Official Title : Prospective, Multi-Center, Single-Arm Post-Market Study of Use of the OMNI® Surgical System in Combination with Cataract Extraction in Open Angle Glaucoma

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Sight Sciences, Inc.

PROSPECTIVE, MULTI-CENTER, SINGLE-ARM POST-MARKET STUDY OF USE OF THE OMNI® SURGICAL SYSTEM IN COMBINATION WITH CATARACT EXTRACTION IN OPEN ANGLE GLAUCOMA

PROTOCOL ID #:	06213
CURRENT REVISION:	Rev F
REVISION DATE:	April 01, 2021
SPONSOR:	Sight Sciences, Inc. 4040 Campbell Avenue, Suite 100, Menlo Park, CA 94025 [redacted]

Agreement of Principal Investigator

I, _____agree to conduct this trial in accordance with this clinical protocol and any amendments.

_____ _____

Signature Date

_____ _____

Center Name City, State, Country

Revision History

Revision	Date Issued	ECO
A	December 19, 2018	[redacted]
B	May 14, 2019	[redacted]
C	May 22, 2019	[redacted]
D	April 02, 2020	[redacted]
E	March 16, 2021	[redacted]
F	April 01, 2021	[redacted]

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1 PROTOCOL SYNOPSIS

Protocol Title	Prospective, Multi-center, Single-Arm Post-market Study of use of the OMNI® Surgical System in Combination with Cataract Extraction in Open Angle Glaucoma
Protocol ID Number	06213
Study Device	OMNI™ Surgical System
Study Objective	To prospectively assess the clinical effect of ab-interno transluminal viscoelastic delivery and trabeculotomy performed using the OMNI Surgical System in combination with Cataract Extraction on intraocular pressure (IOP) and the use of IOP-lowering medications in patients with mild-moderate open angle glaucoma (OAG).
Study Design	Prospective, multicenter, single-arm, post-market study.
Primary Effectiveness Endpoints	• Reduction in mean unmedicated diurnal IOP from baseline to 12 months; and • Reduction in mean number of IOP-lowering medications from screening to 12 months
Secondary Effectiveness Endpoint	• Percent of eyes with a ≥20% reduction in unmedicated diurnal IOP at 12 months • Percent of eyes with unmedicated diurnal IOP between 6 and 18 mmHg inclusive at 12 months
Safety Endpoints	• Rates of ocular adverse events (intraoperative, postoperative) • Reduction in best corrected visual acuity (BCVA) from baseline (note: reduction in BCVA due to PCO will not be treated as a safety event)

Inclusion Criteria	**<u>Inclusion Criteria</u>** (only one eye of each subject is eligible, and all ocular criteria apply to the study eye): 1. Male or female subjects, 22 years or older 2. Visually significant cataract 3. Diagnosed with mild to moderate open angle glaucoma (e.g. primary open angle glaucoma, pigmentary glaucoma, pseudoexfoliative glaucoma) as documented in subjects' medical record per ICD-10 guidelines 4. At screening, a medicated IOP ≤33 mmHg and on 1-4 IOP-lowering medications[1] with a stable medication regimen for two months prior to screening visit 5. At baseline, unmedicated diurnal IOP 21-36 mmHg and IOP at least 3 mmHg higher than screening IOP 6. Scheduled for cataract extraction followed by ab-interno transluminal viscoelastic delivery and trabeculotomy using the OMNI Surgical System 7. Shaffer grade of ≥ III in all four quadrants 8. Potential of good best corrected visual acuity post cataract extraction, in the investigator's judgment 9. Able and willing to comply with the protocol, including all follow-up visits. 10. Understands and signs the informed consent

[1] For combination IOP-lowering medications that consist of two or more IOP-lowering drugs, each IOP-lowering drug component counts as a separate medication.

Exclusion Criteria	(All criteria apply to the study eye; both eyes of a single subject need not be eligible): 1. Any of the following prior treatments for glaucoma: o Laser trabeculoplasty ≤3 months prior to baseline o Implanted with iStent, Cypass, Xen, Express, glaucoma draining device/valve, or Hydrus Device o Prior canaloplasty, goniotomy, trabeculotomy, trabeculectomy, ECP or CPC 2. Normal tension glaucoma 3. Acute angle closure, traumatic, congenital, malignant, uveitic or neovascular glaucoma 4. Severe glaucoma as documented in subjects' medical record per ICD-10 guidelines 5. Use of oral hypotensive medication treatment for glaucoma 6. In the investigator's judgement, predisposed to significant risk because of washout of ocular hypotensive medications 7. Ocular pathology or medical condition which, in the investigator's judgment, would either place the subject at increased risk of complications, contraindicate surgery, place the subject at risk of significant vision loss during the study period (e.g., wet AMD, corneal edema, Fuch's dystrophy, etc.), or interfere with compliance to elements of the study protocol (e.g., returning to investigator's office for follow-up visits) 8. Participation (≤ 30 days prior to baseline) in an interventional trial which could have a potential effect on the study outcome, as determined by the study investigator 9. Women of childbearing potential if they are currently pregnant or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study
Number of Subjects Enrolled and Treated	A total of 145 subjects will be enrolled and treated.
Number of Sites	Up to 20

Study Duration for Each Subject	12 months
Total Study Duration	Approximately 24 months
Schedule of Visits	Screening, Baseline, Surgery (Day 0), Day 1, Week 1, 1 Month, 3 Month, 6 Month, 12 Month, 12 Month Washout (if applicable)
Treatments	Cataract extraction followed by ab-interno transluminal viscoelastic delivery and trabeculotomy using the OMNI Surgical System

2 STUDY OBJECTIVE

The objective of this study is to prospectively assess the impact of ab-interno transluminal viscoelastic delivery and trabeculotomy performed using the OMNI Surgical System in combination with cataract extraction on intraocular pressure (IOP) and the use of IOP-lowering medications in patients with mild to moderate open angle glaucoma (OAG).

3 BACKGROUND AND JUSTIFICATION FOR THE STUDY

Glaucoma is a progressive disease leading to irreversible damage to retinal ganglion cells with the global burden expected to rise to 111.8 million people by the year 2040.[2] OAG is the most prevalent form of glaucoma and it's proven that lowering IOP is the only efficient way to slow down the progressive optic nerve damage and visual field loss.[3] Hypotensive eye drops are commonly used as the first line clinical management for OAG.[4] Ocular side effects such as allergies, ocular surface disorders, blepharitis, pemphigoid, abnormal pigmentation etc. and systemic side effects such as bradycardia, headaches, depression, anxiety, confusion, dysarthria, hallucinations, lethargy, polyuria, weight loss, metabolic acidosis, etc. can occur during long term use of topical medications for management of OAG. [5] There is also a documented low rate of compliance and tolerability with eye drops that results in disease progression and loss of

[2] Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: a systematic review and meta-analysis. Ophthalmology. 2014;121:2081–2090.

[3] European Glaucoma Society. Terminology and guidelines for glaucoma 4th edition Savona, Italy: Editrice PubliComm, 2014.

[4] Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002; 120:701–713.

[5] Kenji Inoue. Managing adverse effects of glaucoma medications. Clin Ophthalmol. 2014; 8: 903–913. Published online 2014 May 12. doi: 10.2147/OPTH.S44708.

vision.[6] The cost of these chronic medications and difficulty administering drops to the eyes contributes to poor compliance.

