June 2nd, 2022

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To Whom It May Concern,

Please see attached, the following document:

Official Title:	**Protocol**
Study ID:	**INN-005**
Dated:	**21Jul2017**
NCT No.	**NCT01881425**

Thank you,

DocuSigned by Haydee Frost
Haydee Frost
I am the author of this document
2022-Jul-08 | 17:53 EDT
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A Randomized Study Comparing the Safety and Efficacy of the InnFocus MicroShunt® Glaucoma Drainage System to Standard Trabeculectomy In Subjects with Primary Open Angle Glaucoma

Protocol INN-005

July 21, 2017

Sponsor:	**InnFocus, Inc.** [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

InnFocus, Inc.

Protocol INN-005

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

Study Synopsis

Study Objective: The study objective is to assess the safety and effectiveness of the InnFocus MicroShunt when used to lower intraocular pressure (IOP) in subjects with primary open angle glaucoma where the IOP is not controlled when using maximum tolerated glaucoma medications.

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

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

A total of **514** subjects will be randomized in Phase II at 3:1 ratio. with a drop-out rate of 6% per year, approximately **480** randomized subjects in Phase II (360 treatments and 120 controls) are expected to have the **12**-month examination and **448** randomized subjects (336 treatments and 112 controls) are expected to have the **24**-month follow-up examination.

The randomization will be stratified by investigational site and within-site by lens status with a target of at least 60 randomized phakic eyes in the treatment group and 20 randomized phakic eyes in the control group at 24 months.

Study Parameters: The study population will consist of subjects diagnosed with open angle glaucoma with IOPs that are not controlled on maximum tolerated glaucoma medications. All subjects will have medicated IOPs of ≥ 15 mmHg and ≤ 40 mmHg.

Subject Population: For Phase II, each investigational site will be asked to enroll at least 23 subjects in the study. Additionally, no study investigator will exceed 25% of the total number of randomized investigational device or control subjects. For study sites with more than one investigator, the total randomization will not exceed 33% of the total number of randomized investigational device or control subjects. Each investigator should enroll at least 10 investigational device subjects and each site will be asked to enroll approximately 23 subjects.

Effectiveness Outcomes:
The primary effectiveness outcome is the proportion of eyes with ≥ 20% decrease in mean diurnal intraocular pressure from screening to 12 months post-operative examination.

The proportion of eyes with ≥ 20% decrease in mean diurnal intraocular pressure from screening to 24 months follow-up will also be compared between treatment group and control group.

The secondary effectiveness outcome is the mean diurnal IOP change from screening to 12 months follow-up.

The mean diurnal IOP change from screening to 24 months post-operative examination will also be compared between the treatment group and control group.

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

1. No light perception vision confirmed on two consecutive visits
2. IOP persistently below 6mmHg (defined as an intraocular pressure below 6mm that is present on two consecutive follow-up visits after the three month visit)
3. Requiring a reoperation in the study eye in an operating room consisting of:
    a. Trabeculectomy
    b. Placement of a drainage device
    c. Bleb revision (other than needling)
    d. Explantation or repositioning of the InnFocus MicroShunt
    e. Iridectomy
    f. Resuturing of the scleral flap
4. Glaucoma laser procedure (e.g., trabeculoplasty, iridotomy)
5. Other glaucoma surgery to reduce IOP
6. Missing 24-month diurnal IOP due to discontinuation from the study prior to the 24-month visit
7. Post-operative introduction of an oral carbonic anhydrase inhibitor

The procedures shown below will be reported as complications but are not failures:

1. Needling of the bleb with or without the use of an injected antifibrotic
2. Laser removal of blockage at the tip of the InnFocus MicroShunt or at the AC 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

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Inclusion Criteria

All criteria apply to the study eye unless otherwise noted:

1) Male or female patient, age 40 to 85 years, inclusive
2) Early to severe primary open angle glaucoma where the mean diurnal intraocular pressure is not controlled on maximum tolerated medical therapy with intraocular pressure ≥ 15 mm Hg and ≤ 40 mm Hg while on glaucoma medications.
   Maximum tolerated medical therapy is defined as:
   a. Three or more classes of topical glaucoma medications (prostaglandin analog, beta–adrenergic antagonist, carbonic anhydrase inhibitor, alpha-adrenergic agonist, parasympathomimetic). Combination glaucoma medications that consist of two or more glaucoma drugs will have each glaucoma drug component counted as a separate drug.
   b. fewer than three classes presently in use if a subject's intolerance to specific glaucoma medications and ineffective medications are included.
3) Primary open angle glaucoma diagnosis based on:
   a. visual field mean deviation of -3dB or worse **and**
   b. glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities documented on slit lamp stereo biomicroscopy or in stereo disc photos:
      - Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles
      - Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles
      - Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
      - Disc rim or peripapillary retinal nerve fiber layer hemorrhages.
4) Prior ab interno conjunctival-sparing glaucoma procedures were conducted more than 6 months prior to enrollment (e.g., iStent, Trabectome, gonioscopy-assisted transluminal trabeculectomy [GATT]).
5) Patient must have signed and dated the Informed Consent form.
6) Patient is willing to attend follow-up visits for two years postoperatively.

Exclusion Criteria

All criteria apply to the study eye unless otherwise noted

1) Patient unwilling or unable to give informed consent, unwilling to accept randomization, or unable to return for scheduled protocol visits through 2 years.
2) Patient < 40 years or >85 years of age.
3) Patient is pregnant or nursing or unable to use appropriate birth control.
4) Vision level of no light perception.
5) Active iris neovascularization, active proliferative retinopathy or other ophthalmic disease that could confound study results.
6) Iridocorneal endothelial syndrome.
7) Epithelial or fibrous downgrowth.
8) Secondary glaucoma such as post-trauma, pseudoexfoliation or pigment dispersion.
9) Chronic ocular inflammatory disease.
10) Subject already enrolled in this or another study (only one eye can participate in this study) or completed their participation in another study within 30 calendar days of the screening exam.
11) Aphakia.
12) Vitreous in the anterior chamber.
13) A history of corneal surgery (including Lasik or PRK), corneal opacities or disease/pathology if accurate IOP measurement may be affected. (Active corneal infection or Fuchs dystrophy are examples.)
14) Severe anterior or posterior blepharitis.
15) Unwilling to discontinue contact lens use after surgery for the duration of the study.
16) Previous incisional ophthalmic surgery involving the conjunctiva.
17) Prior clear corneal cataract, angle or trabecular meshwork surgery conducted within the past 6 months (e.g., iStent, Trabectome, gonioscopy-assisted transluminal trabeculotomy)
18) Presence of an anterior chamber IOL (ACIOL).
19) Prior laser peripheral iridotomy conducted within three months of enrollment.
20) Need for glaucoma surgery combined with other ocular procedures or anticipated need for additional ocular surgery during the investigational period.
21) Fellow eye with poorer than 20/80 best-corrected visual acuity (BCVA) or points in both hemifields within 5 degrees of fixation with sensitivity less than <0 dB.
22) Known allergy or other contraindication to mitomycin C (MMC) drug.
23) Angle closure glaucoma or narrow anatomical chamber angle as identified by gonioscopy and classified as Shaffer Grade 0 or 1.
24) Endothelial cell density at screening for the central reading of the following values:

Phakic	Pseudophakic
Age 40-45< 2200 cells/mm^2	Age 40-45 < 1980 cells/mm^2
Age 46-55 < 2000 cells/mm^2	Age 46-55 < 1800 cells/mm^2
Age 56-65 < 1800 cells/mm^2	Age 56-65 < 1620 cells/mm^2
Age over 65 < 1600 cells/mm^2	Age over 65 < 1440 cells/mm^2

25) Any condition that prevents the investigational device implantation or trabeculectomy in the superior region of the study eye (e.g., peripheral anterior synechiae, scleral staphyloma or conjunctival scarring).
26) Diagnosed degenerative visual disorders not associated with existing glaucoma condition (e.g., advanced dry or wet macular degeneration or other retinal disorders, central retinal artery or vein occlusion) or choroidopathy (e.g., choroidal detachment, effusion, choroiditis, or neovascularization).
27) Central corneal thickness that is less than 450 microns or greater than 620 microns.
28) Previous cyclodestructive procedure
29) Prior retinal laser procedure conducted for any purpose other than treatment of retinal tear or hole.
30) Conditions associated with elevated episcleral venous pressure such as active thyroid orbitopathy, cavernous sinus fistula, Sturge-Weber syndrome, orbital tumors, orbital congestive disease.
31) Clinically significant sequelae from trauma (e.g., chemical burns, blunt trauma, etc.)
32) Ocular pathology or medical condition for which, in the investigator's judgment, the following factors would either place the subject at increased risk of complications or contraindicate device implantation or interfere with compliance to elements of the study protocol (e.g., ophthalmic examinations, follow-up visits),
    a. inability to reliably complete visual field testing over the course of the study,
    b. uncontrolled systemic disease (e.g. diabetes, hypertension) that could compromise their participation in the study.
    c. Disorders that pose a fall risk, as well as compromise ability to take a visual field exam and take glaucoma medications (e.g., Parkinson's disease),
    d. inability to discontinue use of blood thinners.
    e. immunodeficiency concerns.
    f. known corticosteroid responders whose pressure increases would not allow them to withstand the postop corticosteroid regimen.
33) Intraocular silicone oil.
34) Ocular steroid use in the planned study eye or systemic steroid use anytime within three months of the procedure. (This would not include the use of inhaled or dermatologic steroids.)
35) Completion of chemotherapy within six months of the screening visit.
36) Use of oral hypotensive glaucoma medications for treatment of fellow eye.
37) A requirement of general anesthesia for the procedure.
38) ALT/SLT within 90 days of enrollment.

Study Visits and Parameters for Study Eyes

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

[1] **Diurnal IOP**

Examination Schedule:

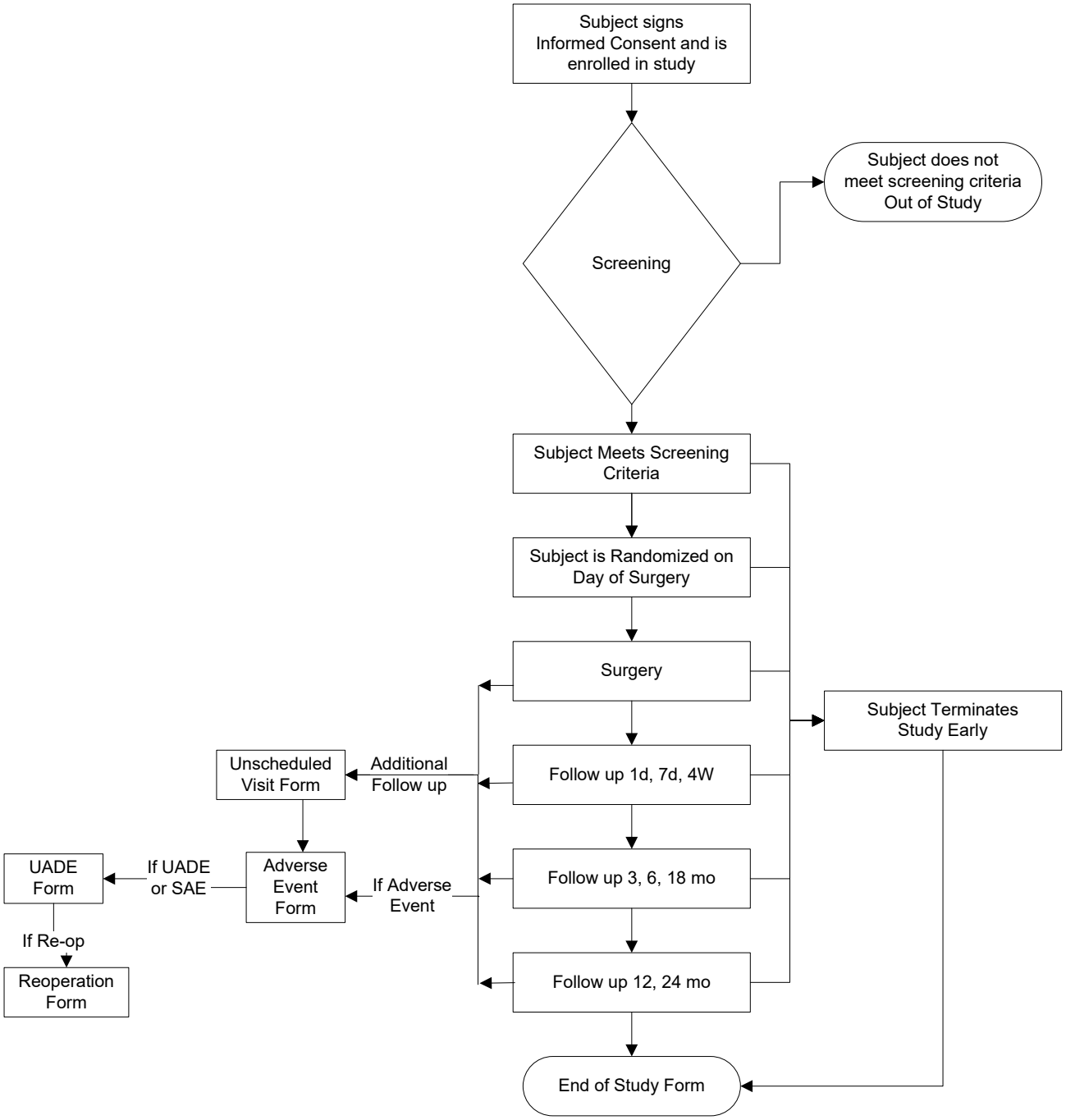
1. Screening Evaluation
2. Operative Procedure
3. 1 Day
4. 1 Week
5. 4 Weeks
6. 3 Months
7. 6 Months
8. 12 Months
9. 18 Months
10. 24 Months

The fellow eye will be managed according to the items listed and data will be gathered on the case report forms.

Activities Conducted on Fellow Eye During Clinical Study

Activities	Screening	Follow-up Evaluation							
		1 D	1W	4W	3 M	6 M	12M	18M	24M
Ophthalmology Exam	X								
Ocular Medical History	X								
Ocular Medication Assessment	X	X	X	X	X	X	X	X	X
History/Demographics	X								
Visual Field	X						X		X
Dilated Fundus Exam	X					X	X		X
Vertical C/D Ratio	X					X	X		X
Optic Disc Photo	X					X	X		X
Slit Lamp Exam	X					X	X	X	X
Manifest Refraction	X			X	X	X	X	X	X
Visual Acuity (Snellen or Pinhole)		X	X						
BCVA (ETDRS)	X			X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X
Pachymetry	X						X		X
Endothelial Cell Density	X				X		X		X
Motility	X						X		X
Observations Recorded	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X

INN-005 Flow Chart



LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Argon Laser Trabeculoplasty
BCVA	Best Corrected Visual Acuity
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
FE	Fellow Eye
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HVF	Humphrey Visual Field
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
LASIK	Laser in situ keratomileusis
MMC	Mitomycin
MR	Manifest Refraction
NRS	Numeric Rating Scale
OD	Oculus Dextrus (Right Eye)
OS	Oculus Sinister (Left Eye)
OU	Oculus Uterque (Both Eyes)
PI	Principal Investigator
POAG	Primary Open Angle Glaucoma
SE	Study Eye
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

InnFocus Study INN-005
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1.0 Study Objective

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

2.0 Study Design

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

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

A total of **514** subjects will be randomized in Phase II at 3:1 ratio with a drop-out rate of 6% per year, about **480** randomized subjects (360 treatments and 120 controls) are expected to have the **12**-month examination and **448** randomized subjects (336 treatments and 112 controls) are expected to have the **24**-month follow-up examination..

If a 40% screening failure is considered, at least 170 subjects should be enrolled for Phase I and 687 subjects should be enrolled for Phase II. Therefore, total of at least 857 subjects will be enrolled for this study in order to have at least 514 subjects be randomized and at least 416 randomized subjects reach the 24-month visit.

The randomization will be stratified by investigational site and within-site by lens type, with a target of at least 60 randomized phakic eyes in the treatment group and 20 randomized phakic eyes in the control group at 24 months. Each investigator is requested to conduct at least 10 InnFocus MicroShunt procedures and each site will be requested to enroll approximately 23 subjects.

3.0 Rationale for the Study

Trabeculectomy with MMC is one of the established treatment methods and for many years has been the gold standard treatment for individuals with glaucoma who are uncontrolled

on maximum tolerated glaucoma medications, and is generally considered the first incisional surgery choice. The latest poll of U.S. glaucoma specialists done in 2008 [9] indicates that 84% of primary trabeculectomies use MMC and 90% of combined phacoemulsification/trabeculectomy procedures use MMC. The effectiveness and safety have been documented in numerous studies. Data from a recent pilot studies are indicative that safety and effectiveness comparable to or better than trabeculectomy with MMC can be obtained with the use of the InnFocus MicroShunt.

This prospective, randomized, controlled, open-label, multi-center trial directly comparing trabeculectomy with MMC to the InnFocus MicroShunt has been designed to establish the comparable safety and effectiveness of the InnFocus MicroShunt and trabeculectomy with MMC. Trabeculectomy with and without MMC has been used previously as the literature control to prove comparability to another glaucoma drainage device that was granted FDA premarket approval (PMA), i.e., the Aquaflow™ Collagen Glaucoma Drainage Device by Staar Surgical. By using a randomized active control in the InnFocus MicroShunt study, a better comparison than literature controls can be made because there will be clearly defined and comparable subject populations in the two arms of the study.

