Early *BIrd*

Early Feasibility Study of the Brown Glaucoma Implant in Patients with Severe Visual Impairment or No Light Perceived

Protocol Identifying Number: 4039

Sponsor: MicroOptx Inc

IDE #: G170205 / NCT03469297

Funded by: MicroOptx Inc

Version Number: v 9.0

January 27, 2019

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LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AH	Aqueous Humor
ALT	Argon Laser Trabeculoplasty
ANSI	American National Standards Institute
BGI	Brown Glaucoma Implant
CFR	Code of Federal Regulations
CRF	Case Report Form
CS	Clinically Significant
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECP	Endoscopic Cyclophotocoagulation
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
HVF	Humphrey Visual Field
IFU	Instructions for Use
IOP	Intraocular Pressure
IRB	Institutional Review Board
ISO	International Organization for Standardization
LogMAR	Logarithm of the Minimum Angle of Resolution
MIGS	Minimally Invasive Glaucoma Surgical
mm	Millimeters
mmHg	Millimeters of Mercury
NCS	Not Clinically Significant
NLP	No Light Perception
NSAID	Nonsteroidal Anti-Inflammatory Agent
OCT	Optical Coherence Tomography
OSD	Ocular Surface Diseases
PEG	Polyethylene Glycol
PI	Principal Investigator
PGVA	Present Glasses Visual Acuity
rNFL	Retinal Nerve Fiber Layer
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SITA	Swedish Interactive Thresholding Algorithm
SLT	selective Laser Trabeculoplasty
TASS	Toxic Anterior Segment Syndrome
TSQ	Treatment Satisfaction Questionnaire
UADE	Unanticipated Adverse Device Effect
UCVA	Uncorrected Visual Acuity
µm	Micrometer
US	United States
USADE	Unanticipated Serious Adverse Device Effect

SPONSOR SIGNATURE PAGE

INVESTIGATOR SIGNATURE PAGE

Investigator Acknowledgement Signature:

I have received and reviewed this Clinical Investigational Plan. I will conduct the Trial as described.

_____	_____
Investigator's Name (print)	Site Number
_____	_____
Investigator's Signature	Date

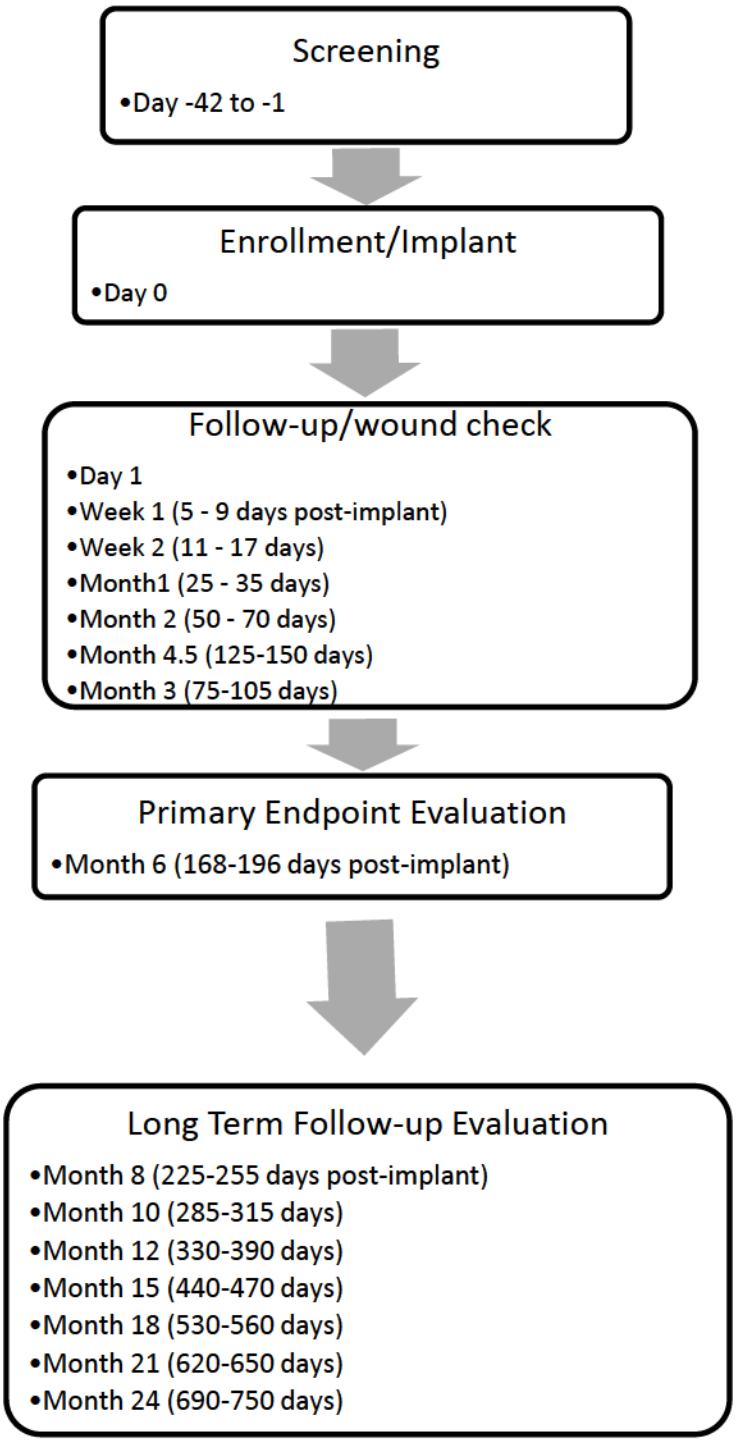
1 PROTOCOL SUMMARY

Title:	**Early BIrd**: Early Feasibility Study of the Brown Glaucoma Implant in Patients with Severe Visual Impairment or No Light Perception and Elevated Intraocular Pressure
Study Purpose:	To assess the safety and feasibility of lowering intraocular pressure with the Brown Glaucoma Implant.
Study Design:	Prospective, non-randomized, single-arm, multi-center (3), early feasibility study.
Description of Study Device :	The Brown Glaucoma Implant (BGI) is an implantable device designed to lower intraocular pressure (IOP) in glaucoma patients by shunting aqueous humor from the anterior chamber of the eye to the surface of the eye. Because there are no physiologic sources of outflow resistance, the device can be engineered to target an IOP that is low enough to halt the progression to blindness in a patient suffering from glaucoma.
Eligibility Criteria:	***Inclusion Criteria*** 1. Age 22 years and older. 2. Best corrected visual acuity of 20/400 or worse.in the study eye. 3. Fellow eye with visually acuity of 20/200 or better and the visual field no worse than the study eye. If the study eye has no light perception, the fellow eye may have no light perception or better. 4. Intraocular pressure in the study eye greater than or equal to 21 mmHg and less than or equal to 50 mmHg. 5. Primary open-angle glaucoma (confirmed by gonioscopy). 6. Glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities: (1) Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles with or without disc hemorrhage; (2) Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles; or (3) Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue 7. Humphrey Visual Field (HVF) demonstrating visual field defects consistent with glaucomatous optic nerve damage: <u>For moderate glaucomatous loss</u> - Meant deviation $\geq$ -6 and $\leq$ -12 dB - Fewer than 37 points depressed below the 5% probability level and fewer than 20 points below the p<1% level - No absolute deficit in the central 5 degrees

	- Only one hemifield with sensitivity of < 15 dB in the 5 central degrees For advanced Glaucomatous loss - MD > -12 dB - More than 37 points depressed below the 5% probability level and more than 20 points below the p<1% level - Absolute deficit in the central 5 degrees - Sensitivity < 15 dB in the 5 central degrees in both hemifields 8. At least two contiguous clock hours of intact conjunctiva near the limbus between clock hours of 9:00 and 03:00 in the study eye. 9. Adequate space in the anterior chamber of the study eye sufficient to support implant with the BGI, defined as two contiguous clock hours of scleral spur visualization via goinioscopy, without compression, in the superior 180 degrees of the anterior angle. 10. Able and willing to comply with protocol requirements. 11. Able to understand and sign the Informed Consent form. ***Exclusion Criteria*** 1. Active Neovascular Glaucoma in the study eye. 2. Pigmentary Glaucoma in the study eye. 3. Pseudoexfoliative Glaucoma in the study eye. 4. Corneal conditions in the study eye that may inhibit normal incisional healing (e.g. Fuch's dystrophy) or impair visualization of the implant inside the anterior chamber. 5. Anticipated need for ocular surgery within one year in the study eye. 6. Requirement of a combined glaucoma procedure in the study eye. 7. Contact lens use in the study eye. 8. Clinically significant inflammation or infection in the study eye within 60 days prior to the preoperative visit (e.g., blepharitis, conjunctivitis, keratitis, uveitis, herpes simplex infection) or any systemic infection. For purposes of this study, clinically significant is considered any such condition requiring prescription therapy. 9. Other clinical conditions: a. Poorly controlled diabetes (Type I or Type II) as determined by HbA1c >8. b. Cancer requiring treatment during the duration of the study. c. Any drugs (e.g.: immunosuppressive drugs) or co-morbidity that might inhibit wound healing. 10. Participation in any other clinical trial during participation in this trial. 11. Life expectancy <1 year. If both eyes of a prospective trial participant are eligible, only the eye with the highest intraocular pressure will be selected for implant.

Washout period:	There will be no washout period of IOP-lowering medications. Rather, all medications for treatment of glaucoma will be stabilized 30 days prior to the Implant visit.
Number of Sites enrolling participants:	Three sites in the United States of America.
Study Size:	10 subjects.
Primary Effectiveness Endpoint:	Overall responder rate, with responder defined as achieving at least 20% reduction from baseline in IOP.
Secondary Effectiveness Endpoints:	• Mean change from baseline in IOP • Responder rate, with responder defined as achieving follow-up IOP less than or equal to 14 mmHg • Change in IOP-lowering medications
Exploratory Endpoints:	• Changes from baseline in the Schirmer Tear Test • Treatment satisfaction questionnaire at six months post implant (TSQ)
Safety Endpoint:	Rate of all AEs, ADEs, SAEs, SADEs and UADEs through the six months post-implant visit, with continuing follow up of ADEs, SAEs, SADEs and UADEs throughout the study.
Study Schedule:	• Screening visit which includes Informed Consent, eligibility, and baseline data collection • Implant visit with surgical implantation of BGI within 42 days of screening; may be same day as baseline data collection • One day post-implant • One week visit: 5-9 days post-implant • Two week visit: 11-17 days post-implant • 1 month visit: 25-35 days post-implant • 2 month visit: 50-70 days post-implant • 3 month visit: 75-105 days post-implant • 4.5 month visit: 125-150 days post-implant • 6 month visit: 168-196 days post-implant – Primary End Point evaluation • 8 month visit: 225-255 days post-implant • 10 month visit: 285-315 days post implant • 12 month visit: 330-390 days post-implant • 15 month visit: 440-470 days post implant • 18 month visit: 530-560 days post implant • 21 month visit: 620-650 days post implant • 24 month visit: 690 – 750 days post-implant
Study Duration:	Primary endpoints will be evaluated at six months, and all subjects will be followed through 24 months post-implant. Expected subject accrual is one to three months.
Participant Duration:	24 months, though study subjects may be enrolled in a long-term follow-up registry after the 24 month visit.

SCHEMATIC OF STUDY DESIGN



KEY ROLES

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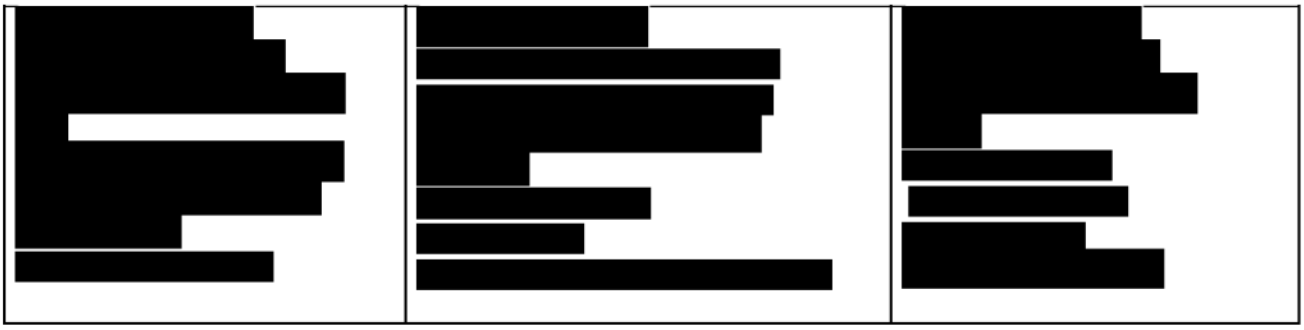

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Clinical Study Manager/Monitor:

[redacted]

The Medical Director will review all Serious Adverse Events within one week of being reported, and will review all adverse events every two months.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

2.1.1 GLAUCOMA

Glaucoma is the leading cause of irreversible blindness worldwide, afflicting up to 105 million people – the World Glaucoma Congress expects this number to double in the next 20 years due to an aging population. Available treatments – medications, surgeries, lasers and implantable devices – are expensive and have been shown to, at best, only manage this relentlessly progressive condition. Despite the consequences and economic burden associated with untreated glaucoma, the World Health Organization has eliminated routine screening due to the lack of universally accepted as safe and effective therapies. Glaucoma represents a major world-wide unmet need.

Damage to the optic nerve caused by glaucoma may cause permanent vision loss. The most common cause of damage to the optic nerve is excessive intraocular fluid and resultant elevated intraocular pressure (IOP). The increased intraocular fluid pressure results from a variety of causes, including blockage of drainage ducts and narrowing or closure of the drainage angle between the iris and cornea.

