit and the time of consent, that are still ***ongoing*** at the time of consent, and for which surgery, physical intervention, or medication changes was required, will be documented as AEs at the Enrollment Visit.

All SAEs and ocular AEs that occurred between the Month 24 Visit and the time of consent, for which, surgery, physical intervention, or medication changes was required, and which are ***resolved*** at the time of consent, shall be captured in the subject's Medical/Surgical history at the Enrollment Visit.

If the action taken to address an ongoing AE at the time of consent was to administer medication more than 30 days prior to consent, the concomitant medication should be recorded on the CRF.

FOLLOW-UP:

All SAEs occurring during the study from the time of consent for the INN-005-EXT study will be assessed at each of the follow-up visits. SAEs, whether they are considered to be device- or procedure-related or not, must be documented.

All ocular AEs occurring during the study from the time of consent will be assessed at the follow-up visits. Ocular AEs in both the study and fellow eye, whether they are considered to be device- or procedure-related or not, must be documented.

All AEs must be followed until resolution or until a stable clinical outcome is reached. Additional follow up information may be needed if an event has not resolved or is not stable at the time of study completion. Subjects with ongoing AEs at the time of study completion may exit the study if the Principal Investigator deems the subject to be stable.

13.1. Anticipated Adverse Events

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. Specific examples of anticipated adverse events include:

1. **Hypotony;** defined as IOP <6mmHg.
2. **Increased intraocular pressure requiring medical or surgical intervention**; Increased intraocular pressure will be considered an adverse event if a subject has an IOP higher than the preoperative medicated screening pressure or 21mmHg, whichever is lower. At this IOP level, the Investigator will intervene either physically or with the addition of glaucoma medication. There may also be cases where intervention for increased IOP is done at a lower IOP level than stated above because of other patient-related factors; these will also be adverse events.
3. **Decrease of BCVA**; BCVA decreases of 2 lines or more should not be reported as adverse events until they occur at two consecutive visits unless surgical or medical intervention is required. If the first decrease is noted at the Study Exit Visit, the subject will be exited and not brought back. In this case, the decrease will not be documented as an adverse event. (Note: a loss of BCVA in conjunction with posterior capsular opacification, followed by Nd:YAG capsulotomy and improvement of BCVA, is not considered an adverse event.)

13.2. Post-operative Anticipated Adverse Events

- Anterior chamber puncture
- Aqueous humor misdirection (malignant glaucoma)
- Blebitis
- Bleb leak
- Bleb related complications e.g. cystic bleb, flat bleb
- Cataract progression
- Choroidal effusion/detachment
- Choroidal hemorrhage
- Chronic iritis
- Chronic pain

- Clinically significant corneal damage
- Clinically significant iris damage
- Confirmed worsening in the visual field of mean deviation (MD) of ≥2.5 dB compared to the MD used to determine subject eligibility (confirmed on at least 2 out of 3 visual field tests performed after 3 months post procedure)
- Conjunctival dehiscence
- Conjunctival dissection
- Corneal abrasion
- Corneal edema
- Diplopia
- Device malfunction
- Encapsulated bleb
- Endophthalmitis
- Erosion of the device through the conjunctiva
- Event requiring unplanned glaucoma-related ocular surgical intervention
- Event requiring unplanned surgical intervention for reason other than glaucoma
- Flat anterior chamber
- Hyphema at any time (including microhyphema)
- Hypotony (IOP<6mmHg at any time)
- Hypotony maculopathy
- Implant migration
- Increase in C/D ratio of ≥0.3 units on slit lamp biomicroscopic examination
- Increased IOP requiring treatment
- Leakage of wound site
- Loss of light perception
- Loss of 2 lines or more of BCVA on 2 consecutive follow-up visits
  (Note: a loss of BCVA in conjunction with posterior capsule opacification, followed by Nd:YAG capsulotomy and improvement of BCVA, is not considered an adverse event)

- Macular edema
- Optic disc hemorrhage
- Posterior capsule opacification
- Proptosis
- Ptosis
- Pupillary block
- Retinal complication (dialysis, flap tears, detachment, decompression or proliferative retinopathy)
- Shallow anterior chamber
- Strabismus
- Subconjunctival bleeding at any time
- Suture abscess or other local infection
- Tube obstruction, partial or complete, regardless of how long the obstruction is present
- Tube touching cornea
- Tube touching iris
- Use of a viscoelastic to limit aqueous flow
- Vitreous hemorrhage

13.3. Sight-Threatening Anticipated Adverse Events

Sight-threatening Adverse Events include, but are not limited to, events such as:

1. Endophthalmitis
2. Corneal decompensation
3. Severe retinal detachment
4. Severe choroidal hemorrhage
5. Severe choroidal detachment
6. Aqueous misdirection

14. Adverse Event Reporting

14.1. Safety Reporting Information Requirements

Each subject will be carefully evaluated by the Investigator for Adverse Events. Any complication occurring, whether or not related to the device, will be considered an Adverse Event and will be recorded on the Adverse Event Form. The Investigator will document the Adverse Event's severity classification and relationship to the device and procedure on the Form. The following Adverse Event attributes must be assigned by the Principal Investigator:

- Adverse event (diagnosis if known, signs and symptoms if not known)
- Date of onset
- Date of resolution
- Outcome
- Severity
- Relationship to the device and/or device explantation procedure

Assessment of Severity:

The description of the severity of the adverse event on the Adverse Event Form should use the following scale:

Mild: Any event that results in minimal transient impairment of body function or damage to a body structure, and does not require intervention other than monitoring

Moderate: Any event that results in moderate transient impairment of body function or damage to a body structure, or requires intervention to prevent permanent impairment of body function or damage to a body structure

Severe: Any event which is life threatening, which results in permanent impairment of a body function or damage to a body structure, or which requires significant intervention (e.g., a major surgery), to prevent permanent impairment of a body function or damage to a body structure.

Assessment of Relatedness:

All Adverse Events will be classified by the Principal Investigator with respect to attribution of causality according to the following classifications:

Device Related:
An adverse event that is directly related to the use, presence and/or performance of the PRESERFLO® MicroShunt.

Procedure Related:
An adverse event that is directly related to the initial study surgical procedure (PRESERFLO® MicroShunt, Trabeculectomy, or general surgical complications).

Not related:
The adverse event was not caused by the device, its explantation, or the procedure.

- **Definite:** Follows a reasonable temporal sequence from device delivery/retrieval and cannot be reasonably explained by known characteristics of the subject's clinical data or the surgical procedure applied.
- **Probable:** Follows a reasonable temporal sequence from device delivery/retrieval that is unlikely to have been produced by the subject's clinical state or by the surgical procedures regardless of the device.
- **Uncertain:** Follows a reasonable temporal sequence from device delivery/retrieval but could have been produced by the subject's clinical state or by the surgical procedures regardless of the device
- **None:** Temporal association is such that the device is not likely to have had any reasonable association with the observed event.

14.2. Adverse Event Reporting Procedures

All Adverse Events should be documented in the EDC by completing the Adverse Event Form and, if applicable, an IRB/IEC-specific form. Identification and collection of adverse event information will be the joint responsibility of the study Sponsor, the CRO, and the study investigators. The Sponsor, Investigator, and the CRO will all follow the Declaration of Helsinki in order to ensure the safety of all subjects.

14.2.1. Adverse Events

Adverse Events, regardless of whether they are deemed device- or procedure-related, should be documented as soon as possible after learning of the event by completing the Adverse Event Form.

14.2.2. Serious Adverse Events

All Serious Adverse Events, regardless of whether they are deemed device- and procedure-related, should be **reported immediately (within 24 hours of becoming aware of the event)** to the Sponsor, or designee:

[redacted]

All SAEs should also be documented in the EDC as soon as possible after learning of the event, by completing the Adverse Event Form and designating the event as **serious**. All SAEs should be assessed for whether or not they meet the definition of a UADE. If yes, the Adverse Event Form should be completed accordingly. The Investigator should adhere to the following reporting guidelines when completing the Adverse Event Form for SAEs:

a) A detailed description of the Serious Adverse Event will be recorded in the Adverse Event Form and the subject's research records.
b) Serious Adverse Events unresolved following this period would be followed up until resolved. Subjects with ongoing AEs at the time of study completion may exit the study if the Principal Investigator deems the subject to be stable.
c) The Investigator should inform InnFocus, or its designee, within 24 hours of any finding with the use of the study product that may suggest significant hazards, contraindications, and precautions pertinent to the safety of the study product.
d) The Investigator should notify the IRB/IEC about Serious Adverse Events according to their standard procedures.
e) A copy of the IRB/IEC report will be filed with the subject's binder, if applicable.
f) The Investigator will comply with any local regulations regarding the reporting of Serious Adverse Events.
g) Preliminary reports, by telephone and in writing, should be followed up on later with detailed descriptions which may include copies of expiration summaries, autopsy reports, or other documents where applicable.

14.2.3. Sight-threatening Adverse Events

Sight-threatening Adverse Events will be reported to InnFocus, Inc. **immediately (within 24 hours of becoming aware of the event)** and to the Investigator's IRB/IEC as soon as possible, but no later than **10 working days** after the Investigator first learns of the event.