Trabeculectomy and tube-shunt implantations remain the gold standard for surgical management of IOP.[7] These interventions are associated with a long list of potential complications such as sclero-conjunctival scarring, hypotony, hypotony maculopathy, choroidal detachment, conjunctival leak, hyphema, and bleb related complications.[8] Surgical techniques that re-establish the aqueous outflow through the physiological pathways without the need for a bleb are gaining acceptance among glaucoma surgeons.[9] Canaloplasty is one such procedure that is intended to restore the natural aqueous outflow system through microcatheterization and viscodilation of the entire length of the Schlemm's canal with a well-documented safety and efficacy profile in reducing IOP.[10,11] Trabeculotomy is another such procedure that relieves the resistance to aqueous flow by cleaving the trabecular meshwork and the inner walls of Schlemm's canal.[12]

The OMNI™ Surgical System (Sight Sciences Inc, Menlo Park, CA) is a 510K-cleared manually operated device indicated for the delivery of small amounts of viscoelastic fluid and to cut trabecular meshwork tissue during trabeculotomy procedures. The

[6] Newman-Casey PA, Robin AL, Blachley T, Farris K, Heisler M, Resnicow K, Lee PP. The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. Ophthalmology. 2015 Jul; 122(7):1308-16.

[7] Gedde SJ, Singh K, Schiffman JC, Feuer WJ. The Tube Versus Trabeculectomy Study: interpretation of results and application to clinical practice. Curr Opin Ophthalmol. 2012 Mar; 23(2):118-26.

[8] Zahid S, Musch DC, Niziol LM, Lichter PR, Collaborative Initial Glaucoma Treatment Study Group. Risk of endophthalmitis and other long-term complications of trabeculectomy in the Collaborative Initial Glaucoma Treatment Study (CIGTS). Am J Ophthalmol. 2013 Apr; 155(4):674-680, 680.e1.

[9] American Academy of Ophthalmology. Preferred practice pattern®. Primary open-angle glaucoma. San Francisco, CA. 2015.

[10] Klink T, Sauer J, Körber NJ, et al. Quality of life following glaucoma surgery: canaloplasty versus trabeculectomy. Clin Ophthalmol. 2014;18;9:7-16.

[11] Lewis RA, von Wolff K, Tetz M, Körber NJ, Kearney JR, Shingleton B, Samuelson TW. Canaloplasty: circumferential viscodilation and tensioning of Schlemm's canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults: interim clinical study analysis. J Cataract Refract Surg 2007; 33:1217–1226

[12] Grover DS, Godfrey DG, Smith O, Feuer WJ, Montes de Oca, Fellman RL. Gonioscopy-Assisted Transluminal Trabeculotomy, A Novel Ab Interno Trabeculotomy: technique report and preliminary results. Ophthalmology. 2014; 121:855-861.

OMNI™ Surgical System allows doctors to perform viscodilation of Schlemm's canal in conjunction with trabeculotomy through single clear corneal incision.[13,14,15]

Cataract is often seen as a comorbidity present in patients with glaucoma and together they serve as leading causes of blindness worldwide.[16] Cataract accounts for 33% of visual disability worldwide and may have a causal relationship with increased IOP in OAG.[17] Cataract surgery is known to reduce IOP in glaucoma patients. A review of cataract surgery in glaucoma patients found that in U.S. patients, cataract surgery (not involving washout of IOP-lowering medications) was associated with a reduction in IOP ranging between 0.6 to 2.5 mm Hg at one year.[18,19,20] Studies that involved pre-operative washout of IOP-lowering medications report a larger reduction in IOP for cataract surgery at 12 months, 6.7 mmHg ± 3.6 mmHg (N =118) in iStent inject study (P170043)[21] and 6.3 mmHg ± 4.0 mmHg (N = 187) in Hydrus study (P160024)[22].

[13] Clara Martinez-Rubio, Ioan Alexandru Placinta, Rodrigo Molina-Pallete, Paula Martínez Lopez-Corell, Jorge Vila-Arteaga. OMNI-an initial experience with a new surgical glaucoma treatment device. ESCRS 2018.

[14] Iwona Grabska-Liberek, Julita Majszyk-Ionescu, Agnieszka Skowyra, Monika Rogowska, Anna Plichta, Patrycja Duda, Ingrid Kane OMNI 360TM in Open-Angle Glaucoma Treatment: A 6-month Follow-up. ESCRS 2018.

[15] Paula Martínez Lopez-Corell, Rodrigo Molina-Pallete, Clara Martinez-Rubio, Ioan Alexandru Placinta, Jorge Vila-Arteaga Procedural Steps For OMNI, A New Surgical Technique For Glaucoma Treatment, In Combination With Cataract Surgery ESCRS 2018.

[16] Resnikoff S, Pascolini D, Etya'ale D, Kocur I, Pararajasegaram R, Pokharel GP, Mariotti SP Bull World Health Organ. Global data on visual impairment. 2016 Nov; 82(11):844-51.

[17] Bourne RRA, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990-2010: a systematic analysis. Lancet Glob Heal. 2013;1:339–349.

[18] Francis BA, Berke SJ, Dustin L, et al. Endoscopic cyclophotocoagulation combined with phacoemulsification versus phacoemulsification alone in medically controlled glaucoma. J Cataract Refract Surg. 2014;40:1313–1321.

[19] Arthur SN, Cantor LB, Wudunn D, et al. Efficacy, Safety, and Survival Rates of IOP-lowering Effect of Phacoemulsification Alone or Combined With Canaloplasty in Glaucoma Patients. Journal of Glaucoma. 2013;23:316–320.

[20] Armstrong JJ, Wasiuta T, Kiatos E, Malvankar-Mehta M, Hutnik CML. The Effects of Phacoemulsification on Intraocular Pressure and Topical Medication Use in Patients With Glaucoma: A Systematic Review and Meta-analysis of 3-Year Data. J Glaucoma. 2017 Jun;26(6):511-522. doi: 10.1097/IJG.0000000000000643. Review.

[21] https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170043b.pdf

[22] Samuelson TW, Chang DF, Marquis R, Flowers B, Lim KS, Ahmed IIK, Jampel HD, Aung T, Crandall AS, Singh K; HORIZON Investigators. A Schlemm Canal Microstent for Intraocular Pressure Reduction in Primary Open-Angle Glaucoma and Cataract: The HORIZON Study. Ophthalmology. 2018 Jun 23. pii: S0161-6420(17)33810-1. doi: 10.1016/j.ophtha.2018.05.012.

Combined glaucoma and cataract surgery often result in a greater decrease in IOP and use of glaucoma medications compared with cataract surgery alone. [21,22,23,24] When a patient with glaucoma also requires surgical intervention for cataract, the ophthalmologist often performs simultaneous cataract and glaucoma surgery.

This prospective, multicenter, single-arm, post-market clinical study will evaluate the impact of ab-interno transluminal viscoelastic delivery and trabeculotomy using OMNI™ Surgical System in conjunction with cataract surgery on IOP and the use of hypotensive medications in patients with mild to moderate open angle glaucoma.