The primary types of glaucoma include open-angle and closed angle glaucoma. Open angle refers to the intraocular drainage angle between the iris and cornea being as wide open as it should be. Open angle glaucoma features slow clogging of the drainage canals in the drainage angle and results in increased intraocular pressure and progressive optic nerve damage. In open/wide-angle glaucoma, flow is reduced through the trabecular meshwork due to the degeneration and obstruction of the trabecular meshwork, whose original function is to absorb the aqueous humor. Loss of aqueous humor absorption leads to increased resistance and thus a chronic, painless buildup of pressure in the eye. This is the most common type of glaucoma, accounting for 90% of cases in the United States, but fewer in Asian countries. It is this primary open-angle glaucoma that the MicroOptx technology will initially address.

2.1.2 GLAUCOMA TREATMENTS

The modern goal of glaucoma management is to avoid nerve damage, and thus preserve sight. Although intraocular pressure is only one of the major risk factors for glaucoma, lowering it via various pharmaceuticals and/or surgical techniques is currently the mainstay of glaucoma treatment.

2.1.2.1 MEDICAL

Medical management is the most common treatment for glaucoma. Intraocular pressure can be lowered, at least for a time, with medications - usually eye drops. Several classes of medications are used to treat glaucoma, with several medications in each class. These medicines may have local and systemic side effects. Adherence to a medication protocol can be confusing and expensive; if side effects occur, the patient must be willing either to tolerate them, or to communicate with the treating physician to improve the drug regimen. Poor compliance with medications and follow-up visits is a major concern in glaucoma patients. These medications include:

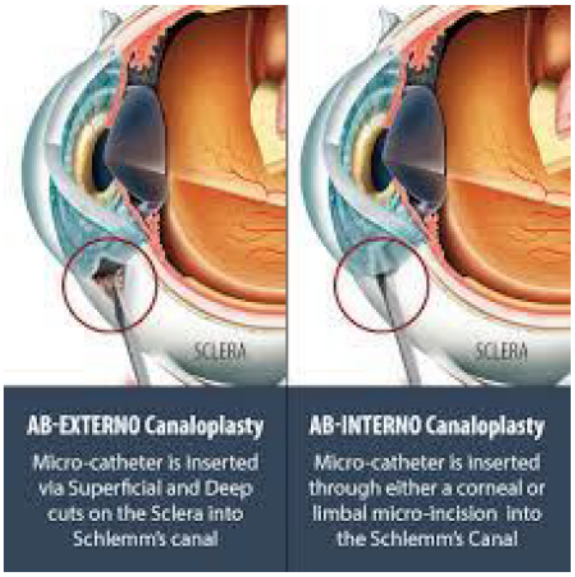
- Prostaglandins –which increase scleral outflow of aqueous humor
- Beta-adrenergic receptor antagonists which decrease aqueous humor production
- Alpha2-adrenergic agonists which decrease aqueous humor production AND increase scleral outflow
- Alpha agonists – which generally decrease aqueous humor production
- Miotic agents such as pilocarpine which cause ciliary contraction and opening of the drainage angle
- Carbonic anhydrase inhibitors lower production of aqueous humor

Through disease progression, poor compliance, side effects, and sometimes limited benefit, medical management often becomes inadequate and surgical interventions are then required to slow the progression to blindness. Generally, these operations provide only a temporary solution because scarring, blockage and infections limit their effectiveness.

2.1.2.2 SURGICAL

Current surgical procedures generally involve some form of trabeculectomy or device based drainage implant. The devices and procedures may be approached through ab externo (outside in) or ab interno (inside out) procedures. Figure 1 illustrates graphically both the ab externo and ab interno approaches as they relate specifically to a canaloplasty procedure.

Figure 1: ab externo and ab interno approach



The most common conventional surgery performed for glaucoma is trabeculectomy. In traditional trabeculectomy, a partial thickness flap is made in the scleral wall of the eye, and a window opening is made under the flap to remove a portion of the trabecular meshwork. The scleral flap is then sutured loosely back in place to allow fluid to flow out of the eye through this opening, resulting in lowered IOP and the formation of a bleb or fluid bubble on the surface of the eye, but under the conjunctiva.

The most common types of tube shunts are the Ahmed Glaucoma Valve, Baerveldt, and Molteno. They are most often used after a failed trabeculectomy.

Lasers can be used to ablate and open the trabecular meshwork. Argon laser trabeculoplasty (ALT) uses a 50-µm argon laser that is aimed at the trabecular meshwork to stimulate opening of the meshwork to allow more outflow of aqueous fluid. A newer type of laser trabeculoplasty is called selective laser trabeculoplasty (SLT) and is thought to cause less damage to the trabecular meshwork, but with comparable efficacy to ALT. Laser peripheral iridotomy is used in patients susceptible to or affected by a closed angle glaucoma. Here, laser energy is used to make a small, full-thickness opening in the iris to equalize the pressure between the front and back of the iris, thus correcting any abnormal bulging of the iris. Diode laser cryoablation is used to reduce aqueous humor secretion by destroying secretory ciliary epithelium.

2.1.2.3 MIGS

Recently, Minimally Invasive Glaucoma Surgical (MIGS) Devices have been developed to enhance physiologic aqueous humor outflow, utilizing minimally invasive surgical procedures. Complications and lack of long term effectiveness of traditional trabeculectomy and tube shunt surgeries have led to the emergence of several new MIGS under development or recently introduced to the market.

The devices small sizes minimize trauma and allow for the surgical intervention of less severe glaucoma patients compared with the typical indication for trabeculoplasty. The main advantage of MIGS is that these procedures are less invasive and safer. Infection is the most dreaded complication and can occur at any time, even years after surgery. The main limitation of MIGS, however, are that these procedures do not typically produce as large a pressure lowering effect as trabeculectomy does. In addition, the resulting effect is not as reliable as that achieved with traditional filtering procedures. Therefore, currently available MIGS are generally reserved for patients with less advanced disease, or used in combination with cataract surgery.

To attempt to lower IOP, MIGS shunt AH into enclosed spaces within the eye: into Schlemm's canal, the subconjunctival space, or the suprachoroidal space. Since they are implanted completely internal to the eye, they are subject to encapsulation due to inflammatory foreign body response. In addition, they must contend with episcleral venous pressure as the fluid is absorbed and returned to the bloodstream. Although they seem to be relatively safe, none has been able to consistently lower IOP to a level that halts glaucoma progression, i.e., threshold IOP (≤12mm Hg). The iStent was the first MIGS device to receive CE Mark and FDA approval. Comparing an iStent implanted in conjunction with cataract surgery to cataract surgery alone, little difference was found in post-op IOPs. After one year, there were 20% less medications needed in the study arm with the iStent plus cataract surgery in this unmasked study, but after two years even this small difference had disappeared.[1] David Friedman "cautioned that there is limited evidence regarding the efficacy of these newer glaucoma procedures".[2] David Epstein wrote about Schlemm's canal surgery that "it is important to remember that these operations may not get the IOP as low as desired."[3]

MIGS devices can be also be classified as ab externo (outside in) or ab interno (inside out).

The ab externo MIGS include:

- Early valved implants such as the Ahmed Glaucoma Valve implant. They work by utilizing a small flow tube that is inserted into the anterior chamber of the eye which is connected to a subscleral plate implanted underneath the conjunctiva to allow flow of aqueous fluid out of the eye into a chamber called a bleb.
- The Ex-PRESS glaucoma filtration device (Alcon): is a 0.4 x 3 mm stainless steel mini-shunt drains aqueous fluid into the subconjunctival space and is used in conjunction with standard trabeculectomy surgery. It is placed under the scleral flap and into the anterior chamber so no sclerectomy or iridectomy is required.
- Canaloplasty (iScience Interventional. This is accomplished by passing a 9-0 or 10-0 prolene suture 360 degrees through Schlemm's canal with the aid of a micro-catheter and viscoelastic to dilate the canal. The suture is tied tightly in order to keep the canal open.
- Endoscopic Cyclophotocoagulation –ECP-(Endo Optiks): endolaser cyclophotocoagulation is used for selective ablation of the pigmented ciliary epithelium to reduce aqueous production.

The ab interno surgeries include:

- iStent trabecular micro-bypass (Glaukos): this small trans trabecular titanium stent drains aqueous fluid into Schlemm's canal. The device is placed through a clear corneal incision with the aid of a gonioscopy lens.
- CyPass (Transcend Medical): this supraciliary microstent increases uveoscleral outflow. It is implanted through a clear corneal incision and can be combined with cataract surgery.
- Gold micro-shunt (SOLX): this is a 3 x 6 mm device that is less than 0.1 mm thick. It is placed into the supraciliary space through a 3 mm incision to increase uveoscleral outflow.
- Trabectome (NeoMedix): this is a thermal cautery device with irrigation and aspiration and a protective footplate. It is used to ablate a 2- to 4-clock hour segment of trabecular meshwork and Schlemm's canal under direct visualization
- XEN Gel Stent (AqueSys): this is a 6 mm long by ~100 micron wide micro shunt that is injected through a small self-sealing corneal incision to shunt fluid to a bleb in the subconjunctival space. The XEN is in premarket phase in the US.
- InnFocus MicroShunt (InnFocus): this is an 8.5 mm long tube with a 350 micron diameter that shunts aqueous from the anterior chamber to a subconjunctival/sub-tenon flap. It is in premarket phase in the US.

2.1.3 DEVICE DESCRIPTION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.2 RATIONALE

Glaucoma is the leading cause of irreversible blindness in the world, and remains a largely unmet clinical need. Today's treatments are generally temporary in effect, associated with high rates of complications, or do not lower IOP sufficiently to halt the progression to blindness without concomitant therapies. MicroOptx has developed the BGI – promising technology that is engineered to safely, consistently lower IOP to below threshold (12 mmHg), low enough to halt further damage to the optic nerve and preserve vision. This clinical investigation is a first-in-human feasibility study, in subjects without useful vision, to confirm findings from rigorous bench and animal studies, and to determine if further investigation and development of the BGI is warranted.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

Known **potential risks of** the BGI and the associated implant procedure may include:

- ***Adverse Result to Patient***
- ***Aborted Procedure***
- ***Bleeding***
- ***Cataract formation or progression***
- ***Choroidal detachment***
- ***Choroidal effusion requiring surgical drainage***
- ***Channel blockage***
- ***Chronic iritis***
- ***Corneal Haze/Opacity***
- ***Corneal false tract above Descemet's membrane***
- ***Corneal Neovascularization***
- ***Conjunctival overgrowth***
- ***Corneal endothelial touch***
- ***Death***
- ***Delayed Procedure***
- ***Deposits on device***
- ***Device malfunction***
- ***Device Migration or Dislodgement***
- ***Device Rejection***
- ***Endophthalmitis***
- ***Flat anterior chamber requiring anterior chamber reformation***
- ***Focal conjunctival hyperplasia***
- ***Infection***
- ***Inflammation including iris, macular and corneal edema***
- ***Hematoma or Hemorrhage including suprachoroidal or vitreous hemorrhage***
- ***Hyphema***
- ***Hypotony (IOP < 6 mmHg when conscious)***
- ***Hypotony maculopathy***
- ***Increased tearing***
- ***Ocular Trauma***
- ***Peripheral flow/ wound leak***
- ***Permanent Loss of Vision***
- ***Phthisis / atrophy (shrinkage of the eye)***
- ***Ptosis***
- ***Pyrogenic***
- ***Re-intervention***
- ***Retinal Detachment***
- ***Secondary surgical interventions***
- ***Substantial increase in IOP vs. baseline***
- ***Severe Irritation including Chronic Iritis***
- ***Temporary Hypotony associated with General Anesthesia***
- ***Temporary Loss of Vision***
- ***Toxicity***
- ***User Dissatisfaction***
- ***Retrograde flow and increased IOP with swimming/diving***

There may also be other risks related to the BGI and associated implant procedure that are not listed or that are not known at this time. This study will help characterize the adverse events associated with the BGI implant.

2.3.2 KNOWN POTENTIAL BENEFITS

Known potential benefits of the BGI include:

- Clinically meaningful reductions in IOP
- Lubrication of cornea, providing relief/treatment of ocular surface diseases (OSD) including dry eye
- Reduced need for IOP lowering medications
- Reduced need for OSD medications
- Pain (resulting from excessive IOP) relief
- Limited post-operative follow-up care requirements

2.3.3 STUDY RISK MITIGATION

The following measures will be taken in the clinical study to mitigate or minimize risks to study subjects that may be associated with implantation of the BGI and have been identified in a formal risk assessment:

1. Implanting Investigator surgeons will receive didactic training from MicroOptx prior to performing study implants.
2. Implanting Investigator surgeons will receive preclinical cadaver and/or animal model implantation training from MicroOptx prior to performing study implants.
3. As part of preclinical training for Investigators, simulated fragment removal will be presented.
4. The protocol and Investigator training will instruct to visually examine the BGI device after removal for evidence of delamination and/or bond failure under the operation microscope.
5. Investigators will be trained prior to follow-ups on the normal appearance of a device implant site.
6. The protocol and Investigator training will describe looking for abnormal findings such as uveitis, corneal hazing and flare, and formation of fibrin in the anterior chamber as signs of potential loss of biocompatibility.
7. MicroOptx will proctor the first three implants at each enrolling center.
8. Implanters must be certified by MicroOptx after training and proctored implants, prior to performing implants on their own.
9. Ease of implant will be assessed on the Implant case report form.
10. Patient follow-ups, inclusive of a slit lamp examination, occur at Baseline, Day 1, Week 1, Week 2, and Months 1, 2, 3, 6, 12, and 24 as described in ANSI-Z80[5], and will include an assessment for epithelial ingrowth in the anterior segment.
11. Aqueous flow through and not around the device will be assessed via the Seidel fluorescein test at all patient follow-ups starting with the Week 1 visit.
12. The implant procedure will use 1.4 mm keratome which, due to the cross bar tab, will prevent internal migration of the device.
13. The Instructions for Use (IFU) will describe the process and criteria for device inspections by the implanting surgeon.
14. This protocol and the IFU will provide general recommendations for explant procedure.
15. The protocol requires continued follow-up of subjects after removal until healing is stabilized.