14.2.4. Unanticipated Adverse Device Effects

All Unanticipated Adverse Device Effects (UADEs) will be reported to the study Sponsor, InnFocus, Inc. by email and/or telephone, and to the reviewing IRB/IEC as soon as possible but no later than **10 working days** after the Investigator first learns of the event. The UADE should be documented in the EDC as a Serious Adverse Event using the Adverse Event Form. The date of event, its severity, treatment if any, and the assessed relationship of the event to the study device will be recorded on the Adverse Event form. The Sponsor will conduct an evaluation of all reported UADEs. The Sponsor shall report the results of such an evaluation to the FDA, and to all reviewing IRBs/IECs and participating investigators, within **10 working days** after the Sponsor first receives notice of the effect. If the Sponsor determines that the UADE presents an unreasonable risk to subjects, the parts of the investigation presenting risk will be terminated. Termination will occur no later than **5 working days** after the Sponsor makes such a determination and no later than **15 working days** after the Sponsor first received notice of the effect.

Any UADEs involving a reoperation in the study eye, requiring the following should be documented on the Reoperation Form:

a. Trabeculectomy
b. Placement of a drainage device
c. Bleb revision (other than needling)
d. Explantation or repositioning of the PRESERFLO® MicroShunt
e. Iridectomy
f. Re-suturing of the scleral flap

The following procedures should be documented as the action taken for an Adverse Event:

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

The following procedures should be documented as the action taken for an Adverse Event:

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

14.3. Follow-Up of Subjects after Adverse Events

Adverse Events will be followed until resolved or considered medically stable. The Principal Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as possible the nature and/or causality of the Adverse Event.

The Investigator is responsible for recommending the type and duration of follow-up for each subject who experiences an Adverse Event. All events must be followed until complete resolution, resolution with sequelae, or the subject exits from the study. Subjects with ongoing AEs at the time of study completion may exit the study if the Principal Investigator deems the subject to be stable. All details must be documented on the Adverse Event Form. It will be up to the Principal Investigator's clinical judgment to determine whether an Adverse Event is of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment after what he or she perceives is an intolerable Adverse Event. If either of these situations arises, the subject should be strongly advised to remain under supervision until the condition becomes medically stable.

If a subject requires an additional glaucoma surgery, the subject shall continue to be seen for the required follow-up visits so that safety can continue to be monitored. Unscheduled visits may be conducted at the Investigator's discretion to provide the necessary standard of care treatment.

Subjects who are terminated from the study due to the adverse events will be followed until their medical outcome is determined, and the Adverse Event Form updated accordingly. Unscheduled visit forms are not required to be entered after termination. Written reports will be provided to the Sponsor by the Investigator.

15. Medical Monitor

An independent Medical Monitor will be utilized for this clinical study. The Medical Monitor will not be an Investigator in the study. The Medical Monitor will be a certified ophthalmologist with a glaucoma specialization. The Medical Monitor will review Adverse Events and determine if the appropriate actions have been or are being taken and may request additional follow-up information. Subjects with ongoing AEs at the time of study completion may exit the study if the Principal Investigator deems the subject to be stable. This determination may be made without consulting with, and seeking approval from, the Medical Monitor.

16. Data Safety Monitoring Board (DSMB)

A Data Safety Monitoring Board (DSMB), consisting of members with pertinent expertise, will be utilized for this clinical study. The DSMB established for the INN-005 clinical study will be used and will be governed by a separate study-specific DSMB Charter. The DSMB consists of three members and was established by the Sponsor.

The DSMB will periodically review safety data in order to advise the Sponsor regarding the long-term safety of study subjects. The DSMB will not be masked to subjects' treatment assignments. After DSMB review of safety data, the DSMB Chair will provide the Sponsor with the Board's observations.

The DSMB is expected to meet at least once a year throughout the duration of the study but may be convened on an *ad hoc* basis at any time in response to safety signals.

17. Protocol Deviations

17.1. Protocol Deviation Handling

An Investigator must not make any changes to or deviate from this Clinical Investigation Plan (CIP), except to protect the life or physical well-being of a subject in an emergency. An Investigator shall notify the Sponsor and the reviewing IRB/IEC of any emergency deviation from the CIP as soon as possible, but in any event **no later than 5 working days after the emergency occurred**. All deviations from the clinical protocol, including those related to inclusion or exclusion criteria, conduct of the investigation, subject management, or subject assessment, must be documented and reported to the Sponsor using the Protocol Deviation Form, with the reason for the deviation and the date of occurrence. The investigative site may also be required to report deviations to their IRB/IEC per their policies.
Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, and appropriate corrective and preventive actions (including notification, site re-training, or discontinuation) will be put into place by the Sponsor.

17.2. Major Protocol Deviations

A major protocol deviation is a protocol violation that 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.

17.3. Minor Protocol Deviations

A minor protocol deviation is a protocol violation that does not adversely affect the risk/benefit ratio of the study, the rights, safety, or welfare of the participants or others, or the integrity of the study.
Examples of minor protocol deviations include:

- Study procedure conducted out of timeframe
- Study visit out of timeframe
- Copy of consent form not given to participant during informed consent process
- Site over-enrollment
- Missing original signed consent, but have a copy of the participant signed consent

17.4. Fellow Eye Deviations

A "Fellow Eye Only" protocol deviation only impacts the fellow eye.

18. Regulatory and Ethics Obligations

18.1. Statements of Compliance

This study will be conducted in accordance with the relevant sections of the ICH Guidelines for Good Clinical Practice, ethical principles that have their origins in the Declaration of Helsinki, FDA 21 CFR Part 812, ISO 14155:2011, and any applicable local regulatory requirements. The study shall not begin until the required IRB/IEC approval has been obtained. The IRB/IEC will review all appropriate investigational documentation in order to safeguard the rights, safety, and well-being of the subjects. The investigation will only be conducted at sites where IRB/IEC approval has been obtained. The clinical protocol, informed consent, written information given to the subjects, safety updates, progress reports, and any revisions to these documents, will be provided to the IRB/IEC by the Investigator. Any additional requirements imposed by the IRB/IEC shall be followed, if appropriate.

18.2. Investigator Responsibilities

The Principal Investigator of an investigative site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical protocol, ISO 14155:2011, FDA 21 CFR Part 812, ethical principles that have their origins in the Declaration of Helsinki, and any conditions of approval imposed by the reviewing IRB/IEC, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following:

- Prior to beginning the study, sign the Investigator Agreement and Protocol Signature Page documenting his/her agreement to conduct the study in accordance with the protocol.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical study.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical study-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.
- Record, report, and assess every Adverse Event.
- Report to the IRB/IEC and Sponsor any SAEs, and supply InnFocus with any additional information related to the safety reporting of a particular event.
- Maintain the study product accountability records, ensuring that study product disposition is tracked appropriately.
- Allow the Sponsor to perform monitoring and auditing activities and be accessible to the monitor and respond to questions during monitoring visits.
- Allow and support regulatory authorities and the IRB/IEC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with this protocol and IRB/IEC requirements.

- Inform the subject of any new significant findings occurring during the clinical study, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that the investigative site facilities and study team are adequate and are maintained and documented for the duration of the clinical study.

18.3. Delegation of Responsibilities

When specific tasks are delegated by the Principal Investigator, including but not limited to conducting the informed consent process, where appropriate, the Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. Delegation or responsibilities will be assigned and recorded on the Delegation of Authority Log. Any changes to responsibilities must be approved by the Investigator. The Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

18.4. Institutional Review Board/Independent Ethics Committee

Prior to gaining approval to enroll subjects in the study, the investigative site will provide the Sponsor with documentation verifying that their IRB/IEC is registered. A copy of the written IRB/IEC approval of the protocol and Informed Consent Form must be received by the Sponsor before enrollment of subjects into the study. Prior approval must also be obtained for other materials that will be provided to the subject. Annual IRB/IEC approval and renewals will be obtained throughout the duration of the study as required by the IRB/IEC. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be provided to the Sponsor.

18.5. Deviations from Clinical Investigation Plan

Protocol modifications may occur during the study. Each will be approved by the Sponsor before implementation and will undergo IRB/IEC review and approval as necessary, per section 17.1.

18.6. Informed Consent

The informed consent document and consent process will be compliant with the requirements in ISO14155:2011 and Good Clinical Practice. An Informed Consent Form template will be provided by InnFocus, Inc. Any updates to the template made by the site will be communicated to InnFocus, Inc. by the site will be approved by the Sponsor prior to IRB/IEC submission. The final informed document to be used in the consent process must be prepared in the native language(s) of the subject population(s) being studied at the investigative site.

Before any study-related procedures are performed, the Principal Investigator is responsible for obtaining written informed consent from the subject, or legally authorized representative (LAR), after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study.

The informed consent discussion need not be performed by the Principal Investigator, if not required by law, but the individual who performs the discussion must be listed on the site's Delegation of Authority Log as being approved to obtain informed consent for this study.

18.7. Communication with Institutional Review Boards and Independent Ethics Committees

A copy of the Clinical Investigation Plan (CIP), proposed Informed Consent Form, and other written information or materials given to subjects, must be submitted to the IRB/IEC for written approval. A copy of the written approval must be received by InnFocus before enrollment of any subjects into the study.

The Principal Investigator must submit to, and where necessary obtain approval from, the IRB/IEC for all subsequent amendments and changes to the CIP, or the informed consent document. As outlined in ISO14155:2011, the Principal Investigator must notify the IRB/IEC of significant deviations from the protocol and any reportable Adverse Events occurring at the investigative site, and similar reportable events that occur at other study sites, as received in periodic reports from InnFocus.

The Principal Investigator will be responsible for obtaining annual IRB/IEC approval renewal throughout the duration of the study. Copies of the Principal Investigator's reports, and the IRB/IEC continuance of approval, must be sent to InnFocus.