4 STUDY DEVICE

4.1 INDICATIONS FOR USE

The OMNI Surgical System has been 510k cleared by the US Food and Drug Administration (FDA) for the following indication for use[25]:

> The OMNI® Surgical System is indicated for canaloplasty (microcatheterization and transluminal viscodilation of Schlemm's canal) followed by trabeculotomy (cutting oftrabecular meshwork) to reduce intraocular pressure in adult patients with primary open-angle glaucoma. .

4.2 DEVICE DESCRIPTION

The OMNI™ Surgical System ("OMNI") is a sterile, single use, manually operated instrument used by ophthalmologists to deliver small, controlled amounts of viscoelastic into the anterior segment of the eye during ophthalmic surgery. It is also indicated to cut trabecular meshwork tissue during trabeculotomy procedures.

The OMNI is designed to function with commonly used viscoelastic fluids made commercially available by companies such as Abbott Medical Optics (AMO), Bausch & Lomb, and Alcon. The OMNI dispenses fluid on the principle of exchanging volumes much like a syringe. The handheld instrument includes a cannula, microcatheter, internal reservoir and plunger tube, and finger wheels. The finger wheels on the handle of the device are used to advance and retract the microcatheter. In addition, when the device is being used to deliver viscoelastic, retraction of the microcatheter causes the

[23] Zhang ML, Hirunyachote P, and Jampel H. Combined surgery versus cataract surgery alone for eyes with cataract and glaucoma. Cochrane Database Syst Rev. 2015; 7: CD008671

[24] Vold S, Ahmed II, Craven ER, Mattox C, Stamper R, Packer M, Brown RH, Ianchulev T; CyPass Study Group. Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts. Ophthalmology. 2016 Oct;123(10):2103-12. doi: 10.1016/j.ophtha.2016.06.032.

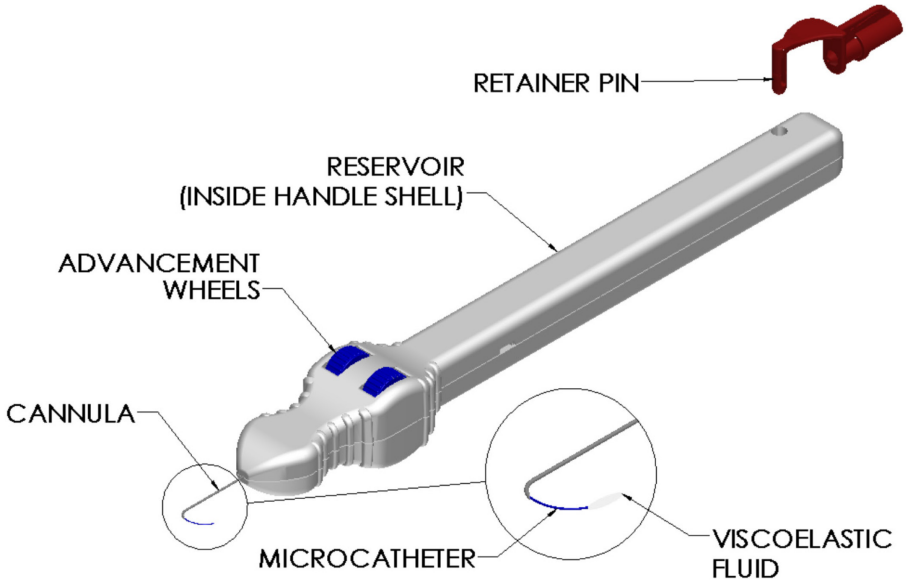
[25] OMNI 510k K202678 approval
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K202678

plunger tube to advance into the viscoelastic fluid reservoir thereby dispensing viscoelastic fluid.

The microcatheter can be advanced/retracted up to 20 mm per cycle. The microcatheter can be fully advanced/retracted up to 5 times (i.e. 5 full cycles of 20 mm each). Dispensation of viscoelastic can only occur during the first two 20-mm cycles.

The wheels are located on both sides of the handle. This allows the OMNI device to be used in either eye (OD or OS) and in either hand of the surgeon (left or right), by turning the device 180 degrees along its vertical axis.

Figure 1: OMNI Surgical System



4.3 TRAINING

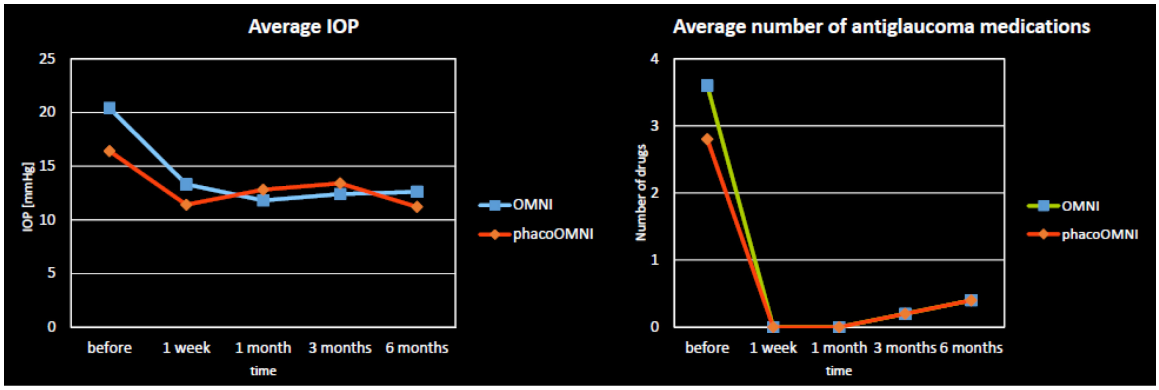
Investigators participating in the study must be experienced in using the OMNI Surgical System (i.e. they must have performed at least 5 procedures with the OMNI Surgical System). All study staff will receive training on the protocol and execution of the study according to applicable regulations and Good Clinical Practices.

5 PRIOR INVESTIGATIONS

Several case series studies have been performed to evaluate the results of ab-interno transluminal viscoelastic delivery and trabeculotomy performed with the OMNI device in patients with open angle glaucoma.

Grabska-Liberek, et al reported on 10 eyes (9 patients) with open angle glaucoma.[26] Five eyes were treated with OMNI surgery alone and 5 eyes underwent OMNI surgery plus cataract extraction (OMNI + CE). In the 5 OMNI alone eyes, IOP declined from and average of 20.4 mmHg pre-op to 12.6 mmHg at 6 months (38.2% decline) and in the OMNI + CE, IOP declined from 16.4 mmHg pre-op to 11.2 mmHg at 6 months (31.7% decline). Use of IOP-lowering medications also declined in both groups: from an average of 3.6 pre-op to 0.4 at 6 months (OMNI surgical) and 2.8 to 0.4 in the OMNI+CE group. Early post-operative complications included IOP spikes (5 cases), hyphema (6 cases), and fibrin in the anterior chamber (1 case). IOP spikes were observed 1-2 days after surgery and were treated with systemic drugs (e.g. acetazolamide or mannitol). Hyphema resolved within the first week post-op.