16. Ease of explant will be assessed on the Explantation case report form.
17. Hypotony management strategies are described in this protocol and IFU, including medical management or device explantation.
18. Best Corrected Visual Acuity will be assessed at Baseline, Week 1, Week 2, and Months 1, 2, 3, 6, 12, and 24.
19. Optic nerve image analysis will be performed at Baseline and Months 6, 12, and 24.
20. Perimetry will be performed at Baseline and Months 6, 12, and Month 24.
21. The TSQ patient questionnaire will be completed at Baseline and Months 1, 3, 6, 12, and 24.
22. The clinical trial Implant and follow-up case report forms will include a forced choice option for the presence or absence of debris and, if present, a prompt to record a description of debris and source if known.
23. The Explant case report form will include a forced choice option to describe if the device is intact, partially intact, or not intact based upon examination under the operating microscope.
24. Explanted devices will be returned to MicroOptx for performance testing, including assessment of the hydrogel layer and flow.Sensitization will be monitored via: Best Corrected Visual Acuity, Applanation Tonometry, Central Corneal Thickness, IOP measurements, Gonioscopy, lens status, slit lamp examinations, Vertical C/D Ratio Assessments, dilated fundus exams, optic nerve image analysis, perimetry, and a patient questionnaire at follow-up examinations as described in the study protocol.
25. Monitor for signs of implantation site effects at Baseline, Day 1, Week 1, Week 2, and Months 1, 2, 3, 4.5 6, 8, 10 12, 15, 18, 21and 24, per protocol.
    a. Follow-up case report forms will have a forced choice option to describe the implant site as normal or abnormal and ask for a description.
    b. Follow-up case report forms will have a standardized scale for assessment of the implant site.
26. Monitor for signs of elevated body temperature Baseline, Day 1, Week 1, Week 2, and Months 1, 2, 3, 4.5 6, 8, 10, 12, 15, 18, 21 and 24, and presence of an identifiable etiology for the fever.
27. Monitor for signs of abnormal response to implant or signs of toxicity at Baseline, Day 1, Week 1, Week 2, and Months 1, 2, 3, 4.5 6, 8, 10 12, 15, 18, 21 and 24 follow-up visits.
28. Specific protocol requirements at follow-up examinations include the slit lamp and dilated fundus examinations that can detect the presence of loss of biocompatibility and an abnormal response to the device.
    a. Signs of an abnormal response include hyperplastic and necrotizing tissue reactions as discoverable by slit lamp and dilated fundus examinations at scheduled follow-ups.
29. Investigators can refer to infectious specialists or other ophthalmic specialists such as retinal surgeons, if needed.
30. The protocol includes assessment for signs of TASS, including symptoms of severe anterior chamber inflammation within 12-48 hours' post-operative period indicated by:
    a. Corneal edema extending from limbus to limbus.
    b. Dilated or irregular pupil.
    c. Increased intraocular pressure.
    d. Hypopyon.
31. Subjects will be examined for signs of ocular pathology at each scheduled follow-up visit.

2.3.4 SUMMARY OF BENEFIT VERSUS RISK

Given the design and intended use of the device, infection and hypotony are perhaps the most serious risks posed. Extensive bench and animal studies (greater than 50 implants) suggest that design features of the device, particularly the highly hydrophilic hydrogel construct of the inner flow channel, are effective in resisting infection – with no clinical evidence of any infection, confirmed by negative culture. No cases of hypotony have been observed, even in the presence of multiple implants in a single eye.

Device dislodgments have been observed with earlier versions of the device. In all cases of dislodgment, the wound spontaneously healed with no clinical sequelae – including infection. Also in all cases, dislodgements were preceded by visual signs of conjunctival hyperplasia and peripheral leakage of aqueous humor around the device. With respect to dislodgments, it is important to note that the incision made at implant is less than half the size of those made during cataract surgery, and those are done without suturing after the procedure. The BGI – flat, at just 150 microns thick - is placed through the small incision, filling the incisional space. Upon dislodgment, the original incision has spontaneously closed - just as in the case with the larger incisions made during cataract surgery.

The intended patient population for this feasibility study are patients with elevated IOP but who have lost useful vision. These patients may be on medicated eyedrops that can cause pain, irritation, and discomfort on the eye. Finally, some of these patients may even experience pain resulting from excessive IOP, despite medications and other pressure-reducing therapies.

The BGI has the potential to reduce intra-ocular pressure in these patients, relieving pressure-associated pain and sparing whatever vision may be left. The BGI will also provide lubrication to the surface of the eye, relieving pain and irritation associated with medicated eye drops or other form of ocular surface disease. While implantation of a BGI is associated with risks (e.g. infection, hypotony, dislodgment, etc.), the potential benefit of BGI implantation should offset those risks in this patient population, particularly considering useful vision has already been lost.

3 OBJECTIVES AND PURPOSE

The purpose of this clinical study is to assess the safety and feasibility of lowering intraocular pressure with the Brown Glaucoma Implant. The objectives are to demonstrate feasibility of effectiveness by observing a clinically meaningful reduction from baseline in diurnal IOP, and to demonstrate feasibility of safety by observing a safety profile that is sufficient to warrant further study. Study subjects will be with best corrected visual acuity of severe visual impairment (20/400) or worse,, have elevated IOP, and may or may not have glaucoma.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This Clinical Investigation Summary is developed with reference to ISO 14155:2011, the American National Standard for Ophthalmics – Implantable Glaucoma Devices (ANSI Z80.27-2014), FDA's Premarket Studies of Implantable Minimally Invasive Glaucoma Surgical (MIGS) Devices Guidance document, and other sources.

The trial is a prospective, non-randomized, single arm, multi-center (3), early feasibility study in subjects with elevated IOP but who have lost useful vision. All subjects will be followed through two years post-implant, but may then be enrolled in a long-term follow-up registry.

Only one eye per study subject will be implanted with a BGI. If both eyes are eligible, the eye with the highest intra-ocular pressure will be selected for implant.

4.1.1 PRIMARY ENDPOINT

The primary effectiveness end point is a responder outcome, with a responder defined as a subject with a reduction in intra-ocular pressure of at least 20% from baseline to six months post-implant. Because this feasibility study is not statistically powered, this endpoint will be evaluated qualitatively, and no formal tests of hypothesis are planned.

Any IOP-lowering medications should be stabilized at least 30 days prior to baseline measurements. The incremental effectiveness of the BGI in reducing IOP relative to stable medical therapy will be assessed.

Safety will be evaluated by assessing the rate of all AEs, SAEs, ADEs, SADEs and UADEs - as well as evaluation of procedure-related complications, slit lamp and fundus examination findings, and specular microscopy findings - through the six-month post-implant visit. All such safety outcomes will be collected and summarized for the 6 month time point. Safety data will continue to be collected and summarized in any update reports beyond six months.

4.1.2 SECONDARY ENDPOINTS

Because this feasibility study is not statistically powered, no formal tests of hypothesis are planned and no method to control type I error for the family of secondary endpoints is necessary. Specific secondary endpoints of interest are:

- Mean change from baseline in diurnal IOP
- Responder rate, with responder defined as achieving follow-up IOP less than or equal to 14mm Hg
- Changes in IOP-lowering medications

4.1.3 EXPLORATORY ENDPOINTS

Exploratory endpoints include:

- Changes from baseline in the Schirmer Tear Test
- Treatment satisfaction questionnaire at six months post implant (TSQ)

Other data to be reported include a cumulative proportion of responder analysis, so that the entire distribution of treatment response is depicted in a graph of the proportion of responders for all percentages of IOP reduction. In this manner, the number of patients with ≥50% IOP reduction can be determined, for example.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Inclusion Criteria

1. Age 22 years and older.
2. Best corrected visual acuity of 20/400 or worse in the study eye.
3. Fellow eye with visually acuity of 20/200 or better and the visual field no worse than study eye. If the study eye has no light perception, the fellow eye may have no light perception or better.
4. Intraocular pressure in the study eye greater than or equal to 21 mm Hg and less than or equal to 50mm Hg.
5. Primary open-angle glaucoma (confirmed by gonioscopy).
6. Glaucomatous optic nerve damage as evidenced by any of the following optic disc or retinal nerve fiber layer structural abnormalities:
   (1) Diffuse thinning, focal narrowing, or notching of the optic disc rim, especially at the inferior or superior poles with or without disc hemorrhage;
   (2) Localized abnormalities of the peripapillary retinal nerve fiber layer, especially at the inferior or superior poles; or
   (3) Optic disc neural rim asymmetry of the two eyes consistent with loss of neural tissue
7. Humphrey Visual Field (HVF) demonstrating visual field defects consistent with glaucomatous optic nerve damage:

   <u>For moderate glaucomatous loss</u>
   - Mean deviation $\geq$ 6dB $\leq$ -12 dB
   - Fewer than 37 points depressed below the 5% probability level and fewer than 20 points below the p<1% level
   - No absolute deficit in the central 5 degrees
   - Only one hemifield with sensitivity of < 15 dB in the 5 central degrees

   <u>For advanced Glaucomatous loss</u>
   - Mean deviation > -12 dB
   - More than 37 points depressed below the 5% probability level and more than 20 points below the p<1% level
   - Absolute deficit in the central 5 degrees
   - Sensitivity < 15 dB in the 5 central degrees in both hemifields

in
8. At least two contiguous clock hours of intact conjunctiva near the limbus between clock hours of 9:00 and 03:00 in the study eye.
9. Adequate space in the anterior chamber of the study eye sufficient to support implant with the BGI, defined as two contiguous clock hours of scleral spur visualization via gonioscopy, without compression, in the superior 180 degrees of the anterior angle.
10. Able and willing to comply with protocol requirements.
11. Able to understand and sign the Informed Consent form.

5.2 PARTICIPANT EXCLUSION CRITERIA

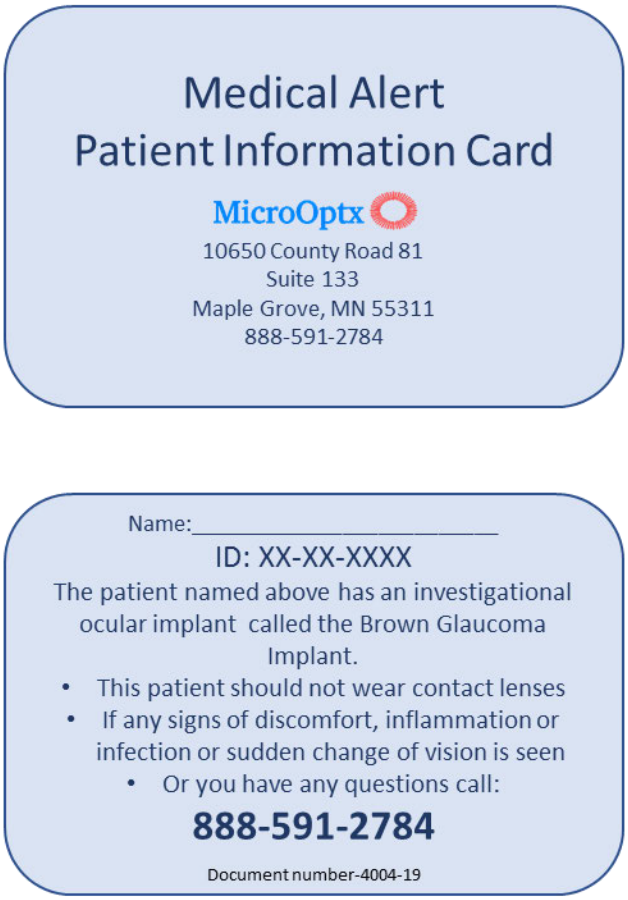
1. Active Neovascular Glaucoma in the study eye.
2. Pigmentary glaucoma.
3. Pseudoexfoliative glaucoma.
4. Corneal conditions in the study eye that may inhibit normal incisional healing (e.g. Fuch's dystrophy) or impair visualization of the implant inside the anterior chamber.
5. Anticipated need for ocular surgery within one year in the study eye.
6. Requirement of a combined glaucoma procedure in the study eye.
7. Contact lens use in the study eye.
8. Clinically significant inflammation or infection in the study eye within 60 days prior to the preoperative visit (e.g., blepharitis, conjunctivitis, keratitis, uveitis, herpes simplex infection) or any systemic infection. For purposes of this study, clinically significant is considered any such condition requiring prescription therapy.
9. Other clinical conditions:
    a. Poorly controlled diabetes (Type I or Type II) as determined by HbA1c >8.
    b. Cancer requiring treatment during the duration of the study.
    c. Any drugs (e.g.: immunosuppressive drugs) or co-morbidity that might inhibit wound healing.
10. Participation in any other clinical trial during participation in this trial.
11. Life expectancy <1 year.

If both eyes of a prospective trial participant are eligible, only the eye with the highest intra-ocular pressure will be selected for implant. (NOTE: only one eye per subject may be implanted with the investigational device).