18.8. Document Requirements

The Principal Investigator is responsible for forwarding the following documents to InnFocus (or designee) for review before enrollment of subjects can occur:

a) Copy of the IRB/IEC-approval of the protocol and any subject-facing study materials
b) Copy of IRB/IEC-approved informed consent form
c) Signed and dated Protocol Signature Page
d) Signed Clinical Trial Agreement
e) Signed Financial Disclosure Form
f) Up to date CV of Principal Investigator and all Sub-Investigators
g) Up to date Medical License of Principal Investigator and all Sub-Investigators
h) GCP Training certificates for all Investigators and study staff
i) Other documents as required by local regulations

18.9. Direct Access to Source Data/Documents

It is required that the Principal Investigator and institution permit authorized representatives of the Sponsor company, regulatory agency(ies), and the IRB/IEC, to have direct access to the subject's original medical records for verification of study-related procedures and data. Direct access includes analyzing, verifying, and reproducing any reports that are important to the evaluation of the study.

18.10. Subject Confidentiality

The Principal Investigator must ensure that the subject's confidentiality is maintained. On the eCRFs and all other documents submitted to InnFocus, subjects will be identified by the subject identification number.

Any original or reproductions of subject medical records, provided by the investigative site for the purposes of verifying study-related procedures, will have personally identifying information redacted in a way that preserves subject confidentiality. The Principal Investigator is obligated to inform and obtain

the consent of the subject to permit such named representatives to have access to the subjects' study-related records.

18.11. CIP Amendments

This clinical protocol is to be followed exactly. If a protocol revision is necessary, an amendment is required. Appropriate IRB/IEC approval of the revised protocol must be obtained prior to implementation. Any change that would require alteration of the Informed Consent form must receive approval from all persons who approved the original clinical investigational plan and from the IRB prior to implementation. If it is necessary to amend the clinical protocol, the CRFs will also be reviewed to determine if an amendment of these forms is also necessary.

Deviations from the CIP shall not be allowed except when necessary to ensure subject safety. CIP deviations will be listed by the CROs monitoring group using forms including the deviation, the reason why it was done, and corrective action plan. The form will have a signatory line by the sponsor's medical monitor and the Principal Investigator or designee. The study monitoring plan will have criteria for Principal Investigator disqualification for continuing the study.

Protocol deviations, except where necessary to eliminate an immediate hazard to subjects, must be approved by InnFocus prior to implementation. The IRB/IEC must approve all protocol amendments and amendments to the informed consent. The Principal Investigator must send a copy of the IRB/IEC approval letter for such amendments to InnFocus. The FDA, and as applicable, and the National Competent Authority will review and approve the amendment and will not become effective at the site until such approval.

19. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the monitor will verify that study records are adequately maintained, and that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively.

19.1. Site Monitoring

InnFocus or its designee(s) will monitor the study in a manner consistent with applicable health authority regulations and the clinical research standards adopted by InnFocus. Study monitoring will involve the following elements:

a) InnFocus or its designee(s) will meet with Investigators prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the Investigator with the study protocol and Good Clinical Practices.
b) InnFocus or its designee(s) may meet with the Investigator(s) at the time the investigative site begins to enroll in order to ensure that subjects are being properly enrolled, and that study data are being correctly recorded.

c) InnFocus or its designee(s) will visit the investigative site at any time during the study to review and/or collect the Case Report Forms.
d) Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure proper study progress and documentation of study findings.

Monitoring will be done during a Site Initiation Visit, a Site Closeout Visit, and at Interim Monitoring Visits throughout the study. The monitor is responsible for performing source document verification at regular intervals throughout the study to verify adherence to the CIP, as well as completeness, accuracy and consistency of the data, and adherence to ISO 14155:2011, GCP, and local regulations. Monitoring visits will include ongoing review of adequacy of site facilities, investigational device security and accountability, changes in site staff, and safety reporting. The monitor must have access to the subject medical records and other study-related records in order to verify the entries on the eCRF as part of the source document verification process.

The monitor will issue reports from these visits that will be reviewed by InnFocus. In these reports' problems will be identified, and resolution by corrective action, will be tracked and documented. The Principal Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing the CRFs/EDC pages are resolved.

19.2. Source Documents

The Investigator/Institution guarantees direct access to original source documents, including imaging documentation, by InnFocus, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is being seen by a non-study physician at a non-study institution, photocopies of the original source documents must be made available for review. Paper versions of the study case report forms will be provided and may be used as source documents to record subject data. If paper CRFs are used as source, they need to be signed and dated by either the Principal Investigator or the site staff member conducting the assessment.

19.3. Clinical Monitoring Plan

A Clinical Monitoring Plan (CMP) will be developed prior to the initiation of the investigation which outlines the extent and nature of monitoring appropriate for the clinical study, including the frequency of visits and the strategy for source data verification, based on considerations such as the objective, design, complexity, size, critical data points, and endpoints of the clinical study. All data will be verified against source documents during the monitoring process. The site monitoring for this study will be performed by InnFocus or a CRO designee in accordance with requirements in ISO 14155:2011 and GCP.

19.4. Audits

The study may be subject to a quality assurance audit by InnFocus or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study staff are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

This study may be selected for audit by quality assurance representatives from InnFocus or an authorized designee. Inspection of site facilities (e.g., investigational device storage, laboratories) and

review of study-related records will occur during such audits in order to evaluate the trial conduct and compliance with the CIP, ISO 14155:2011, GCP and applicable local regulatory requirements.

20. Data Management

A separate Data Management Plan (DMP) will govern all aspects of data management including the creation of CRFs and other electronic data capture methods; database design; data security; data retention and backup/recovery plan; process for data entry into the CRF/EDC; the data validation process including query management; database audit plan, and database acceptance criteria.

All documents and data shall be produced and maintained in a way that assures control and traceability. All documents and subsequent versions related to the clinical study shall be identifiable, traceable, and appropriately stored to provide a complete history of the clinical investigation. The Principal Investigator shall ensure accuracy, completeness, legibility, and timeliness of the data reported to InnFocus on the eCRF and in all other reports required by this CIP. The data recorded on the eCRF shall be derived from source documents and any discrepancies shall be explained in writing. The eCRF shall be electronically signed by the Principal Investigator or authorized designee. Any change or correction to source data reported on a CRF shall be dated, initialed or explained if necessary, and shall not obscure the original entry.

20.1. Recording Data

The study data will be recorded on electronic case report forms (eCRF). Source documents, and any worksheets used as source documents, will be filed in the subject's medical record. Office visit data will be recorded by the Investigator, or a designated representative.

A Regulatory Binder (Investigator Site File) will be provided to store all study documents and forms. All of the data will be properly recorded in standard hospital charts and forms as well as in the eCRFs. The data will include the examination and evaluation methods described in this protocol such as:

- Results of study procedures
- Subject imaging photos
- Adverse event reporting (if applicable)
- Deviation reporting (if applicable)
- Reoperations (if applicable)

Consented subjects will be entered on the subject Screening and Enrollment Log. Consented subjects who are deemed eligible for participation in the study based on the enrollment process will continue to use the subject identification numbers assigned during the INN-005 study, in order to track individual subject data.

20.2. Data Handling and Record Keeping

20.2.1. Subject Identification

Subjects will be identified by a five (5) digit Subject ID number composed of a one-digit study identification number, a two-digit center identification number, followed by a two-digit sequential subject number. The subject ID will be the same number given when the subject originally enrolled under the INN-005 study. Subject initials may also be included on eCRFs, in accordance with local regulations.

20.2.2. Subject Accountability

All subjects enrolled in this clinical study shall be monitored for the duration of the investigation. The clinical study shall be considered completed when all subjects that have been enrolled in the investigation, including subjects whose device was removed or replaced, have completed the Month 60 Follow-Up Visit.

20.2.3. Confidentiality

All medical records associated with the clinical study will be made available for review by InnFocus personnel, its Contract Research Organization (CRO), and any governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area at the Investigator's facility, the CRO, and at InnFocus, Inc.

20.2.4. Source Data and Electronic Case Report Forms

All investigative sites will be given instructions by a trained InnFocus designee on case report form completion at the site initiation visit and/or interim monitoring visits. Source documents are to be maintained at the site in the Subject Binder. All entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. All source worksheets, used as source documents, must be completed and signed and dated by either the Principal Investigator or the site staff member conducting the assessment. No correction fluid or correction tape is to be used on the source documents. The source document will be used by the Sponsor to verify data submitted on the eCRFs. The source document data will be entered into a validated Electronic Data Capture (EDC) system at each site by trained study staff in accordance with 21CFR Part 11 requirements.

20.3. Data Management

The study database will be designed to be compliant with 21 CFR Part 11 and relevant guidance documents. The electronic database will be developed and maintained by an independent Contract Research Organization (CRO), Promedica International Inc.

The database will incorporate time-stamped audit trails, protection of human subjects, restricted access, and data security at the component level. Each database module, including each individual eCRF, will be validated by conducting a series of standard tests that demonstrate usability and correctness of the database system. The database will be maintained on an ongoing basis and will be routinely backed up with both onsite and offsite storage.

21. Statistical Analysis and Methods

This is a concurrent controlled, open-label, long-term follow-up study of the safety of the PRESERFLO® MicroShunt device. All inferential statistics will be provided at the 5% nominal significant level. Data generated in this study may be continuous with data generated in the INN-005 study. The primary analysis of the INN-005 protocol has already been conducted and additional labeling claims are not intended to be made from analyses performed for this Extension study. Detailed analyses will be provided in the Statistical Analysis Plan (SAP).

21.1. Sample Size Considerations

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, this study.