The MMC concentration of 0.2mg/mL and 2 minutes of exposure were selected based on the recent NDA approval of the Mobius Therapeutics Mitosol™ Mitomycin C kit for use as an adjuvant to glaucoma filtering surgery. This is the only approved source of MMC for this purpose. Prior pilot studies conducted on the InnFocus MicroShunt used 0.4mg/mL and 3 minutes of application and there were no safety issues related to the concentration or application time of the MMC. Review of the literature shows the MMC has been used over a wide range of MMC concentrations and application times from 0.1-0.5mg/mL and 1-5 minutes application times. Results of the various studies have shown no clear advantage of 0.4mg/mL versus 0.2mg/mL; therefore, it is appropriate for this study to utilize the only approved source of MMC for the specific purpose of providing an adjuvant to glaucoma filtering surgery.

The allowance of at least 6 months from the time of IOL placement for the pseudophakic subjects in the study was to assure that most of the healing from the surgery had occurred and there would be no residual inflammation or rapid endothelial cell configuration changes.

Investigational sites for the clinical study have been selected to assure that an appropriate balance of gender, minority, and age are obtained during the study. Many of the sites are in metropolitan settings, which assist greatly in providing this balance. Also, the sites are distributed across the country to minimize any geographic differences. The inclusion and exclusion criteria of the study will inherently result in the majority of subjects in the 60-80 years of age range where the most subjects on maximum tolerated glaucoma medications would be expected to be. Based on not allowing any subject less than 40 years of age in the study, there is not expected to be a significant effect on enrollment of women in the study because of the one exclusion “subject is pregnant or nursing or unable to use appropriate birth control”.

4.0 Potential Risks and Benefits

InnFocus has reviewed the potential risks and benefits associated with the InnFocus MicroShunt Glaucoma Drainage System. The risks have been evaluated and design and procedure recommendations implemented to mitigate these risks where applicable.

The following potential risks have been identified:

a. The cornea or iris could be damaged during the implantation procedure or post implantation. Based on prior clinical data, no cornea or iris damage has been observed although occasionally the device has made direct contact with the iris. Additionally, surgeons are instructed on the proper insertion method. This potential contact risk with the iris or cornea is similar to presently commercialized aqueous shunts (Ahmed, Baerveldt, Molteno) as they require placement of the proximal end of the tube in the same location as the InnFocus MicroShunt.

b. The device may not be inserted completely into the anterior chamber. If this occurs, the device may be relocated to a different access tract or another device may be implanted. In either case, this would result in an overall longer procedure. There has only been one case with the present device in which a second insertion location adjacent to the original location was required with the same device with a corresponding longer procedure time. No other complications were observed.

c. Tube obstruction is a risk with the InnFocus MicroShunt surgery. The device could clog if it remains in contact with the iris with resultant low flow and increased IOP. Although contact with the iris has been observed with the present device, flow has been maintained. If the tip does become clogged, the physician can use a standard laser to remove the iris material from the tip of the device. Also, fibrin that develops during surgery can occlude the device. There has been one transient tube obstruction from fibrin in a combined InnFocus MicroShunt implantation and cataract surgery in an ongoing study that was resolved with a flush of the AC end of the tube during the initial surgery. This risk of clogging is also present with the proximal end of commercial aqueous shunts, which can contact the iris, or cornea and lasers are routinely used to clear debris from the proximal end.

d. The bleb that is typically created by the aqueous flow into the Tenon/subconjunctival pocket may develop excessive scarring (bleb encapsulation or also called “Tenon’s cyst”) which can result in lower aqueous flow through the bleb and increased IOP. The implantation procedure has been refined to provide for a large pocket that is resistant to fibrosis and scarring. One bleb encapsulation was observed in prior InnFocus MicroShunt studies and was successfully needled. A similar risk of scarring is observed with trabeculectomy.

e. Choroidal effusion may occur and lead to an observable choroidal detachment. This has been observed in 2 prior InnFocus MicroShunt cases during combined surgery with cataract removal and resolved with the use of cycloplegics. There was no incidence of suprachoroidal hemorrhage in studies to date but this should be considered a risk of this surgery, as it is with trabeculectomy.

f. Flat or shallow chambers may occur as the result of low pressure in the anterior chamber. Two cases of shallow chambers were observed in studies to date and resolved spontaneously with no observable damage to the cornea or iris.

g. Wound leaks may occur shortly after surgery and may be related to the suturing of the conjunctiva to the limbus. One short-term wound leak was observed but resolved spontaneously within the first three weeks after surgery. No long-term wound leaks have been observed in existing studies of this device.
h. No blebitis has been observed in clinical studies to date but is a risk whenever a bleb is developed as a result of the surgery.
i. No endophthalmitis has been observed but it is a risk of this type of surgery, especially in the event that blebitis develops.
j. Hyphema has been observed in several cases but not at a level of 10% or more of the anterior chamber and typically resolves within one week of surgery.
k. Aqueous misdirection is a potential risk of filtering surgery but has not been observed in existing studies of the device.
l. Decompression retinopathy has not been observed but remains a risk with this type of surgery.
m. Persistent hypotony is defined as an intraocular pressure below 6mmHg that is present on two consecutive follow-ups after three months. This can lead to hypotony maculopathy. No persistent hypotony or hypotony maculopathy have been observed in studies to date.
n. Corneal decompensation from MMC exposure could occur if MMC reached the corneal endothelium as has been reported in an animal model in the literature and is another risk. Avoiding contact of MMC with the cornea endothelium by rinsing MMC out of the subconjunctival pocket prior to entry of the needle into the AC should assure no entry of MMC and therefore no effect on the endothelium. Corneal decompensation has not been observed in InnFocus MicroShunt clinical studies to date.
o. A thin-walled avascular bleb may be associated with low IOP. This has not been observed in the prior InnFocus MicroShunt studies.
p. Tube erosion over time resulting in a break in the conjunctival barrier and potential infection is a risk in the InnFocus MicroShunt arm of the study. There have been no tube erosions in the ongoing studies of the InnFocus MicroShunt.
q. Chronic or recurrent iritis is a risk associated with filtering surgery. No chronic or recurrent iritis has been observed in the ongoing InnFocus MicroShunt clinical studies.
r. Migration of device out of anterior chamber. There have been no clinical cases of InnFocus MicroShunt migration out of the anterior chamber, but there has been one case where the surgeon inadvertently moved the InnFocus MicroShunt out of the anterior chamber during conjunctival closure at time of the original procedure.

The following potential benefits have been identified (please note we do not necessarily intend to seek specific claims for all these potential benefits):

a. The surgical procedure does not require extensive cutting into the sclera, as does the trabeculectomy in the creation of a sclera flap and in punching an internal ostium, and where if the cut is too deep, there is a risk of hemorrhage and loss of the eye. In this regard, the InnFocus MicroShunt is less invasive.
b. The aqueous outflow through the InnFocus MicroShunt is controlled by the diameter and length of the InnFocus MicroShunt tube and does not rely on subjective tensioning of sutures as does trabeculectomy.

c. If the implanted device is effective and reduces intraocular pressure, the subject may reduce or eliminate glaucoma medication therapy. Reduction of glaucoma medication is desirable as more than half of the patients on glaucoma medications do not comply with their regimens and vision loss continues. If the implanted device is effective and reduces intraocular pressure, the subject may not require additional glaucoma surgery and further vision loss may be avoided.
d. Based on the minimally invasive procedure and the characteristics of the device, there may be fewer complications. Historical clinical data suggests that the short term control of IOP with the InnFocus MicroShunt may be better than trabeculectomy with MMC with less inflammation and bleb scarring and less hypotony and associated concerns.

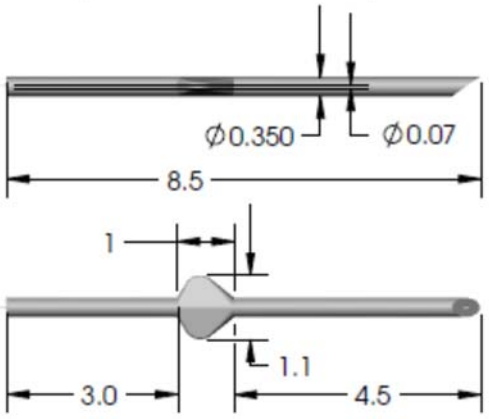
5.0 Device Description

This study evaluates the InnFocus MicroShunt Glaucoma Drainage System, which includes the InnFocus MicroShunt device and associated components. There is only one device model in the clinical study. The InnFocus MicroShunt can be stored at room temperature. Brief descriptions of each are presented below:

5.1 InnFocus MicroShunt device

The lumen of the device as shown below is approximately 70 microns in diameter with an outer diameter of 350 microns and a length of approximately 8.5mm. It is designed to allow aqueous flow from the anterior chamber to a bleb (blister-like formation below the conjunctiva/Tenons).

InnFocus MicroShunt
(All dimensions in mm)



It is packaged in a thermoform tray that is enclosed in a sealed Tyvek pouch.

5.2 Double Step Incision Knife

This disposable stainless steel knife has a 1.0mm wide cutting edge and 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.

5.3 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 InnFocus MicroShunt thermoform tray and enclosed in a sealed Tyvek pouch.

5.4 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 InnFocus MicroShunt System Box.

5.5 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 InnFocus 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 InnFocus MicroShunt kit.

5.6 Outer Packaging

The ethylene oxide sterilized InnFocus MicroShunt and 3mm marker are packaged in a unit box with the other purchased and separately packaged sterilized components for shipment to the clinical site.

6.0 Primary Effectiveness Outcome

The primary effectiveness outcome is the proportion of eyes with ≥ 20% decrease in mean diurnal intraocular pressure from screening to 12 months follow-up.

The proportion of eyes with ≥ 20% decrease in mean diurnal intraocular pressure from screening to 24 months follow-up will also be compared between treatment group and control group.

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

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

4. Glaucoma laser procedure (e.g., trabeculoplasty, iridotomy)
5. Other glaucoma surgery to reduce IOP
6. Missing 24-month diurnal IOP due to discontinuation from the study prior to the 24-month visit
7. Post-operative introduction of an oral carbonic anhydrase inhibitor.

The procedures shown below will be reported as complications but are not failures:

1. Needling of the bleb with or without the use of an injected antifibrotic
2. Laser removal of blockage at the tip of the InnFocus MicroShunt or at the AC 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

7.0 Secondary Effectiveness Outcome

The secondary effectiveness outcome is mean diurnal IOP change from screening to 12 months follow-up post-operative examination.

The mean diurnal IOP change from screening to 24 months post-operative examination will also be compared between the treatment group and control group.

8.0 Safety Outcome

Safety will be evaluated at one year follow-up as a comparison of all adverse events between the investigational device and control groups and will also be compared at 2 years follow-up.

9.0 Protocol Parameters

9.1 Number of Study Centers

A total of 30 centers will be recruited to participate in the study to assure enrollment in a reasonable timeframe. Thirteen centers are identified for the Phase I activities and will continue into Phase II as part of the total of 30 centers. A maximum of 6 centers of the thirty are planned to be outside of the United States.

9.2 Study Population Characteristics

All of the following ophthalmic criteria apply to the study eye unless otherwise noted. The study population will consist of subjects diagnosed with open angle glaucoma. Subjects will be currently taking ocular hypotensive medications and have IOPs that are not controlled. Pseudophakic participants must have at least 180 days between cataract surgery and study enrollment. All subjects must have IOPs that are not controlled on maximum

tolerated glaucoma medications. The term "maximum tolerated glaucoma medications" is defined for this study as three or more classes of topical glaucoma medications (prostaglandin analog, beta blocker, carbonic anhydrase inhibitor, alpha agonist, miotic). If a subject is intolerant to specific glaucoma medications or the medications are ineffective, "maximum tolerated glaucoma medications" may be fewer than three classes presently in use. In cases where one or more of the classes of glaucoma medications have been used unsuccessfully because of ineffectiveness or allergic reaction or intolerable side effects, this will be noted on the Screening form. Combination glaucoma medications that consist of two or more glaucoma drugs will have each glaucoma drug component counted as a separate drug.

The rationale for adopting these criteria is derived from the observed outcomes in the Advanced Glaucoma Intervention Study (AGIS)[1-3], the Early Manifest Glaucoma Treatment study (EMGT) [4-5] and the Collaborative Initial Glaucoma Treatment Study (CIGTS)[6-8]. These studies taken together have shown that most eyes with primary open-angle glaucoma will progress to a clinically significant degree without treatment, that visual field progression in glaucomatous eyes is intraocular pressure dependent, and that visual field loss can be stabilized in a large majority of eyes with optimal pressure reduction, which is best obtained with pressures in the low-normal range (11-13 mm Hg) for eyes with advanced damage, and no higher than the mid-normal (14-17 mm Hg) range for eyes with mild-moderate damage. All subjects will have medicated IOPs of $\geq$ 15mmHg and $\leq$ 40mmHg at time of screening. In addition, all subjects will be in compliance with the inclusion and exclusion criteria presented below.

9.2.1 Inclusion Criteria (All criteria apply to the study eye)

9.2.1.1 Male or female patient, age 40 to 85 years, inclusive

9.2.1.2 Patient has early to severe primary open angle glaucoma where the mean diurnal intraocular pressure is not controlled on maximum tolerated medical therapy with the intraocular pressure $\geq$ 15 mm Hg and $\leq$ 40 mm Hg while on glaucoma medications.

Maximum tolerated medical therapy is defined as:

9.2.1.2.1 Three or more classes of topical glaucoma medications (prostaglandin analog, beta–adrenergic antagonist, carbonic anhydrase inhibitor, alpha-adrenergic agonist, parasympathomimetic). Combination glaucoma medications that consist of two or more glaucoma drugs will have each glaucoma drug component counted as a separate drug.

9.2.1.2.2 Fewer than three classes presently in use if a subject's intolerance to specific glaucoma medications and ineffective medications are included.

9.2.1.3 Primary open angle glaucoma diagnosis based on:

9.2.1.3.1 visual field mean deviation of -3dB or worse **and**

9.2.1.3.2 glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities documented on slit lamp stereo biomicrosopy or in stereo disc photos:

- Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles
- Diffuse or localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles
- Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
- Disc rim or peripapillary retinal nerve fiber layer hemorrhages

9.2.1.4 Prior ab interno conjunctival-sparing glaucoma procedures were conducted more than 6 months prior to enrollment (e.g., iStent, Trabectome, gonioscopy-assisted transluminal trabeculectomy [GATT]).

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

9.2.1.6 Patient is willing to attend follow-up visits for two years postoperative.

9.2.2 Exclusion Criteria (All criteria apply to the study eye unless otherwise noted)

9.2.2.1 Patient unwilling or unable to give informed consent, unwilling to accept randomization, or unable to return for scheduled protocol visits through 2 years.

9.2.2.2 Patient < 40 yr or >85 years of age.

9.2.2.3 Patient is pregnant or nursing or unable to use appropriate birth control.

9.2.2.4 Vision level of no light perception.

9.2.2.5 Active iris neovascularization or active proliferative retinopathy or other ophthalmic disease that could confound study results.

9.2.2.6 Iridocorneal endothelial syndrome.

9.2.2.7 Epithelial or fibrous downgrowth.

9.2.2.8 Secondary glaucoma such as post-trauma, pseudoexfoliation or pigment dispersion.

9.2.2.9 Chronic ocular inflammatory disease.

9.2.2.10 Subject already enrolled in another study (only one eye can participate) or completed their participation in another study within 30 calendar days of the screening exam.

9.2.2.11 Aphakia.

9.2.2.12 Vitreous in anterior chamber for which a vitrectomy is anticipated.

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

9.2.2.14 Severe anterior or posterior blepharitis.

9.2.2.15 Unwilling to discontinue contact lens use after surgery for the duration of the study.

9.2.2.16 Previous incisional ophthalmic surgery involving the conjunctiva

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

9.2.2.18 Presence of an anterior chamber IOL (ACIOL).

9.2.2.19 Prior laser peripheral iridotomy conducted within 3 months of enrollment.

9.2.2.20 Need for glaucoma surgery combined with other ocular procedures or anticipated need for additional ocular surgery during the investigational period.

9.2.2.21 Fellow eye with poorer than 20/80 best-corrected visual acuity (BCVA) or points in both hemifields within 5 degrees of fixation with sensitivity <0 dB.

9.2.2.22 Known allergy or other contraindication to use of mitomycin C (MMC) drug.

9.2.2.23 Angle closure or narrow angle as identified by gonioscopy and classified as Shaffer Grade 0 or 1.

9.2.2.24 Endothelial cell density for the central reading at screening of the following values:

Phakic	Pseudophakic
Age 40-45< 2200 cells/mm^2	Age 40-45 < 1980 cells/mm^2
Age 46-55 < 2000 cells/mm^2	Age 46-55 < 1800 cells/mm^2
Age 56-65 < 1800 cells/mm^2	Age 56-65 < 1620 cells/mm^2
Age over 65 < 1600 cells/mm^2	Age over 65 < 1440 cells/mm^2

9.2.2.25 Any condition that prevents the investigational device implantation or trabeculectomy in the superior region of the study eye (e.g., peripheral anterior synechiae, scleral staphyloma or conjunctival scarring).

9.2.2.26 Diagnosed degenerative visual disorders not associated with existing glaucoma condition (e.g., advanced dry macular degeneration or other retinal disorders, central or branch retinal artery or vein occlusion) or choroidopathy (e.g., choroidal detachment, effusion, choroiditis, or neovascularization).

9.2.2.27 Central corneal thickness that is less than 450 microns or greater than 620 microns.

9.2.2.28 Previous cyclodestructive procedure

9.2.2.29 Prior retinal laser procedure conducted for any purpose other than treatment of retinal tear or hole.

9.2.2.30 Conditions associated with elevated episcleral venous pressure such as active thyroid orbitopathy, cavernous sinus fistula, Sturge-Weber syndrome, orbital tumors, orbital congestive disease.