5.4 PATIENT ENROLLMENT CARD

After enrolling into the Early Bird study and receiving a BGI implant, each subject will be issued a Patient Card. This card identifies receipt of the BGI and recommends signs to watch for that suggest trouble or risk to the subject and require physician follow-up. The card also provides contact information for the subject and health care providers.

Figure 6: Patient Card



5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Prior to trial recruitment, the Sponsor and investigational centers will develop study start-up recruitment and retention procedures to determine tactics that will be employed to recruit and retain study subjects. Tactics may include Sponsor-provided materials for prospective subjects and site staff, a communication plan, minimal long-term data collection requirements, and use of physician referral networks.

5.6 PARTICIPANT WITHDRAWAL OR TERMINATION

5.6.1 REASONS FOR WITHDRAWAL OR TERMINATION

All subjects enrolled in the clinical study, including those withdrawn from the clinical study, terminated, or lost to follow-up, shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. Reasons for withdrawal may include, but are not limited to:

- Subject found not to meet eligibility criteria
- Subject did not receive implant
- Subject choice to withdraw consent
- Investigator discretion
- Lost to follow-up, despite best efforts to locate the subject
    - Three documented attempts to contact the subject, including one certified letter, are required to declare a subject lost to follow up.
- Death (see Section 8.6 for reporting requirements).

If a subject withdraws from the clinical investigation, the reason(s) shall be reported on the End of Study electronic case report form (eCRF) in the EDC system. Data up to the point of withdrawal will be collected. If any SAEs, SADEs or USADEs are open, every effort should be made to follow the subject until resolution. If this is not possible, any open event should be closed or documented as chronic. Normal manufacturer vigilance monitoring of device performance will take place after a subject is withdrawn.

5.6.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Upon withdrawal, the subject and physician may elect to have an implanted device explanted. If the device is explanted, the subject should continue to be followed at least through 3 months post-explant or until the wound is healed, whichever is longer.

5.7 PREMATURE TERMINATION OR SUSPENSION OF STUDY

In the event of premature termination or suspension of the study, the Sponsor will promptly notify the investigational center and communicate a plan for orderly termination or suspension. Elective explants of implanted devices shall be performed under this protocol, prior to study close-out.

6 STUDY DEVICE

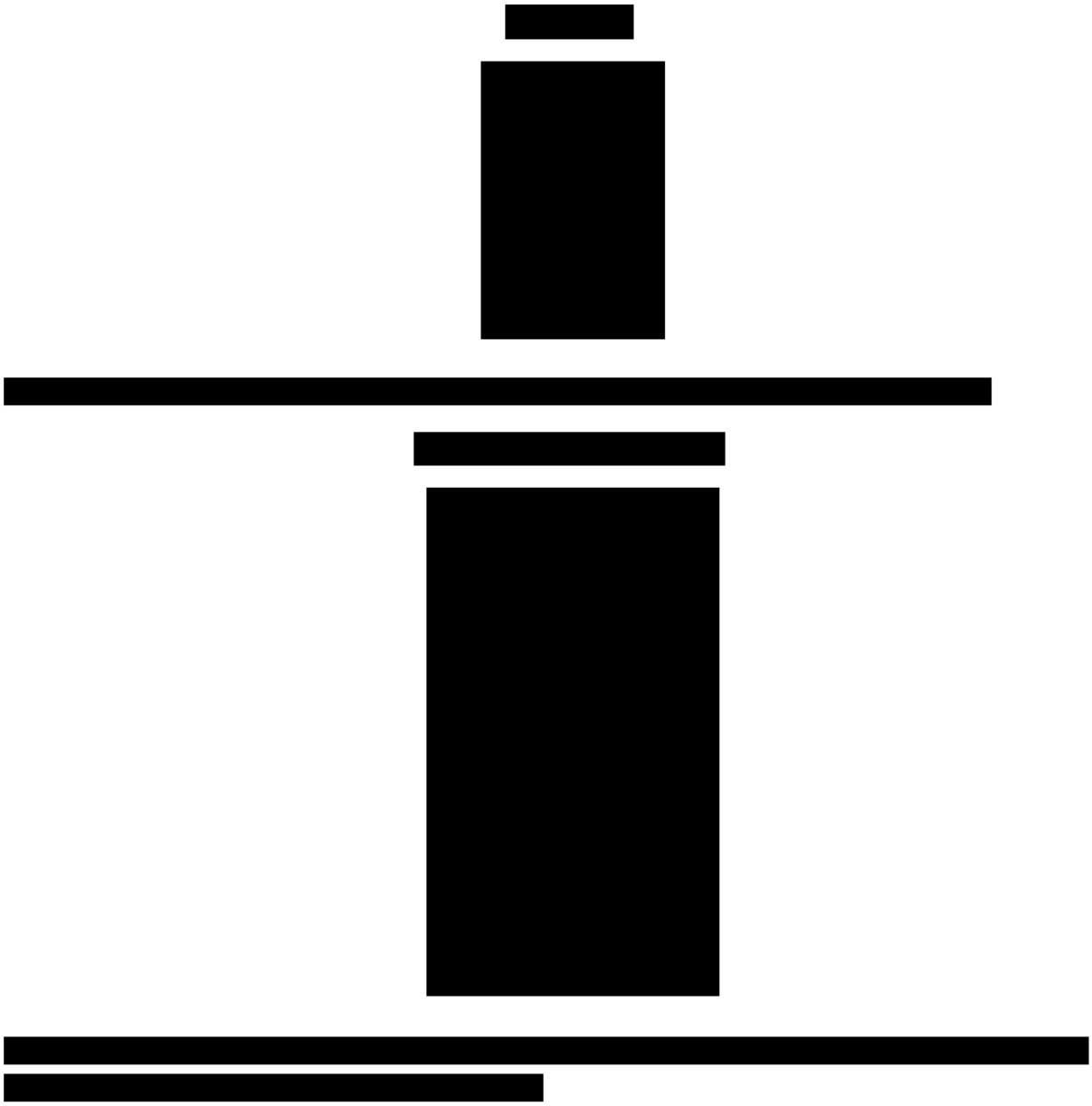
6.1 STUDY DEVICE DESCRIPTION

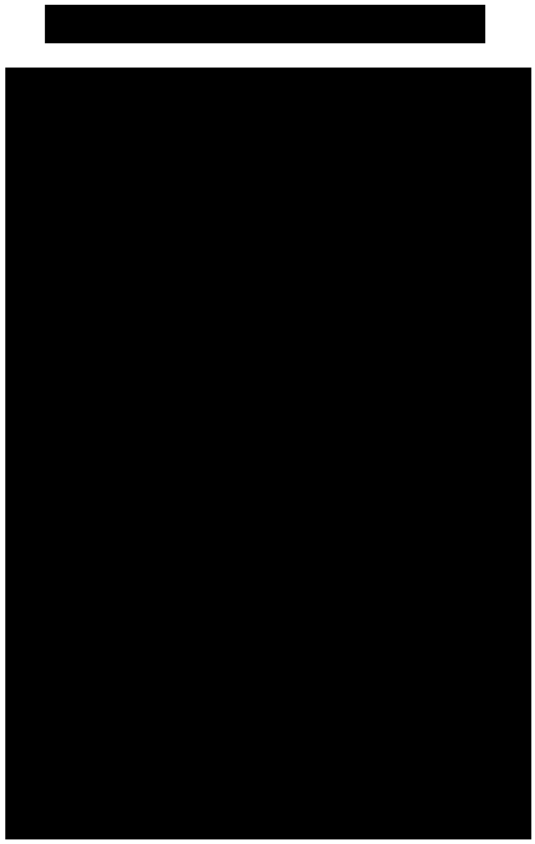
6.1.1 ACQUISITION

Study devices will be hand-delivered to study site by Sponsor personnel.

6.1.2 APPEARANCE, PACKAGING, AND LABELING

[redacted]



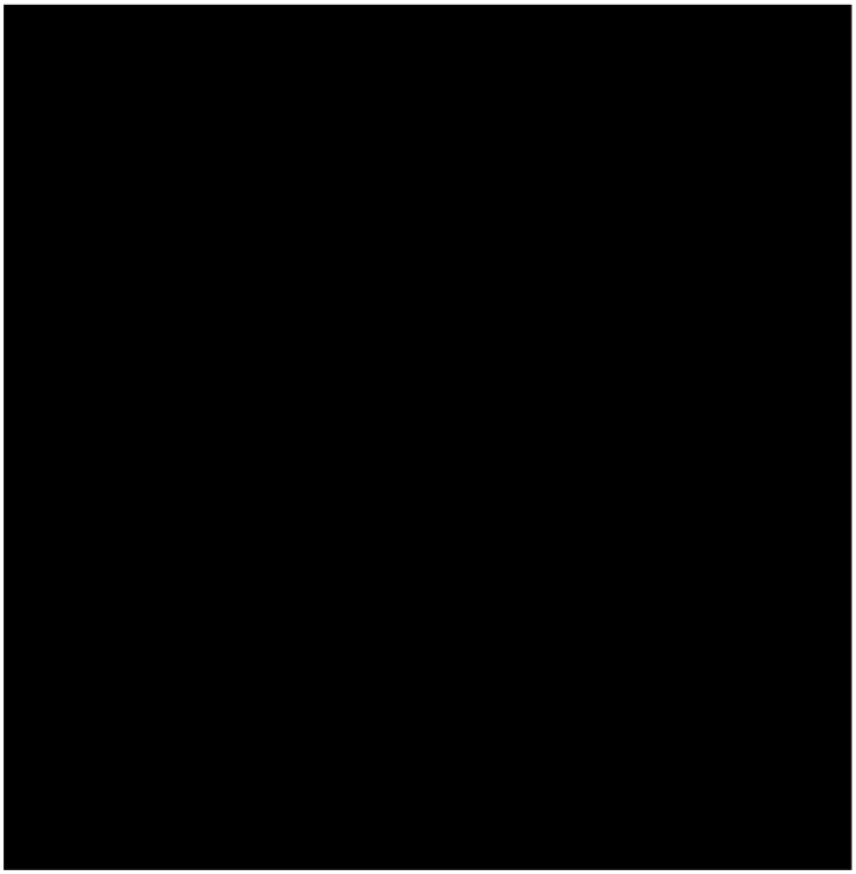


[redacted]

Figure 10: Labels

[redacted]

[redacted]



6.1.3 PRODUCT STORAGE AND STABILITY

[redacted]

6.1.4 IMPLANT PROCEDURE

The Brown Glaucoma implant is intended for single use. It is supplied sterile and individually.

All physicians implanting the MicroOptx Brown Glaucoma Implant must be MicroOptx approved Investigators and implanters in a MicroOptx clinical trial, and have previously completed required didactic and simulated implant training in animals or cadavers. In addition, the first three patient implants of the MicroOptx Brown Glaucoma Implant must be performed with the assistance of a MicroOptx surgical proctor.

[redacted]

[redacted]

To implant the Brown glaucoma Implant:

Surgical Field Preparation

All procedures will be performed using aseptic technique.

The affected eye will be individually prepped with a lid/lash scrub using 5% povidone-iodine solution.

The gowned and gloved surgeons/techs will then drape the eye with a self-adhesive ophthalmic aperture drape such as the 3M ophthalmic "Steri-Drape".

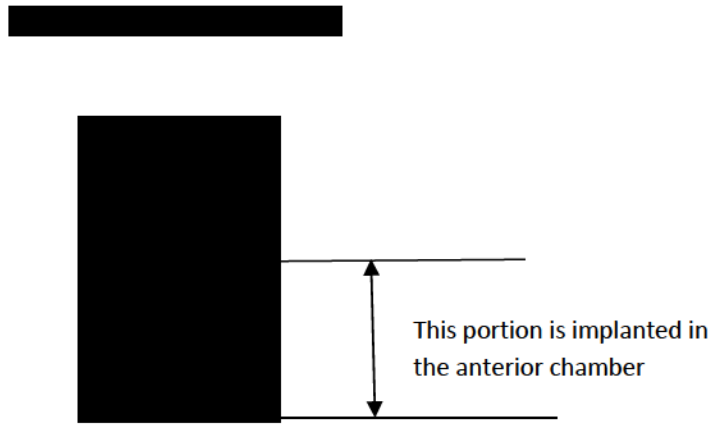
An operating microscope with photographic or digital imaging required for the implantation procedure is positioned over the eye.

Test Device Implant Procedure

Pre-implant photomicrographs of the eye will be collected. Topical ophthalmic drops of ofloxacin or vigamox , ketorolac and prednisolone will be given three times in the interval between sedation and commencement of surgery. A lid speculum is placed to open the ocular field.

[redacted]

[redacted]



The final implant position of the BGI should be visualized microscopically and verified by gonioscopy. The angle of insertion is recorded on the implantation case report form. Photographs of the implant will be taken to document positioning and location.

6.2 DEVICE DISPOSITION PROCEDURES

Device accountability shall be in compliance with ISO 14155 and FDA regulations.

The Sponsor will control the availability of all investigational devices by hand-delivering devices only to trained study site personnel. The Sponsor shall keep records to document the physical location of all investigational devices from delivery of investigational devices to the investigation site until return or disposal. Devices are not transferable between Investigators unless prior approval is obtained from the Sponsor. Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigation Plan.

The site Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

1. the date of receipt,
2. identification of each investigational device (batch number/serial number or unique code),
3. the expiry date,
4. the date or dates of use,
5. Subject identification,
6. date on which the investigational device was returned/explanted from the Subject, if applicable, and
7. the date of return of unused, expired or malfunctioning investigational devices, if applicable.