21.2. Safety Outcome Measures

This long-term safety study does not specify any hypotheses to evaluate the study outcome measures. Descriptive statistics will be used to summarize safety, effectiveness, and ancillary data. The Primary Safety Outcome Measure is incidence of sight-threatening adverse events, as defined in sections 12 and 13.3.

21.3. Effectiveness Outcome Measures

Evaluating long-term effectiveness is a secondary outcome measure of the study. The main effectiveness outcome measure is the overall success rate, which is defined as the proportion of study eyes with ≥ 20% decrease in intraocular pressure from INN-005 study screening to 60 months of post-operative follow-up without increasing the number of glaucoma medications. This proportion, along with the 95% confidence interval will be summarized for the treatment group and the control group. Further details will be provided in the SAP.

Analyses of effectiveness outcomes will consider subjects that fall into a failure category. **Failure** is defined as a subject with one or more of the following:

1. No light perception vision confirmed on two consecutive follow-up visits
2. IOP persistently below 6mmHg (defined as an intraocular pressure below 6mm that is present on two consecutive study follow-up visits)
3. Requiring a reoperation in the study eye, performed in an operating room, consisting of the following:
   a) Trabeculectomy
   b) Placement of a drainage device
   c) Bleb revision (other than needling)
   d) Explantation or repositioning of the PRESERFLO® MicroShunt
   e) Iridectomy
   f) Resuturing of the scleral flap
   g) Glaucoma laser procedure (e.g. trabeculoplasty, iridotomy)

h) Other glaucoma surgery to reduce IOP
i) Introduction of an oral carbonic anhydrase inhibitor

The procedures below will be reported as **complications** but will **not** be considered **failures**:

1. Needling of the bleb with or without the use of an injected antifibrotic
2. Laser removal of the blockage at the tip of the PRESERFLO® MicroShunt or at the Anterior Chamber entry point for a trabeculectomy
3. Use of a viscoelastic to limit aqueous flow

The following procedures will **not** be considered as **failures or complications** but will be documented:

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

Other effectiveness outcome measures will include the following:

- 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 (complete, qualified). Complete success is defined as patients with 20% reduction in IOP from Screening, without glaucoma medication supplement. Qualified success is defined as patients with 20% reduction in IOP from Screening with glaucoma medication supplement.
- Change in the number of glaucoma medications from INN-005 study screening.
- For categorical endpoints, frequencies and percentages will be used. For continuous endpoints, mean, median, standard deviation, minimum, and maximum will be used. As previously stated, no labeling claims will be made from these analyses.

21.4 Interim Analyses

An annual interim analysis will be performed after the last subject completes his/her Month 36 and 48 Visit. The final analysis will be performed after the last subject completes his/her Month 60 Visit. Each interim analysis and final analysis will include the evaluation of safety and effectiveness of MicroShunt and Trabeculectomy as outlined above. All statistical analyses will be performed at the nominal 5% significant level without multiplicity adjustment.

22. Study Administration

22.1. Suspension or Early Termination

InnFocus reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons, and reasons related to the protection of subjects.
Investigators, associated IRBs/IECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.
Possible reasons for premature study termination include, but are not limited to, the following:

- The occurrence of unanticipated adverse events that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of InnFocus to suspend or discontinue the surveillance of the product.

Both InnFocus and the Principal Investigator reserve the right to terminate the study according to the study contract and the requirements specified in ISO14155:2011 and relevant sections of Title 21 CFR Part 812. The Principal Investigator should notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to InnFocus.

22.1.1. Termination of Study Participation by the Investigator or Withdrawal of IRB/IEC Approval

Any Investigator in the study may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to InnFocus. Investigators, associated IRBs/IECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

In the event an IRB/IEC terminates an investigative site's participation in the study, participating Investigators, associated IRBs/IECs, and regulatory authorities, as applicable, will be notified in writing. Information on how enrolled subjects will be managed thereafter will be provided by InnFocus.

22.1.2. Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by InnFocus. The IRB/IEC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event that an Investigator terminates participation in the study, study responsibility will be transferred to a Sub-Investigator, if possible. In the event there are no opportunities to transfer Investigator responsibility, information on how enrolled subjects will be managed thereafter will be provided by InnFocus. The Investigator must return all documents to InFocus, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.1.3. Criteria for Suspending/Terminating an Investigative Site

InnFocus reserves the right to close an investigative site at any time due to non-enrollment, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions. The IRB/IEC should be notified. All subjects enrolled in the study at the investigative site will continue to be followed until their next follow-up visit. The Principal Investigator at the investigative site must make provision for these follow-up visits unless InnFocus otherwise notifies the study site.

22.2. Record Retention

The Principal Investigator or the investigative site will maintain, at the site, in their original format all supporting study documents and source documentation for data collected on study subjects. All records associated with this clinical study will be maintained for a minimum period of two years after the study has been completed or discontinued, unless otherwise mandated per institution policy.

Source documents are original documents, data and records from which the patient's CRF/EDC data are obtained. These include but are not limited to original paper, copied paper, or electronic versions of hospital records, clinic and office charts, laboratory and pharmacy records, diaries, radiographs and correspondence, along with completed versions of any site source document created from a template produced either by the site or provided by InnFocus specifically for use in the study.

The Principal Investigator and study staff are responsible for maintaining a centralized system of filing all essential documentation suitable for inspection at any time by InnFocus or applicable regulatory authorities

No study document should be destroyed without prior written agreement between InnFocus and the Principal Investigator. Should the Principal Investigator wish to assign the study records to another party or move them to another location s/he must notify InnFocus before moving materials in writing of the new responsible person and/or the new location.

All study documents will be retained for a period of time in accordance with ISO14155:2011, GCP or local regulations, whichever is longer.

22.3. Record Custody

If the Investigator withdraws from the study or relinquishes his/her responsibility for maintaining the study essential documents, custody must be transferred to an individual who will assume responsibility and InnFocus must receive written notification of the custodial transfer.

23. Publication Policy

In accordance with InnFocus' corporate policy, the company requires disclosure of its involvement as a Sponsor or financial supporter in any publication or presentation relating to an InnFocus study or its results. All publications or presentations including manuscripts, abstracts, oral/slide presentations, and book chapters based on the study, must be submitted to InnFocus for review.

24. References

1. Friedman NJ, Kaiser PK. Glaucoma. In: *Essentials of Ophthalmology*. 1st ed. Philadelphia, PA: Saunders Elsevier; 2007:201-212. Santen training slides: "Introduction to Glaucoma".
2. Peters D, Bengtsson B, Heijl A. Lifetime risk of blindness in open-angle glaucoma. Am J *Ophthalmol*. 2013; 156(4):724-730.
3. Kanski JJ, Bowling B. Glaucoma. In: *Clin Ophthalmol.*: A Systematic Approach. 7th ed. London, UK: Elsevier Saunders; 2011:312-400.
4. DuBois L. Tonometry. In: *Clinical Skills for the Ophthalmic Examination*: Basic Procedure. 2nd ed. Thorofare, NJ: SLACK Incorporated; 2006:72-82.
5. Sommer A, Tielsch JM, Katz J, et al. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol*. 1991; 109(8):1090-1095.
6. Zangwill LM, Ayyagari R, Liebmann JM, et al. The African Descent and Glaucoma Evaluation Study (ADAGES): III. Contribution of genotype to glaucoma phenotype in African Americans: Study design and baseline data. *Ophthalmol.* 2019; 126(1): 156-170.
7. Li Z, He Y, Keel S, et al. Efficacy of a Deep Learning System for Detecting Glaucomatous Optic Neuropathy Based on Color Fundus Photographs. *Ophthalmol.* 2018; 125(8): 1199-1206.
8. Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. *Ophthalmol*. 2014;121(11):2081-2090.
9. Allingham R, Damji K, Freedman S, et al. Optic Nerve, Retina, and Choroid. In: Shield's Textbook of Glaucoma. 5th Edition ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:73-115.
10. *American Academy of Ophthamology* (AAO). Preferred Practice Pattern® Primary Open-Angle Glaucoma. San Francisco, CA. Prepared by the American Academy of Ophthalmology Glaucoma Panel. 2015:P41-P110.
11. Moghimi, S, Zangwill LM, Penteado RC, et al. Macular and Optic Nerve Head Vessel Density and Progressive Retinal Nerve Fiber Layer Loss in Glaucoma. *Ophthalmol.* 2018; 125(11): 1720-1728.
12. Allingham R, DamjiK, Freedman S, et al. Chronic Open-Angle Glaucoma and Normal-Tension Glaucoma. In: Shield's Textbook of Glaucoma. 5th Edition ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:197-216.
13. Canadian Ophthalmological Society (COS). Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of glaucoma in the adult eye. Canadian Ophthalmological Society (COS); 44:1-S93.
14. King A, Zuara-Blanco A, Tuulonen A. Glaucoma. *BMJ*. 2013; 346:f3518.
15. European Glaucoma Society (EUGS). Terminology and Guidelines for Glaucoma. 4th Edition. Savona, Italy. 2014:1-195.
16. Cvenkel B. Laser treatment in glaucoma. In: Glaucoma. 8 ed. Basel, Switzerland: Karger AG; 2016:76-90.
17. 2017 Glaucoma Surgical Device Report: A Global Market Analysis for 2016 to 2022. Saint Louis, MO. Market Scope®, LLC. August 2017:1-294.
18. Anderson DM, Novak PD, Keith J, et al, eds. Dorland's Illustrated Medical Dictionary. 32nd ed. Philadelphia, PA: Elsevier Saunders; 2012.
19. Lee JW, Yau GS, Yick DW, et al. MicroPulse Laser Trabeculoplasty for the Treatment of Open-Angle Glaucoma. Medicine (Baltimore). 2015; 94(49):e2075.