9.2.2.31 Clinically significant sequelae from trauma (e.g., chemical burns, blunt trauma, etc.)

9.2.2.32 Ocular pathology or medical condition for which, in the investigator's judgment, the following would be either at risk or contraindicate device implantation or compliance to elements of the study protocol (e.g., ophthalmic examinations, follow-up visits),

a. inability to reliably complete visual field testing over the course of the study,
b. uncontrolled systemic disease (e.g. diabetes, hypertension) that could compromise their participation in the study.

c. Disorders that pose a fall risk, as well as compromise ability to take a visual field exam and take glaucoma medications, (e.g., Parkinson's disease)
d. inability to discontinue use of blood thinners
e. immunodeficiency concerns.
f. known corticosteroid responders whose pressure increases would not allow them to withstand the postop corticosteroid regimen.

9.2.2.33 Intraocular silicone oil.

9.2.2.34 Ocular steroid use in the planned study eye or systemic steroid use anytime within three months of the procedure. (This would not include the use of inhaled or dermatologic steroids.)

9.2.2.35 Completion of chemotherapy within six months of the screening visit.

9.2.2.36 Use of oral hypotensive medications for treatment of fellow eye.

9.2.2.37 A requirement of general anesthesia for the procedure.

9.2.2.38 ALT/SLT within 90 days of enrollment.

9.3 Study Entry Procedures

9.3.1 Informed Consent

The InnFocus and IRB approved informed consent form (ICF) will be presented and explained to each prospective subject by the investigator or a trained clinical professional before study-specific tests have been performed. The investigator or a trained clinical professional will explain the elements of the informed consent form, including the risks or discomforts, the fact that he or she will be randomized and therefore may or may or may not receive a device and he or she will not know their randomization treatment until the 2 year visit is completed.

Once the subject has been informed of all aspects of the study, the potential subject will be given the opportunity to ask questions, and allowed time to consider the information provided. The subject's willingness and ability to meet follow-up 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, the HIPAA (Health Insurance Portability and Accountability Act) authorization, and other applicable local documentation (e.g., California Bill of Rights), the subject can then proceed with the screening evaluation. The subject has the right to withdraw from the study at any time without consequences, as indicated in the Informed Consent document.

Subjects are enrolled upon signing the informed consent document even if they subsequently fail to meet the eligibility criteria. Subjects will be added to the enrollment log, and assigned a subject number.

The principal investigator(s) 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. **Note:** Subjects will remained masked throughout the two year

follow-up period to the treatment they will received, this will be explained to the subject prior to their signing the informed consent document.

9.3.2 Screening Evaluation

After obtaining an understanding of the purpose of this study, then reviewing and signing the informed consent form, all potential subjects will undergo a series of standard clinical tests to determine their eligibility for the study.

Subjects who do not meet the screening exam eligibility criteria will be exited from the study. An ocular and non-ocular medication or supplements (including vitamins) assessment will be performed at screening visit and collected on CRF for the duration of the study. Subjects who are intolerant to maximum tolerated medications should have history glaucoma medications recorded on CRF.

The screening examination will consist of the activities included in Table 1. The study eye and fellow eye of each subject will undergo the tests as indicated in Table 1.

Table 1. Activities Conducted During Screening Evaluation

Activity	Study eye Screening Evaluation	Fellow Eye Screening Evaluation
Informed Consent	X	X
Demographics	X	X
Ocular Medical History	X	X
Systemic Disease History	X	X
Ocular Medication Assessment	X	X
Ophthalmology Exam	X	X
BCVA (ETDRS)	X	X
Lens Evaluation (LOCS III)	X	
Diurnal Medicated IOP	X	
Medicated IOP (during first IOP for study eye)		X
Gonioscopy	X	
Optic Nerve Head Imaging	X	X
Vertical C/D Ratio	X	X
Pachymetry	X	X
Diplopia Evaluation	X	
Motility Evaluation	X	
Visual Field (only if < 3 mo. is not available)	X	X
Pregnancy Test (as applicable)	X	
Endothelial Cell Density	X	X
Ocular QOL Questionnaire	X	
General Health Questionnaire	X	

If both eyes meet the applicable inclusion and exclusion criteria, the eye that has the greater visual field defect will be in the study. If the mean deviations are within 1dB of each other, then the eye with the worse BCVA (or PAM result in phakic eyes in which the visual acuity is not 20/25 or better) will be selected.

The other eye will be excluded based on the first eye already being included in the study.

Note: If a subject does not meet the eligibility criteria, he/she may be re-screened after 30 calendar days. Subject should be exited from the study and pertinent clinical data to the screening exam will be recorded on the appropriate CRFs. If the subject is screened the second time, another subject identification number will be assigned.

During the screening process, the surgeon will prospectively decide at what postoperative interventional IOP he/she will want to reinitiate glaucoma medication or physically intervene. In this manner, the decision will be set before randomization, such that there will be no bias on the group to which the subject is randomized.

- Default interventional IOP: IOP > 21 mm Hg (or > the preoperative medicated IOP if that was lower than 21mm Hg) is the default IOP for reinitiating glaucoma medication or physically intervening.

- Alternate interventional IOP: IOP chosen by the surgeon above which he/she will reinitiate glaucoma medication or physically intervene.

(If the alternate interventional IOP was chosen and the post-procedure IOP exceeds the surgeon's choice, the subject will be asked to come back for a second visit within 1 week to confirm the IOP before reinitiating glaucoma medication or physically intervening. If the IOP also exceeds the default interventional IOP, such that safety is a concern, a second visit is not required before taking any action.)

9.3.3 Surgery and Subject Randomization

On the day of the surgery, the subject is randomized to participate in the Treatment or Control groups using a pseudo-random number generator with subjects enrolled according to a predetermined list. Each investigational site will be provided envelopes with randomization assignments. The Treatment group will receive the InnFocus MicroShunt with MMC. The Control group will receive trabeculectomy with MMC. **Note:** The subject will not be informed of what procedure he/she will receive. Neither the investigator nor the investigational staff will reveal the treatment assignment to the study subject for the duration of their participation in the clinical study

9.3.4 Evaluation Methods

The following background information is provided to assist with appropriate screening and follow-up for all subjects in this study:

a. Measurement of intraocular pressure
Each time IOP is measured, the physician or technician is to utilize a Goldmann tonometer; however, the individual operating the tonometer should not view the dial during the measurement and another individual who is masked to the treatment should read the measurement and then record the measurement to minimize observer bias. At each visit, IOP will be measured prior to gonioscopy 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.

In order to determine the mean diurnal intraocular pressure (IOP) measurements at screening, 12 months and 24 months, values should be taken at 9:00AM $\pm$ 1.5 hours, 12:00PM $\pm$ 1 hour, and 4:00PM $\pm$ 2 hours. The three IOP measurements should then be averaged to determine the mean diurnal IOP.

Standard postoperative IOP measurements (i.e., taken at Day 1, Week 1, Week 4, Months 3, 6 and 18), only 1 set of pressure measurements will be needed. Every attempt should be made to have these values taken at the same time interval for each visit.

b. Visual Field Examination
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 the pre-operative evaluation and all subsequent evaluations,

Visual fields must be reliable at screening for eligibility, defined as $\leq$ 33% false positives, false negatives, and fixation losses. (These are the acceptance criteria used in the previous OHTS study.) A visual field done within 90 days prior to the subject informed consent date and in accordance with the 24-2 SITA Standard requirements can be used for the screening evaluation. For visual fields that do not meet the reliability standards, the test should be repeated within two weeks.

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 screening, it should be performed at all subsequent visual field examinations. However, dilation should not be performed before the IOP measurement on the appropriate visits.

Visual field interpretation will be documented on the Screening form and one of the choices in the following categories will be marked (Mills GSS criteria were referenced to obtain these choices):

Mean Deviation
Early defect outside of inclusion range = MD of > -2.99 dB
Early defect within inclusion range = MD of -3.00 dB to - 6.00 dB
Moderate defect = MD of -6.01 to -12.00 dB
Advanced defect = MD of -12.01 dB to -20.0 dB
Severe defect = MD of ≤ -20.01 dB

Central Defects <0 dB within 5^{o} of fixation
None
1 in one hemifield only
2 in one hemifield only
1 in both hemifields
2 in one hemifield and 1 in the other hemifield
2 in one hemifield and 2 in the other hemifield

c. Pachymetry
Pachymetry is performed to determine central corneal thickness at screening, Months 12 and 24. For each evaluation, three measurements are taken utilizing an electronic pachymeter and annually thereafter. The measurements and the mean value will be recorded in the source documents.

Follow-up measurements conducted at the 12 and 24 month visits should be performed using the same instrument that acquired the screening data if at all possible. These measurements should be performed on the study eye.

d. Distance Visual Acuity
During the screening visit, Best Corrected Visual Acuity (BCVA) should be measured (BCVA must be 25 or more letters equivalent to 20/80 or better in the fellow eye) 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. At all subsequent follow-up visits from 1 month and longer where BCVA measurements are required, LogMAR measurement (utilizing ETDRS) should be documented. MR must be performed prior to BCVA using the ETDRS charts and will be performed at all visits except Operative, Day 1, and Week 1 visits. The Snellen or Pinhole visual acuity is used for the 1 day and 1 week post-op values.

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 are directed to refer to the instructions on the commercial ETDRS charts and the Visual Acuity Testing Manual.

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 investigational 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.

e. Dilated fundus examination

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 in support of a glaucoma indication as defined in the inclusion criteria and reported on the Screening form. A measurement of the vertical cup-to-disc ratio should be made and reported. All methods used to assess nerve abnormalities at screening must also be used at all required postoperative exams.

The optic disc photos should be performed using HRT, OCT, GDx or other method (such as stereo disc photography with either true stereo or sideways displacement of the camera). Note: Assessment of nerve abnormalities conducted $\leq$ 6 months of screening visit can be used as part of the subject's evaluation for inclusion in (or exclusion from) the study.

The examination will be conducted at the prescribed intervals in the activity list 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.

f. Endothelial Cell Density

Each subject must have a screening density of the central endothelium in accordance with the clinical study inclusion criteria to participate in the study. Endothelial cell densities are to be taken before gonioscopic testing 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) located at the Department of Ophthalmology and Visual Sciences, Case Western Reserve University School of Medicine, Cleveland, Ohio.

Cornea Image Analysis Reading Center (CIARC) will certify technicians and approve specular microscopes for study participation. 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 investigational site must be confirmed by the CIARC prior to conducting the first readings. CIARC will provide sites a detailed site manual.

All technicians at CIARC conducting endothelial cell reading will be masked to the treatment group. Investigational site technicians will be masked to the treatment group for imaging as well.

For each subject, central images of the study eye will be collected at screening, 3 months, 6 months, 12 months and 24 months follow-ups. Fellow eye central images will be collected at screening, 3, 12 and 24 months.

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 patient to lean in comfortably.
3. The axis of head should be perpendicular to the forehead bar.
4. Ask the patient to focus on the green indicator light.
5. Ensure the patient's pupil is within the target circle on the monitor in upper right of screen.
6. Once adjusted, tell the patient 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 patient 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 patient 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 patient's eyelid interferes with photograph, hold the lid for patient while keeping the forehead against the forehead bar, or lightly tape the eyelid up still allowing the patient to be able to blink.
d. IOLs can reflect multiple beams of light into the camera interfering with the photograph. If so, have patient look slightly off (right/left/up/down) from indicator light until white reflections coalesce into one or two reflection spots and then take picture.

g. Slit Lamp Examination

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 and pigment dispersion should also be evaluated and noted.

For patients 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 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.

h. Gonioscopy

Gonioscopy will be conducted as part of the screening process to verify that the subject has an open angle and to identify any anterior synechiae as well as determine if there is any pigment dispersion. A Zeiss, Sussman or similar lens should be used and gonioscopy 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.

Gonioscopy may also be used post-surgery with a trabeculectomy if an elevated IOP is observed to determine if the sclerostomy is filling with iris or fibrin before adding glaucoma medications.

i. Ocular Hypotensive Medications
Each ocular hypotensive medication will be recorded on the case report form. If subjects are taking combination medications such as Cosopt® this is to be counted as two medications even though this is only in 1 bottle.

j. Pregnancy Testing, Nursing and Contraceptives
Women of childbearing potential are excluded from participation if they are currently pregnant, have a positive urine pregnancy test at screening, or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study ((hormonal – oral, implanted, transdermal, or injected contraceptives)(mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD)). All women are considered to be of childbearing potential unless one or more of the following criteria are met:

- Postmenopausal for at least 1 year
- Surgically sterile

For non-sexually active females, abstinence may be regarded as an adequate method of birth control; however if the patient becomes sexually active during the study, she must agree to use adequate birth control methods as define above prior to sexual activity and for the remainder of the study.

Females of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study. Should this occur, the investigator must immediately contact the sponsor.

k. Ocular Quality of Life (QOL) Questionnaire
A patient questionnaire is being used in this study to evaluate visual function and local eye effects related to the surgeries. The questionnaire has been derived from the Collaborative Initial Glaucoma Treatment Study {CIGTS} (*Ophthalmology 1999;106:653–662)*and identified in a draft manuscript (yet to be published) as potentially useful for QOL evaluation based on the CIGTS history. The questionnaire was provided to InnFocus by one of the authors of the manuscript.

The questionnaire contains 2 subgroups, consisting of 18 separate items: 11 on Visual Function and 7 on the Local Eye, that have been extracted from the 43 question QOL questionnaire used in CIGTS. The visual function subscale (11 items) includes symptoms and health problems deemed by clinical center ophthalmologists to be related to glaucoma as a disease process independent from any treatments or side effects: difficulties going from light to dark, blurred vision, difficulty seeing in dark places, difficulty with near vision, trouble seeing when stepping down, problems with distance vision, dimming of vision, problems with depth perception, visual distortion,

difficulty with bright lights or sunlight, and trouble with color vision. The local eye subscale (7 items) includes such problems as eye irritation and burning, excessive tearing, and red eyes.

After enrollment during screening, the patient will be initially interviewed using the questionnaire. The statements to be used are at the beginning of the questionnaire and should be followed closely to assure consistency of response. Document the patient responses directly on the questionnaire.

The interviewing process will be conducted again at several intervals in accordance with the testing schedule.

l. General Health Questionnaire (EQ-5D-5L)
A second questionnaire will also be used to document the general health of the subject before and after surgery. This questionnaire, in association with the questionnaire in item k above will be used to compare the overall health status of the subject as a result of the surgery. Both questionnaires will also be used as part of a health economics comparison of the InnFocus MicroShunt surgery and trabeculectomy. This questionnaire was selected based on the well-documented history of its use and the relative ease of questionnaire completion. The subject completes this questionnaire without the assistance of an interviewer initially after enrollment and during the screening process. The subject again completes the questionnaire at the defined follow-up points in the test schedule.

The EQ-5D-5L consists of a cover page and 2 pages to complete – the EQ-5D-5L descriptive system (page 2) and the EQ Visual Analogue scale (EQ VAS) (page 3). The descriptive system comprises 5 dimensions (mobility, self care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

9.4 Study Procedures

9.4.1 Training
Before any site may begin actual device implantation, all investigators will participate in an InnFocus investigator training session. Investigators will gain familiarity with the InnFocus MicroShunt through the use of animal or human cadaver eyes. Further training will be provided to the study coordinators at each site by an InnFocus trained designee.

9.4.2 Material and Equipment
A listing of general equipment and materials required at the investigational site for the preoperative, operative, and postoperative steps of the investigational study is provided below.

1. InnFocus MicroShunt Glaucoma Drainage System
2. Goldmann Applanation Tonometer
3. Humphrey Visual Field Analyzer
4. Goniolens (Zeiss, Sussman or similar, not Goldmann to screen for angle closure)
5. Ultrasound Pachymeter
6. Slit lamp and fundus contact lens, Hruby lens or 90 diopter lens
7. Indirect ophthalmoscope
8. ETDRS Visual Acuity System/Snellen Visual Acuity System
9. Specular Microscope (Konan XL)
10. Fully equipped surgical suite equipped with operating microscope
11. Video equipment in operating room
12. Fundus camera
13. Mobius Therapeutics Mitosol MMC Kit
14. Light Meter

The Goldmann tonometer should be calibrated at each investigational 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.

9.4.3 InnFocus MicroShunt Surgical Procedure

Mark the location of the implant on the study eye sketch in the source documents. The following provides an overview of the surgical procedure for implantation of the InnFocus MicroShunt. If possible, each surgical procedure should be videotaped.

A. Anesthesia

The type of anesthesia will be at the surgeon's discretion except general anesthesia is excluded and the type will be documented on the Operative form.

B. Preparation of InnFocus MicroShunt

Carefully examine the package containing the InnFocus MicroShunt for signs of damage that could compromise sterility. If damaged, discard the device.
Remove InnFocus MicroShunt from sterile packaging onto sterile field. No more than 2 devices should be opened for each case. Wet the InnFocus MicroShunt using a solution of Balanced Salt Solution (BSS).

Note: No cutting or modification of the InnFocus MicroShunt is allowed.

C. Preparation of Mitomycin C

Follow the instructions for use of the Mobius Therapeutics Mitosol Kit.
Prepare a syringe or line that can flush copious amounts of BSS (≥20ml). (Training on the Mitosol kit will be provided prior to study initiation).

D. Corneal Traction and Conjunctival Flap

Perform corneal traction with 7-0 Vicryl suture at surgeon's discretion.

In the planned surgical area, dissect a fornix-based subconjunctival//subTenon pouch over a circumference of 90º-120º at least 8mm deep.

E. Application of MMC

Apply the MMC in accordance with the Mobius Therapeutics Mitosol Kit instructions for use. Use only 4 half-moon sponges in the kit to prepare with MMC and place under the subconjunctival/subTenon's flap. Rinse with generous amounts of BSS (≥20mL). **Note:** Assure that the conjunctival wound edge does not come into contact with antimetabolite.