Figure 2: Results for OMNI Surgery (Grabska-Liberek et al)

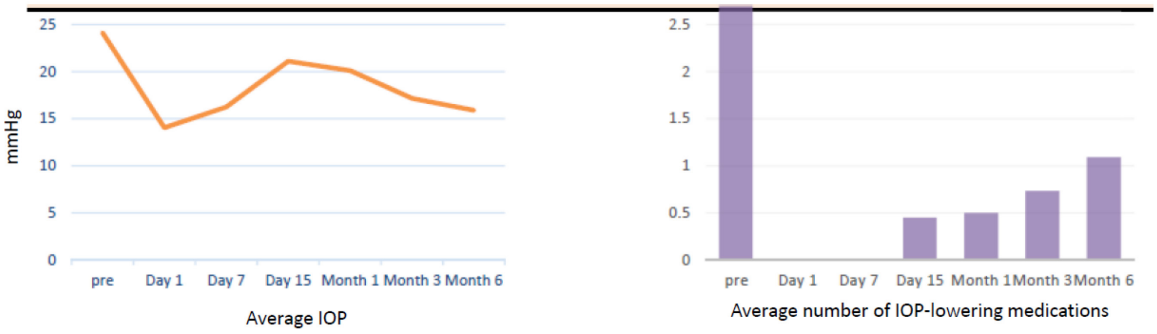


Martinez-Rubio, et al[27] reported early safety and efficacy of viscodilation and trabeculotomy using the OMNI Surgical System in 20 eyes with primary open angle glaucoma, 13 of which were treated with the OMNI device and cataract surgery and 7 who were only treated with the OMNI device. Mean pre-operative IOP was 24.2 ± 6.3 mmHg and the mean number of preoperative antiglaucoma drugs used by patients was 2.7. At 6 months, pressure had been reduced to an average of 15.9 ± 3.3 and medications were reduced to an average of 1.1. Early postoperative complications included one case of transient toxic anterior segment syndrome (TASS) and one case of transient hyphema. Early follow-up data showed a reduction of IOP, with medication reduction, in treatment of moderate glaucoma in adults.

[26] Grabska-Liberek I, et al. OMNI 360 in Open-Angle Glaucoma Treatment: A 6-Month Follow-Up. European Society of Cataract & Refractive Surgeons (ESCRS) 2018.

[27] Martinez-Rubio, et al. OMNI-an initial experience with a new surgical glaucoma treatment device. European Society of Cataract & Refractive Surgeons (ESCRS) 2018.

Figure 3: Results for OMNI Surgery (Martinez-Rubio et al)



6 STUDY DESIGN

This is a prospective, multicenter, single-arm, post-market study.

6.1 STUDY DEVICE

The study device is the OMNI Surgical System. Subjects enrolled in the study will undergo ab-interno transluminal viscoelastic delivery and trabeculotomy using the OMNI Surgical System in conjunction with cataract extraction.

6.2 STUDY SITES

This study will be conducted at up to 20 sites in the United States. No center will have more than 25% of the target enrollment.

7 STUDY ENDPOINTS

7.1 EFFECTIVENESS ENDPOINTS

The **Primary effectiveness endpoints** are:

- Reduction in mean unmedicated diurnal IOP from baseline to 12 months; and
- Reduction in mean number of IOP-lowering medications from screening to 12 months

The **Secondary effectiveness endpoints are**:

- Percent of eyes with a ≥20% reduction in unmedicated diurnal IOP at 12 months
- Percent of eyes with unmedicated diurnal IOP between 6 and 18 mmHg inclusive at 12 months

7.2 SAFETY ENDPOINTS

Safety will be assessed by evaluating the following measures over time:

- Rates of ocular adverse events (intraoperative, postoperative)
- Reduction in best corrected visual acuity (BCVA) from baseline (note: reduction in BCVA due to PCO will not be treated as a safety event)

8 STUDY SELECTION CRITERIA

8.1 INCLUSION CRITERIA

For inclusion in this study, subjects must meet all the following criteria (only one eye of each subject is eligible, and all ocular criteria apply to the study eye only unless otherwise indicated):

1. Male or female subjects, 22 years or older
2. Visually significant cataract
3. Diagnosed with mild to moderate open angle glaucoma (e.g. primary open angle glaucoma, pigmentary glaucoma, pseudoexfoliative glaucoma) as documented in subjects' medical record per ICD-10 guidelines
4. At screening, a medicated IOP ≤33 mmHg and on 1-4 IOP-lowering medications with a stable medication regimen for two months prior to screening visit[28]
5. At baseline, unmedicated diurnal IOP 21-36 mmHg and IOP at least 3 mmHg higher than screening IOP
6. Scheduled for cataract extraction followed by ab-interno transluminal viscoelastic delivery and trabeculotomy using the OMNI Surgical System
7. Shaffer grade of ≥ III in all four quadrants
8. Potential of good best corrected visual acuity post cataract extraction, in the investigator's judgment
9. Able and willing to comply with the protocol, including all follow-up visits
10. Understands and signs the informed consent.

8.2 EXCLUSION CRITERIA

A subject who meets any of the criteria listed below (in the study eye, unless otherwise indicated) will be excluded from the study:

(All criteria apply to the study eye; both eyes of a single subject need not be eligible):

1. Any of the following prior treatments for glaucoma:

[28] For combination IOP-lowering medications that consist of two or more IOP-lowering drugs, each IOP-lowering drug component counts as a separate medication.

   - Laser trabeculoplasty ≤3 months prior to baseline
   - Implanted with iStent, Cypass, Xen, Express, glaucoma draining device/valve, or Hydrus Device
   - Prior canaloplasty, goniotomy, trabeculotomy, trabeculectomy, ECP or CPC
2. Normal tension glaucoma
3. Acute angle closure, traumatic, congenital, malignant, uveitic or neovascular glaucoma
4. Severe glaucoma as documented in subjects' medical record per ICD-10 guidelines
5. Use of oral hypotensive medication treatment for glaucoma
6. In the investigator's judgement, predisposed to significant risk because of washout of ocular hypotensive medications.
7. Ocular pathology or medical condition which, in the investigator's judgment, would either place the subject at increased risk of complications, contraindicate surgery, place the subject at risk of significant vision loss during the study period (e.g., wet AMD, corneal edema, Fuch's dystrophy, etc.), or interfere with compliance to elements of the study protocol (e.g., returning to investigator's office for follow-up visits)
8. Participation (≤ 30 days prior to baseline) in an interventional trial which could have a potential effect on the study outcome, as determined by the study investigator.
9. Women of childbearing potential if they are currently pregnant or intend to become pregnant during the study period; are breast-feeding; or are not in agreement to use adequate birth control methods to prevent pregnancy throughout the study

9 STUDY PROCEDURES

9.1 STUDY SCHEDULE

Table 1: Study Visit Schedule

Note: The fellow eye should be followed per the PI's usual practice based on the ocular health of the fellow eye.