20. Ahmed I. Excellent safety profile of MicroPulse Laser Trabeculoplasty (MLT) for glaucoma. Glaucoma Today. 2014; November/December 2014:1-2.
21. Eldaly MA, Bunce C, Elsheikha OZ, et al. Non-penetrating filtration surgery versus trabeculectomy for open-angle glaucoma. Cochrane Database Syst Rev. 2014; 1(2):CD007059.
22. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311(18):1901-1911.
23. Roy S, Mermoud A. Deep sclerectomy. In: *Glaucoma Surgery*. 2nd ed. Basel, Switzerland: Karger; 2017:36-42.
24. Grieshaber M. Viscocanalostomy and canaloplasty: ab Externo Schlemm's Canal Surgery. In: *Glaucoma Surgery*. 2nd ed. Basel, Switzerland: Karger; 2017:113-126.
25. Francis B, AkilH, Bert B. Ab interno Schlemm's canal surgery. In: *Glaucoma Surgery*. 2nd ed. Basel, Switzerland: Karger; 2017:127-146.
26. Aref A, G S, Budenz D. Glaucoma drainage implant surgery. In: *Glaucoma Surgery*. 2nd ed. Basel, Switzerland: Karger; 2017:43-52.
27. Riva I, Roberti G, Oddone F, et al. Ahmed glaucoma valve implant: surgical technique and complications. *Clin Ophthalmol*. 2017; 11:357-367.
28. Richter GM, Coleman AL. Minimally invasive glaucoma surgery: current status and future prospects. *Clin Ophthalmol*. 2016; 10:189-206.
29. NardiM, Posarelli C, Nasini F, et al. Mini drainage devices for anterior and intermediate filtration. In: *Glaucoma Surgery*. 2nd ed. Basel, Switzerland: Karger; 2017:90-99.
30. InnFocus MicroShunt® Glaucoma Drainage System *Instructions for Use*. Miami, FL: InnFocus; 2012.
31. Batlle JF, Fantes F, Riss I, et al. Three-Year Follow-up of a Novel Aqueous Humor MicroShunt. *J Glaucoma*. 2016; 25(2):e58-e65.
32. Desai, Practice Preferences for Glaucoma Surgery: A Survey of the American Glaucoma Society in 2008, Ophthalmic Surg Lasers Imaging 2011;42:202-208.
33. Musch, DC, Lichter, PR, Guire, KE, et al. The Collaborative Initial Glaucoma Treatment Study: Study Design, Methods, and Baseline Characteristics of Enrolled Patients. *Ophthalmol*. 1999; 106:653-661.
34. Musch, DC, Tarver, ME, et al. Development of an 19-Item Measure of Symptom Burden in Patients with Glaucoma From the Collaborative Initial Glaucoma Treatment Study's Symptom and Health Problem Checklist. *JAMA Ophthalmology*. December 2017; 153:1345-1351.
35. Wilson FM. Practical Ophthalmology: A Manual for Beginning Residents. *American Academy of Ophthalmology*. 4th Ed. 1996.

25. Appendices

25.1. Appendix A: Glaucoma Background

GLAUCOMA Glaucoma is a group of optic neuropathy disorders involving progressive loss of retinal nerve cells and consequent damage to the optic nerve. The main consequence is peripheral visual field (VF) loss without the loss of central visual acuity (1). Glaucoma can progress to irreversible blindness, with the biggest risk factor being increased intraocular pressure (IOP). However, optic nerve damage and VF loss are required for a glaucoma diagnosis. Early stages of glaucoma are mostly asymptomatic and painless. Symptoms are usually only experienced in later stages of the disease and are dependent on the speed at which IOP increases (1). Glaucomatous neural damage is caused by increased IOP, which causes biomechanical stress to the posterior eye structures (2). It begins with cell death in the retinal nerve fiber layer (RNFL) and structural damage to the optic nerve, eventually progressing and leading to loss of the peripheral VF and central VF. Glaucoma can be congenital (developmental) or acquired, however, congenital glaucoma is rare and only affects 1 in 10,000 births (3). Acquired glaucoma can be classified into two categories, depending on whether the anterior chamber angle is open or closed (3). Glaucoma is further classified into primary glaucoma, distinguished by no underlying disease, and secondary glaucoma, characterized by the contribution of a drug or disease to the elevation of IOP (3). The balance between the rates of aqueous humor production and outflow determine the optimal IOP range. In patients with glaucoma, abnormal drainage in the anterior chamber can be caused by a variety of factors, resulting in increased IOP (3,4,5).

GLAUCOMA EPIDEMIOLOGY Glaucoma increases with age. Up to 2% of people over 40 years old, and up to 10% of people over 80 years old are affected by the disease (3). Glaucoma is the leading cause of irreversible blindness worldwide, corresponding to an estimated 64.3 million individuals (6). By 2020, approximately 76 million people will be affected by glaucoma compared to 64.3 million people in 2013 (6,9,8). With population growth and aging, this number is expected to increase to 112 million by 2040 (2). Glaucoma is the second leading cause of irreversible blindness in all Americans, and the leading cause of irreversible blindness in individuals of African descent (7). Fortunately, most vision loss resulting from glaucoma can be avoided by employing early detection and treatment strategies. Despite the availability of early detection and treatment strategies to help curtail vision loss, glaucoma still represents a significant financial burden worldwide. By 2020, over 11 million people will be bilaterally blind, up from 8.4 million in 2010 (9).

PRIMARY OPEN-ANGLE GLAUCOMA (POAG) Primary open-angle glaucoma in adults, can result in chronic and progressive damage to the optic nerve, characterized by atrophy of the optic nerve and loss of retinal ganglion cells and their axons (10). This condition is associated with an open anterior chamber angle as assessed by gonioscopy. Although many patients with POAG present with elevated intraocular pressure (IOP), nearly 40% of those with POAG may not have elevated IOP measurements (10). Most patients with POAG also present with optic disc changes or disc and visual field changes.

POAG is the most prevalent type of glaucoma and accounts for 60% to 70% of cases (1) and may be caused by mechanical damage, when retinal nerve fibers are compressed against the lamina cribrosa at the optic nerve head, or vascular damage when optic nerve head blood vessels are compressed (3). In POAG, increased IOP is due to obstruction of aqueous outflow (12). POAG is characterized by IOP > 21 mmHg, open anterior chamber angle, optic nerve damage, and progressive VF loss (3).

While elevated intraocular pressure (IOP) has been identified as a major risk factor for POAG, and current treatments focus on reducing the IOP to limit disease progression, it is well documented that some patients continue to worsen despite IOP lowering (11). Ischemia to the optic nerve and reduced ocular blood flow have also been linked to the pathogenesis and progression of glaucoma. Moreover, decreased ocular perfusion pressure has been associated with an increase in POAG prevalence, incidence, and progression (11). These observations therefore suggest that the origin of glaucoma progression is multifactorial.

Potential POAG mechanisms include (12):

- Alterations of the collagen in the trabecular meshwork
- Mutations in stress response markers, such as in endothelial cells in the trabecular meshwork and in vacuole presence and pore density in Schlemm's canal
- Collapse of Schlemm's canal
- Alterations of the intrascleral channels
- Abnormal composition of aqueous humor
- Immunoregulatory abnormalities at the level of the trabecular meshwork, ganglion cell bodies and optic nerve axons, retinal vessels, or lamina cribrosa
- Abnormalities in blood flow to the posterior segment of the eye
- Apoptotic susceptibility of ganglion cells
- High flow resistance in the scleral venous plexus
- High flow resistance in the episcleral veins

POAG EPIDEMIOLOGY Primary open-angle glaucoma is a significant public health concern and it is estimated that 45 million people worldwide have open-angle glaucoma (10). In 2004, the prevalence of POAG for adults aged 40 and older in the United States was estimated to be about 2%. Open-angle glaucoma (OAG) affects an estimated 2.2 million people in the United States, and as the population ages, that number is likely to increase to 3.3 million in 2020 (7). It is worth noting that the prevalence of glaucoma in the United States differs greatly among different ethno-racial groups, with a threefold higher prevalence of OAG observed in African Americans relative to non-Hispanic whites. OAG is also the leading cause of blindness in African Americans (3). Furthermore, the prevalence of OAG is even higher in Afro-Caribbeans relative to African Americans. Recent evidence on Hispanics/Latinos suggests that they have comparable prevalence rates of OAG relative to Asian Americans (10).

POAG RISK FACTORS The findings of epidemiological investigations and clinical trials provide a framework for assessing the risk factors associated with POAG. The important risk factors associated with POAG are as follows (1,3,11):

- Higher intraocular pressure (IOP)
- Older age (≥ 60 years; African Americans ≥ 40 years)
- Family history of glaucoma (first-degree relatives)
- African race or Latino/Hispanic ethnicity
- Thinner central cornea
- Lower ocular perfusion pressure
- Type 2 diabetes mellitus
- Myopia
- Lower systolic and diastolic blood pressure
- Vascular disease
- Disc hemorrhage
- Larger cup-to-disc ratio
- Higher pattern standard deviation on threshold visual field testing

GOALS The primary goal of glaucoma treatment is to stop or delay disease progression to prevent blindness and preserve health-related quality of life. Recall that glaucoma refers to a group of chronic eye conditions characterized by degeneration of retinal ganglion cells (RGCs) that can result in damage to the optic nerve, loss of visual field, and blindness. It is often associated with increased intraocular pressure (IOP) (1,13,14)

The goals of managing patients with POAG are to achieve the following (10):

- Controlled of IOP in the target range
- Stable optic nerve/retinal nerve fiber layer (RNFL) status
- Stable visual fields

A number of population-based studies have demonstrated that IOP reduction decreases the risk of VF progression in OAG. Moreover, treated eyes with greater IOP fluctuation may be at an increased risk of disease progression. Despite the correlation between the level of IOP and POAG, there is significant variation between individuals with respect to susceptibility of the optic nerve to IOP-related damage (10). Population-based studies further indicate that a varying proportion of patients with IOP greater than 21 mmHg have glaucomatous optic nerve damage. This suggests that an IOP level of greater than 21 mmHg may be a relatively poor predictive value in the utilization of a specific IOP cutoff as a measure for screening or diagnosis of POAG (10).