F. Preparation of Anterior Chamber Entrance Site

Mark a point 3mm from the limbus, utilizing 3mm scleral marker and marker pen. At the marked point, use a 1mm double step knife in one motion to create both a scleral track into the anterior chamber (AC) so as to enter the angle just above the iris plane and a shallow scleral pocket at the mark just big enough to tuck the fin portion of the InnFocus MicroShunt.

G. Insertion of InnFocus MicroShunt into Anterior Chamber

Gently insert the InnFocus MicroShunt tube with the bevel facing toward the cornea through sclera track using forceps and holding close to the track entrance while keeping the fin face parallel to the scleral surface and tuck the fin into the scleral pocket. If there is resistance to the placement of the InnFocus MicroShunt after multiple attempts to position it, use a 25G blunt tip cannula to re-enter the sclera track and assure it is open. Then attempt placement of the InnFocus MicroShunt again.

If the InnFocus MicroShunt is damaged during the procedure, use a new InnFocus MicroShunt and repeat the insertion step using the same tract. If not accessible, another track can be made. After successful insertion of the InnFocus MicroShunt, check that the InnFocus MicroShunt tube position in the AC is not in contact with the cornea or iris and that there is flow of aqueous. If flow is not visible, place the 23G cannula over the distal end of InnFocus MicroShunt up to the fin while applying slight pressure and inject BSS to prime the tube. Confirm flow, tuck the distal end of the InnFocus MicroShunt tube under the subconjunctival/Tenon's flap on scleral surface making sure it is not caught in Tenons.

H. Conjunctival Closure

Reposition the Tenon's and conjunctiva to the limbus and suture using sutures with a long history of successful use by glaucoma specialists (i.e., nylon, vicryl). A moistened fluorescein strip is used to check for a conjunctival leak, which may be closed with additional sutures.

Verify the presence of the proximal end of the InnFocus MicroShunt in the anterior chamber.

Pull corneal traction suture out if it was used.

Apply antibiotic and steroidal medication post-op per clinical protocol requirements.

After use, dispose of product and packaging in accordance with hospital, administrative, and/or local government policy.

Follow the Mobius Therapeutics Mitosol Kit instructions for use for proper disposal of the MMC and kit components.

Warnings and Precautions:

- For one-time use only. Do not reuse or re-sterilize.
- Long term effects of MMC with the use of this device have not been evaluated. Necessary precautions on the use of MMC are highly recommended.
- All types of Viscoelastics have not been tested with this device. However, in an emergency when all other therapies have failed, the use of hydroxyl methyl-cellulose (HPMC) may be an option. Use of HPMC should be a last resort to correct a flat chamber with the InnFocus MicroShunt and may risk loss of flow through the device for one or more weeks after use necessitating close or more frequent observation of IOP.
- Should the InnFocus MicroShunt appear deformed, folded and/or distorted, do not use. Avoid use of toothed forceps to handle device. McPherson type forceps are recommended.
- Do not use knife if it has been hit against or in contact with other parts than the eyeball. Such knife may be damaged and lose sharpness.
- Do not resterilize the device.

9.4.4 Trabeculectomy with MMC Surgical Procedure

1. Investigators should use the following procedure for conducting the trabeculectomy procedure with the use of MMC: Anesthesia type is at the surgeon's discretion except general anesthesia is excluded.
2. Conjunctival flap – the trabeculectomy is performed in a superior quadrant. A fornix-based conjunctival flap is used. A corneal traction suture or superior rectus traction suture may be used to rotate the globe inferiorly and improve exposure.
3. Mitomycin C application –The MMC is prepared and used in accordance with the Mobius Therapeutics Mitosol Kit instructions for use, again using 4 half-moon sponges for delivery of the MMC under the subconjunctival flap. The mitomycin may be applied before or after the scleral flap creation dependent on the investigator's standard practice (Training on the Mitosol Kit will be conducted prior to study initiation).
4. Scleral flap – A corneal-based scleral flap is dissected approximately one-half scleral thickness. The shape and size of the scleral flap is determined by the

surgeon in keeping with his or her usual practice and should be kept consistent throughout the study.

5. Paracentesis tract – A peripheral clear cornea paracentesis tract is made.
6. Excision of Limbal tissue – A block of limbal tissue is excised from underneath the trabeculectomy flap using a sharp blade and Vannas scissors or a Kelly punch. The amount of limbal tissue excised is at the surgeon's discretion.
7. Peripheral iridectomy – A peripheral iridectomy is performed unless a specific rationale is provided as to why it is not required. The sclerostomy opening is inspected for entrapped iris tissue, and a cellulose sponge is used to test for the presence of vitreous. Vitreous presenting to the surgical wound is excised. The method used to remove the vitreous present at the surgical site is at the surgeon's discretion. Document any presence of vitreous observed.
8. Scleral flap closure – The scleral flap is reapproximated to the scleral bed with interrupted or releasable 10-0 nylon suture. The number and tension of the scleral flap sutures is determined by the surgeon. Following injection of balanced salt solution into the anterior chamber through the paracentesis tract, the anterior chamber should remain formed with a visible leak present around the scleral flap at equilibrium.
9. Conjunctival flap closure – The type of suture material and needle used for the conjunctival flap closure is of the surgeon's choice. Either a double layered closure (conjunctiva and Tenon's closed separately) or single layered closure (conjunctiva and Tenon's together) may be performed.
10. Reformation of the Anterior Chamber and Bleb Elevation – Balanced salt solution is injected through the paracentesis tract to deepen the anterior chamber and elevate the bleb. A moistened fluorescein strip is used to check for a conjunctival leak or leakage from the paracentesis tract, which may be closed with additional sutures.
11. Intraoperative medications – The use of intraoperative medications is at the surgeon's discretion.

9.4.5 Post-operative Instructions

A. Following surgery, the subjects will be instructed to adhere to the following antibiotic/anti-inflammatory regiment and the frequency will be documented on the Concomitant Medication form:

- Topical polymyxin B sulfate and trimethoprim ophthalmic solution combination (e.g., Polytrim) antibiotic or fourth generation fluoroquinolone (e.g., gatifloxacin [Zymar], or moxafloxacin [Vigamox], for one week postoperatively by instilling one drop in the operated eye four (4) times per day distributed during the waking hours. All subjects at a given investigational site must use the same antibiotic regimen unless contraindicated by allergy.
- Anti-inflammatory medication (prednisolone acetate 1% ophthalmic suspension):

- Weeks 1-4: at least four (4) times per day for the first 4 weeks. .
- Weeks 5-8: two (2) times per day for the next 4 weeks
- Weeks 9-12: one time per day for the next 4 weeks.

NOTE:

1. Anti-inflammatory medications may be increased to ≥ 4 times a day for the first month. If frequency is increased during the first month, consideration should be given to the appropriate tapering schedule at follow-up visits.
2. In the event of an adverse event during post-operative medication regimen, consideration should be given to the appropriate tapering schedule.

At the 3 months follow-up, the investigator will determine if further treatment is needed. Alternate antibiotic and anti-inflammatory medication regimens are allowed when the patient does not respond well to the initial regimen. Cycloplegics may also be used for patients as needed during the initial healing phase or in phakic eyes.

B. At follow-up visits, there are some fairly routine practices that are done by the investigator to assure a diffuse bleb and lower IOP. These are not considered as adverse events in the study. They are as follows:
   1. Eye massage done by the investigator will be documented on the follow-up form. **Eye massage should only be done by investigators and not by subjects.**
   2. Laser suture lysis is commonly used to lyse one or more sutures in the first week or later 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. The suture lysis is also documented on the follow-up form.
   3. 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 will be allowed and will be documented on the appropriate case report form as needed. The use of a topical 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 follow-up form.

C. Interventional techniques are employed if the IOP increases to the default interventional IOP value of greater than 21mmHg or greater than the pre-surgery medicated IOP if lower than 21mmHg for any subject.

   As described in the Screening section earlier in the protocol, the investigator may have established an alternate interventional IOP for the subject on the screening

form prior to randomization, and in this case, the investigator will use this value as the maximum value before considering intervention.

All investigators will intervene in a consistent manner per the pre-established interventional IOP point for each subject in the treatment and control groups and only when necessary to control IOP. (If the alternate interventional IOP was chosen and the post-procedure IOP exceeds the surgeon's choice, the subject will be asked to come back for a second visit within 1 week to confirm the IOP before reinitiating glaucoma medication or physically intervening. If the IOP also exceeds the default interventional IOP, such that safety is a concern, a second visit is not required before taking any action.)

There may be cases where the investigator needs to bring the IOP down when the subject has not exceeded the interventional IOP. In these cases, the Medical Monitor will consult with the physician to understand the rationale for the intervention and it will be documented by the investigator on the source document. For the intervention, the reason for the decision will be noted on the case report form as one or more of the following: IOP> default interventional IOP or alternate interventional IOP, visual field change, optic nerve change or temporary glaucoma med use pending suture lysis. A field for "Other" will be used to document any other reason for the intervention.

Physical intervention should 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 subconjunctival pocket. In these cases, The InnFocus 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 is documented as a complication on the Adverse Event form).
    a. 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 with both arms of 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 documented in the concomitant medications log and needling with an antifibrotic is indicated on the adverse event form.

2) Laser removal of blockage at the tip of the InnFocus MicroShunt or at the AC entry point for a trabeculectomy is another possibility and is documented as a complication on the Adverse Event form.

D. Glaucoma medications are added if common physical interventional techniques have been employed, but do not decrease the IOP below the target IOP for any subject, or if physical intervention is not attempted at all to reduce the IOP.

E. If glaucoma medications need to be re-introduced, glaucoma medications to which the subject is naïve should be deferred until after previously used medications have been introduced. Barring interfering factors regarding the method of re-introduction of glaucoma medications post-surgery, the recommended sequence is to first add a beta blocker, then a prostaglandin, and either an alpha adrenergic agonist or a carbonic anhydrase inhibitor as a third medication. As routine practice, medications should be added one at a time and the IOP lowering effect determined 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 follow-up form field identified as "Investigator rationale for medication re-introduction or discontinuation" and the Medical Monitor will discuss the rationale with the investigator as needed to assure consistency.

Based on the sequence of drug re-introduction, there should not be a case where an oral carbonic anhydrase inhibitor will be required, but if it is, it will be counted as a failure. It is unlikely that any subject will be on oral carbonic anhydrase inhibitors at the effectiveness determination, since they would be the last drug added.

Medications which have been re-started by the investigator may be discontinued if the investigator's judgment is that the target intraocular pressure 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 follow-up form by the investigator and the Medical Monitor will follow up with the investigator as needed to assure consistency within the study parameters. For medication discontinuation, the reason for the decision will be noted on the case report form as IOP controlled or allergy to medication. A field for "Other" will be used to document any other reason for glaucoma medication discontinuation.

F. 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 screening, there is no persistent choroidal detachment, the anterior chamber is not flat with lens corneal

touch, or the patient 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 as a complication on the Adverse Event form.)

G. A secondary procedure that is performed including a trabeculectomy, repositioning of a InnFocus MicroShunt, Tenon's resection, glaucoma laser, 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.

H. If the InnFocus 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 suture to seal the track. The limbus should then be resutured in a similar manner as the original surgery. The removed InnFocus MicroShunt should be returned to InnFocus, Inc. for analysis in accordance with the explanted device procedure.

If the InnFocus MicroShunt is removed, another InnFocus MicroShunt should **not** be implanted in the same subject. Use an alternate procedure.

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 over the two years period under the protocol schedule will be part of the safety analyses. Any extra visits to evaluate the patient due to the secondary procedure will be considered "Unscheduled Visits" if performed outside of the standard visit windows in the protocol and the Unscheduled Visit form will be used to document the visit.

I. 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.

Unless a post-surgery visit coincides with the standard protocol follow-up visit, the visits will be handled as "Unscheduled Visits" and the Unscheduled Visit form will be used to document the visit.

9.5 Follow-up

All subjects will participate in defined follow-up visits throughout two years. A follow-up case report form shall be completed from source data gathered at the time the subject is examined. Unscheduled or interim visits should also be recorded using the appropriate forms. Table 5 provides an overview of all activities to be conducted during the clinical study. Table 5a indicates the testing that should be conducted on the fellow eye during the study. All attempts should be made to conduct each follow-up evaluation within the specified time intervals shown in Table 6. Evaluations conducted outside the prescribed time period will be considered protocol deviations. Visits conducted outside scheduled timeframes will be considered an additional visit and must be documented using the Unscheduled Visit form.

Table 5. Study Visits and Parameters for Study Eyes

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

[1]**Diurnal IOP**

Testing of the fellow eye will be conducted as per the table below and data will be gathered on the case report forms.

Table 5a. Activities Conducted on Fellow Eye During Clinical Study

Activities	Screening	Follow-up Evaluation							
		1 D	1W	4W	3 M	6 M	12M	18M	24M
Ophthalmology Exam	X								
Ocular Medical History	X								
Ocular Medication Assessment	X	X	X	X	X	X	X	X	X
History/Demographics	X								
Visual Field	X						X		X
Dilated Fundus Exam	X					X	X		X
Vertical C/D Ratio	X					X	X		X
Optic Disc Photo	X					X	X		X
Slit Lamp Exam	X					X	X	X	X
Manifest Refraction	X			X	X	X	X	X	X
Visual Acuity (Snellen or Pinhole)		X	X						
BCVA (ETDRS)	X			X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X	X
Pachymetry	X						X		X
Endothelial Cell Density	X				X		X		X
Motility	X						X		X
Observations Recorded	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X

Follow-up Examination Schedule

Table 6. Examination Schedule

Activity	Acceptable Time Interval in Days
Post Surgery Evaluations	
1 Day	1
7 Days	5-9
4 Weeks	21-35
3 Months	70-98
6 Months	168-196
12 Months	330-420
18 Months	510-600
24 Months	690-780

9.6 Withdrawal Criteria

All subjects have the right to withdraw at any point during the treatment 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 patient 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.

9.7 Lost-to-Follow-up Subjects

Subjects who do not show up for a follow-up must be contacted to attempt to have them come for the follow-up. For those subjects who cannot be reached, at least 3 phone call attempts should be made and documented. If still no response, a registered letter shall be sent to the 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 a further communication by the subject.

9.8 Device Return

If an InnFocus device needs to be returned, the Device Return Form must be completed and returned with the product as instructed by the Device Return Procedure (located in the Regulatory Binder). Prior to explantation or return, please contact InnFocus as soon as possible. Reasons for return could include any of the following:

1. Device has exceeded the labeled expiration date.
2. Implant was not present or damaged in packaging.
3. Implant was damaged or contaminated before or during surgical procedure.
4. Implant could not be inserted during surgical procedure.
5. Flow was never observed prior to closing the flap (implying an obstruction in the device)
6. Implant was removed during post-operative/secondary surgical intervention.
7. Unused inventory upon completion of the study or site exiting from the study.

For any device to be returned that has been exposed to blood or tissue, a special package will be provided by InnFocus, Inc. for return of the device.

9.9 Protocol Modifications and Deviations

Protocol modifications may occur during the study. Each will be approved by the sponsor before implementation. Each will undergo Institutional Review Board (IRB) review and approval as necessary.

Any deviations from this protocol intended to protect the life or physical well-being of a subject in an emergency are to be reported to InnFocus, Inc. as well as the IRB as soon as possible, and no later than 5 working days after the emergency occurred.

All protocol deviations will be documented using Protocol Deviation form.

10.0 Data Handling and Recordkeeping

10.1 Subject Identification

The subjects will be identified by a five digit subject 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 identification will be assigned when ICF is obtained. The initials for each subject will also be included on CRFs. In this way, information contained in the study records will be kept as confidential as possible.

10.2 Subject Accountability

All subjects randomized in this clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation, including subjects whose device was removed or replaced, have reached the final reporting period.

10.3 Confidentiality

All medical records associated with the clinical investigation will be made available for review by InnFocus personnel, its contract research organization (CRO) and 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.

10.4 Source Data and Electronic Case Report Forms

All sites will be given instructions by a trained InnFocus designee on source data completion at site initiation visit and/or interim monitoring visits.

Source data forms are to be maintained at the site in the subject records. 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 documents must be completed and signed by the authorized study personnel (e.g., study coordinator). 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 CRFs.

The source data will be entered into a validated electronic Case Report Form system at each site by trained study personnel in accordance with 21CFR Part 11 requirements. The following forms will be utilized to collect source data during this clinical investigation

<u>Source Data Forms</u>

Screening
Operative
1 Day
7 Day
1M
3M
6M

12M
18M
24M
Unscheduled Visit
Adverse Event/ Unanticipated Adverse Device Effect (UADE)
Protocol Deviation
Re-operation
End of Study Form
Glaucoma Medication
Concomitant Medication
Ocular QOL Questionnaire
EQ-5D-5L Health Questionnaire

10.5 Device Accountability

With each shipment of investigational devices, InnFocus will include a Packing List that will give the amount shipped and the lot numbers. This packing list must be reconciled by the investigational site with the contents of the shipment and then complete the Inventory Logs for the InnFocus MicroShunt and the Mobius Mitosol (these logs are contained within the regulatory binder at the site). All investigational products (IMS) at the site must be stored in a secured/locked area. The InnFocus MicroShunt and Mobius Mitosol Kits may be stored at room temperature. Device reconciliation activities will also be conducted periodically in conjunction with site monitoring visits.

The investigator must maintain accurate records of the receipt of all devices shipped by InnFocus, including the date and lot numbers received with the use of the device inventory tracking log. The use of devices will also be recorded. An extra label provided with the device may be placed in the patient records. Any unused inventory will be returned to the Sponsor upon completion of a given procedure, expiration, or Sponsor's request.

10.6 Record Retention

Clinical sites are to retain any and all clinical trial material (documentation, photographs, etc.) for a period of two years from the date the marketing application is approved or two years after the investigation has been discontinued and the FDA notified, or as directed by their institutional document retention requirements, whichever is the longest. After that time, the items may be returned to InnFocus for archiving. Unused medical devices are to be returned to the sponsor at the conclusion of the enrollment period.