PROCEDURE	SCREENING (DAY -45 TO -6)	BASELINE (DAY -7 TO 0)	SURGERY (DAY 0)	1 DAY (DAY 1)	1 WK (DAY 5-9)	1 M (DAY 21-35)	3 M (DAY 70-98)	6 M (DAY 150-210)	12 M (DAY 330-420)	12 M WASHOUT [29] (DAY 330-420)
Informed Consent	X									
Demographics	X									
Medical & Ocular History	X	X								
Medication Log	X	X	X	X	X	X	X	X	X	X
BCVA (ETDRS), with manifest refraction	X	X			X	X	X	X	X	
Visual Field (Humphrey 24-2 SITA)	X								X	
IOP (Goldmann)	X			X	X	X	X	X	X[30]	
Unmedicated diurnal IOP (Goldmann)		X							X[31]	X
Slit Lamp Exam	X	X		X	X	X	X	X	X	
Gonioscopy	X				X	X	X	X	X	
Dilated Fundus Exam/C:D Ratio	X								X	
Eligibility Assessment	X	X								
Cataract Extraction + ab-interno transluminal viscoelastic delivery and trabeculotomy			X							
AE Assessment	X	X	X	X	X	X	X	X	X	X

[29] The 12 month washout visit is only required for subjects who are taking hypotensive medications at the 12 month visit.
[30] This is only required for subjects who are taking hypotensive medications at the 12 month visit.
[31] If subject is not on any hypotensive medications, a diurnal IOP measurement should be obtained at the 12 month visit as unmedicated IOP.

9.2 NUMBER OF SUBJECTS, DURATION OF FOLLOW-UP AND STUDY DURATION

A total of 145 subjects will be enrolled in the study. Assuming a 40% screen failure rate, approximately 245 subjects will be enrolled and screened to obtain 145 enrolled and treated subjects. All subjects will be followed for 12 months.

It is anticipated that enrollment in the study will take approximately 12 months. Including the 12-month follow-up period, the study is expected to last 24 months.

9.3 INFORMED CONSENT AND POINT OF ENROLLMENT

The IRB-approved informed consent will be presented and explained to each prospective subject by the investigator or a trained clinical professional. Once the subject has had ample time to read the consent form, has been informed of all aspects of the study, and has had an opportunity to ask questions, the subject will be given a choice to voluntarily confirm his or her participation in the study as documented by completion of the Informed Consent. After signing the Informed Consent and the HIPAA (Health Insurance Portability and Accountability Act) authorization, the subject can then proceed with the screening visit. The subject has the right to withdraw from the study at any time without consequences, as indicated in the Informed Consent Document.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. Subjects are enrolled upon signing the ICD even if they subsequently fail to meet the eligibility criteria.

The principal investigator(s) must retain the original, signed written Informed Consent Document. A copy of the written Informed Consent Document must be given to the subject.

9.4 SCREENING VISIT

After obtaining an understanding of the purpose of this study, then reviewing and signing the Informed Consent Document, all potential subjects will undergo an initial screening examination in order to determine their eligibility for the study. Exams and tests listed in the Screening column of Table 1 should be performed. Refer to Appendix A for instructions for performing the exams.

If both eyes meet the applicable inclusion and exclusion criteria, the eye with higher IOP is recommended to be included in the study. In case of both eyes with same IOP at screening, investigator will select the study eye. The other eye will be excluded based on the first eye already being included in the study.

Once the study eye is identified, subjects will undergo the washout procedure described in Section 9.5 before the Baseline visit.

Note: If a subject does not meet the inclusion/exclusion criteria, he/she may be re-screened after 30 calendar days. Subject should be exited from the study and assigned another subject identification on second screening.

Exam data collected on subjects prior to enrollment as part of the routine clinical practice may serve as Screening data as long as it was collected within 15 days prior to the visit. The only exceptions to this are:

- IOP and IOP-lowering medications. These data must be collected at the Screening visit.
- Visual field: Visual Fields conducted per the protocol method (Humphrey 24-2 SITA standard) within 90 days of the Baseline visit may serve as the Baseline exam.

9.5 WASHOUT OF HYPOTENSIVE MEDICATIONS

Subjects who meet all screening eligibility criteria will be instructed to discontinue their ocular hypotensive medication regimen in the study eye only, and to return for a Baseline visit after completing the appropriate washout period. Glaucoma medication discontinuation can be staged (for patients on multiple medications) so that the pressure increase duration is minimized to the greatest possible extent during the washout period. For example, if a patient is on a prostaglandin (PGA) and a Carbonic Anhydrase Inhibitor (CAI), the PGA could be discontinued 4 weeks prior to the Baseline visit but the allowed to continue until 5 days before Baseline.

If the study subject fails to remember to not use ocular hypotensive medication for the study eye per the required washout period, they can be reinstructed to washout and return for the Baseline or 12-month washout IOP visit as long as it falls within the specified visit window.

The minimum wash-out periods are specified in Table 2 below. Note: The maximum washout period is 6 weeks. Therefore, if the study procedure cannot be scheduled within one week of the end of the washout period, the subject should be restarted on glaucoma medication until the Day 0 visit (but after the washed-out diurnal IOP has been obtained).

Table 2: Ocular Hypotensive Medication Washout Periods

Brand Name/Chemical Name	Minimum washout period
Carbonic Anhydrase Inhibitors	
Diamox® (Acetazolamide) – oral Rx	5 days
Neptazane® (Methazolamide) – oral Rx	5 days
Azopt® (Brinzolamide)	5 days
Trusopt® (Dorzolamide Hydrochloride)	5 days
Muscarinic Agonists	
Salagen, Pilocar (Pilocarpine)	5 days
Alpha Adrenergic Agonist	
Alphagan® (Brimonidine)	14 days
Iopidine® (Apraclonidine Hydrochloride)	14 days
Beta Blockers	
Betagan® (Levobunolol Hydrochloride)	28 days
Betoptic® (Betaxalol Hydrochloride)	28 days
OptiPranolol® (Metipranolol)	28 days
Timoptic/Betimol® (Timolol Maleate)	28 days
Prostaglandin Analogs	
Lumigan® (Bimatoprost)	28 days
Travatan® (Travoprost)	28 days
Xalatan® (Latanoprost)	28 days
Zioptan® (Tafluprost)	28 days
Vyzulta® (Latanoprostene Bunod)	28 days
Rho Kinase Inhibitor	
Rhopressa® (Netarsudil)	28 days
Combined Medications	
Combigan® (Brimonidine Tartrate/Timolol Maleate)	28 days
Cosopt® (Dorzolamide Hydrochloride/ Timolol Maleate)	28 days
Simbrinza® (Brinzolamide/Brimonidine Tartrate)	28 days
Other	Contact Sponsor

9.6 BASELINE VISIT

During the Baseline visit, the exams and tests listed in the Baseline column of Table 1 should be performed. Refer to Appendix A for instructions for performing the exams.

9.7 SURGICAL PROCEDURE

During the surgical procedure, cataract extraction should be performed following the surgeon's standard practice. Then, 360° ab-interno transluminal cohesive viscoelastic

delivery followed by 180° trabeculotomy[32] using the OMNI Surgical System should be performed only in eyes with uneventful cataract extraction. Eyes with complications related to cataract extraction or IOL implantation should be exited from the study. The region where the trabeculotomy procedure is performed (e.g. superior hemisphere) shall be recorded on the case report forms.

Surgeons should follow their standard peri-operative medication regimen. All the medications should be administered in the form of ocular drops. Any other means of medication administration such as intracameral or intravitreal routes should be avoided.

9.8 FOLLOW-UP VISITS

Follow-up visits should be performed according to the schedule provided in Table 1 (page 17). All attempts should be made to conduct each follow-up visit within the time interval specified in Table 1. Evaluations conducted outside the prescribed time period will be considered protocol deviations.

9.9 MANAGEMENT OF IOP AFTER SURGERY

This protocol recommends that no IOP-lowering medications should be administered to subjects after the surgery (0 meds on postop day 1) unless medically warranted. Investigators should use their clinical judgement in determining when and why IOP-lowering medications should be reintroduced and if a subject requires surgical re-intervention to manage IOP.