Since elevated IOP is a treatable cause of POAG damage, one can expect to reduce the risk of disease progression in many patients by lowering the IOP by means of medication, laser therapy, or incisional glaucoma surgery. Results from randomized controlled trials and other studies reinforce this expectation and provide evidence that the more the IOP is lowered, to a certain threshold, the more likely it is to slow the rate of progression of POAG.

Management is a challenge for the patient and the doctor, because POAG is a chronic, often asymptomatic, condition that may require frequent use of multiple and expensive medications that may cause side effects or may require laser or incisional surgery. The effects of treatment, the patient's quality of life, and the patient's life expectancy are important to consider when choosing therapy. The diagnosis, severity of the disease, prognosis and management plan, and likelihood of long-term therapy should be discussed with the patient. Substantial visual field loss in glaucoma is associated with a decrease in quality of life measures.

Target IOP for Patients with POAG The goal of glaucoma treatment is to maintain the IOP in a range at which a patient is likely to remain stable or at which worsening of glaucoma will be slow enough that the risk of additional intervention is not justified. The estimated upper limit of this range is considered the "target pressure." The initial target pressure is an estimate and a means toward the ultimate goal of protecting the patient's vision. The target pressure is unique for each eye of every patient and is a compromise between reducing the risk of symptomatic vision loss and the consequences of the chosen therapy. Therefore, when selecting an initial treatment, it is important to consider relevant patient characteristics. A lower target IOP is necessary in more advanced disease to maximize preservation of remaining vision, often requiring aggressive treatment to achieve large IOP reduction (15). In addition to being individualized, the target pressure may also need to be adjusted during the course of the disease (10). The adequacy and validity of the target pressure are periodically reassessed by comparing optic nerve status (by optic disc appearance, quantitative assessments of the disc and nerve fiber layer, and visual field tests) with previous examinations. If progression occurs at the target pressure, undetected IOP fluctuations and adherence to therapy can be re-evaluated before adjusting the target IOP.

When initiating therapy, the ophthalmologist assumes that the measured pretreatment pressure range contributed to optic nerve damage and is likely to cause additional damage in the future. Lowering the pretreatment IOP by 25% or more has been shown to inhibit progression of POAG. It is reasonable to select an initial target pressure at least 25% lower than pretreatment levels. Choosing an even lower target IOP can be justified if there is more severe optic nerve damage, if the damage is progressing rapidly, or if other risk factors such as family history, age, or disc hemorrhages are present. Choosing a less aggressive target IOP may be reasonable if the risks of aggressive treatment outweigh the benefits (e.g., if a patient does not tolerate medical therapy well and surgical intervention would be difficult or if the patient's life expectancy is short). In a study of newly diagnosed patients with moderate to advanced glaucoma, a subset of patients randomized to initial lowering of IOP by surgery did better than those assigned to medical treatment over an 8-year period, and this could be due to the lower mean post-treatment IOP in the surgery group (10).

THERAPEUTIC CHOICES Currently, treatment of glaucoma entails reducing IOP to minimize glaucoma progression and preserve visual function. Given the permanent nature of glaucomatous damage, disease progression is more manageable when treatment begins at an early stage (13,14). Initial therapy for glaucoma to lower IOP is typically pharmacologic alone or in combination with laser surgery. Exceptions include patients with more advanced glaucoma, who may require incisional surgery to achieve the IOP lowering necessary to preserve vision. In those patients, regular monitoring of IOP level is required to

evaluate the effectiveness of treatment and determine whether treatment modification is required (13,15). Pharmacologic, laser, and surgical methods reduce IOP by increasing aqueous humor outflow or by decreasing its production (13,14). The choice of initial therapy depends on numerous considerations, including the degree of optic nerve damage, level of IOP control required, disease progression, patient age, and compliance by the patient to the treatment (13,14). Comorbidities that need to be considered include asthma/chronic obstructive pulmonary disease, cardiac arrhythmia, or depression (10).

MEDICAL TREATMENT Treatment with medications is currently the most commonly employed initial intervention for lowering IOP. A number of drugs are available for initial therapy and the choice of medication is typically influenced by its potential cost, side effects, dosing schedules, and the degree of IOP pressure lowering required. If the target IOP cannot be achieved with one medication, the ophthalmologist will either switch or add medications, depending on whether the patient has responded to the first medication or not, with the first medication typically not being kept in the regimen if the patient has had no response in IOP lowering (10). Prostaglandin analogs are the most frequently prescribed initial eye drops for lowering IOP because they are the most efficacious, are well-tolerated, are instilled once daily, and are relatively safe. Alternative agents include beta-blockers, alpha2 adrenergic agonists, parasympathomimetics, and topical and oral carbonic anhydrase inhibitors (CAIs) (10).

SURGICAL TREATMENTS

Laser Treatment:

Laser treatment is typically considered by ophthalmologists as the first-line therapy as an alternative for patients at high risk for nonadherence to pharmacologic treatment due to cost, memory problems, difficulty with instillation, or intolerance to the medication (10). Laser therapy can also be selected as an alternative when pharmacologic treatment fails to prevent disease progression. Laser treatment involves targeting a focused beam of light to remove tissue in the eye to reduce IOP. The degree of tissue removal depends on the duration of application, laser spot size, laser power setting, and pigmentation of the tissue. Several different laser treatments may be used to treat glaucoma (16,17,18). The following are used to treat POAG:

- *Argon laser trabeculoplasty (ALT)* uses an argon laser to induce biological changes in the trabecular meshwork through discrete laser burns. This increases aqueous outflow from the trabecular meshwork into the Schlemm's canal, thereby reducing IOP (3,16,17).
- *Selective laser trabeculoplasty (SLT)* uses a neodymium:yttrium-aluminum-garnet (Nd:YAG) low-energy laser that targets pigmented cells in the trabecular meshwork. Nonpigmented cells are unaffected by the thermal damage. SLT has a lower exposure time than ALT and may cause less thermal damage to the structure of the trabecular meshwork. It also allows for easier tissue targeting, which offers safer repeatability and a lower rate of complications (3,10).
- *MicroPulse laser trabeculoplasty (MLT)* is a newer alternative to ALT and SLT. It uses a low-energy diode laser that targets pigmented cells in the trabecular meshwork. The procedure increases the permeability of the trabecular meshwork, resulting in reduction of IOP. Like SLT, MLT has a lower exposure time, appears repeatable, has a low rate of complications, and does not cause scarring of the trabecular meshwork. However, MLT is able to thermally affect the

pigmented cells of the trabecular meshwork without destroying them by allowing a cooling period between laser pulses (19,20).

Incisional Surgery:

Incisional surgery is usually performed when pharmacologic or laser treatment is unlikely to stop or delay progression of glaucoma. The goal of incisional surgery is to achieve a target IOP to preserve vision while simultaneously reducing or eliminating the medication load for the patient (13,15). Surgery can be approached from either inside the eye (ab interno) or from outside the eye (ab externo).

Filtration Surgery:

Filtration Surgery is typically used when medical and laser therapies are insufficient to control the progression of glaucoma, and when visual function declines rapidly enough to impair the patient's quality of life. Filtration procedures aim to reduce IOP by increasing the outflow of aqueous humor (21). Filtration procedures create an alternative pathway for the outflow of aqueous humor by cutting through the sclera to reduce IOP. The choice of filtration procedure is a compromise between the desired level of IOP reduction and the risk for complications (1,15).

- ***Ab externo trabeculectomy*** is one of the most widely used surgical procedure to reduce IOP. The procedure involves removal of a small portion of the trabecular meshwork and adjacent scleral tissue. Aqueous humor then drains into the subconjunctival space, creating a bleb on the external part of the eye, where it diffuses away. Antiproliferative agents are often used to reduce postoperative fibrosis and increase rates of success (1,22).
- ***Deep sclerectomy*** creates a window in the Descemet membrane, allowing the flow of aqueous humor from the anterior chamber to a shallow subconjunctival filtration bleb. The roof of Schlemm's canal is removed, then a collagen or viscoelastic space maintainer is inserted into the scleral bed to prevent collapse. In nonpenetrating filtration surgery, such as deep sclerectomy, the anterior chamber is not entered, and the internal trabecular meshwork is preserved. This reduces the incidence of postoperative over-filtration, hypotony, and the need for anti-scarring agents. However, the surgery is technically challenging and IOP reduction is less than that achieved by trabeculectomy, such that pharmacologic treatments are often still needed (3,23).
- ***Canaloplasty*** is a nonpenetrating, blebless, filtration surgery where a microcatheter is inserted into the Schlemm's canal to enlarge it. Canaloplasty can be performed ab externo by cutting the conjunctiva and sclera or ab interno through a corneal incision. Like deep sclerectomy, canaloplasty is a technically challenging procedure. Canaloplasty is not associated with bleb-related complications, and antimetabolites are not required. Canaloplasty may be combined with cataract surgery. It may also be a surgical option in patients who are at risk for complications (3,15,24,25).