10.7 Database Management

The 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, Promedica International.

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 CRF, 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.

11.0 Assessment of Safety

11.1 Adverse Events

Adverse Events are defined below. Adverse events that occur in the study eye during the trial as well as other non-ocular events whether they are considered to be device related or not must be documented in the subject's records. Date of the 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. Conditions which exist at the time the subject is enrolled do not need to be recorded on the Adverse Event Form as adverse events unless they increase in severity during the study.

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 hypotony, increased intraocular pressure requiring medical or surgical intervention and decrease of BCVA. 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. BCVA decreases of 2 lines or more should not be reported as adverse events until two consecutive standard visits after the 3-month follow-up visits unless surgical or medical intervention is required. (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.)

Intraoperative adverse events:

- Hyphema (≥10% of anterior chamber)
- Choroidal effusion/detachment
- Choroidal hemorrhage
- Corneal abrasion during surgery
- Failure to implant the device
- Tube touching iris
- Tube touching cornea
- Iris abrasion during surgery
- Globe perforation during the implantation or anesthesia
- Flat anterior chamber
- Needle damaged corneal endothelium

Post-operative adverse events:

- Anesthesia-related complications
- Anterior chamber puncture
- Aqueous humor misdirection (malignant glaucoma)
- Blebitis
- Bleb leak based on Seidel positive test
- Choroidal effusion/detachment
- Choroidal hemorrhage
- Chronic pain
- Clinically significant corneal damage
- Clinically significant iris damage
- Conjunctival dehiscence
- Conjunctival dissection
- Corneal edema
- Diplopia
- Encapsulated bleb causing increased IOP
- Endophthalmitis
- Erosion of the device through the conjunctiva
- Flat anterior chamber
- Hypotony (IOP<6mmHg at any time)
- Hypotony maculopathy
- Implant migration
- Inadequate pain control following surgery
- Increased IOP requiring Needling
- Increased IOP requiring Needling with 5FU/MMC post-surgical injection of bleb area.
- Increased IOP requiring addition of glaucoma medications
- Increased IOP requiring treatment with oral or intravenous medications
- Prolonged inflammation resulting from surgery defined as requiring anti-inflammatory medication with duration and dosage in excess of protocol post-op instructions
- Loss of 2 lines or more of BCVA on 2 consecutive standard follow-ups 90 days or more after implantation
  (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)
- Loss of light perception
- Macular edema
- Posterior capsule opacification
- Proptosis
- Pupillary block
- Re-suture scleral flap
- Retinal complication (dialysis, flap tears, detachment, decompression or proliferative retinopathy)
- Shallow anterior chamber
- Subconjunctival bleeding or hyphema at any time (including microhyphema)

- Event requiring unplanned surgical intervention for reason other than glaucoma
- Tube obstruction, partial or complete, regardless of how long the obstruction is present
- Tube touching iris
- Tube touching cornea
- Vitreous hemorrhage
- Leakage of wound site based on Seidel test
- Suture abscess or other local infection
- Significant increase in IOP vs. screening ≥10 mmHg occurring at any visit
- Strabismus
- Event requiring unplanned glaucoma-related ocular surgical intervention
- Device malfunction
- Increase in C/D ratio of ≥0.3 units on slit lamp biomicroscopic examination
- 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)
- Laser removal of blockage at the tip of MicroShunt or at the AC entry point for trabeculectomy
- Use of a viscoelastic to limit aqueous flow
- Other – complete AE description

Sight-Threatening Adverse Events

Sight-threatening AEs included but are not limited to events such as endophthalmitis and corneal decompensation, globe perforation during the implantation or anesthesia, severe retinal detachment, severe choroidal hemorrhage, severe choroidal detachment and aqueous misdirection.

Sight-threatening AEs will be reported to InnFocus and to the investigator's IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event. Subjects who are terminated from the study due to the adverse experiences will be followed until their medical outcome is determined; written reports will be provided to the sponsor by the investigator.

Unanticipated Adverse Device Effect

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. Date of event, its severity, treatment if any, and the assessed relationship of the event to the study device will be recorded on the AE form.

11.2 Reporting Adverse Events and Unanticipated Adverse Device Effects

All unanticipated adverse device effects (UADE) will be reported to the study sponsor, InnFocus, Inc., [redacted] or by e-mail and to the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. A

UADE should be documented as an adverse event using the Adverse Event form and then also documented on the UADE form. All adverse events should be documented by completing the Adverse Event form and, if applicable, a specific IRB AE 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, the investigator, and the CRO will all follow the Declaration of Helsinki in order to ensure the safety of all subjects.

The sponsor will conduct an evaluation of unanticipated adverse device effects. If the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, parts of the investigation presenting risks will be terminated. Termination will occur not later than 5 working days after the sponsor makes such a determination and not later than 15 working days after the sponsor first received notice of the effect.

11.3 Type and Duration of Follow-up after Adverse Events
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. All details must be documented on the Adverse Event Form.

If a subject in either study arm requires an additional glaucoma surgery, the subject shall continue to be seen for the required follow-up visits so that safety and effectiveness can continue to be monitored.

12.0 Monitoring Plan

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:

12.1 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

12.2 InnFocus or its designee(s) may meet with the investigator(s) at the time the site begins to enroll in order to ensure that subjects are being properly selected and that study data are being correctly recorded.

12.3 InnFocus or its designee(s) will visit the clinical site at any time during the study to review and/or collect the Case Report Forms.

12.4 Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.

12.5 A close-out monitoring visit will be conducted at the completion of the study or study termination.

13.0 Statistical Plan

The statistical analysis plan has been detailed in a separate document.

14.0 Medical Monitor

An independent Medical Monitor will be used in the 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 action have or are being taken. In cases where there was an IOP increase and intervention or glaucoma medication was initiated or in cases where medication was discontinued, the Monitor will assure that the actions of the investigator met the intent of the protocol and were appropriate for the specific subject involved.

15.0 Data Safety Monitoring Board

A clinical trial DSMB will be used for this clinical study with pertinent expertise and will review on a regular basis accumulating data from this clinical study. The DSMB will advise the sponsor regarding the continuing safety of trial subjects and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

The DSMB will review the Phase I study results and provide their recommendations directly to FDA for continuing the study into Phase II. The Phase I interim report will be provided to them in a masked fashion for review. Only in the event of unexpected safety findings will the data be unmasked for further study.

DSMB meetings will be scheduled to review the status of the study. After review of the first 75 subjects at 3 months follow-up in the Phase I study, DSMB meetings will be scheduled at least every six months to review interim results including 1 year Phase II results. All data reviews by the DSMB will be masked to the treatment group.

A charter and operational procedures will be established for the DSMB. The DSMB will consist of at least three members and will be established by the sponsor. No DSMB member will have a conflict of interest in maintaining objectivity in study evaluation.

16.0 Compliance with Protocol

An investigator shall conduct this investigation in accordance with the signed agreement with the sponsor, the investigational plan, the IDE regulation and other applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA.

17.0 References

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18.0 Supplementary Information – Ophthalmic Definitions

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

Aqueous Flare: A clinical sign occurring when there is increased protein content at the aqueous. It occurs when there is increased protein content in the aqueous fluid indicating a breakdown of the blood/aqueous barrier.

Aqueous Humor: Clear, watery fluid that fills the space between the back corneal surface and the front vitreous surface, bathing the lens. Produced by ciliary processes: nourishes the cornea, iris, and lens and maintains the ocular pressure.

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

Choroid: The layer of major blood vessels (vascular layer) of the eye, which lies between the retina and sclera and provides nourishment to the outer layers of 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

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.

Gonioprism: A special type of contact lens with prism that permits examination of the periphery of the anterior chamber or the peripheral retina.

Intraocular Pressure (IOP): Pressure of the fluid inside the eye, which varies among individuals.

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.

Low Vision: Visual loss, which cannot be corrected with eyewear or contact lenses and interferes with daily living activities.

Lumen: The space within the inside of any tubular structure, e.g., the inside walls of the arteries ore veins or tubular medical device.

Open-angle glaucoma (OAG): Glaucoma not associated with mechanical coverage of the trabecular meshwork by iris.

Optic cup: The white depression in the center of the optic disc; usually occupies about one-third or less of the total disc diameter.

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

Persistent Hypotony - intraocular pressure below 6mm that is present on two consecutive follow-ups after three months post-surgery.

Posterior Chamber: The space between the back of the iris and the front face of the vitreous; filled with aqueous fluid.

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.

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).

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.

Tonometry: The procedure that measures intraocular pressure in the eye. The various types of devices measure the pressure by indenting the cornea and are as follows: applanation, indentation, pneumotonometer, and pneumatic tonometer.

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.

Uvea, Uveal Tract: The pigmented layers of the eye (iris, ciliary body and choroid) that contain the majority of the blood vessel supply.

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: The vertical and horizontal extent of visual perception of specific targets, measured in degrees in each direction from fixation.

Vitrectomy: Surgical procedure for the removal of vitreous fluid, blood, or membranes from the vitreous cavity in the posterior of the eye, usually performed by entering through the pars plana with a needle-like rotary cutter that has fluid injection and suction capabilities.

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.

APPENDIX 1

1.0 Background on POAG, Management, and Rationale for the Study

1.1 Background on Primary Open Angle Glaucoma

The following summary in this section has been excerpted from the American Academy of Ophthalmology Preferred Practice Patterns for Primary Open Angle Glaucoma, October, 2010. Additional information and specific literature references can be obtained by going to the following website:
http://one.aao.org/ce/practiceguidelines/ppp_content.aspx?cid=93019a87-4649-4130-8f94-b6a9b19144d2

EPIDEMIOLOGY
Primary open-angle glaucoma is a significant public health problem. It is estimated that 45 million people in the world have open-angle glaucoma (OAG). Glaucoma (both open-angle and angle-closure) is the second leading cause of blindness worldwide, with approximately 8.4 million people blind from glaucoma. Overall in 2004, the prevalence of POAG for adults 40 and older in the United States was estimated to be about 2%. Open-angle glaucoma affects an estimated 2.2 million people in the United States, and that number is likely to increase to 3.3 million in 2020 as the population ages. However, large differences exist in the prevalence of glaucoma among different ethnic groups. Overall, there appears to be a threefold higher prevalence of OAG in African Americans relative to non-Hispanic Whites in the United States. It is also the leading cause of blindness in African Americans. Further, the prevalence of OAG is even higher in Afro-Caribbeans relative to African Americans. Recent evidence on Hispanics/Latinos suggests that they have high prevalence rates of OAG that are comparable to African Americans. There are no data on the prevalence of OAG in Asians in the United States.

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:

- Intraocular pressure level
- Older age
- Family history of glaucoma
- African ancestry or Latino/Hispanic ethnicity
- Thinner central cornea
- Low ocular perfusion pressures
- Type 2 diabetes mellitus
- Myopia
- Genetic mutations

Intraocular Pressure
Several population-based studies have demonstrated that the prevalence of POAG increases as the level of IOP increases. These studies provide strong evidence that IOP plays an important role in the neuropathy of POAG. Furthermore, studies have demonstrated that reduction in the level of IOP lessens the risk of visual field progression in OAG. In addition, treated eyes that have a greater IOP fluctuation may be at increased risk of progression, although this has not been shown consistently.

In spite of the relationship between the level of IOP and POAG, there is great inter-individual variation in the susceptibility of the optic nerve to IOP-related damage. Population-based studies indicate that a variable proportion of patients with IOP greater than 21 mmHg (Northern Italy [13%], Los Angeles [18%], Arizona [20%], Blue Mountains [25%], Melbourne [39%], Baltimore [45%], Rotterdam [61%], Barbados [71%]) have glaucomatous optic nerve damage. This suggests that an IOP level of greater than 21 mmHg is an arbitrarily defined level and highlights the poor value of utilizing a specific IOP cutoff as a measure for screening and diagnosing POAG.

Age
Older age is another important risk factor for the presence of POAG. A number of epidemiological studies demonstrate that the prevalence of glaucoma increases dramatically with age, particularly among individuals of Latino/Hispanic and African descent (see Table 1, Figures 1 and 4). African Americans 73 to 74 years old and 75 and older had a prevalence of 5.7% and 23.2%, respectively. Similarly, the prevalence of OAG was 3.4% for white individuals 73 and 74 years old and 9.4% for those 75 and older.

Family History
Family history is a risk factor for glaucoma. In the Rotterdam Eye Study, where all siblings of glaucoma cases and controls were examined, the odds of having POAG was 9.2-fold higher for individuals who have a first-degree relative (sibling or parent) with medically confirmed POAG. Other studies in which family members were not physically examined depend on patient reports of the status of family members, and these are known to be subject to several biases. Nonetheless, they support the concept that first degree relatives of those with OAG are at greater risk. For example, in the Baltimore Eye Survey and the Los Angeles Latino Eye Study (LALES), for individuals with POAG the odds were twice as high (1.92 and 2.85, respectively) of reporting a first-degree relative (parent, child, or sibling) with glaucoma compared with individuals who did not have glaucoma. However, the odds increased to over three times as high if they reported that they had a sibling with glaucoma (LALES 3.47, Baltimore 3.7). Interestingly, the odds rose to fivefold higher if there were two or more siblings who were reported to have a history of glaucoma.

Race or Ethnicity
For POAG, ethnicity is an important risk factor. The prevalence of POAG is higher in individuals of West African, Afro-Caribbean, or Latino/Hispanic origin than of other groups. The prevalence is three times higher in African Americans and Hispanics of Mexican ancestry compared with non-Hispanic Whites. Blindness from glaucoma is at least six times more prevalent in African Americans than in Caucasian Americans.

Central Corneal Thickness
Because applanation tonometry measurements are derived from resistance to corneal indentation and corneal stiffness, differences in central corneal thickness (CCT) may introduce artifacts in IOP measurement. The mean CCT in healthy human eyes varies by race/ethnicity. The average CCT measured ultrasonically in Caucasian Americans is 556 μm, in Latinos it is 546 μm and in African Americans it is 534 μm. If IOP is underestimated in those with thinner CCT, the relationship between IOP level and OAG damage may be underestimated, since the IOP is actually higher than measured. Conversely, if IOP is overestimated in those with a non-edematous thicker CCT, the relationship between IOP level and OAG damage may be overestimated, since the IOP is actually lower than measured. Although several tables and figures have been published, no standard nomogram correcting applanation IOP measurements for CCT has yet been fully validated.

A thinner central cornea has been reported as an independent risk factor (independent of IOP) associated with POAG, though not in all studies. In LALES, the risk of having OAG was higher in persons with thinner CCT compared with those with normal or thicker CCT even after adjusting the IOP. Studies show that differences in corneal biomechanics across individuals may have a greater impact on IOP measurement errors than CCT.

Low Ocular Perfusion Pressure
Ocular perfusion pressure is the difference between blood pressure (at systole or diastole) and the IOP. It has been hypothesized that low ocular perfusion pressures lead to alterations in blood flow at the optic nerve head and contribute to progressive glaucomatous optic nerve damage. Population-based studies in African Americans, Hispanics, and non-Hispanic Whites have provided evidence that low diastolic perfusion pressure (<50 mmHg) is associated with a higher prevalence of POAG. In addition, in the Early Manifest Glaucoma Treatment Study, low systolic perfusion pressure (≤125 mmHg) was associated with a higher risk of glaucoma progression (relative risk of 1.42) over an 8-year period.

Type 2 Diabetes Mellitus
While there are some conflicting data on the association between type 2 diabetes mellitus (type 2 DM) and POAG, there is increasing evidence from population-based studies suggesting that type 2 DM is an important risk factor for POAG. Population-based assessments of Hispanics (in Los Angeles, California), non-Hispanic Whites (in Beaver Dam, Wisconsin and Blue Mountains, Australia), and a large cohort enrolled in the Nurses Health Study have shown that persons with type 2 DM are more likely (40% higher odds in Hispanics, twofold higher odds in non-Hispanic Whites) to have POAG. Further, in the LALES, longer duration of type 2 DM was associated with a higher risk of having POAG. One explanation for this observation is that microvascular changes in the optic nerve may contribute to the greater susceptibility of optic nerve damage in persons with type 2 DM.

Myopia
Large cross-sectional epidemiologic studies in Afro-Caribbeans, Hispanics, non-Hispanic Whites, Chinese, Asian Indians, and Japanese suggest that persons with myopia have a higher prevalence of OAG than those without myopia. More recently, data from the

LALES have provided evidence of an independent relationship between longer axial length (axial myopia) and a higher prevalence of OAG. The underlying hypothesis is that individuals with axial myopia have weaker scleral support at the optic nerve, and this contributes to a greater susceptibility of the optic nerve to glaucomatous damage.

Genetic Factors
The first gene to be linked to POAG was the myocilin gene (*MYOC)* on chromosome 1. In one study, 3% to 4% of cases with POAG were found to have mutations in the myocilin gene. Several chromosomal regions have now been linked to POAG and additional genes identified. However, a majority of the cases with POAG do not have an identified genetic abnormality, suggesting that glaucomatous optic nerve damage may be multifactorial in its development, with different genes modifying the impact of various factors such as age, IOP, and blood flow.

Other Factors
In addition, migraine headache and peripheral vasospasm have been identified as risk factors for glaucomatous optic nerve damage. The association between POAG and factors such as concurrent cardiovascular disease and systemic hypertension has not been demonstrated consistently.

1.2. Management of Primary Open Angle Glaucoma

Goals
The goals of managing patients with POAG are to achieve the following:

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

Because 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, the more likely is it 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[181] 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 field loss in glaucoma is associated with a decrease in quality of life measures.

Target Intraocular Pressure 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 should be individualized and may need adjustment during the course of the disease.

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.

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. However, target pressure is an estimate, and all treatment decisions must be individualized according to the needs of the patient.