Re-introduction of hypotensive medications should follow the guidelines below:

- The same medication class(es) as used preoperatively should be re-introduced. Dependent on preoperative IOP medication use, the reintroduction/addition of IOP medications postoperatively should follow the order below:

  1. Prostaglandin Analogues
  2. Alpha Agonists
  3. Beta Blockers
  4. Rho Kinase Inhibitor
  5. Carbonic Anhydrase Inhibitors (CAIs)

- No more than one ocular hypotensive agent should be added at a single visit or within a 2-week period.

[32] 180° trabeculotomy should be attempted in every eye enrolled in the study. There is a possibility that 180° trabeculotomy may not be possible in each case.

In the event of a steroid response (IOP increase), the usual guidelines requiring a reproducible increase in IOP should be followed; however, topical hypotensive medications should be discontinued once the topical steroid has been discontinued.

If a pressure rise is observed, a paracentesis may be performed as necessary. If a paracentesis is performed and there is no protocol-defined adverse event, the paracentesis will be documented in the subject's medical record, the applicable visit CRF and the Ocular Procedures log. If, however, the paracentesis is performed in conjunction with an AE, then the AE is recorded as such, and the paracentesis is also recorded on the AE CRF as a treatment for the protocol-defined AE (as well as the other CRFs mentioned above).

Medications which have been re-started by the investigator may be discontinued if the investigator's judgment is that the target intraocular pressure has been reached and the continued use of some or all of the therapy may not be required. Discontinuation of medications after re-introduction is recommended to be in the reverse order of re-introduction. The rationale for discontinuation will also be documented on the follow-up form by the investigator.

A record of all ocular hypotensive medications added, discontinued or changed will be documented on the appropriate Case Report Form for each scheduled visit or on a Case Report Form for an Unscheduled Visit, if necessary.

Another potential reason for intervention is hypotony. Intervention should only be considered if the hypotony has caused or is likely to cause sequelae such as a flat chamber. No intervention is indicated when the vision is unchanged from screening, there is no persistent choroidal detachment, the anterior chamber is not flat with lens corneal touch, or the patient is asymptomatic. No intervention should be undertaken for hypotony which is not causing, or threatening to cause, a reduction in vision.

Secondary IOP-Lowering Interventions to Control IOP

If the subject requires another glaucoma procedure to control their IOP, the subject should continue to be followed according to standard of care until the adverse event resolves or 1 month post-re-intervention, whichever is longer. Following this, the subject should be withdrawn from the study.

Subjects who have a secondary IOP-lowering intervention will be considered treatment failures for the purpose of the secondary endpoint analyses. These subjects will be included in the Safety Endpoint analyses through their withdrawal from the study.

9.10 WITHDRAWAL AND DISCONTINUATION

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

If a subject withdraws from the study post-baseline but prior to surgery, then that subject may be replaced in the study by a newly enrolled subject.

9.11 SUBJECTS LOST TO FOLLOW-UP

Subjects who do not show up for a follow-up must be contacted to attempt to have them come for the follow-up. For those subjects who cannot be reached, at least 3 phone call attempts should be made and documented. If still no response, a registered letter shall be sent to the address on file for the subject in an attempt to make contact. If a subject misses two consecutive follow-up visits without any contact with the study staff, the subject will be considered lost-to-follow-up unless there is a further communication by the subject.

10 ADVERSE EVENTS (AES)

Adverse Events are defined below. Adverse events that occur in the eye during the trial, whether they are considered to be device related or not, must be documented in the subject's records. Date of the event, its severity, treatment (if any) and the assessed relationship of the event to the study device will be recorded on the Adverse Event Form. Conditions which exist at the time the subject is enrolled do not need to be recorded as adverse events unless they increase in severity during the study.

10.1 DEFINITIONS OF AE, SAE, SADE, USADE

Adverse Event	Any untoward medical occurrence in a subject who has been treated with the device that does not necessarily have causal relationship with the treatment.
Adverse Device Effect	Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that is possibly related to the study device.
Serious Adverse Event (SAE)	Any untoward medical occurrence that: • Results in death

	• Is life-threatening • Requires in-patient hospitalization or prolongs existing hospitalization • Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure • Sight threatening
Unanticipated Adverse Device Effect	Any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the clinical investigational plan; or any other serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)). Any sight-threatening event, whether listed in the protocol or not, is considered to be reportable as a UADE

10.2 LIST OF ANTICIPATED POTENTIAL ADVERSE EVENTS

Anticipated potential adverse events listed below include those that might reasonably be expected to occur in this study because they are associated with glaucoma, cataract surgery, ab-interno transluminal viscoelastic delivery, trabeculotomy, and/or the risk analysis for OMNI System. Adverse events may occur intra-operatively or post-operatively.

- Layered Hyphema ≥ 1mm (Microhyphema or Hyphema <1mm is expected and will not be considered an AE)
- IOP increase ≥ 10 mmHg above baseline IOP at ≥1 month visit[33]
- IOP increase requiring management with systemic medication at ≥1 month visit[32]
- Need for secondary surgical intervention to manage IOP[32]
- Hypotony (IOP <6 mmHg)[34] with at least one of the following conditions:
    a) Flat anterior chamber requiring anterior chamber reformation
    b) Corneal folds
    c) Choroidal effusions requiring or undergoing surgical drainage
    d) Suprachoroidal hemorrhage

[33] To avoid double counting an event, events of IOP ≥ 10 mmHg above baseline IOP at ≥1 month visit that require management with systemic medication or secondary surgical intervention should be reported as "IOP increase requiring management with systemic medication at ≥1 month visit" or "Need for secondary surgery intervention to manage IOP," respectively.

[34] Hypotony is defined as "early" if it occurs within 2 weeks of surgery and "late" if it occurs more than 2 weeks after surgery

e) Maculopathy

- Corneal injury
- Corneal edema after 1 week
- Corneal abrasion
- BCVA loss of ≥10 letters (ETDRS) at or after 3 months postoperative
- Descemet's membrane tear or detachment
- Chronic anterior uveitis (inflammation of grade 1+ or worse persisting for more than 3 months post-operatively or that recurs less than three months after discontinuing treatment)
- Wound leak
- IOL dislocation and/or damage
- Intracorneal Hematoma
- Posterior capsular tear
- Pupillary block
- Cyclodialysis
- Iridodialysis or significant iris damage
- Peripheral Anterior Synechiae >1 clock hour
- Suture abscess or other local infection
- Flat or shallow anterior chamber requiring anterior chamber reformation
- Aqueous misdirection
- Choroidal detachment
- Choroidal effusion requiring surgical drainage
- Choroidal hemorrhage
- Suprachoroidal hemorrhage
- Vitreous hemorrhage
- Perforation of sclera
- Clinically significant cystoid macular edema
- Retinal detachment
- Retinal tear
- Chronic pain present later than 3 months after the surgery
- Increase in C/D ratio of > 0.3 units compared to baseline on slit lamp exam
- TASS
- Endophthalmitis

10.3 Reporting Adverse Events and Unanticipated Adverse Device Effects

Identification, collection and reporting of adverse event information is the responsibility of the principal investigator. The investigator records the date of the event, its severity,

treatment (if any) and the assessed relationship of the event to the study device on the Adverse Event Case Report Form (AE CRF).