Tube Shunts:

Tube shunts enable drainage of the aqueous humor through an artificial filtering device consisting of a silicone tube connected to an episcleral plate which can be made from silicone or polypropylene. The aqueous humor drains to a space between the end plate and an overlying fibrous capsule that develops

postoperatively. Reduction in IOP results from passive flow of aqueous humor across the capsular wall (3,26). While tube shunts can be used as a primary surgical procedure, they are often reserved for patients with risk factors that would result in a poor outcome with trabeculectomy (15). Both non-valved and valved implants are used in patients at high risk for failure with standard trabeculectomy with antifibrotic agents (26).

- ***Nonvalved implants*** Non-valved implants have no resistance to anterior chamber aqueous humor outflow. The fibrous capsule that forms postoperatively provides the primary resistance to aqueous flow. Aqueous flow may also be restricted using sutures (17,26). Examples of popular nonvalved implants are the Baerveldt® Glaucoma Implant and Molteno® Glaucoma Implant devices.
- **Valved implants** are designed with a valve system that provides flow resistance to reduce the incidence of postoperative low IOP that may occur with non-valved implants (17,27). The Ahmed Valve is currently the only valved glaucoma drainage device.

Minimally-Invasive Glaucoma Surgeries (MIGS):

Minimally invasive glaucoma surgery (MIGS) aims to provide a safer, less invasive means of reducing IOP than traditional surgery, with concomitant reduction in topical medication use. Often, MIGS can be combined with phacoemulsification cataract surgery, during which a corneal incision is already created and the anterior chamber is filled with a viscoelastic fluid. These techniques are typically performed in selected glaucoma patients with early-to-moderate disease (15,28). The following are the surgical targets of various MIGS procedures (28):

- Increasing trabecular outflow/Schlemm's canal drainage - Procedure removes a portion of the trabecular meshwork and inner wall of the Schlemm's canal to increase trabecular outflow.
- Subconjunctival Filtration - Subconjunctival stent creates a nonphysiologic route for aqueous outflow
- Increasing uveoscleral outflow - Suprachoroidal stents direct aqueous outflow to the suprachoroidal space, thereby increasing uveoscleral outflow.
- Reducing aqueous humor production - The anterior ciliary processes are laser-treated to the point of tissue shrinkage to reduce aqueous humor production.

Microstents:

Microstents are drainage devices that target one of the eye's internal drainage sites to improve outflow through an ab interno corneal incision (25). Ab interno microstents have a high safety profile but are, aside from the XEN® Gel Implant, not indicated for low target IOPs . Ab externo microstents aim to mimic the IOP reduction of trabeculectomy, while improving the safety profile (29).

The PRESERFLO® MicroShunt, formerly called the InnFocus MicroShunt®, is an Ab externo microstunt formed from a flexible polymer called poly(Styrene-block-IsoButylene-block-Styrene); (SIBS). It shunts aqueous humor from the anterior chamber to a flap formed under the conjunctiva and Tenon's capsule. The accumulation of fluid in this space is called a bleb (30,31). The PRESERFLO® MicroShunt may be implanted alone or in combination with cataract surgery.

25.2. Appendix B: Investigational Device

Manufacturer

The PRESERFLO® MicroShunt device is manufactured by InnFocus, Inc., located in Miami, FL.

Intended Population

The PRESERFLO® MicroShunt is indicated for the reduction of intraocular pressure (IOP) in eyes of patients with primary open-angle glaucoma where IOP is not controlled by maximum tolerated glaucoma medications.

Device Form and Route of Administration

The PRESERFLO® MicroShunt is surgically implanted into the subject's eye.

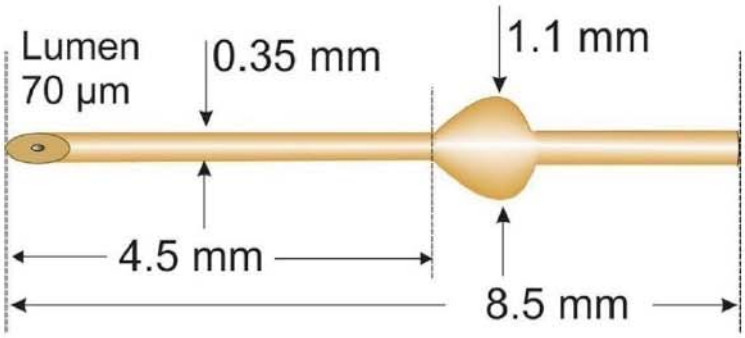
Device Components:

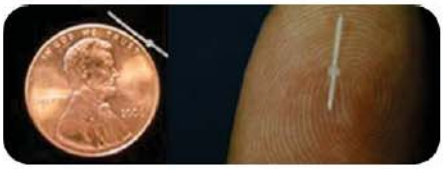
PRESERFLO® MicroShunt device

The PRESERFLO® MicroShunt is an implantable glaucoma drainage device made of an extremely flexible polymer called poly(Styrene-block-IsoButylene-block-Styrene); (SIBS), with a tube of 350 µm outer diameter and a lumen of 70 µm. It has triangular fins that prevent migration of the tube into the anterior chamber (AC). The device is designed to be implanted under the subconjunctival/Tenon space to allow aqueous flow from the AC to a bleb (blister-like formation below the conjunctiva/Tenons).

PRESERFLO® MicroShunt

Device Diagram - Dimensions





Device System Components

The PRESERFLO® MicroShunt is shipped with the following Class I accessories: Incision knife, Scleral marker, Marker pen, and 25 Gauge needle or 23 Gauge cannula.

Two different kit configurations were used in Phase I and Phase II of the INN-005 study, as indicated in the table below:

Phase I (US)	Phase II (US only)	Phase II (EU only)
3mm Scleral Marker	3mm Scleral Marker	3mm Scleral Marker
1mm Slit Angle Knife	1mm Double Step Knife	1mm Slit Angle Knife
25 Gauge Needle	23 Gauge Cannula	25 Gauge Needle
Marker Pen	Marker Pen	Marker Pen

Incision Knife & 25 Gauge Needle

The disposable stainless-steel 1.0mm slit angle knife is used to create a shallow scleral flap just large enough to tuck the fin portion of the PRESERFLO™ MicroShunt. In addition to the 1.0mm wide cutting edge, the disposable stainless-steel double step incision knife has a separate 0.5mm wide cutting edge at the distal end of the knife. This double cutting edge allows a track to be completed through the sclera into the anterior chamber while simultaneously creating a 1mm wide scleral pocket for the fin to be located. In surgeries that employed the 1.0mm wide slit knife instead of the double step knife, the 25 Gauge needle was used to create the track into the anterior chamber.

3mm Scleral Marker

This disposable component is made from stainless steel. The gentian violet from the marker pen is transferred to the tips of the marker during surgery. The marker is lined up with the limbus and a point on the sclera 3mm from the limbus is marked with the marker. The marker is packaged in the PRESERFLO® MicroShunt thermoform tray and enclosed in a sealed Tyvek pouch.

Marker Pen

The disposable marker pen contains gentian violet to be used with the 3mm marker to identify the point of entry for the knife. It is provided in a separate sealed and sterilized package in the PRESERFLO® MicroShunt System Box.

23 Gauge Thin Wall Cannula

This stainless-steel cannula can be attached to a syringe filled with balanced sterile saline (BSS) and placed over the distal end of the PRESERFLO® MicroShunt to flush saline through the lumen of the device and aid in initiating flow of aqueous. The cannula is supplied in a separate sterile package in the PRESERFLO® MicroShunt System Box.

Device Packaging

The PRESERFLO® MicroShunt device is packaged in a thermoform tray that is enclosed in a sealed Tyvek pouch. The ethylene oxide sterilized PRESERFLO® MicroShunt and 3mm marker are packaged in a unit box, along with the other purchased and separately packaged sterilized class I accessories, prior to shipment.

Device Receipt and Tracking

No devices will be shipped to sites. PRESERFLO® MicroShunt devices, previously provided to sites as part of the INN-005 clinical study and implanted into each subject randomized to the treatment arm, are traceable by the device lot number. All un-used devices shipped in conjunction with the IDE G130028 INN-005 clinical investigation have been returned and accounted for by InnFocus.
Device Accountability

PRESERFLO® MicroShunt devices were securely maintained, controlled, and used in the INN-005 clinical study. A Device Accountability Log was employed to track subjects and product allocations during the study. For this long-term follow-up study, records shall be kept by the Principal Investigator, or an authorized designee, to document INN-005 study device explantation and return, using the Product Return Packing and Tracking Form.

Device Return

Every effort shall be made by the Principal Investigator, or an authorized designee, to return explanted PRESERFLO® MicroShunt devices to InnFocus, Inc. If a device needs to be returned, the Device Return Packing Slip and Tracking Form must be completed and provided with the returned device as instructed by the Device Return Procedure (located in the Regulatory Binder). If possible, InnFocus should be contacted prior to explantation or return. If the device cannot be returned, the reason should be documented on the Device Return Packing Slip and Tracking Form. Not returning a device will not constitute a protocol deviation. A special package will be provided by InnFocus, Inc., for any returned device that has been exposed to blood or tissue.

Device Training Requirements

Investigators were previously trained as part of the INN-005 study prior to implanting the PRESERFLO® MicroShunt into subjects randomized to the treatment arm. No device training is required for this long-term study.