Therapeutic Choices
The IOP can be lowered by medical treatment, laser therapy, or incisional glaucoma surgery (alone or in combination). The choice of initial therapy depends on numerous considerations, and discussion of treatment with the patient should include the relative risks and benefits of the three options.

Medical treatment
Unless contraindicated, medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, and dosing schedules Patient adherence to therapy is enhanced by using eyedrops with the fewest side effects as infrequently as necessary to achieve the target IOP. If target IOP is not achieved by one medication, then additional separate medications, combination therapies, or switching of treatments may be considered to reach the target IOP.

Prostaglandin analogs and beta-blockers are the most frequently used initial eye drops for lowering IOP in patients with glaucoma. Prostaglandin analogs are the most effective drugs at lowering IOP and can be considered as initial medical therapy unless other

considerations such as cost, side effects, intolerance, or patient refusal preclude this. Other agents in addition to prostaglandin analogs and beta-blockers include alpha2 adrenergic agonists, parasympathomimetics, and topical and oral carbonic anhydrase inhibitors.

The ophthalmologist should consider the balance between side effects and effectiveness in choosing a regimen of maximal effectiveness and tolerance to achieve the desired IOP reduction for each patient. Frequent dosing and side effects (such as depression, exercise intolerance, and impotence with topical beta-blockers) may affect adherence to therapy.

Adequate treatment of glaucoma requires a high level of adherence to therapy. Frequently this is not achieved; studies indicate relatively poor adherence to therapy. Even with instruction, free medication, once-daily administration, use of a dosing aid, and electronic monitoring of adherence, nearly 45% of patients in one study took fewer than 75% of their prescribed doses. Instilling eyedrops correctly is difficult for patients, and their ability to do so may worsen as glaucoma progresses. Repeated instruction and counseling in proper techniques for using medication as well as a clearly written medication regimen and follow-up telephone calls may improve adherence to therapy.

Laser trabeculoplasty

Laser trabeculoplasty can be considered as initial therapy in selected patients or an alternative for patients who cannot or will not use medications reliably due to cost, memory problems, difficulty with instillation, or intolerance to the medication. Laser trabeculoplasty lowers IOP by improving aqueous outflow and can be performed using argon, diode, and frequency-doubled YAG lasers.

Argon and diode laser trabeculoplasty

Studies using continuous-wave argon laser with a wavelength spectrum that peaks at 488 nm (argon laser trabeculoplasty [ALT]) found that treatment increases aqueous outflow and provides a clinically significant reduction of IOP in more than 75% of initial treatments of previously unoperated eyes. Since these initial studies, more compact solid-state diode lasers have mostly replaced the original argon laser with equal IOP lowering efficacy. For patients initially treated with ALT, the amount of medical treatment required for glaucoma control is reduced. Results from long-term studies of patients receiving maximum medical therapy who subsequently had laser and incisional surgery indicate that 30% to more than 50% of eyes require additional surgical treatment within 5 years after ALT. For eyes that have failed to maintain a previously adequate response, repeat ALT has a low long-term rate of success, with failure occurring in nearly 90% of these eyes by 2 years. After previous applications to the full circumference of the anterior chamber angle, repeat ALT has a lower success rate than initial therapy in eyes that have not had a reduction in IOP for at least a year following the first laser surgery. Compared with initial laser trabeculoplasty, there is an increased risk of problems and complications such as IOP spikes after repeat laser trabeculoplasty.

Selective laser trabeculoplasty

The introduction of selective laser trabeculoplasty (SLT) is most likely responsible for the increase in use of laser trabeculoplasty in 2001 after a previous decline. Selective laser

trabeculoplasty uses a Q-switched, frequency doubled, 532 nm Nd:YAG laser that delivers less energy and is purported to be selectively absorbed by pigmented cells in the trabecular meshwork. These attributes appear purportedly to produce less thermal damage to the trabecular meshwork compared with ALT. However, several prospective and retrospective studies indicate that SLT appears comparable to but not better than ALT in lowering IOP. Selective laser trabeculoplasty also appears to be comparable in efficacy to medical therapy with prostaglandin analogs, although in one prospective study, SLT was only comparable to latanoprost when 360 degrees of the trabecular meshwork was treated. In this study, latanoprost had a better IOP-lowering effect compared with 90 and 180 degrees of treatment.

It has been claimed that SLT has greater success than ALT with repeated treatments, but no controlled, randomized clinical trial has shown that this is true. Only one study with a significant sample size has studied the results of SLT repeated after prior SLT treatment. This was a retrospective study of repeat 360 degree SLT after prior successful 360-degree SLT. In the postoperative period, repeat SLT treatment lowered IOP, but the effect was less than that with initial SLT treatment at 1 to 3 months and 5 to 8 months. These results suggest that repeat SLT may be less efficacious compared with primary treatment, but further studies are needed to clarify this issue. The safety profile of SLT appears to be good, with mild anterior chamber inflammation after treatment and less ocular discomfort compared with ALT. Intraocular pressure spikes have been noted after SLT in 4.5% to 27% of eyes in various studies.

Incisional glaucoma surgery
Trabeculectomy
Filtering surgery is effective in lowering IOP; it is generally indicated when medicine or laser therapy is insufficient to control disease and can be considered in selected cases as initial therapy.

Filtering surgery provides an alternative path for the escape of aqueous humor, and it often reduces IOP and the need for medical treatment. Estimates of success rates over time range from 31% to 56% in different populations. The failure rate of filtering surgery, without the use of adjunctive antifibrotic medications, alone or combined with medical therapy in a previously unoperated eye in the Advanced Glaucoma Intervention Study reached approximately 30% in African American patients and 20% in Caucasian American patients over a 10-year period. While long-term control is often achieved, many patients may require further therapy or a reoperation, which carries a higher failure rate. Furthermore, filtering surgery increases the likelihood that phakic eyes may undergo cataract surgery. In eyes that have undergone previous cataract surgery involving the conjunctiva, the success rate of initial glaucoma surgery is reduced.

Antifibrotic agents may be used intraoperatively and postoperatively to reduce the subconjunctival scarring after filtration surgery that can result in failure of the operation. The use of intraoperative mitomycin-C reduces the risk of surgical failure both in eyes at high risk of surgical failure and in eyes that have not undergone previous surgery. Some studies have demonstrated a benefit of intraoperative 5-fluorouracil and others have not.

The use of postoperative injections of 5-fluorouracil also reduces the likelihood of surgical failure in both high-risk eyes and eyes that have not undergone previous surgery.

The use of an antifibrotic agent carries with it an increased likelihood of bleb-related complications such as hypotony, hypotony maculopathy, late-onset bleb leak, and late-onset infection that must be weighed against the benefits when deciding whether or not to use these agents. These complications may be even more common in primary filtering surgery of phakic patients.

Aqueous shunts

All commercialized aqueous shunts (also known as tube shunts, glaucoma drainage devices, and setons) consist of a tube that diverts aqueous humor to an end plate located in the equatorial region of the eye. The primary resistance to flow through these devices occurs across the fibrous capsule that develops around the end plate. Aqueous shunts differ in their design with respect to the size, shape, and material from which the end plate is made. They may be further subdivided into valved and non-valved shunts, depending on whether or not a valve mechanism is present to limit flow through the shunt if the IOP becomes too low. Examples of non-valved implants are the Baerveldt glaucoma implant (Abbott Medical Optics, Santa Ana, CA) and the Molteno implant (Molteno Ophthalmic Ltd., Dunedin, New Zealand). Examples of the valved implants are the Ahmed glaucoma valve (New World Medical, Inc., Rancho Cucamonga, CA) and the Krupin implant (Eagle Vision, Inc., Memphis, TN).

Aqueous shunts have traditionally been used to manage medically uncontrolled glaucoma when trabeculectomy has failed to control IOP or is deemed unlikely to succeed. This includes eyes with neovascular glaucoma, uveitic glaucoma, extensive conjunctival scarring from previous ocular surgery or cicatrizing diseases of the conjunctiva, and congenital glaucoma in which angle surgery has failed. However, the indications for using aqueous shunts have been broadening, and these devices are being increasingly utilized in the surgical management of glaucoma. Medicare data show a steady rise in the number of shunts placed from 1995 to 2004, while there has been a concurrent decline in the number of trabeculectomies performed. Recent surveys of the American Glaucoma Society membership have also demonstrated a progressive increase in the number of surgeons using tube shunts.

A systematic review concluded that aqueous shunts are comparable with trabeculectomy for IOP control and duration of benefit, that larger end-plate surface area provides better IOP control, and that there appears to be no advantage to the use of antifibrotic agents or systemic corticosteroids as adjuncts to aqueous shunt procedures. The need for comparative studies and long-term follow-up was identified by the authors.

Several studies have compared aqueous shunts with trabeculectomy. A retrospective study evaluating surgical results in matched patient groups reported similar IOP reduction with the single-plate Molteno implant and trabeculectomy with 5-fluorouracil. However, another retrospective case-control study observed a higher 5-year success rate after trabeculectomy with mitomycin-C than with Ahmed glaucoma valve implantation. A randomized clinical

trial in Sri Lanka comparing the Ahmed implant and trabeculectomy in patients with primary open-angle and angle-closure glaucoma found comparable IOP reduction and success rates with a mean follow-up of 31 months. The Tube Versus Trabeculectomy (TVT) Study is a multicenter, prospective, randomized clinical trial that compared the safety and efficacy of tube-shunt surgery using the 350-mm2 Baerveldt glaucoma implant and trabeculectomy with mitomycin-C in patients with previous cataract extraction and/or failed trabeculectomy. Tube-shunt surgery had a higher success rate than trabeculectomy (85% vs. 69%) after 3 years of follow-up as defined by loss of vision, and/or IOP less than or equal to 5 mmHg or greater than or equal to 21 mmHg. Both surgical procedures were associated with similar IOP reduction and use of supplemental medical therapy at 3 years. Postoperative complications occurred more frequently after trabeculectomy compared with tube-shunt surgery, but the rate of serious complications associated with vision loss and/or reoperation to manage the complication was similar with both procedures.

Aqueous shunts are associated with intraoperative and postoperative complications that are similar to those that occur with trabeculectomy. In addition, they have unique complications related to implantation of a foreign body. Erosion of the tube may occur through the conjunctiva, and this typically develops a few millimeters behind the limbus following anterior chamber insertion. Diplopia may result from extraocular muscle fibrosis or a mass effect of the bleb overlying the end plate. Tube-cornea touch can lead to progressive endothelial cell loss and persistent corneal edema. The risk of postoperative infection appears to be less with aqueous shunts than after trabeculectomy with an antifibrotic agent.

Other glaucoma surgeries

Nonpenetrating glaucoma surgery is an alternative to trabeculectomy. The precise role of nonpenetrating surgery in the surgical management of glaucoma remains to be determined. The two main types of nonpenetrating glaucoma surgery are viscocanalostomy and nonpenetrating deep sclerectomy. The rationale for nonpenetrating glaucoma surgery is that by avoiding a continuous passageway from the anterior chamber to the subconjunctival space, the incidence of complications such as bleb-related problems and hypotony can be reduced. The nonpenetrating procedures have a higher degree of surgical difficulty compared with trabeculectomy and require special instrumentation. Randomized clinical trials comparing viscocanalostomy with trabeculectomy generally suggest greater IOP reduction with trabeculectomy, but more complications with viscocanalostomy.
One randomized clinical trial found that trabeculectomy was more effective than nonpenetrating deep sclerectomy at lowering IOP, and several others found that the two surgeries were equally effective.

Other glaucoma surgical procedures currently in use are canaloplasty with a tensioning suture (Prolene [Ethicon Inc., Somerville, NJ]), ab interno trabeculotomy using the Trabectome (NeoMedix, Tustin, CA), trabecular meshwork bypass stent (i-Stent, Glaukos Corp., Laguna Hills, CA) and the Ex-PRESS mini glaucoma shunt (Alcon Laboratories, Inc., Ft. Worth, TX).

Cyclodestructive surgery
Cyclodestructive procedures reduce the rate of aqueous production. There are several ways to reduce ciliary body function, such as cyclocryotherapy, transscleral and noncontact Nd:YAG laser, and transscleral and noncontact endodiode laser cyclophotocoagulation.

Cyclodestructive procedures have traditionally been used for refractory glaucomas, and success rates have been reported in the range of 34% to 94%. They have been associated with a subsequent decrease of visual acuity and, rarely, cases of sympathetic ophthalmia. Disadvantages of cyclodestructive procedures include postoperative inflammation, IOP spike, and the frequent need for repeat treatment weeks or months later. Compared with cyclocryotherapy, laser cyclophotocoagulation causes less postoperative pain and inflammation. Therefore, cyclocryotherapy is now rarely used. Laser cyclodestructive procedures have advantages over filtration surgery that include technical ease and reduced postoperative care.

In 2005, 47% of all Medicare cyclophotocoagulation procedures were performed endoscopically; in 2006, 58%; and in 2007, 65%. Endoscopic cyclophotocoagulation (ECP) consists of a solid-state 810-nm laser, a video camera, aiming beam, and a xenon light source housed together in a fiberoptic cable that can be introduced inside the eye for direct visualization and treatment of the ciliary processes. Theoretically, this allows better titration of laser treatment. The efficacy of ECP appears to be good, with IOP reduction reported in the range of 34% to 57%. It appears that treating 270 to 360 degrees of the ciliary body is necessary to achieve significant IOP lowering. Fibrin exudates, hyphema, cystoid macular edema, vision loss, hypotony, choroidal detachment, and phthisis have been noted after ECP in eyes with advanced glaucoma, but more recent studies involving eyes with less advanced glaucomatous damage seem to report fewer of these complications.

APPENDIX 2

2.0 Prior Pre-clinical and Clinical Testing

2.1 Pre-clinical Studies

The studies were designed and implemented by InnFocus or independent contractors to ensure that all reasonable concerns regarding human implantation were mitigated. These tests evaluated not only the basic safety of the device and the feasibility of performing the surgery with the associated surgical instruments, but also the fit and expected performance to assure the highest likelihood of success in reducing intraocular pressure in glaucomatous eyes.

2.1.1 Physical Stability

Accelerated Hydrolysis Testing

The testing was conducted on three lots of InnFocus MicroShunt facsimiles. The test was conducted for a 5 year equivalent timeframe at two temperatures, 85±2°C and 100±2°C, for 20 and 57 days, respectively. No significant weight loss was observed. The bond strength of the tube to the fins of the device did not change from the hydrolysis. After incubation, each recovered sample group was evaluated for changes in appearance relative to un-aged samples. SEM at 500x magnification and optical microscopy at magnifications of 20x and 30x were both applied and no significant changes were detected with either imaging method. No significant analytes were detected in the hydrolysates from either incubation. These methods consistently demonstrated the chemical hydrolytic stability of the poly(styrene-b-isobutylene-b-styrene) thermoplastic hydrophobic elastomer (SIBS) from which the device is made.

2.1.2 Pressure/Flow Characteristics

Studies were conducted to verify that the 70 micron internal diameter and 8.5mm length of the InnFocus MicroShunt tube provide adequate aqueous flow to reduce intraocular pressure. The study of three lots of sterilized InnFocus MicroShunts demonstrated that the internal diameter and length will provide at least 2 microliters/minute of flow at 6mmHg pressure.

2.1.3 Structural Integrity

The fins on the InnFocus MicroShunt are heat fused to the tube. Testing was conducted on three lots pre and post sterilization to verify the fusion was adequate. All bonds met the specification of >50grams or >0.5Newtons. An overall average increase in bond strength of 11.2% was observed after sterilization.

2.1.4 Chemical Testing

Exhaustive Extraction of InnFocus MicroShunt in Isopropyl Alcohol

InnFocus MicroShunt facsimiles were exhaustively extracted in isopropyl alcohol, a strong but non-dissolving solvent for the SIBS thermoplastic material. The test facsimiles, over three lots tested, displayed an average weight loss of approximately 0.2%. The overall sensitivity level of the chromatographic and spectroscopic methods applied in this study was approximately 1 ppm or less for relevant compounds used in the manufacture of the device. The study provides documented evidence at baseline levels showing only dimethylsiloxanes which are related to the packaging materials, and 2-phenylphenol and benzophenone at trace levels. None of these was considered to be significant and do not impact the biocompatibility of the device. No other compounds were detected. There were no significant differences in the extractable fractions of the three different lots tested.

Leachable Testing

This study quantified and identified the aqueous and lipophilic leachable fractions for the InnFocus MicroShunt. Samples were incubated at a temperature of 35±2ºC for 72±2h in both aqueous and lipophilic solvents. Extractions in these two solvents cover the possible polarity range that the implant could be exposed to in the intraocular environment. HPLC-grade isopropyl alcohol (IPA) was used as the lipophilic solvent and HPLC-grade water was used as the aqueous solvent. The leachates from test and control extractions were analyzed spectroscopically using UV/VIS spectrophotometry and chromatographically using HPLC/PDA (photodiode array UV detection), GC/FID (flame ionization detection), and GC/MS techniques.

Low molecular weight siloxanes, ethylene glycol, benzophenone, 2-phenylphenol, and a low molecular weight alkyl polyol were detected in the lipophilic leachates at very low concentrations. These are related to the packaging materials and the sterilization process. Glycerin, which is applied to the device to improve handling, was in the leachate at a concentration of 0.5-0.6 weight%. Only the water-soluble compounds, glycerin, ethylene glycol, and the alkyl polyol, were detected in the aqueous leachates. None of these was considered to be significant and do not impact the biocompatibility of the device.

Insoluble Inorganics Analysis of InnFocus MicroShunt product

Because the processes used to manufacture the InnFocus MicroShunt involve contact with metallic equipment, three lots of the sterilized InnFocus MicroShunt were sent for inductive coupled plasma/mass spectrophotometry analysis for metallic content. The data indicated that there is a low level of metallic contaminants from the manufacturing processes. None of the levels of the contaminants is near or above any known toxic levels for the particular inorganics observed. Additionally, the biocompatibility tests separately conducted by InnFocus used samples that had been prepared with the same equipment. Those samples passed all of the biocompatibility tests as will be discussed later in this document.