An out-of-service product is defined as any implantable products (e.g. device) removed or rendered inactive. Out-of-service product includes but is not limited to devices that do not function appropriately at implant, and explanted product. Whenever possible, any out-of-service product should be returned to

the Sponsor for analysis. In the event of a Subject death, every effort should also be made to return explanted product to MicroOptx.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STANDARD OF CARE STUDY PROCEDURES

Informed consent must be obtained from each subject prior to enrollment into the study and prior to any study-specific procedures that are not part of routine standard of care for glaucoma patients. The process for obtaining informed consent shall be in compliance with FDA regulations (21CFR 50) and ISO 14155.

7.1.2 STUDY SPECIFIC PROCEDURES

Subject contact will be according to the schedule outlined in Section 7.2. Any unscheduled visits will be recorded.

Note: All data collection shall be done as the first thing in the follow up visit, prior to any other procedures.

Note: Adverse event data will be collected at each visit after the Screening/Baseline Visit.

7.1.3 OPHTHALMIC EXAMINATIONS

All patients will receive periodic ophthalmic examinations including slit lamp evaluations, indirect ophthalmic examinations and intraocular pressure tonometry measurements. Each eye will be examined and photographs taken of the implanted test device. Pre-implant photographs will be collected on the day of (but prior to) implant.

The pupil of each eye must be sufficiently dilated to allow indirect ophthalmic evaluations. Topical mydriatics (Tropicanimide and Phenylephrine, or equivalent) may be used to achieve this if needed based upon preferences of the examiner. The ophthalmic examinations will be recorded on the appropriate case report forms.

The ophthalmic examinations will include:

- Best Corrected Visual Acuity
- Applanation Tonometry
- Body Temperature
- Central Corneal Thickness
- Slit Lamp Examination

- Indirect Ophthalmic Examination with dilation
- Vertical C/D ratio
- Corneal Endothelial Cell Count
- Gonioscopy
- Optic Nerve Image Analysis
- Perimetry
- Seidel's Test
- Schirmer Tear Test
- Lens status for phakic eyes
- Treatment Satisfaction Questionnaire
- Implant Photomicrograph

7.1.3.1 BEST CORRECTED VISUAL ACUITY

Best Corrected Visual Acuity is performed to a standard Early Treatment Diabetic Retinopathy Study (ETDRS) testing protocol, and requires a dedicated 4 meter distance full research lane and ETDRS Equipment for visual acuity standard protocol.

In this test, the following measures are made in both the test and contralateral eyes:

- Uncorrected Visual Acuity (UCVA)
- Present Glasses Visual Acuity (PGVA)
- Manifest Refraction

LogMAR is calculated for each according the the calculation:

LogMAR VA = 0.1 + LogMAR value of the best line read – 0.02 X (number of letters read).

To confirm that the study subject perceives no light in the study eye, completely occlude or cover the fellow eye to prevent light scatter that might be perceived by the non-study eye. Using a bright, narrow beamed light source such as a Finhoff muscle light or indirect ophthalmoscope, shine the light in the study eye and question the subject on whether or not light is perceived. Repeat this test, with light on and off, at least 10 times.

7.1.3.2 APPLANATION TONOMETRY

Intraocular pressures (IOPs) of the test and control eyes are measured with a Goldman Applanator according to the Goldman method. Two measures are taken from each eye and the average is calculated. Diurnal IOPs may be collected, as described above, for three measurements taken four hours apart, and recorded in a 24 hour clock format.

7.1.3.3 BODY TEMPERATURE

Body temperature is recorded in degrees fahrenheit at each follow-up.

7.1.3.4 CENTRAL CORNEAL THICKNESS

Central corneal thickness is measured in both eyes using an ultrasound pachymeter. Three measurements are made and averaged for both the test and contralateral eye.

7.1.3.5 GENERAL EXTERNAL OHPTHALMIC EXAM

The test and control eyes will be examined with special attention to the following parameters:

- Evaluation of the cornea
- Evaluation of the test eye device and whetether it is visible or healed over
- Evaluation of periorital skin
- Evaluation of the eye lids
    - The lids and margins will be examined for erythema and for edema.
    - To describe erythema the following scale is used:
        - □ 0= Normal
        - □ 1= Mild (redness localized to small region of the lids margin or skin)
        - □ 2= Moderate (redness of most or all lid margin or skin)
        - □ 3= Severe (redness of most or all lid margin and skin)
        - □ 4= Very Severe (marked diffuse redness of both lid margin AND skin)
    - To describe edema the following scale is used:
        - □ 0= Normal
        - □ 1= Mild (localized to small region of the lid)
        - □ 2= Moderate (diffuse, most or all lid but not prominent / protruding)
        - □ 3= Severe (diffuse, most or all lid and prominent/protruding)
        - □ 4= Very Severe (diffuse AND prominent/protruding AND reversion of the lid)
- Evaluation of the conjunctiva
    - The conjunctiva will be examined for erythema and for edema.
    - To describe erythema the following scale is used:
        - □ 0= None (normal)
        - □ 1= Mild (a flush reddish color)
        - □ 2= Moderate (more prominent red color)
        - □ 3= Severe (definite redness)
    - To describe edema the following scale is used:
        - □ 0= None (normal)
        - □ 1= Mild (slight localized swelling)
        - □ 2= Moderate (moderate medium localized swelling or mild diffuse swelling)
        - □ 3= Severe (severe diffuse swelling)
        - □ 4= Very Severe (very prominent / protruding diffuse swelling)
- Evaluation of the sclera
    - The Sclera will be examined for erythema.
    - To describe erythema the following scale is used:
        - □ 0= None (normal)
        - □ 1= Mild (a flush reddish color)

□ 2= Moderate (more prominent red color)
□ 3= Severe (definite redness).

7.1.3.6 SLIT LAMP OPHTHALMIC EXAMINATIONS

The slit lamp ophthalmic evaluations will include assessment of:

- Status of the implanted device
- Evaluation of the eye being normal or infected
- Evaluation of the cornea
- Evaluation of the anterior chamber
- Evaluation of the iris
- Evaluation of the lens
- Corneal surface staining
- Conjunctival erythema
- Measurement of Vertical C/D ratio

The cornea will be evaluated and objectively scored according to the scales developed bt Hackett and McDonald[1]. These scoring criteria are as follows:

Corneal Exam Findings Score

0 -Normal cornea. Appears with the slit-lamp adjusted to a narrow slit image as having a bright gray line on the epithelial surface and a bright gray line on the endothelial surface with a marble-like gray appearance of the stroma.

1- Some loss of transparency. Only the anterior half of the stroma is involved as observed with an optical section of the slit-lamp. The underlying structures are clearly visible with diffuse illumination, although some cloudiness can be readily apparent with diffuse illumination.

2-Moderate loss of transparency. In addition to involving the anterior stroma, the cloudiness extends all the way to the endothelium. The stroma has lost its marble-like appearance and is homogenously white. With diffuse illumination, underlying structures are clearly visible.

3- Involvement of the entire thickness of the stroma with endothelium intact. With optical section, the endothelial surface is still visible. However, with diffuse illumination the underlying structures are just barely visible (to the extent that the observer is still able to grade flare and iritis, observe for pupillary response, and note lenticular changes).

4- Involvement of the entire thickness of the stroma with endothelium damaged. With the optical section, cannot clearly visualize the endothelium. With diffuse illumination, the underlying structures cannot be seen. Cloudiness removes the capability for judging and grading flare, iritis, lenticular changes, and pupillary response.

[1] Hackett RB, McDonald TO. 1991. Eye irritation. In: Advances in Modern Toxicology: Dermatoxicology. 4th ed. (Marzulli F, Maibach H, eds.). Washington, DC:Hemisphere Publishing Corporation, 749–815

Corneal Opacity Area Score

0- Normal cornea with no area of cloudiness
1- 1% to 25% area of stromal cloudiness
2- 26% to 50% area of stromal cloudiness
3- 51% to 75% area of stromal cloudiness
4- 76% to 100% area of stromal cloudiness

The lens will be evaluated and objectively scored according to a modified methodology previously described by Chlack, et. Al in the LOCS III method[2]. The following assessments will be performed using a decimalized scale ranging from 0 (indicating a completely clear or colorless lens) to 5 (indicating complete opacification on the cortex or posterior capsule for C or P scales) and 5 indicating advanced opacification and brunescence of the nucleus for NO or NC scales). Each assessment will be recorded to the nearest single digit as determined by the ophthalmologist.

Table 1 Modified LOCS Scoring

Nuclear Color	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Nuclear opalescence	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Cortical	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
Posterior Capsular	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5	☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

[2] **Chylack,L.T; et.al; The Lens Opacities Classification System III, Arch. Ophthalmol.; vol 111, 831-836, 1993**

The existence or absence of uveitis will be documented using standardized uveitis nomenclature as reported by Jabs[6] et. Al. If uveitis exists, it will be classified as follows:

Table 2 Jab Uveitis Scoring

- **Anterior Uveitis**

Grade	Cells in field
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26 -50
4+	>50

- **Anterior Chamber Flare**

Grade	Description
0	none
1+	faint
2+	moderate (iris and lens detail clear)
3+	marked (iris and lens detail fuzzy)
4+	intense (fibrin or plastic aqueous)

- **Intermediate Uveitis**

Grade	Description
1+	faint
2+	mild
3+	moderate
4+	severe

- **Posterior Uveitis**

Grade	Description
1+	faint
2+	mild
3+	moderate
4+	severe

- **Panuveitis**

Grade	Description
1+	faint
2+	mild
3+	moderate
4+	severe

7.1.3.7 VERTICLE C/D RATIO

The vertical and horizontal C/D ratio will be assessed utilizing a 90 diopter lens during the slit lamp examination.

7.1.3.8 INDIRECT OPHTHALMIC EXAMINATIONS

The indirect ophthalmic evaluations of both the test and contralateral eyes will include assessment of:

- Evaluation of the iris
- Evaluation of the retina
- Evaluation of the vitreous
- Evaluation of the optic cup and disc
- Evaluation of the macula

Results of each of these examinations will be scored on the following scale for both the test and contralateral eyes.

□ Normal
□ Abnormal NCS – Not Clinically Significant
□ Abnormal CS – Clinically Significant

7.1.3.9 CORNEAL ENDOTHELIAL CELL COUNT

The corneal endothelial cell count will be assessed for both the test and contralateral eye utilizing Specular Microscopy. The result will be expressed as cells/mm^2.

To address differences in location of the image within a given area of the cornea, three acceptable images should be taken at each visit. The density from at least one preferred image should be determined.

Non-contact specular microscopes are strongly recommended. The same model of specular microscope should be used at each site. Images should be stored on 35 mm slides, half-inch video, or in electronic format. Specular cameras that can record digitized images on disk or to e-mail are preferable for ease of data transfer.

To capture a good image:

- make sure the subject is comfortable;
- instruct the subject to blink;
- instruct the subject not to move and to open eyes wide;
- instruct the subject to focus on the fixation light; and,
- if necessary, use the manual setting. (Note that the use of the manual setting may require additional training.)

The technician performing the image analysis should be advised of the following recommendations:

- A minimum of 100 cells (ideally 150 cells) in a contiguous area should be counted. The center method for counting cells is recommended;
- The quality of cells in an image is critical. When selecting cells to count, use the area with the fewest distortions (not in shadow, washed-out, or blurred).
- Follow the same methodology for all subjects at all visits.

7.1.3.10 GONIOSCOPY

Gonioscopy evaluations will be performed on both the test and contralateral eyes. The following positions on the anterior angles will be assessed: supertemporal, superonasal, inferotemporal, and inferonasal. The results will be scored based on the Shaffer Classification:

Grade 4: The angle between the iris and the surface of the trabecular meshwork is 45°.

Grade 3: The angle between the iris and the surface of the trabecular meshwork is greater than 20° but less than 45°.

Grade 2: The angle between the iris and the surface of the trabecular meshwork is 20°. Angle closure is possible.

Grade 1: The angle between the iris and the surface of the trabecular meshwork is 10°. Angle closure is probable in time.

Slit (S): The angle between the iris and the surface of the trabecular meshwork is less than 10°. Angle closure is very likely.

0: The iris is against the trabecular meshwork. Angle closure is present.

7.1.3.11 OPTIC NERVE IMAGE ANALYSIS

The optic nerves of both the test and contralateral eyes will be imaged and analyzed by Optical Coherence Tomography (OCT). The following parameters will be measured:

- VerticalDisc Diameter
- Vertical Cup Diameter
- Superior retinal Nerve Fiber Layer (rNFL)
- Inferior retinal Nerve Fiber Layer (rNFL)
- Temporal retinal Nerve Fiber Layer (rNFL)

7.1.3.12 PERIMETRY

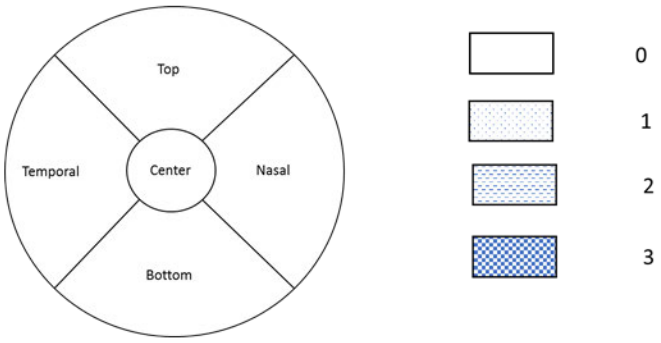
The visual perimetry of the contralateral non-implanted eyes will be assessed utilizing automated Humphrey Visual Field (HVF) testing. For this testing the eye should not be dilated uless it is miotic (the pupil is<3mm open). With Investigator approval, the eye may be dilated, however all remaining HVF follow-up evaluations of that eye should also be dilated. For the HFV testing the standard Swedish Interactive Thresholding Algorithm (SITA) testing algorithm should be used. +/1 mean deviations will be reported.