25.3. Appendix C: Ophthalmic Definitions

Angle-closure glaucoma: Glaucoma due to obstruction of the trabecular meshwork by peripheral iris tissue.

Anterior Chamber: The fluid filled space filled with aqueous fluid between the iris and back surface of the cornea.

Aqueous humor: The transparent watery fluid that fills the anterior and posterior chambers of the eye. This fluid is produced by the ciliary body. Its main functions are maintaining intraocular pressure (the pressure within the eye), maintaining eyeball shape, and supplying nutritional elements for the avascular cornea and lens.

Argon laser: A laser with ionized argon as the active medium whose beam is in the blue and green visible light spectrum, with two energy peaks, at 488 and 514 nm.

Best Corrected Visual Acuity (BCVA): Measurement of vision obtained with the best possible lens correction.

Bleb: A large blister or vesicle filled with fluid. It is also called bulla.

Cannulation: Introduction of a tube through a passageway, allowing the escape of fluid.

Cataract: An opacity of the lens of the eye, usually occurring as a result of aging, trauma, endocrine or metabolic disease, or intraocular disease, or as a side effect of the use of tobacco or certain medications (such as steroids).

Choroid: The highly vascular tissue between the sclera and the retina that supplies nutrition to the retina. It appears brown due to melanocytes, which prevent reflection and scattering of light within the eye, resulting in a sharp and clear image on the retina.

Ciliary Body: The circumferential tissue inside the eye composed of ciliary muscle and ciliary processes that produce aqueous fluid.

Ciliary Processes: The innermost, epithelial portion of the ciliary body that secretes aqueous fluid and serves as attachment site of suspensory ligaments of the lens (zonules).

Collagen: Protein fibrils within the corneal tissue that help sustain its shape.

Conjunctivitis: An inflammation of the conjunctiva (mucus membranes that cover the white portion of the eye and inner surfaces of the eyelids). Characterized by discharge, grittiness, redness and swelling. Contagious, usually viral in origin.

Cornea: The outer, transparent, front segment of the cornea often having specific signs and symptoms with a known cause.

Corneal Ulcer: Area of epithelial tissue loss from the corneal surface: associated with inflammatory cells in the cornea and anterior chamber and usually caused by bacterial, fungal or viral infection.

Cystic Bleb – thin, avascular blister under the conjunctiva.

Encapsulated Bleb - dome-shaped, elevated, tense, thick-walled, demarcated area centered over the trabeculectomy or other, subconjunctival wound site.

Endoscopy: Visual inspection of any cavity using an endoscope—an instrument used for examination of the interior of a body cavity.11
Episcleral: Overlaying the sclera of the eye.41

Endothelium: The most posterior part of the cornea, consisting of a single layer of endothelial cells that act as metabolic pumps to regulate normal corneal water content. They normally have hexagonal shapes, are uniform in size, and have very little ability to regenerate.

Epithelium: Tissue covering the outer surfaces of the cornea, conjunctiva, and eyelid surfaces.

Filtering Bleb: A surgical procedure causing a bubble-like blister of the conjunctiva overlying a tunnel that leads to inside of the eye: formed by a surgical drainage procedure. The most common form of filtering surgery is trabeculectomy.

Glaucoma: Damage to the optic nerve and to retinal nerve fiber diagnosed by excavation of the optic nerve head and documented by typical visual field defects. A common cause of preventable vision loss. Elevated intraocular pressure is the only modifiable risk factor.

Goldmann Applanation Tonometer: Instrument device that measures intraocular pressure and usually attaches to a slit lamp.

Gonioscopy: Gonioscopy is a painless eye exam administered by an ophthalmologist for viewing the drainage system (anterior chamber angle) of the eye to evaluate, classify, and manage normal and abnormal angle structures. Gonioscopy uses a goniolens (also known as a gonioscope), together with a slit lamp or operating microscope to view the iridocorneal angle, or the anatomical angle formed between the eye's cornea and iris. It is an important technique in diagnosing and monitoring various eye conditions associated with glaucoma.

Hyphema: Layer or clot of red blood cells in the anterior chamber of the eye, in front of the iris. It is often caused by a contusion from a fast-moving object but may sometimes occur spontaneously, as in patients with diabetes mellitus or intraocular tumors.

Intraocular Pressure (IOP): The pressure that maintains the shape of the eyeball and prevents it from collapsing. It is produced primarily by aqueous humor. Pressure of the fluid inside the eye, which varies among individuals.

Iris: The colored portion of the eye that functions as an aperture to control the amount of light entering the eye.

Iritis: An inflammation of the colored part of the eye (iris) that can cause pain, tearing, blurred vision, a small pupil and a red, congested eye, which is sensitive to light.

Keratitis: Corneal inflammation, characterized by the loss of luster and transparency, and cellular infiltration.

Lens: The natural crystalline lens of the eye: transparent, bioconvex intraocular tissue that helps bring rays of light to focus on the retina. Suspended by fine ligaments (zonules) attached between the ciliary processes.

Limbus: The transitional zone, about 1-2 millimeters wide, where the cornea joins the sclera and the bulbar conjunctiva attaches to the eyeball.

Neodymium:yttrium-aluminum-garnet(Nd:YAG): A laser whose active medium is a crystal of yttrium, aluminum, and garnet doped with neodymium ions, and whose beam is in the near infrared spectrum at 1060 nm. It is used for photocoagulation and photoablation.

Neuropathy: A functional disturbance or pathologic change in the peripheral nervous system.40
Optic cup: A depression in the center of the optic nerve through which the blood vessels pass.41
Open-angle glaucoma (OAG): A form of glaucoma in which the anterior chamber drainage angle is open. Open-angle varieties include primary open-angle glaucoma, the most common form of glaucoma, as well as many secondary types in which ocular or non-ocular diseases contribute to IOP increase.

Optic disc: The area of the retina where the optic nerve enters. It is also called the blind spot because it does not contain photoreceptor cells.

Optic Disc/Optic Nerve Head: The exit site of the retinal nerve fibers from the eye.

Optic nerve: The nerve that transmits information from the eye to the visual centers of the brain. It is composed of approximately 1.2 million axons formed from retinal ganglion cells and usually appears as yellowish-orange in color.

Pupil: The variable-size, circular opening in the center of the iris; regulating the amount of light that enters the eye.

Retina: The part of the eye, that converts images (from the eye's optical system) into electrical impulses sent along the optic nerve for transmission back to the brain. It consists of many named layers that include cones, rods, bipolar cells, amacrine cells, ganglion cells, horizontal cells, Mueller cells, and all interconnecting nerve fibers.

Retinal ganglion cells (RGCs): A group of nerve cell bodies located outside the central nervous system, near the inner surface of the retina. It receives visual information from photoreceptors. Its long axons extend posteriorly to the optic disc and exit the eye as the optic nerve.

Retinal nerve fiber layer (RNFL): The innermost layer of the fundus that contains retinal ganglion cell axons and collects the visual impulses that travel from photoreceptors through the ganglion cells.

Schlemm's canal: The circular channel deep in the corneo-sclera junction (limbus); collecting aqueous fluid from the anterior chamber of the eye and delivering it through a series of veins into the blood stream. Passageway in which aqueous fluid leaves the eye.

Sclera: The opaque, fibrous, protective outer layer of the eye; contains collagen and elastic fibers. This is directly continuous with the cornea (interiorly) and with the sheath covering the optic nerve (posteriorly).

Scotoma: An area of lost or depressed vision within the visual field, surrounded by an area of less depressed or of normal vision.

Slit lamp: The common name for the binocular microscope that has been designed to give a magnified view of the anterior segment of the eye.

Stroma (Iris): The primary substance of the iris and contains pigment cells that determine eye color, and two non-striated muscles: the ring-shaped sphincter and the radially-fibered dilator.

Subconjunctival: Beneath the conjunctiva.

Suprachoroidal: Superior to or over the choroid of the eye.

Synechia: Adhesion of the iris to the cornea or to the lens.

Tomography: The recording of internal body images at a predetermined plane by means of an apparatus for moving a light source in one direction as the film is moved in the opposite direction, thus showing the tissue in detail while blurring or eliminating detail in other planes.40
Visual field (VF): The spatial area within which stimuli produce the sensation of sight when the eye is in a straight-ahead position.

Trabecular meshwork: The mesh-like structure inside the eye bridging the anterior chamber angle between the cornea and the sclera. The trabecular meshwork, associated glycosaminoglucans, and the endothelium of Schlemms canal comprise the outflow resistance for aqueous leaving the anterior chamber and entering into the canal of Schlemm.

Trabeculectomy: Type of filtering procedure used in the treatment of glaucoma. Involves the formation of an opening or hole under the conjunctiva and scleral flap into the anterior chamber, such that aqueous humor is drained onto the outer surface of the sclera.

Visual Acuity (VA): The measurement of the eye's ability to distinguish objects, details and shapes. This is assessed by the smallest identifiable letters that can be discerned at a specified distance (usually 20 feet or 14 inches).

Visual Field (VF): Visual Field: The vertical and horizontal extent of visual perception of specific targets, measured in degrees in each direction from fixation. The spatial area within which stimuli produce the sensation of sight when the eye is in a straight-ahead position.

Vitreous: The transparent, colorless gelatinous mass of fine collagen fibrils and hyaluronic acid filling the rear two-thirds of the interior of the eyeball, between the lens and the retina.

Zonules: Radially arranged fibers that suspend the lens from the ciliary body and hold it in position.

26. Version History

Version	Summary of Changes	Author(s)/Title
Version 1.0	New	[redacted]
Version 2.0	Included Gonioscopy as an additional assessment at the Month 60 follow-up visit.	