2.1.5 Dimensional and Surface Quality

Pre and post sterilization dimensional and visual testing was conducted on three separate manufacturing lots of InnFocus MicroShunts. The testing included length, outside diameter, inside diameter, and surface characteristics. All InnFocus MicroShunts met the specifications pre and post sterilization. Insignificant shrinkage of post sterilization samples was observed.

2.1.6 Evaluation of the Effect of Viscoelastics in Anterior Chamber

Studies were conducted with implanted InnFocus MicroShunts in rabbits to determine if viscoelastics will flow through the lumen. One Healon version and methyl cellulose were the only types studied. The studies determined that it requires over one week for these viscoelastics to degrade adequately so that flow is initiated. Based on this data, warnings were included in the study protocol regarding the use of viscoelastics.

2.1.7 Aging and Transport testing

Transport Testing

Standard packaged InnFocus MicroShunt units were sent to a contract lab for transport testing to assure there is no damage to the product or packaging during shipment. The packaged units met the test requirements.

Accelerated Aging Study

Units were aged at 60ºC for 11.1 weeks to simulate 3 years of real time aging and subsequent testing confirmed that the product met specifications supporting a 3 year expiration date.

2.1.8 EO Sterilization residuals

Testing of sterilized InnFocus MicroShunts was conducted to assure ethylene oxide residuals met specifications. The devices passed the test requirements.

2.1.9 Pyrogen Testing

Testing of sterilized InnFocus MicroShunts was conducted to assure that levels of pyrogenic material were below acceptable levels. All the devices passed the test requirements.

2.1.10 Biocompatibility (ISO 10993)

Biocompatibility tests were conducted on SIBS polymer samples that had been processed through simulated InnFocus MicroShunt manufacturing steps. The SIBS used for the testing included an additive to aid in manufacturing processing. After EtO sterilization, the samples were sent to an outside laboratory for a series of ISO 10993 GLP biocompatibility studies as shown below. The processed and 2x EtO sterilized samples passed all of these tests.

1. Cytotoxicity – ISO Elution Method
2. In Vitro Inhibition of Cell Growth – L-929 Mouse Fibroblast

3. ASTM Hemolysis
4. ASTM Partial Thromboplastin Time
5. ISO Maximization Sensitization Study – Saline
6. ISO Maximization Sensitization Study – Sesame Oil
7. ISO Muscle Implantation Study – 2 weeks
8. Genotoxicity – Bacterial Reverse Mutation Study – DMSO Extract
9. Genotoxicity – Bacterial Reverse Mutation Study – Saline Extract
10. USP Pyrogen Study – Material Mediated
11. USP and ISO Systemic Toxicity Study – Saline
12. USP and ISO Systemic Toxicity Study – Sesame Oil
13. ISO Intracutaneous Study – Saline
14. ISO Intracutaneous Study - Sesame Oil

2.1.11 Animal and clinical studies on prior InnFocus MicroShunt prototypes

A series of chronic ocular implantation rabbit studies were conducted to evaluate the safety of InnFocus glaucoma drainage device prototypes. These studies were conducted on various internal diameter and external diameter tubes. In some prototypes, a tab located on one side of the tube was present. In one study, a small SIBS plate was attached to the distal end of the device.

The chronic ocular implantation studies consisted of device implantation and follow-ups at 1 and 7 days, 4 weeks, and 3 and 6 months during which the rabbits were examined by slit lamp for healing characteristics and IOP was measured. At the end of each study, histology was conducted on explanted devices and surrounding tissue to evaluate the healing response. In all of these studies, the prototypes demonstrated excellent biocompatibility.

Clinical feasibility studies were conducted in France and Dominican Republic. Each of these studies had one year follow-up. Based on the outcome of these studies on prior prototypes which identified specific safety and functional improvements as well as providing confirmation of many design components, the final InnFocus MicroShunt Glaucoma Drainage System design was established and additional clinical studies initiated that are described below.

2.1.12 Ongoing InnFocus MicroShunt Clinical Studies

Dominican Republic Study (Protocol INN-003)

The first study which utilizes the present design of the InnFocus MicroShunt (formerly called the MIDI Arrow) study was initiated in Santo Domingo, Dominican Republic in 2010. Twenty-three (23) subjects were enrolled. The patients averaged 59.8$\pm$15.3 years of age, IOP of 24.0$\pm$5.4 mmHg and 2.2$\pm$0.9 glaucoma meds at baseline. The subjects had no prior incisional glaucoma surgery and 1 of 23 had prior glaucoma laser surgery. A total of 14 InnFocus MicroShunt only cases and 9 combined InnFocus MicroShunt and cataract surgery cases were performed. The study will continue through 3 years of

follow-up for each subject. As of December 2012, 2 year data are available for 15 subjects with 1 year data available for all other subjects. This study used the present version of the device except that the length was trimmed to 8-9mm at time of implantation versus the pre-cut length of 8.5mm planned for the U.S. study.

The data from the InnFocus MicroShunt study provided below are based on 15 subjects at 24 months follow-up, 7 subjects at 12 months follow-up and one lost to follow-up after 12 months follow-up. The definition of success in the study was based on ≥20% drop in IOP and IOP ≤ 21mmHg with or without glaucoma medication usage. At 12 months follow-up, the success rate was 100% with an average IOP decrease of 55.4%. The mean IOP for the InnFocus MicroShunt only cases at 12 months was 11.3 ± 2.9 mmHg, and 9.7 ± 2.4 mmHg for the combined InnFocus MicroShunt and cataract cases. Glaucoma meds usage for the total group at 12 months was an average of 0.3 meds/patient with only 3 patients requiring any glaucoma medications. At two years, the success rate was 87% with an average IOP drop of 49.1%. The mean IOP at 2 years was 12.2 ± 3.9 mmHg for the InnFocus MicroShunt only cases (9) and 12.1 ± 4.4 mmHg for the combined group (6). Glaucoma meds usage for the total group at 24 months was an average of 0.5 meds/patient with only 3 patients on any glaucoma medications. Of the three failures at 24 months, 2 failures were due the subjects only having an IOP decrease of 19% and 1%. The third failure was due to increased IOP, which resulted in the need for another glaucoma surgery.

Complications of specific interest in the study are summarized below and a table presenting all complications is on the following page.

Intra-operative adverse events: There was one intra-operative adverse event that occurred when the tip of the InnFocus MicroShunt tube in the anterior chamber was observed to have blood and fibrin on it. A paracentesis was made and the tip was flushed with balanced sterile saline to successfully clear the tip of blood. A bleb was not present at 1 and 7 days post-surgery, but the bleb was present from 21 days post-surgery forward.

Post-operative Adverse Events: There were a total of 58 mostly mild, post-operative ocular adverse events to date in the study. The most common event was transient acute hypotony where all cases cleared up spontaneously without intervention. Hypotony was defined as <6mmHg in the study. The historical data from the literature has used either <6mmHg or <5mmHg as a limit. Also the historical data is variable on when to start reporting hypotony, i.e., at Day 1, Day 7 or later. Because of these reporting differences and the fact that any associated adverse events from hypotony tend to increase as the pressure moves downward from <6mmHg, special mention is given to the data as to the extent of lower pressure.

Hypotony Resolution	No. of Subjects
Transient Hypotony	
< 7 Days	4 (17%
< 90 Days	5 (22%)
< 180 Days	1 (4%)
Chronic Hypotony > 180 Days	0

Hypotony resolved in 4 subjects by day 7, in 5 subjects by day 90 and in 1 subject by day 180. When patients with IOP values at exactly 5 or with hypotony at 1 day postop only are excluded, there were only 3 cases or 13% transient hypotony. All the patients with transient hypotony < 5 mmHg (excluding Day 1) were combined MIDI Arrow procedures with cataract surgery.

No chronic hypotony, defined as two consecutive visits after 90 days follow-up with IOP $\leq$ 6 mmHg has been observed to date. Shallow or flat anterior chambers were observed in 13% (3/23) subjects with all cases resolved within 14 days with no associated adverse events. The tube in contact with the iris was observed in 13% (3/23) of the cases, but has not led to any occlusion of the tube or other adverse event.

In the combined surgery group, there were 2 choroidal effusions, 4 cases of acute corneal edema, 2 cases of posterior capsule opacification, 2 cases of Descemet striae, 1 case of fibrin strands, 2 cases of posterior synechiae, 1 case of vitreous hemorrhage and 2 cases of IOL pupillary capture. All are likely related to the cataract surgery or the added IOP drop from the cataract surgery. All of these resolved spontaneously or were treated successfully.

There were two cases of elevated IOP that required physical intervention. In one combined surgery case with elevated IOP, the anterior chamber was "burped" with the use of a 27G needle on Day 1 post surgery to alleviate the high pressure. The pressure immediately dropped below 5 mmHg and was back above 6 mmHg on Day 7. The pressure increase at Day 1 was thought to be due to fibrin in the anterior chamber from the cataract surgery that may have blocked the InnFocus MicroShunt tube temporarily until the fibrin resorbed. The second elevated IOP case resulted in needling of a cystic bleb at the slit lamp on Day 90, wherein the pressure returned to the prior reduced level. Both of these adverse events are considered severe and are denoted with an "S" in Table 6.

There were 3 cases of increased IOP that were treated with glaucoma medication.

One exposed Tenon's capsule was observed at Day 1 post surgery in a patient with thin conjunctiva and was resolved by Day 21 without intervention. A second potential exposed Tenon's capsule was reported in a subject approximately 9 months post-surgery with no Seidel positive. The subject was prescribed lubricant drops, and intact

conjunctiva was clearly observed over the Tenon's capsule within the next 3 months with no other issues or action taken.

There was one bleb leak not related to the device that resolved within 2 weeks.

Additional visual field loss of >2.5dB in mean deviation (MD) was classified as an adverse event and was based on the latest follow-up of subjects with measurable visual fields. At 12 months for 6 patients, 0 of the 6 had additional VF loss of >2.5dB. At the latest follow-up of 24 months for 10 patients, 2 of 10 had additional VF loss of >2.5dB.

One patient with a baseline MD of -19.2dB had additional loss of 12.2dB at 2 years follow-up with no bleb and an IOP of 19mmHg. Based on the excavation of the optic nerve (C:D=0.9) and the continuing excellent visual acuity of 20/20, the subject was scheduled for surgery to minimize further optic nerve damage and was put on 3 glaucoma medications until surgery. The contralateral eye had been on 3 glaucoma medications for 12 months.

The second patient with a baseline of -25.0dB had additional loss of 7.1dB at 2 years follow-up. The subject had an IOP of 11.5mmHg with a bleb present and visual acuity of 20/25. The contralateral eye had been on 3 glaucoma medications for 2 years. No further action was indicated.

Adverse Events in Dominican Republic Study

Non-Ocular Adverse Events	Number of events
Angina pectoralis	1

Adverse events in study eye	MIDI Arrow Only Surgery N=14	Combined Cataract and MIDI Arrow Surgery N=9	Overall	% of Eyes N=23
Corneal edema	0	4	4	17.4
BCVA loss of at least 2 lines at or after the three month visit	1	0	1	4.3
Tube in contact with iris	3	0	3	13.0
Transient Hypotony resolved by D7	3	1	4	17.4
Transient Hypotony resolved by D90	4	1	5	21.7
Transient Hypotony resolved by D180	0	1	1	4.3
Chronic hypotony >180 Days	0	0	0	0.0
Shallow or flat AC	1	2	3	13.0
Posterior capsule opacification	0	2	2	8.7
Hyphema	1	1	2	8.7
Elevated IOP requiring needling of bleb or AC	1	1	2	8.7
Descemet striae	0	2	2	8.7
Tube obstruction by iris, blood, fibrin, etc.	1	0	1	4.3
Elevated IOP requiring treatment with glaucoma medication	3	0	3	13.0
Vitreous hemorrhage	0	1	1	4.3
Dry eye	1	0	1	4.3
Flat bleb	1	1	2	8.7
Tearing	1	0	1	4.3
Exposed Tenon's capsule	2	0	2	8.7
Cystic bleb	2	0	2	8.7
Bleb leak	1	0	1	4.3
Pain	2	1	3	13.0
Fibrin strand	0	1	1	4.3
Choroidal effusion or detachment	0	2	2	8.7
Posterior synechiae	0	2	2	8.7
IOL pupillary capture	0	2	2	8.7
Endophthalmitis	0	0	0	0.0
New cataract or progression	0	0	0	0.0
Allergic conjunctivitis	1	0	1	4.3
Corrective Surgery	1	0	1	4.3
Visual field loss > 2.5dB at 1 yr	0	0	0	NA[1]
Visual field loss > 2.5dB at 2 yr	2	0	2	NA[1]
Totals	**32**	**27**	**59**	

[1]Not all subjects had visual fields that could be measured

Clinical Study of InnFocus MicroShunt in Bordeaux, France

INN-004 Clinical Study of the Safety and Performance of the Miami InnFocus Drainage Implant (MIDI Arrow) to Relieve Glaucoma Symptoms
(REP-INF-0152-00 is in Volume 8; Briefcase summaries are in REP-INF-0153-00)

An additional clinical trial of the InnFocus MicroShunt implant is being conducted in Bordeaux, France under the direction of Professor Isabelle Riss. The subjects for the study are inadequately controlled on maximum tolerated medical therapy with intraocular pressures ≥18mmHg to ≤ 40mmHg. The subjects had no prior incisional ophthalmic surgery other than uncomplicated cataract surgery. There are 37 eyes in the study of a total of 20 males and 16 females; one patient had both eyes treated with the InnFocus MicroShunt. As shown in the second table below, 32 of 37 eyes had prior non-incisional glaucoma procedures. The study is planned for two years of follow-up. To date, a total of 41 eyes of 36 subjects have received InnFocus MicroShunt devices (Four of these InnFocus MicroShunts were implanted outside of the study protocol in fellow eyes of subjects in the study for which the surgeon believed the InnFocus MicroShunt to be the best choice). The data below summarizes the 37 eyes of 36 subjects that are in the clinical study. The exceptions to this are the adverse event summary and tables that include all 41 eyes implanted. A total of 19 eyes are phakic and 18 eyes in the study are pseudophakic. The mean age of the subjects is 62.6 years (SD 13.0). All patients are Caucasian.

Table 1: Demographics and Baseline Characteristics for INN-004 Population

	Overall
Number of Eyes	37
Age (Years)	
Mean	62.6
Std. Dev.	13.0
Minimum	38
Maximum	86
Race	
Caucasian	36
Status of Test Eye	
Phakic	19
Pseudophakic	18
Base line IOP	
Mean	22.8
Std. Dev.	4.3
Minimum	18
Maximum	35
Visual Acuity in Test Eye	
Mean	7.3
Min, Max	1-10
Glaucoma Diagnosis	
POAG	23
Number of Glaucoma Meds	
Mean	3.4

Std. Dev	1.2
Min, Max	1 - 6
Systemic Diseases	
Hypertension	10
Diabetes	0
Hypertension and Diabetes	1
HTN + Other	3
Other	13

Prior Non-Incisional Glaucoma Procedures

Procedure	Number of Eyes
Selective laser trabeculoplasty (SLT)	15
Laser peripheral iridotomy (LPI)	6
SLT and LPI	7
SLT and unspecified non-incisional procedure (NIP)	2
SLT, LPI and NIP	1
NIP	1
Total	**32**

Follow-ups are shown below:

Length of Follow-up	No. of Eyes
1 Year	12
9 Months	9
6 Months	10
< 6 Months	6

For eyes with baseline IOP >18 to < 21 mmHg, success is defined as an IOP reduction of 20% or greater with no reoperation for glaucoma or loss of light perception vision. For eyes with baseline IOP >21 mmHG, success is defined as IOP<21 mmHg and IOP reduction from baseline of 20% or greater with no reoperation for glaucoma or loss of light perception vision.

For the 12 eyes that have reached 12 months follow-up, the surgical success rate is 75%.

The baseline medicated IOP for the 37 eyes is 22.8±4.3mmHg. The mean decreases in IOP are shown below at 6 and 12 months follow-up.

Measurement Timepoint	N	IOP		
		Mean	SD	% Decrease
Baseline	37	22.8	4.3	NA
6 Months	31	15.3	3.4	33
12 Months	12	15.5	5.2	32

As shown below, the glaucoma medication reduction from an average of 3.4 meds per patient is 82% for those subjects at 12 months follow-up and 79% overall.

Glaucoma Medication Usage

	N	No. Eyes on Meds	Avg. Meds/Eye	% Reduction
All Eyes Post Surgery	37	11	0.7	79
Subjects at 12 months follow-up	12	5	0.7	82

Adverse events related to the treated eye in the study as well as those outside the study are summarized below for the 41 eyes:

There was one case of corrective surgery due to the InnFocus MicroShunt being dislodged during closure of the conjunctiva without being noticed by the surgeon. Upon observing an IOP of 26mmHg, the next day the surgeon observed that the tip of the device was not in the anterior chamber. Review of the video showed that the device was dislodged by the forceps as the conjunctiva was pulled forward to suture. Because of the presence of blood, the surgeon did not observe this. One week after the original procedure, a new procedure was successfully performed to place the same device back into the anterior chamber with flow observed through the device prior to conjunctival closure. The patient responded well initially and at 12 months follow-up, the IOP was 19mmHg with one glaucoma medication.

Hypotony was observed infrequently with a total of 3 eyes with transient hypotony for an overall rate of 7.3%, and all were resolved by the 3 week follow-up.