7.1.3.13 FLUORESCEIN STAINING

The surface and corneas of both the test and contralateral eyes will be stained with fluorescein and the surfaces examined by fluorescient light evaluation. The evaluation should be performed approximately 2.5 minutes after fluorescein instillation in the eye. The physician should use broad beam cobalt blue illumination and a yellow barrier filter hand held in front of the objective to observe corneal staining.

Based upon the evaluations, the five regions of the cornea will be scored (0-3) as shown below:

Figure 12 Corneal Fluorescein Scoring

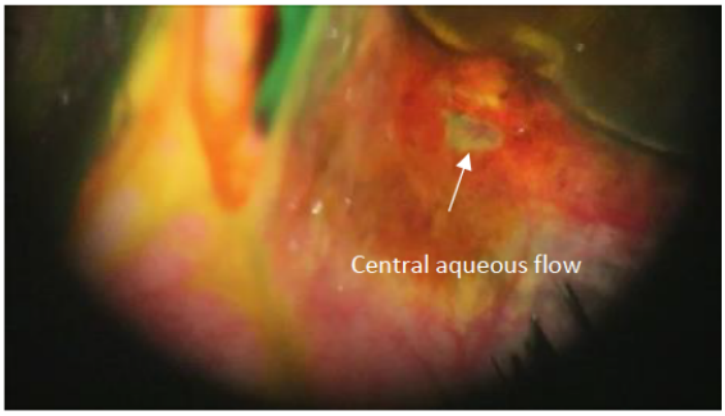


7.1.3.14 SEIDEL'S TESTING

Topical fluorescein will be applied to the cross bar tab of each test device post-implant at each follow-up exam and observed under magnification to assess device patency (central flow) and peripheral flow. Typically, this is accomplished by wetting the sterile fluorescein strip with sterile ophthalmic topical anesthetic agent and touching the paper fluorescein applicator to the cross bar tab and vicinity of the implant site. Proper aqueous flow from the center of the cross bar tab (central flow) may be verified directly under magnification and without fluorescent lamp illumination. Fluorescent illumination with cobalt blue lamp illumination from the slit lamp or other cobalt blue light sources may enhance visualization of exiting aqueous humor.

Figure 13: Fluorescein applicator

Figure 14: Positive Seidel's Test



7.1.3.15 SCHIRMER TEAR TEST

A standard Schirmer tear test will be performed in both the test and contralateral eye to assess tear production status. The measurement interval will be 5-minutes duration.

7.1.3.16 LENS STATUS FOR PHAKIC EYES

The lens status for phakic eyes will be described for both the test and contralateral eye if applicable.

A modified LOCS III grading system utilizing a 0-5 single digit scoring system will be used to evaluate all eyes for lens changes and to evaluate those changes over time. Standardized definitions in this instrument will be used to determine "change".

7.1.3.17 TREATMENT SATISFACTION QUESTIONNAIRE

The modified Treatment Satisfaction Questionnaire (TSQ) will be given to the patient at the beginning of the follow-up visit and prior to initiation of testing procedures. The coordinator should attempt to administer the questionnaire in a consistent fashion.

This questionnaire will attempt to measure the study subject's overall satisfaction with the implanted device and procedure. Data will be summarized using simple, descriptive frequency tables.

7.1.3.18 SYMPTOM AND HEALTH PROBLEM CHART FROM CIGTS

The Symptom and Health Problem Chart from the Collaborative Initial Glaucoma Treatment Study (CIGTS)[3] will be given to the patient at the beginning of the follow-up visit and prior to initiation of testing procedures. The coordinator should attempt to administer the questionnaire in a consistent fashion.

Currently permission to utilize the survey is not yet secured from the CIGTS Authors. The instrument will be administered once permission is secured prospectively only.

[3] Janz, J.K; et. al. Quality of Life in Newly Diagnosed Glaucoma Patients; Ophthalmology Volume 108, Number 5, May 2001

7.2 STUDY SCHEDULE

7.2.1 SCREENING/BASELINE

Subjects will be provided with the Subject Information and Informed Consent Form which advises that data will be collected for evaluation of eligibility for inclusion in the Trial. Subjects are told that if the criteria are met and the subject consents, then the Brown Glaucoma Implant will be implanted. If the subject agrees to inclusion for data collection, the subject Informed Consent will be signed and recorded in the subject's records as part of the Screening/Baseline visit. The subject will be assigned a unique study identifier.

The Screening/Baseline evaluation may be completed after the patient has reviewed, understood, and signed the Informed Consent. The Baseline assessments may be performed at any time prior to the Implant visit. If the implanting physician determines that the subject is not a suitable candidate for the procedure, then the subject shall not be scheduled for implant, will be withdrawn from the trial, and will not be included in the analysis.

Data to be collected during the Screening/Baseline visit include:

- Informed Consent Form
- Documentation of eligibility
- Medical History (including Physical Exam)
- Medications (all medications including indication)
- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Central corneal thickness
- Diurnal IOP assessment
- Gonioscopy
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Vertical C/D ratio assessment
- Corneal surface stain
- Optic nerve image analysis
- Corneal endothelial cell count (specular microscopy)
- Perimetry of non implanted eye
- Lens status for phakic eyes
- Schirmer's Tear Test
- Patient body temperature

Activities to be performed:

- Answer any questions the subject may have, and confirm willingness to proceed if the baseline criteria are verified.
- Verify that the inclusion/exclusion criteria are satisfied.
- Assessment by the Investigator of the subject's suitability for BGI implant (e.g. mental fitness).

If the subject meets the inclusion criteria, the surgery for the BGI implant will be discussed with the subject and scheduled. Investigational staff will ensure the product and equipment necessary for the procedure are available, and schedule support staff.

7.2.2 IMPLANT

If Informed Consent is obtained and eligibility has been performed, the Implant visit should be scheduled. The implant should occur as soon as possible after baseline data is collected, and not more than 30 days after. Baseline data collection on the day of surgery is permitted, but must be collected prior to the surgical procedure.

Data to be collected at implant include:

- Implant location OS/OD
- Patient body temperature
- Procedure Ease
- Procedure start and end times
- Description of surgical challenges
- Seidels Test
- Device information
- Adverse Events
- Implant site photo
- Medication changes

7.2.3 FOLLOW-UP

Post-implant follow-up visits (and corresponding visit windows) will occur according to the following schedule:

- Day 1 (one day)
- Week 1 (5-9 days)
- Week 2 (11-17 days)
- Month 1 (25-35 days)
- Month 2 (50-70 days)
- Month 3 (75-105 days)
- Month 4.5 (125-150 days)
- Month 6 (168-196 days)
- Month 8 (225-255 days)
- Month 10 (285-315 days)
- Month 12 (330-390 days)
- Month 15(440-470 days)
- Month 18 (530-560 days)
- Month 21 (620-650 days)
- Month 24 (690-750 days)

Data to be collected at each visit are summarized below.

Day 1

- Applanation tonometry
- Slit lamp examination
- Seidels Test
- Body temperature
- Implant site photo
- Adverse events

Week 1

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Seidel's test
- Body temperature
- Implant Site photograph
- Adverse events

Week 2

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Seidel's test
- Body temperature
- Implant site photograph
- Adverse events

Month 1

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Seidel's test
- Schirmer Tear Test
- Treatment Satisfaction Questionnaire (TSQ)
- Lens Status for phakic lenses
- Body temperature
- Implant site photograph
- Adverse events

Month 2

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Seidel's test
- Body temperature
- Implant site photograph
- Adverse events

Month 3

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Corneal endothelial cell count (specular microscopy)
- Gonioscopy
- Seidel's test
- Schirmer Tear Test
- Lens status for phakic eyes
- Treatment Satisfaction Questionnaire (TSQ)
- Body temperature
- Implant site photograph
- Adverse events

Month 4.5

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 6

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Central corneal thickness
- Diurnal IOP assessment
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Vertical C/D ratio assessment
- Corneal surface stain
- Corneal endothelial cell count (specular microscopy)
- Gonioscopy
- Optic nerve image analysis
- Perimetry of non implanted eye
- Seidel's test
- Schirmer Tear Test
- Lens status for phakic eyes

- Treatment Satisfaction Questionnaire (TSQ)
- Implant site photograph
- Body temperature
- Adverse events

Month 8

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 10

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 12

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Central corneal thickness
- Diurnal IOP assessment
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Vertical C/D ratio assessment
- Corneal surface stain
- Corneal endothelial cell count (specular microscopy)
- Gonioscopy
- Optic nerve image analysis
- Perimetry of non implanted eye
- Seidel's test
- Schirmer Tear Test
- Lens status for phakic eyes
- Treatment Satisfaction Questionnaire (TSQ)
- Implant site photograph
- Body temperature
- Adverse events

Month 15

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 18

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 21

- Applanation tonometry
- Device site evaluation
- Seidel's test
- Implant site photograph
- Adverse events

Month 24

- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Central corneal thickness
- Diurnal IOP assessment
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Vertical C/D ratio assessment
- Corneal surface stain
- Corneal endothelial cell count (specular microscopy)
- Gonioscopy
- Optic nerve image analysis
- Perimetry of non implanted eye
- Seidel's test
- Schirmer Tear Test
- Lens status for phakic eyes
- Treatment Satisfaction Questionnaire (TSQ)
- Implant site photograph
- Body temperature
- Adverse events

7.2.4 EARLY TERMINATION VISIT

If a study subject's participation in the study is terminated early, an End of Study case report form must be completed. Data to be collected include:

- Reason for withdrawal / early termination
- Best corrected visual acuity (ETDRS)
- Applanation tonometry
- Slit lamp examination
- Indirect ophthalmic examination with dilated fundus exam
- Seidel's test
- Schirmer Tear Test
- Lens status for phakic eyes
- Implant site photograph
- Body temperature
- Adverse events

7.2.5 SCHEDULE OF EVENTS TABLE

Table 3 Schedule of Events

Procedures	Screening/Baseline	Implant	Day 1	Week 1	Week 2	Month 1	Month 2	Month 3	Month 6, 12 & 24	Month 4.5, 8, 10, 15, 18, &21	Unscheduled
Informed Consent	X										
Eligibility Verification	X										
Medical History (including physical exam)	X										
BGI Implant		X									
Best Corrected Visual Acuity (ETDRS)	X			X	X	X	X	X	X		X
Applanation Tonometry	X		X	X	X	X	X	X	X	X	X
Diurnal IOP	X								X		
Body Temperature	X		X	X	X	X	X	X	X		X
Central Corneal Thickness	X								X		
Slit Lamp Examination	X		X	X	X	X	X	X	X		X
Vertical C/D Ratio	X								X		
Corneal Surface Stain	X								X		
Indirect Ophthalmic Examination/Dilated Fundus Exam	X				X	X	X	X	X		X
Corneal Endothelial Cell Count	X							X	X		
Gonioscopy	X							X	X		
Optic Nerve Image Analysis	X								X		
Perimetry of non implanted eye	X								X		
Seidel's Test		X	X	X	X	X	X	X	X	X	X
Schirmer Tear Test	X					X		X	X		
Lens Status for Phakic Eyes	X					X		X	X		
Treatment Satisfaction Questionnaire	X					X		X	X		
CIGTS	X					X		X	X		
Implant Site Photograph		X	X	X	X	X	X	X	X	X	X
Screening CRF	X										
Implant CRF		X									
Day 1 CRF			X								
Week 1 CRF				X							
Week 2/Month 2/Unscheduled CRF					X		X				X
Month 1/Month 3 CRF						X		X			
Month 6/Month 12/Month 24 CRF									X		

Procedures	Screening/Baseline	Implant	Day 1	Week 1	Week 2	Month 1	Month 2	Month 3	Month 6, 12 & 24	Month 4.5, 8, 10, 15, 18, &21	Unscheduled
Month 4.5, 8, 10, 15, 18, and 21 CRD										X	
Adverse events		X	X	X	X	X	X	X	X	X	X
Medication Log	X	X	X	X	X	X	X	X	X	X	X
Device Experience CRF (if applicable)		X	X	X	X	X	X	X	X	X	X
Explantation CRF (if performed)		X	X	X	X	X	X	X	X	X	X
End of Study CRF (when conducted)		X	X	X	X	X	X	X	X	X	X

7.3 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

7.3.1 TREATMENT OF INFECTIONS

Since the MicroOptx Brown Glaucoma Implant is an externally communicating device, special care must be exercised to watch for and treat if necessary any ocular infections. The patient and care providers should be counseled on the signs of infection to watch for which include:

- Redness
- Ocular discomfort
- Headache
- Change in vision
- Discharge at the implant site
- Device migration
- Changes in the external appearance of the eye
- Tissue hyperplasia at the implant site
- Hypopyon
- Hyphema
- Uveitis

Infections of the eye can rapidly damage important functional structures and lead to permanent vision loss or blindness. *Any study subject presenting with signs and symptoms of endophthalmitis (hypopyon and anterior chamber cell and flare, with or without vitreous cell; pain, redness, etc) shall be urgently referred to a vitreo-retinal surgeon, where institutional best practices will be followed* to obtain gram-stains, cultures and sensativities for suspected infections. Broad-spectrum antibiotics should be administered to the appropriate site of infection as soon as possible. Topical drops are preferred for corneal and conjunctival infections. Intravitreal antibiotics, and possibly subconjunctival and parenteral antibiotics, are preferred for endophthalmitis. Parenteral antibiotics are recommended for infection in deep adnexal structures. If infection occurs, culture and sensitivity testing should be undertaken. Medical management, including ophthalmic antibiotics (such as combination aminoglycosides and cephalosporins or fluoroquinolones) or explant can be considered.