Any ocular-related **serious adverse event** (SAE) should be reported to the study sponsor within one working day of learning of the event. Non-ocular-related SAEs should be reported to the study sponsor within two working days of learning of the event. Email the AE CRF to [redacted]

Any **unanticipated adverse device effects (UADE)** must be reported to the following two entities:

1. The study sponsor – Within one working day of the investigator first learning of the event, e-mail the AE CRF to [redacted]; and
2. The reviewing IRB – As soon as possible, but no later than 10 working days after the investigator first learns of the event, report per the IRB's instructions.

The sponsor will conduct an evaluation of unanticipated adverse device effects. If the sponsor determines that an unanticipated adverse device effect presents an unreasonable risk to subjects, parts of the investigation presenting risks will be terminated. Termination will occur no later than 5 working days after the sponsor makes such a determination and no later than 15 working days after the sponsor first received notice of the effect.

11 STATISTICAL CONSIDERATIONS

11.1 HYPOTHESES AND SAMPLE SIZE CALCULATION

11.1.1 SAMPLE SIZE FOR THE PRIMARY EFFECTIVENESS ENDPOINTS

First Primary Effectiveness Endpoint

The first primary effectiveness endpoint is the reduction in the unmedicated diurnal IOP from baseline to 12 months postoperatively. The study objective is to show that the mean unmedicated diurnal IOP reduction of the study treatment (i.e. ab-interno transluminal viscoelastic delivery and trabeculotomy performed with OMNI system performed after uneventful cataract extraction) is superior to that of the cataract extraction alone. Based on recent approved MIGS studies, the mean ± SD unmedicated diurnal IOP reduction at 12 months for the cataract extraction alone is 6.7 mmHg ± 3.6 mmHg (N =118) for Glaukos P170043 and 6.3 mmHg ± 4.0 mmHg (N = 187) for Ivantis P160024. Therefore, the mean ± SD unmedicated diurnal IOP reduction at 12 months for the cataract extraction alone is estimated as 6.5 mmHg ± 3.8 mmHg.

The corresponding statistical hypotheses are as follows:

H0: $\mu_{OMNI} \leq 6.5$ mmHg and Ha: $\mu_{OMNI} > 6.5$ mmHg, where μ_{OMNI} is the mean unmedicated diurnal IOP reduction at 12 months for the OMNI Surgical System in combination with Cataract Extraction.

Based on a one-sample t-test with a one-sided significance level of 0.025 (or two-sided 0.05), a sample size of **116** eyes at 12 months provides a statistical power of 80% at a true μ_{OMNI} of 7.5 mmHg.

Second Primary Effectiveness Endpoint

The second primary effectiveness endpoint is the reduction in the number of IOP-lowering medications from screening to 12 months (before medications washed out if applicable) postoperatively.

The study objective is to show that the mean reduction in number of IOP-lowering medications of the study treatment at 12 months is not inferior to that of the cataract extraction alone. Based on P170043 and P160024, the mean ± SD of reduction in number of IOP-lowering medications at 12 months for the cataract surgery alone is 0.9 ± 0.8 and 1.1 ± 1.1, respectively. Therefore, the mean ± SD of reduction in the number of IOP-lowering medications at 12 months for the cataract surgery alone is estimated as 1.0 ± 1.0. A non-inferiority margin of 0.25 is considered. Therefore, a difference between the mean reduction in number of IOP-lowing medications for the cataract alone (1.0) and the mean reduction in number of IOP-lowing medications for the study treatment (MOMNI), 1.0 - MOMNI, of < 0.25 indicates that the study treatment is not inferior to the cataract alone in reducing the number of IOP-lowing medications.

The corresponding statistical hypotheses are as follows:

H0: $M_{OMNI} \leq 0.75$ and Ha: $M_{OMNI} > 0.75$ (i.e. $1.0 - M_{OMNI} < 0.25$).

Based on a one-sample t-test with a one-sided significance level of 0.025 (or two-sided 0.05), a sample size of 101 eyes at 12 months provides a statistical power of 80% at a true M_{OMNI} of 1.0 medication.

Sample Size for the Primary Effectiveness Endpoints

Both of the alternative hypotheses of the two primary effectiveness endpoints need to be achieved in order to prove the study treatment effect, so the significance level adjustment for the multiplicity is not performed for the primary effectiveness endpoints. Therefore, based on the two primary effectiveness endpoints discussed above, a sample size of 116 eyes at 12 months is needed. Considering a drop-out rate of about 10%, approximately 130 eyes should be enrolled and treated with the study treatment.

11.1.2 SAMPLE SIZE FOR THE SECONDARY EFFECTIVENESS ENDPOINT

The first secondary effectiveness endpoint is the 12-month outcome of ≥ 20% reduction in unmedicated diurnal IOP (medication washed out if applicable) from baseline. Based on P170043 and P160024, the percent of eyes achieving this outcome for the cataract surgery alone is 75.4% (89/118) and 70.1% (131/187). Therefore, the percent of cataract-surgery-alone eyes achieving this secondary effectiveness outcome is estimated as 73%. The corresponding statistical hypotheses are H0: $P1_{OMNI} \leq 0.73$ and Ha: $P1_{OMNI} > 0.73$, where $P1_{OMNI}$ is the probability of eyes achieving the first secondary effectiveness endpoint.

The second secondary effectiveness endpoint is the 12-month outcome of unmedicated diurnal IOP (medication washed out if applicable) of ≥6 mmHg and ≤ 18 mmHg. Based on P170043 and P160024, the percent of eyes achieving this outcome for the cataract surgery alone is 63.6% (75/118) and 47.6% (89/187). Therefore, the percent of cataract-surgery-alone eyes achieving this secondary effectiveness outcome is estimated as 55% (approximate average of 63.6% and 47.6%). The corresponding statistical hypotheses are H0: $P2_{OMNI} \leq 0.55$ and Ha: $P2_{OMNI} > 0.55$, where $P2_{OMNI}$ is the probability of eyes achieving the second secondary effectiveness endpoint.

The formal conclusion of the secondary effectiveness endpoints will not be determined if the primary effectiveness endpoints are not statistically significant. Meanwhile, the conclusion of the second secondary effectiveness endpoint will not be determined if the first secondary effectiveness endpoint is not statistically significant (i.e., using the step-down approach for the secondary effectiveness endpoint). Therefore the significance level is two-sided 0.05 or one-sided 0.025 for both of the secondary effectiveness endpoints.

Based on the binomial distribution with a one-sided significance level of 0.025 (or two-sided 0.05), a sample size of **105** eyes at 12 months provides a statistical power of at least 80% at a true $P1_{OMNI}$ of 0.85, and a sample size of **91** eyes at 12 month provides at least 80% at a true $P2_{OMNI}$ of 0.70. Therefore, at least **105** eyes at 12 months are needed for the secondary effectiveness endpoints.

11.1.3 SAMPLE SIZE OF THE STUDY

Based on the discussion in Section 11.1.1 and 11.1.2 the sample size for the effectiveness endpoints is **130** eyes treated with the study device with the cataract surgery.

With a sample size of 130 eyes, there is a probability of 95% to observe at least one incidence of a safety event with an event rate of about 2.4%.