Increased IOP was observed in a total of 17 eyes with 12 of these having one or more needling procedures with glaucoma medication and the remaining 5 eyes having glaucoma medications only. Needling was conducted in all cases except one with the use of MMC; the one exception was with the use of Healaflow (viscoelastic). Three eyes had over 3 needlings performed (7, 4, 4); the IOP in two of these eyes was brought back into control with IOPs at one year of 7mmHg and 13mmHg and the third remained high at one year with an IOP of 27mmHg.

Keratitis was observed in 6 eyes and a corneal ulcer in 1 patient with resolution in all 7 patients. Five of the corneal edema cases and the corneal ulcer were resolved by the 3 months follow-up, and one corneal edema case was resolved by the 6 months follow-up.

Hyphema was observed in 10 eyes and resolved within the first week after surgery. In one eye, the anterior chamber was flushed to remove the blood.

Conjunctival bleeding was noted in 3 eyes. In one of these eyes, the bleeding was considered significant and it occurred approximately 2 weeks after surgery. It was resolved the same day and was attributed to the procedure and not the device.

There were transient irritation issues in 5 patients, which resolved.

There were 5 cases of posterior capsule opacification in the study eye of pseudophakic patients not believed to be related to the InnFocus MicroShunt that were treated with YAG laser and resolved.

Other notable events included a temporary loss of 2 lines of visual acuity in 1 patient which resolved by 12 months, and a bleb leak caused by cutting a suture within a week of surgery to eliminate irritation that was quickly resolved.

There were 7 non-ocular adverse events that are listed in the second table below.

Adverse Events for Study Eye in Protocol INN-004
(Includes 4 eyes implanted outside of study protocol)

Anticipated adverse event in test eye	IMS Only Surgery N=38	Combined Cataract and IMS Surgery N=3	Overall	% of Eyes (n=41)
Keratitis (Corneal edema)	5	1	6	14.6
Corneal ulcer	1	0	1	2.4
BCVA loss of at least 2 lines at or after the three month visit	1 (temporary)	0	1	2.4
Tube in contact with iris	0	0	0	0
Transient Hypotony (< 7 Days)	1	0	1	2.4
Transient Hypotony (7-180 Days)	2	0	2	4.9
Chronic hypotony (Post 180 Days)	0	0	0	0.0
Shallow or flat AC	1	0	1	2.4
Posterior capsule opacification	5	0	5	12.2
Hyphema	9	1	10	24.4
Intraoperative AC washout of blood	1	0	1	2.4
Elevated IOP requiring needling of bleb with with MMC or Healaflow	32 (11 eyes)	1 (1 eye)	33 (12 eyes)	29.3
Descemet striae	0	0	0	0.0
Tube obstruction by iris, blood, fibrin, etc.	0	0	0	0.0
Elevated IOP requiring treatment with glaucoma medication only	5 (5 eyes)	0	5 (5 eyes)	12.2
Elevated IOP (Other)	2	0	2	4.9
Vitreous hemorrhage	0	0	0	0.0
Dry eye	0	0	0	0.0
Flat bleb	1	0	1	2.4
Tearing	0	0	0	0.0
Exposed Tenon's capsule	0	0	0	0.0
Resuturing of conjunctiva	2	0	2	4.9
Cystic bleb	0	0	0	0.0
Bleb leak	1	0	1	2.4
Irritation	4	1	5	12.2
Conjunctival bleeding	3	0	3	7.3
Dislocation of Device During Procedure	1	0	1	2.4
Fibrin strand	0	0	0	0.0
Choroidal effusion or detachment	1	0	1	2.4
Posterior synechiae	0	0	0	0.0
IOL pupillary capture	0	0	0	0.0
Endophthalmitis	0	0	0	0.0
New cataract or progression	0	0	0	0.0
Corrective Surgery	1	0	1	2.4
Conjunctivitis	1	0	1	2.4
Sinusitis	1	0	1	2.4
Age-related Macular Degeneration	1	0	1	2.4
Totals	**82**	**4**	**86**	

Non-Ocular Adverse Events in Protocol INN-004

Adverse Event	Number	% of Subjects N=37
Abnormal Hemogram during follow-up of Hyperlymphocytosis	1	2.7
Pneumopathy	1	2.7
Psychiatric internment	1	2.7
Emergency cardiac operation	1	2.7
Blood pressure increase during surgery	1	2.7
Hospitalization for alcoholic withdrawal	1	2.7
Headache	1	2.7
Total	**7**	

Effectiveness Comparison to Historical Trabeculectomy/Glaucoma Drainage Device Studies

Literature evaluation was used to study the historical data on glaucoma drainage devices and trabeculectomy with or without the use of MMC. The data collected from these analyses were used to compare the performance and safety versus the InnFocus MicroShunt in the most recent clinical studies in the Dominican Republic (DR) and Bordeaux, and is presented in the tables below. Based on the data from the 23 eyes in the Dominican Republic study and 37 eyes in the Bordeaux study, the performance of the InnFocus MicroShunt is comparable to or exceeds the expected success rate at one year for trabeculectomy with MMC and drainage devices. This is evidenced by the mean IOP, the use of glaucoma medications, and the InnFocus MicroShunt effectiveness at 12 months follow-up as compared to the success rates at one year shown below for trabeculectomy with or without MMC and glaucoma drainage devices.

Further comparison of the InnFocus MicroShunt 2-year data can be made to the trabeculectomy data by adjusting the one-year trabeculectomy success rates downward by 10%, which is generally considered the rate of failure of trabeculectomy per year. The InnFocus MicroShunt results continue to compare favorably at the 2-year timeframe with each of the historical trabeculectomy groups at 12 months follow-up in the table that follows.

Effectiveness Comparison of One Year Follow-up Data Summaries from Literature Search of Trabeculectomies at One Year Follow-up with InnFocus MicroShunt Data at 12 months follow-up

Effectiveness Parameter	Type of Value	Trab[a] (Cochrane data @12mo follow-up)		Trab w/MMC[a] (Cochrane Data @12mo follow-up)		Trab w/MMC (12mo follow-up in historical studies from REP-INF-0117-00) Table 4	IMS at 12 months (n=23) DR	IMS at 12 months (n=12) Bordeaux
		High[b] Risk	Primary[c]	High Risk	Primary			
Surgical Success (% of N)	Mean	49.5	72.0	84.4	92.2	78.6	100	75
	Range	26-71	29-78	71-90	86-100	64-89		
IOP	Mean	20.7	17.4	13.8	12.0	13.0	10.7	15.5
	Range	18.6-23.9	16.4-18.4	12.5-14.6	11.1-12.8	9.9-16.0		
Reduction in IOP (%)	Mean	40.7	35.3	59.5	55.4	51.2	55.6	30
	Range	40-42	28-42	55-64	50-61	28-63		
Glaucoma Meds Reduction (%)	Mean	NR		NR		85.8	91	79
	Range	NR		NR		48-96		

[a]The values in this column do not include any combined glaucoma and cataract surgery.

[b]High risk = previous glaucoma drainage surgery or previous surgery involving anything more than trivial conjunctival incision, including cataract surgery; patients with one or more of the following forms of glaucoma: glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma.

[c]Primary = people who have received no previous surgical intervention. This group may include people who have had previous medical therapy, laser procedures or both.

Effectiveness Comparison of One Year Follow-up Data Summaries from Literature Search of Various Aqueous Shunt Studies with InnFocus MicroShunt Data at 12 months follow-up

Effectiveness parameter	Type of Value	Aqueous shunts w/reservoir	Optonol Ex-Press Shunt	Staar Aquaflow	IMS DR	IMS Bordeaux
IOP at one year (mmHg)	Mean	15.7	12.7	13.4	10.7	15.3
	Range	12.1-18.9	11.8-13.5	10.4-16.5		
Surgical success (with or without glaucoma meds) (% of N)	Mean	78.8	91.3	65.3	100	75
	Range	53.7-100	85.6-96.9	44-75		
Glaucoma meds per patient	Mean	0.9	0.6	0.4	0.3	0.7

Extrapolated Surgical Success of Trabeculectomy at 2 years Follow-up vs. 2 year InnFocus MicroShunt Data

Effectiveness Parameter	Type of Value	Trab[a] (Cochrane data)		Trab w/MMC[a] (Cochrane Data)		Trab w/MMC (12mo follow-up in historical studies from REP-INF-0117-00) Table 4	IMS at 24 months (n=23) DR
		High[b] Risk	Primary[c]	High Risk	Primary		
Surgical Success (% of N)	Mean	39.5	62.0	74.4	82.2	68.6	87

[a]The values in this column do not include any combined glaucoma and cataract surgery.

[b]High risk = previous glaucoma drainage surgery or previous surgery involving anything more trivial conjunctival incision, including cataract surgery; patients with one or more of the following forms of glaucoma: glaucoma secondary to intraocular inflammation, congenital glaucoma and neovascular glaucoma.

[c]Primary = people who have received no previous surgical intervention. This group may include people who have had previous medical therapy, laser procedures or both.

Safety Comparisons to Historic Trabeculectomy and Glaucoma Drainage Device Studies

A similar analysis of trabeculectomy with or without MMC and glaucoma drainage devices historic studies was done for safety as compared to the InnFocus MicroShunt in the Dominican Republic and Bordeaux studies, and the two tables below show the complications breakdown. The analysis is based on the data from the 23 eyes in the Dominican Republic study and the 41eyes in the Bordeaux study. The analysis includes adverse events through the latest follow-up including two-year follow-up on 15 eyes in the Dominican Republic and 12 eyes in the Bordeaux study.

The rate of cataract development or progression was noticeably less in InnFocus MicroShunt treated eyes with 0% of eyes at one year follow-up versus trabeculectomy with MMC meta analysis means of 15.6% and 20.1% and aqueous shunt means ranging from 2.5-11.9%.

Visual acuity decreases were less in the InnFocus MicroShunt groups with 2.4% and 4.3% versus a mean of 14.6% in the one trabeculectomy with MMC meta analysis that reported the decreases. The InnFocus MicroShunt groups were also less than the reported aqueous shunt visual acuity decreases ranging from 10.8-21.8%.

Acute hypotony and related adverse events were similar for the trabeculectomy and InnFocus MicroShunt groups, with no chronic hypotony in the InnFocus MicroShunt groups.

Corneal edema was greater in both InnFocus MicroShunt studies with 17.4% and 14.6% as compared to the glaucoma drainage device studies mean values of 7.3% and 3.6%. There was no meta analysis data available for trabeculectomy with or without MMC. The corneal edema value of 17.4% was in the Dominican Republic study and was observed only in combined InnFocus MicroShunt and cataract cases where corneal edema is expected. One of the six cases observed in the Bordeaux study was also a combined surgery case. Four of these cases resolved within the first 3 months with the final one by the six months follow-up.

There were no other notable differences in the comparisons between the two procedures.

Based on this analysis of the relative safety of the InnFocus MicroShunt as compared to commercialized glaucoma drainage devices and trabeculectomy with MMC, the InnFocus MicroShunt has comparable or better safety characteristics.

Safety Comparison of InnFocus MicroShunt to Historic Trabeculectomy Studies

Complications (% of Patient Population)

Complication	Type of Value	Trab[a] (Cochrane data @12mo follow-up)	Trab w/MMC[a] (Cochrane Data @12mo follow-up)	Trab w/MMC (12mo follow-up in historical studies from REP-INF-0117-00 Table 5)	**InnFocus MicroShunt**	
		Combined High Risk and Primary	**Combined High Risk and Primary**		23 eyes DR	41 eyes BORD
Wound leak	Mean	1.0	1.2	5.6	5.0	2.4
	Range	0.0-12.5	0.0-19.5	1.9-11.0		
Chronic Hypotony	Mean	2.9[b] 0.0-10.0	3.7[b] 0.0-10.0	8.3	0.0	0.0
	Range			0-24.3		
Acute Hypotony	Mean			13.3	13.0[c]	7.3
	Range			0-47.9		
Shallow or flat AC	Mean	9.3	7.6	6.2	8.7	2.4
	Range	0.0-26.7	0.0-35.7	0.2-18.1		
Endophthalmitis	Mean	0.0	0.0	1.5	0.0	0.0
	Range	0.0-0.0	0.0-0.0	0.3-3.0		
Suprachoroidal Hemorrhage	Mean	0.0	0.0	3.0	0.0	0.0
	Range	0.0-0.0	0.0-0.0	3.0-3.0		
Cataract Surgery	Mean	6.9	15.6	20.1	0.0	0.0
	Range	0.0-18.2	0.0-26.0	1.0-40.2		
Blebitis	Mean	NR	NR	3.5	0.0	0.0
	Range	NR	NR	1.1-10.8		
Hyphema	Mean	NR	NR	7.8	8.7	24.4
	Range	NR	NR	0.0-24.6		
Bleb Leak	Mean	NR	NR	9.1	4.3	2.4
	Range	NR	NR	1.9-27.0		
Choroidal Effusion or Detachment	Mean	NR	NR	10.4	8.7	2.4
	Range	NR	NR	0.8-28.0		
Encapsulated Bleb	Mean	NR	NR	10.3	8.7	0.0
	Range	NR	NR	1.2-37.0		

Complications (% of Patient Population) (continued)

Complication	Type of Value	Trab[a] (Cochrane data @12mo follow-up)	Trab w/MMC[a] (Cochrane Data @12mo follow-up)	Trab w/MMC (12mo follow-up in historical studies from REP-INF-0117-00 Table 5)	**InnFocus MicroShunt**	
		Combined High Risk and Primary	**Combined High Risk and Primary**		23 eyes DR	41 eyes BORD
Tenon's Cyst	Mean	NR	NR	50.4	0.0	0.0
	Range	NR	NR	40.9-62.8		
Visual Acuity Decrease[d]	Mean	NR	NR	14.6	4.3[e]	2.4[f]
	Range	NR	NR	6.0-28.6		

[a]The values in this column do not include any combined glaucoma and cataract surgery.
[b]These values were not defined as acute or chronic hypotony in the individual studies and therefore have been grouped.
[c]This value excludes patients with IOP values at exactly 5 or hypotony at 1 day postop only.
[d]Defined as ≥ 2 lines of vision loss
[e]Occurred in 1 patient and considered unreliable because of patient mental state
[f]One temporary VA decrease was observed but was not present at 12 months follow-up
NR = Not reported in study

Complications Comparison of InnFocus MicroShunt Data to Historic Aqueous Shunt Studies

Complications (% of patient population)

Complication	**Type of Value**	**Aqueous shunts with reservoir**	**Optonol Ex-Press Shunt**	**Staar Aquaflow**	**InnFocus MicroShunt**	
					23 eyes DR	41 eyes BORD
Acute hypotony	Mean	5.3	9.8	8.9[b] 0-32[b]	13.0[a]	7.3
	Range	2-18.8	4-15.6			
Chronic hypotony	Mean	8.4	2		0.0	0.0
	Range	1-23	0-4			
Shallow or Flat AC	Mean	9.9	3.0	3.8	8.7	2.4
	Range	3-20	2-4.1	0-18		
Hyphema	Mean	9.5	6.7	5.9	8.7	24.4
	Range	0.8-20	2.8-11.5	0-10.3		
Erosions	Mean	6.4	0.0	0	0.0	0.0
	Range	2-12	0-0	0-0		
Goniopuncture	Mean	0	0	38.5	0.0	0.0
	Range	0-0	0-0	21-50		
MMC injections	Mean	NR	NR	23.7	4.3	26.8
	Range	NR	NR	20-31		

Complications (% of patient population)
(continued)

Complication	Type of Value	Aqueous shunts with reservoir	Optonol Ex-Press Shunt	Staar Aquaflow	InnFocus MicroShunt	
					23 eyes DR	41 eyes BORD
Strabismus and diplopia	Mean	3.0	NR	NR	0.0	2.4
	Range	0.0-5.0	NR	NR		
Choroidal detachment (effusion)	Mean	17.5	4	3.2	8.7	2.4
	Range	3.8-52.0	0.0-8.0	0.0-5.0		
Suprachoroidal hemorrhage	Mean	3.3	NR	NR	0.0	0.0
	Range	0.8-7.0	MR	NR		
Retinal detachment	Mean	3.2	NR	NR	0.0	0.0
	Range	1-6.4	NR	NR		
Corneal edema or decomposition	Mean	7.3	NR	3.6	17.4[d]	14.6
	Range	0.0-27.0	NR	3.6-3.6		
Cataract formation or progression	Mean	2.5	NR	11.9	0.0	0.0
	Range	2.5-2.5	NR	0.0-31.0		
Bleb problems (leaks, Tenon's cyst, blebitis)	Mean	3.6	5.6	23.2	8.7	2.4
	Range	1.0-8.2	5.2-6.0	7.7-40.0		
Endophthalmitis	Mean	3.3	2.0	0.0[c]	0.0	0.0
	Range	1.6-5.0	2.0-2.0	0.0-0.0[c]		
Visual acuity decrease[e]	Mean	21.8	NR	10.8[c]	4.3[f]	2.4[g]
	Range	0.0-33.0	NR	10.8-10.8[c]		

[a]This value excludes patients with IOP values at exactly 5 or hypotony at 1 day postop only.

[b]No differentiation between acute and chronic.

[c]Only the PMA study of the Aquaflow included data in these areas.

[d]Corneal edema observed was the result of cataract surgery done at the same time; no decomposition was observed.

[e]Defined as $\geq$ 2 lines of vision loss

[f]Occurred in 1 patient and considered unreliable because of patient mental state

[g]Temporary decrease in VA but resolved by 1 year follow-up

Overall Summary of Ongoing InnFocus MicroShunt Clinical Studies

InnFocus has studied the implantation results of the present device design of the InnFocus Glaucoma Drainage System in the ongoing studies summarized above. The summary of the preliminary findings is as follows:

- No biocompatibility issues have been observed with the device.
- In all cases, the InnFocus MicroShunt was successfully placed through the needle tract without damage to the device.