7.3.2 TREATMENT OF HYPOTONY

Hypotony is a serious condition that can cause damage to the intraocular tissues and optic nerve. It is a serious risk to ocular health and should be immediately treated when it is persistent or associated with clinical signs. Management of hypotony in BGI implant patients should especially be considered when it is diagnosed at more than 2 visits with IOP <5 mm and when associated concomitant hyptonous findings are noted, including:

- Corneal edema/folds
- Shallow anterior chamber
- Hypotonous maculopathy
- Significant choroidal detachments or effusion

The MicroOptx Brown Glaucoma is designed to achieve normotension in the eye. If hypotony develops in a patient with a BGI implant, inadequate healing and peripheral flow of aqueous humor around the tissue device interface should be suspected. Seidels test will usually confirm the presence or absence of aqueous humor peripheral flow.

If hypotony develops after implantation of the BGI and the subject is confirmed to have central flow of aqueous humor through the device, then the physician may medically manage the hypotony as advised through standard treatment protocols.

Hypotony is best managed by correcting the underlying problem. As a temporizing measure, the anterior chamber may be inflated with viscoelastic or a pars plana injection of viscoelastic or gas may be administered. Steroids may be useful in individuals who are prone to a steroid response, and may improve aqueous humor production by decreasing ciliary body inflammation. Increased fluid intake may slightly increase aqueous humor production.

With inflammatory conditions or with recent surgery or trauma, topical prednisolone acetate or difluprednate may be considered. Additional therapy, such as topical or systemic nonsteroidal anti-inflammatory agents (NSAIDs), systemic, sub-Tenon, or intravitreal steroids, or other systemic medications (eg, methotrexate, cyclosporin), may be appropriate. Because steroids can slow wound healing, use should be moderated in the case of peripheral flow around the tissue device interface.

Atropine and other cycloplegics deepen the anterior chamber, lessen iris-corneal touch, and restore normal anatomy of the lens-iris diaphragm and ciliary body. Unfortunately, atropine also increases the uveoscleral outflow and can contribute to increased choroidal effusion.

If significant persistant hypotony persists, the device can be easily removed and a suture can be placed throught the incisions site. This manuever, as well as pharmacologic treatments as noted above, should allow a prompt resolution of the hypotony.

7.3.3 MANAGEMENT OF DEVICE BLOCKAGE

[redacted]

7.3.4 EXPLANTATION OF THE BROWN GLAUCOMA IMPLANT

The MicroOptx Brown Glaucoma Implant should be explanted if any of the following signs are noted:

- Extreme and persistent ocular discomfort
- Clinically significant infection
- Partial external migration of the BGI associated with site inflammation or nodular hyperplasia
- Significant peripheral flow of aqueous humor along the outside device-tissue interface is seen by Seidel testing
- Significant inflammation associated or possibly associated with the device develops
- Any situation the attending ophthalmologist feels might benefit be improved by device explantation

Explantation in settings of complete and normal healing:

[redacted]

[redacted]

Explantation in the setting of a loose device, one with peripheral flow, infection, etc:

[redacted]

7.3.5 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

After implantation of the BGI, intra-ocular pressure should be closely monitored. If pressures fall below 6 mmHg, elimination or reduction of IOP-lowering medications should be considered.

7.3.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Any post-implant procedure or treatment that physically interacts with the BGI either on the surface of the eye or in the anterior chamber should be avoided. This excludes any treatments or procedures described in this protocol for treatment of BGI or BGI implant procedure related adverse device effects.

7.3.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Study subjects will receive topical antibiotic, corticosteroid, and non-steroid anti-inflammatory (NSAID) agents to begin four times a day, one day prior to surgical implantation of the BGI. These same medicaitons will be used post-operatively for two weeks, and which time they will be reduced to twice daily until the bottles are completely empty or until one month from surgery, whichever comes first.

Bottle size should be 5 ml. The examining surgeon(s) can determine if these medicaitons should be prolonged or reduced any sooner than this protocol.

Study subjects will also receive three sets of drops (to include antibiotic, coriticsteroid, and NSAID) three times between induction and commencement of surgery. The first set of these drops can be given in the pre-operative area of the surgical suite, once IV access is obtained.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

All adverse events observed throughout the study will be reported on the Adverse Event CRF.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

The following definition is used:

> Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.
>
> NOTE 1: This definition includes events related to the investigational device or the comparator.
>
> NOTE 2: This definition includes events related to the procedures involved.
>
> NOTE 3: For users or other persons, this definition is restricted to events related to investigationl medical devices.

If an adverse event leads to multiple outcomes that sequentially worsen, only the worst adverse event is reported. For example, abnormal healing leading to infection would be reported as a single AE for the infection.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

The following definition is used:

> Serious Adverse Event (SAE): Adverse event that:
>
> a) led to a death,
>
> b) led to a serious deterioration in health of the subject, that either resulted in: - a life-threatening illness or injury, or — a permanent impairment of a body structure or a body function, or — in-patient hospitalization or prolongation of existing hospitalization,

or — in medical or surgical intervention to prevent life threatening illness or — injury or permanent impairment to a body structure or a body function.

c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition or a procedure required by the protocol (e.g., the index implant procedure), without serious deterioration in health, is not considered a serious adverse event.

8.1.3 ADVERSE DEVICE EFFECT (ADE)

The following definition is used:

Adverse Device Effect (ADE): An adverse event that is related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition also includes any event resulting from use error or from intentional misuse of the investigational medical device.

8.1.4 SERIOUS ADVERSE DEVICE EFFECT (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.1.5 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

The following definition is used:

Unanticipated Serious Adverse Device Effect (USADE): A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

8.1.6 PRE-SPECIFIED LIST OF ADVERSE EVENTS

Adverse events listed below are provided on the case report form along with a method for recording other adverse events not listed, based on the recognized standard ANSI Z80.27-2014.[7]

- Corneal edema
- Progression of cataract requiring cataract extraction

- Wound leak
- Suture abscess or other local infection
- Endophthalmitis
- Chronic iritis
- Hyphema
- Strabismus
- Macular edema
- Vitreous hemorrhage
- Suprachoroidal hemorrhage
- Retinal detachment
- Device malfunction
- Device blockage not requiring surgical revision
- Device blockage requiring surgical revision
- Implant migration (of any kind) not requiring surgical intervention
- Implant migration requiring surgical revision
- Implant exposure or extrusion
- Flat anterior chamber requiring anterior chamber reformation
- Hypotony (e.g., IOP <6 mmHG and associated with concomitant hypotonous findings are noted, including: Corneal edema/folds, shallow anterior chamber, hypotonous maculopathy, significant choroidal detachments or effusion)
- Hypotony maculopathy
- Choroidal effusion requiring surgical drainage
- Substantial increase in IOP vs. baseline (defined as ≥10 mmHg)
- Substantial visual field loss vs. baseline (e.g., 10 db loss)
- Substantial visual acuity loss vs. baseline (e.g. 10 or more ETDRS letters)
- Event requiring unplanned ocular surgical re-intervention

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 RELATIONSHIP TO DEVICE OR PROCEDURE — CAUSALITY

The relationship between the use of the medical device (including the medical — surgical procedure) and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of

confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each AE will be classified according to five different levels of causality. The Sponsor and the Investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device or procedures.

1) Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the investigational device or the procedures;

- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application or the reduction of the level of activation/exposure — when clinically feasible — and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

- harms to the subject are not clearly due to use error;

- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3**) Possible**: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

5) Causal relationship: the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that:

  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

The Sponsor and Iinvestigator will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

Related to Device - Events reasonably anticipated to be related to the physical presence of the device, e.g. erosion, a device deficiency, dislodgment.

Related to Procedure — Events reasonably anticipated to be related to procedures (pertaining to implant) described in this protocol.

NOTE: Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.

In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Ssponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the Sponsor remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as "possible".

Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

All AEs will be collected from the time of informed consent through the end of the study. Death should not be recorded as a separate adverse event, but rather as an outcome of the specific SAE which led to the subject's death. Adverse Events that would be reasonably expected to be associated with any surgical procedure (e.g.: anesthesia associated nausea, surgical site pain) will not be categorized as procedure or device related in the 30 days post the surgical procedure.

Notes:

1. Any current condition that is recorded as a pre-existing condition is not an AE, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
2. Technical observations – an undesirable device event that does not result in a medically undesirable situation for the subject – is not an AE.
3. Planned hospitalization for a procedure required by this protocol is not an AE. However, complications during the course of that planned hospitalization that prolong the anticipated duration of the hospitalization do constitute SAEs.
4. Elective hospitalization for a pre-existing illness does not constitute an SAE unless the illness has worsened in the nature, severity or degree of the condition with respect to baseline.
5. Device dislodgment/expulsion will not be collected as an AE, but rather as a device deficiency. If device migration results in a clinical symptom, report this as an AE in addition to the device deficiency report documenting device dislodgment/expulsion.
6. Lack of efficacy or diminished therapeutic response does not constitute an AE since failure to receive therapeutic benefit is an issue of efficacy, not safety. This includes symptoms that recur in the context of device deficiency leading to loss of therapy.

7. Removal and/or replacement of the device due to malfunction would be considered a device related adverse event

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events will be monitored through study closure. Each scheduled and unscheduled follow-up visit will include active ascertainment of new adverse events, as well as follow-up of previously reported, ongoing adverse events. All study subjects will be educated on the anticipated adverse events associated with the BGI and ocular surgery through the consenting process. They will be instructed to contact their physician if they experience any adverse events during their participation in the trial. All adverse events will be documented on the adverse event forms.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

The Investigator will monitor the occurrence of adverse events for each enrolled Subject. Adverse events reported by the Subject to the Investigator, confirmed by the Investigator, and documented in medical records must be reported on the adverse event form based on the requirements of the study CIP. All ADEs, SAEs, SADEs, and USADEs will be reported to all Investigators and IRBs and/or Ethics Committees participating in the study per their reporting requirements. This is done by means of an interim report or a final study report prepared by the Sponsor.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events are to be reported to the Sponsor by the Investigator within three working days of becoming aware of the event in compliance with MEDDEV 2.7/3 revision 3 May 2015; Guidelines on Medical Devices Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/Eec And 93/42/EEC.

8.5 DEVICE DEFICIENCIES

Device deficiencies are defined as inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

All suspected investigational device deficiencies should be documented on the appropriate CRF. The Sponsor will investigate all suspected device deficiencies.

Note: a device deficiency can include a device malfunction (i.e.: failure to perform to specifications), and may also include other deficiencies (e.g.: ambiguity of labelling).

For the BGI, not all device deficiencies will lead to an explant. For example, if patency is lost but the device is not causing discomfort, the Investigator and study subject may elect to leave the device in place while implanting a second device or seeking alternative treatment. Thus a device deficiency may not necessarily lead to an AE or SAE. If explanted, a device with a suspected malfunction should be returned to MicroOptx for analysis. If it is not possible to return the device, the reason it could not be returned as well as its final disposition should be documented. Note that reporting of device deficiencies shall be separate from adverse event reporting. If there should be an adverse event associated with the device deficiency, then that adverse event should be reported on an adverse event CRF.

8.6 SUBJECT DEATH

A subject death during the study should be reported to the Sponsor as soon as possible and, in any event, within two working days of notification to the Investigator. The center's IRB or Ethics Committee must be notified of any deaths in accordance with that center's IRB or Ethics Committee policies and procedures. Notification of death should include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death and is signed by the principal Investigator or authorized Sub-Investigator. The death letter should include all of the following:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Whether or not the death was witnessed
- Device status at the time of death, if known
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)
- Investigator or sub-Investigator signature and date

Any information listed above that is unavailable or unknown must be specified as such in the death letter. If the subject expired in the hospital, the following documentation should also be submitted:

- A copy of the medical records for that admission (e.g., consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the subject expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to the Sponsor)
- Death certificate (if available)

As applicable per local country regulation, the event should be reported by the Investigator to the appropriate regulatory bodies.

8.7 STUDY HALTING RULES

There are no statistically-based rules related to early trial termination. However, if two of the first five subjects experience a serious device or procedure related adverse event, or if three total subjects experience a serious device or procedure related adverse event, the study will be halted until the time an acceptable (to FDA and sponsor) mitigation can be implemented. If no such mitigation is possible, the study will be terminated. In addition, the Sponsor and independent Medical Director will review safety data every two months, including the emergence of serious adverse events and unanticipated adverse device effects, and will convene a special session of the DSMB if the observed risks appear greater than expected, even if the stopping rule is not met.

8.8 SAFETY OVERSIGHT

A Data Safety Monitoring Board (DSMB) will be assembled to routinely monitor ongoing safety of trial participants. The DSMB will meet at least quarterly and, upon data review, make recommendations to the sponsor to:

- Continue the trial as planned
- Continue the trial with modification(s), or
- Terminate the trial due to safety concerns.

A DSMB charter will be developed separately in a cooperative effort between sponsor and the DSMB.

9 CLINICAL MONITORING

It is the responsibility of the Sponsor to ensure proper monitoring of the study per regulations. Appropriately trained Sponsor personnel or delegates appointed by the Sponsor will perform study monitoring at the investigation site in order to ensure that the study is conducted in accordance with the CIP, the signed Clinical Trial Agreement, and applicable regulatory requirements. The Sponsor must therefore be allowed access to the Subjects' clinic and hospital records when so requested as per the consent form, Privacy Authorization (US only) and Clinical Trial Agreement.

Procedures required in this CIP require source document verification for this study. A separate Monitoring Plan will detail levels of source verification for this study. Monitoring visits will be conducted periodically to assess study progress, the Investigator's adherence to the CIP and regulatory compliance. This includes but is not limited to IRB/EC approval and review of the study, maintenance of records and reports, review of the consent process and review of source documents against Subject case report forms to ensure data points are correct and that adverse events are being reported.

Monitors facilitate site regulatory and study compliance by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Communication with the site personnel occurs during the visit and following the visit via a written follow-up letter. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular center.

Frequency of monitoring visits will occur based on subject enrollment, timing of the study visits, duration of the study, study compliance, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. All active sites will have a closure visit. A closure visit is a visit that occurs after a site's last required follow-up visit. Closure visit activities may include source verification of the data and closure of any findings and/or study-related activities. Storage and accountability of investigational product used for this study will be assessed and monitored throughout the study at each site.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

Because this is a first-in-human feasibility study, no formal Statistical Analysis Plan will be developed.

10.2 STATISTICAL HYPOTHESES

Because this is a small, unpowered, first-in-human feasibility study, no formal tests of hypothesis are planned.

10.3 ANALYSIS DATASETS

Data from all enrolled subjects for whom an implant is attempted will be included in data analysis. Certain exploratory analyses may be conducted that include only subjects who received an implant, or who have retained an implant for a minimum period of time.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

Because this is an unpowered feasibility study, no formal tests of hypothesis will occur. All outcome data will be summarized using appropriate descriptive statistics (e.g. mean, standard deviation and 95% confidence intervals for continuous data; frequency distributions for categorical data). Data will be summarized in a manner that will provide sufficient basis for a risk vs benefit assessment to inform considerations for future study.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is a binary measure of at least 20% reduction from baseline in diurnal IOP at six months. This endpoint will be descriptively summarized as a proportion of subjects meeting this criterion, along with the corresponding 95% confidence interval.

Given the small sample size of this study, the primary efficacy endpoint will be evaluated several different ways to assess the robustness of study conclusions. One analysis will determine whether or not a subject is classified as success (at least 20% reduction in IOP) based strictly on the baseline and follow-up IOP. Another analysis will be conducted that classifies any subject as a failure if, at the time of the endpoint evaluation, the subject:

- is taking increased glaucoma medication over baseline
- has required glaucoma re-operation
- has experienced a clinically significant post-operative hypotony that results in injury (i.e., no hypotony maculopathy, astigmatism, flat anterior chamber, corneal folds, choroidal effusions, suprachoroidal hemorrhage) or requires invasive intervention
- has been unable to receive an implant
- has discontinued trial participation due to the investigational device
- requires oral or intravenous glaucoma medication
- experienced a serious device-related AE.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Because this is an unpowered feasibility study, no formal tests of hypothesis will be conducted for the secondary endpoints. All secondary endpoints will be assessed using appropriate descriptive statistics.

10.4.4 SAFETY ANALYSES

Safety will be assessed by summarizing all adverse events, including summaries according to relatedness and seriousness.

10.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline characteristics and subject demographics will be summarized using appropriate descriptive statistics.

10.4.6 PLANNED INTERIM ANALYSES

10.4.6.1 SAFETY REVIEW

Safety will be assessed on an ongoing basis by the independent Medical Director, Sponsor, and Principal Investigator. No formal interim analyses are planned.

10.4.6.2 EFFICACY REVIEW

Effectiveness will be informally assessed on a periodic basis to ensure an acceptable level of risk for the observed level of efficacy.

10.4.7 ADDITIONAL SUB-GROUP ANALYSES

Due to the small (n=10) sample size, formal sub-group analyses are not possible or planned.

10.4.8 MULTIPLE COMPARISON/MULTIPLICITY

Because no formal tests of hypothesis are planned, the notion of type I error does not exist and controlling for multiple comparisons and multiplicity is not necessary.

10.4.9 TABULATION OF INDIVIDUAL RESPONSE DATA

In addition to tabular descriptive summaries of safety and effectiveness data, line listings of all adverse events and key effectiveness variabiles will provided, by subject.

10.4.10 EXPLORATORY ANALYSES

The ability to perform formal exploratory analyses is limited by the sample size of this trial. All outcome data will be summarized using appropriate descriptive statistics.

10.5 SAMPLE SIZE

This trial is a first-in-human feasibility trial of the Brown Glaucoma Implant. No formal tests of hypothesis are planned, and so sample size is not statistically derived. A total of ten enrolled and implanted subjects are believed to be sufficient to confirm preclinical findings, provide evidence of feasibility of efficacy, and determine whether or not the observed safety profile justifies further study.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

A study subject will be considered enrolled in the study upon signing Informed Consent. If an enrolled subject does not meet all eligibility criteria, the subject will be subsequently withdrawn from the study. Only enrolled subjects for whom an implant is attempted will be followed and reported on. Since this is a single-arm feasibility study, there will be no randomization or masking/blinding procedures.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Investigators are required to maintain on file the accurate, complete, and current records relating to this investigation:

- All correspondence with another Investigator, an IRB or Ethics Committee, MicroOptx, a monitor, or FDA or Competent Authority including required reports
- The signed CIP with any and all amendments
- The approved template of the Subject informed consent form
- Records showing receipt, use, and disposition of all devices, including:
    - Date, quantity, and serial numbers of devices received
    - Names of all persons who received, used or disposed of each device
    - Dates and serial numbers of devices returned to the Sponsor and the reason(s) for return
- IRB or Ethics Committee approval of the CIP and any amendments and renewals
- Competent Authority Approval in those countries where applicable
- The Investigators' agreement and the fee agreement (separate or combined)
- The Report of Prior Investigations and/or the Investigator's Brochure
- The insurance certificate
- Any documentation provided with the device
- Current curriculum vitae for the Principal Investigator and all Sub-Investigators
- Monitoring letters (if applicable)
- Interim/final reports
- Study initiation forms
- Study closure documents

In addition to the study administrative documents, Subject records shall be appropriately filed, including the following:

- Signed informed consent forms
- Source documents used for recording data (e.g., device characteristics at implant and followup)
- Records of any adverse event, including supporting documentation
- Records pertaining to Subject deaths during the study
- Relevant source data
- Any other records required by the Sponsor
- Documents showing the dates and reasons for each deviation from the CIP

MicroOptx and designated personnel (e.g. monitors) shall have access to all records listed above, upon request.

12 ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1 INSTITUTIONAL REVIEW BOARD (IRB)

The primary purpose of the IRB is to ensure that the rights and welfare of research subjects are adequately protected. In executing its purpose, the IRB has the authority to approve, require modifications to secure approval, or disapprove this research study. Also, the IRB has authority to suspend or terminate the trial once it is ongoing if it is not being conducted in accordance with the IRB's requirements, or becomes associated with unexpected serious harm to subjects.

Given the early nature and duration of this trial, the IRB will formally review ongoing data (protocol deviations, AEs, and deaths) every six months. Serious Adverse Events will be reported to the IRB according to the IRB's policy.

12.2 ETHICAL STANDARD – STATEMENTS OF COMPLIANCE

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The trial will be carried out in compliance with ISO standard 14155:2011 – Clinical investigation of medical devices for human subjects – Good Clinical Practice

This trial will be listed in clinicaltrials.gov prior to beginning the trial.

This study will not begin until all required approvals and favorable opinions have been obtained from the EC and other governing regulator bodies. All requirements imposed by the EC or other governing bodies will be followed.

12.3 INFORMED CONSENT PROCESS

12.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed Consent is required from all Subjects (or their legal representatives) prior to the Subject's participation in the study.

Other informational materials provided to study participants will include:

- Patient Manual – important information for trial participants implanted with the Brown Glaucoma Implant, including contact information for questions and concerns
- Patient Card – Medical Alert patient information card

12.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The process of obtaining Informed Consent shall comply with the Declaration of Helsinki, FDA 21CFR 50, ISO 14155-2011 and applicable national regulations (local IRB, Ethics Committee and/or Regulatory bodies, as applicable). The process of obtaining informed consent shall:

a) Avoid any coercion of or undue influence of Subjects to participate,

b) Not waive or appear to waive subject's legal rights,

c) Use native language that is non-technical and understandable to the subject or his/her legal representative,

d) Provide adequate time for the subject to consider participation and ask questions if necessary,

e) Informed consent shall always be signed and personally dated by the subject or legal representative and by the Investigator.

The original signed Informed Consent must be retained on file by the Investigator and a copy given to the subject (Investigator's responsibility).

12.4 PARTICIPANT AND DATA CONFIDENTIALITY

Throughout the study, confidentiality shall be maintained at all times, by all parties involved, and all data shall be secured against unauthorized access. Confidentiality of each subject shall be preserved in reports and any publication of the results. Only authorized personnel and their designees will have access to these confidential files. Subject data may be made available to national and foreign regulatory agencies, health or other governmental authorities, under strict confidentiality condition. The investigational sites shall ensure that data (e.g. worksheets, medical records, digital images) forwarded to the Sponsor do not contain any Subject identifying data (such as name and birth date), other than the Subject ID.

It is required that eCRFs be entered in the electronic data entry system provided by the Sponsor. All eCRFs require the Investigator's electronic signature or the Investigator's designee.

Source documents — as per FDA 21CFR 812 and ISO 14155-2011 — are printed, optical or electronic documents including the information in original records and necessary for the reconstruction and evaluation of the clinical investigation. Original source data should remain at the investigational site.

12.4.1 RESEARCH USE OF STORED HUMAN SAMPLES,SPECIMENS OR DATA

A participating Investigator shall provide direct access to source data and documents for Trial-related monitoring, audits, IRB or Ethics Committee review, and regulatory inspection. All subjects' health information will be kept confidential in accordance with all applicable laws and regulations. Subjects' health information may be used to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of products, new medical research and proposals for developing new medical products or procedures, and other business purposes. Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

12.5 FUTURE USE OF STORED SPECIMENS

There will be no human samples or specimens collected and stored for future use in this study.

13 DATA HANDLING AND RECORD KEEPING

13.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

To ensure data quality and completeness, all required data will be recorded on standardized case report forms (eCRFs) provided by the Sponsor. Case report forms should be completed accurately and completely during and in a timely manner after any treatment in the study. The Principal Investigator or appointed designee must review the case report forms and electronically sign them certifying their accuracy.

MicroOptx follows a data management plan which is on file and available for review. Data will be captured in an electronic data capture system. Data will be reviewed regularly by both study monitors and data associates. Data queries will be issued as needed and require site personnel to make corrections and state the reason for the modification. All entries and modifications will be captured in an electronic system audit trail.

13.2 STUDY RECORDS RETENTION

Source data is retained at the clinical sites until completion of the trial and then will be stored for a period of time as specified by the Sponsor's quality system.

13.3 PROTOCOL DEVIATIONS

An Investigator is required to conduct this study in accordance with the signed Investigator's Agreement, this investigational plan, applicable laws and applicable national regulations, and any conditions of approval imposed by the reviewing IRB or Ethics Committee and regulatory agency (e.g.: FDA or Competent Authority).

Protocol deviations are a fact of life with any clinical trial. Deviations may be anticipated (e.g.: known delay in a follow up visit), inadvertent (e.g.: unplanned delay or miss of a follow up visit due to a family emergency), or unanticipated on an emergency basis (e.g.: trauma may require device removal to accommodate contraindicated procedures). Except in emergency situations, protocol deviations requires prior Sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior IRB or Ethics Committee approval is required. An Investigator shall notify the Sponsor and the reviewing IRB or Ethics Committee of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but no later than five working days after the emergency occurred. All deviations from the investigational plan must be reported to the Sponsor together with the reason for the deviation and possible corrective actions for the deviations. In some circumstances, the center may be required to notify the center's IRB or Ethics Committee, and the Sponsor will notify the appropriate regulatory agencies.

13.4 PUBLICATION AND DATA SHARING POLICY

Publications addressing the Early Bird Study results will be managed by a publications committee. MicroOptx will form the Early Bird Study publications committee to include members of MicroOptx and participating Investigators. The committee shall elect its chair at the first publications meeting, which will be held near the time of study start. Each participating institution may provide one representative to the publications committee. Additional members may be added based on approval of the committee. The committee will develop a publication strategy that will include a final publication plan. The scientific validity and timing of publications will be evaluated in order to maximize the benefits derived from the publication of the world wide clinical data of the Early Bird Study. All publications and strategy will be reviewed and approved by the Publications Committee. In general, publications utilizing study data will be managed as follows:

Authorship Selection

Authors will be selected based on the following criteria:

- The quantity of patients who are enrolled in the study, provided that quality compliant data is collected (i.e., data that is complete, accurate and received within a reasonable time frame)
- Documented Investigators' participation in the study development process
- The quality and quantity of prior publication history in general and with MicroOptx Clinical Research
- At least one MicroOptx author providing substantive contribution to the study shall be considered

Confidentiality

The Committee, MicroOptx, and all Investigators and authors will ensure that no information which would reveal a patient's identity is used in any publication. Information which could be used to establish a patient's identity, should not be provided to MicroOptx. Authors and MicroOptx will take every reasonable precaution to protect the identity of patients enrolled in the trial.

Review and Communication Guidelines

Investigators will receive a communication regarding the authorship selection, the publication co-authors, and to which scientific platform the publication will be submitted.

14 STUDY ADMINISTRATION

14.1 SPONSOR INFORMATION

MicroOptx, Inc
10650 County Road 81
Suite 133
Maple Grove, MN 55369
888-591-2784

Sponsor's Contact:

[redacted]

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APPENDIX

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