In May of 2019, the study protocol was revised to require at least one ocular hypotensive medication at the screening for the study eyes. Since the study has treated

some eyes that did not have ocular hypotensive medications at screening, the planned sample size of the study is increased to approximately 145 eyes.

11.2 ANALYSIS POPULATIONS

The intent-to-treat (ITT) analysis population includes all subjects who are enrolled and treated, regardless of whether or not they have a protocol deviation. Due to the eligibility revision in May of 2019 on requiring at least one ocular hypotensive medication, the modified ITT (mITT) population includes all ITT except for the treated eyes that were not on any ocular hypotensive medication at the screening visit. The per-protocol analysis population (PP) is a subset of mITT, which includes all subjects who have taken at least one ocular hypotensive medication at screening and have uneventful cataract extraction followed by ab-interno transluminal viscoelastic delivery and trabeculotomy, 12 month IOP and medication data, and have no clinically significant protocol deviations. It should be noted that the mITT subjects with an uneventful study procedure but with SSIs before the 12-month visit will be included in the PP population even if they do not have the 12-month IOP and medication data. The primary analyses on the primary and secondary endpoint analyses will be carried out on the per-protocol population.

The safety data will be summarized based on the ITT population. The primary and secondary endpoint analyses will also be performed on the mITT population.

The data will be listed separately for the enrolled subjects that are not treated with OMNI and treated subjects that do not have ocular hypotensive medications at the screening.

11.3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic variables gender, race, ethnicity, and age will be summarized for all enrolled subjects treated with OMNI Surgical System, along with medical history. Descriptive statistical summaries of pre-treatment parameters (min, max, median, mean, standard deviation) will also be provided. The same analyses will be performed for the mITT and PP populations.

11.4 EFFECTIVENESS ENDPOINTS AND ANALYSIS METHODS

Descriptive statistics on continuous variables will include mean, standard deviation, median, minimum, and maximum. Confidence intervals for change from baseline will be included for selected endpoints. Categorical variables will be summarized using frequency counts and percentages. Exact confidence intervals for point estimates may be provided. Statistical testing will be one-sided with a significance level of 0.025 or two-sided significance level of 0.05) unless specify otherwise. Data listings of individual subject data may be provided.

As described above, the primary analyses of the primary and secondary effectiveness endpoints will be based on the PP population (Section 11.2), although the analyses will also be performed on the mITT population. The safety data will be summarized based on the ITT population.

11.4.1 PRIMARY EFFECTIVENESS ENDPOINTS

The IOP reduction from baseline to 12 months postoperatively and the reduction in number of IOP-lowering medications from baseline to 12 months will be calculated for each eye and summarized descriptively. The 95% confidence interval of the mean reduction will be derived based on the t-distribution. The one-sample t-test will be performed for testing the statistical hypotheses described in Section 11.1.1. It should be noted that, for eyes with secondary surgical interventions (SSI) to control IOP or with SSI that can affect the IOP before 12 months, the last available observed data before the SSI will be used to impute the 12-month data. For the analyses based on the mITT population, the following imputation for subjects with missing 12-month data but without SSI may be performed:

- The within-eye worst IOP (collected after 3 months postoperatively or IOP at baseline for the subjects with no data after postoperative 3 months) for the missing 12-month IOP and worst number of IOP lowering medications (collected after 3 months postoperatively or IOP-lowering medication data at baseline for the subjects with no data after postoperative 3 months) for the missing 12-month number of IOP-lowering medications.
- The worst IOP (collected after 3 months postoperatively or IOP at baseline for the subjects with no data after postoperative 3 months) during the study for the missing 12-month IOP and worst number of IOP-lowering medications (collected after 3 months postoperatively or IOP-lowering medication data at baseline for the subjects with no data after postoperative 3 months) during the study for the missing 12-month number of IOP-lowering medications.
- The mean IOP during the study for the missing 12-month IOP and mean number of IOP-lowering medications during the study for the missing 12-month number of IOP-lowering medications.
- The last-observed-carry-forward approach.

11.4.2 SECONDARY EFFECTIVENESS ENDPOINT

The number and percent of eyes achieving the secondary effectiveness endpoint will be calculated. The binomial distribution will be used to derive the exact 95% confidence interval of the percent and to perform the statistical hypotheses for the secondary effectiveness endpoint described in Section 11.1.2. It should be noted that, for eyes with secondary surgical interventions (SSI) to control IOP or with SSI that can affect the

IOP before 12 months, the non-responder (i.e. do not achieve the secondary effectiveness endpoint) will be assumed for the missing 12-month response.

For the analyses based on the mITT population, the IOP and number of IOP-lowering medications imputation for missing data described in Section 11.4.1 will used to derive the corresponding response of the secondary effectiveness endpoint.

11.4.3 COVARIATE ANALYSIS

The following variables will be examined for their prognostic value to the primary and secondary effectiveness endpoints using the PP population with the imputation used for the IOP-related SSIs:

- Age group (based on observed quartiles)
- Gender (male and female)
- Race (White and non-White)
- Ethnicity
- Baseline IOP group (based on observed quartiles)
- Screening Number of IOP-lowing medications (1, 2, 3 and 4)
- Study site

For the primary effectiveness endpoints, one-way ANOVA with one of the factors listed above will be used to check the possible covariate effects. For the secondary effectiveness endpoint, Fisher's test will be performed. A p-value of 0.15 will be used for evaluating the possible covariate effects.

11.4.4 ADDITIONAL EFFECTIVENESS ANALYSES

The analyses will be based on the PP population.

- The IOP, change in IOP, percent change in IOP, number of IOP-lowing medications, and change in number of IOP-lowing medications will be summarized descriptively at each visit along with the 95% confidence intervals based on the t-distribution.
- The outcome of $\geq$ 20% reduction in IOP with no IOP-lowering medications at each visit will be summarized by count and percent of eyes achieving the outcome.
- The outcome IOP of $\geq$6 mmHg and $\leq$ 18 mmHg with no IOP-lowering medications at each visit will be summarized by count and percent of eyes achieving the outcomes.
- The distribution of 12-month unmedicated diurnal IOP percent change from baseline will be prepared for the following categories stratified by the number of IOP-lowing medication change from baseline and the IOP-related SSIs:
  - 40% ≤ Change (i.e. increase ≥ 40%)
  - 30% ≤ Change < 40% (i.e. 30% ≤ increase < 40%)

- 20% ≤ Change < 30% (i.e. 20% ≤ increase < 30%)
- 10% ≤ Change < 20% (i.e. 10% ≤ increase < 20%)
- 0% < Change < 10% (i.e. 0% < increase < 10%)
- Change = 0% (i.e. no change)
- -10% < Change < 0% (i.e. 0% < decrease < 10%)
- -20% < Change ≤ -10% (i.e. 10% ≤ decrease < 20%)
- -30% < Change ≤ -20% (i.e. 20% ≤ decrease < 30%)
- -40% < Change ≤ -30% (i.e. 30% ≤ decrease < 40%)
- -50% < Change ≤ -40% (i.e. 40% ≤ decrease < 50%)
- Change ≤ -50% (i.e. decrease ≥ 50%)

- The distribution of 12-month unmedicated diurnal IOP will be prepared for the following categories stratified by the number of IOP-lowing medication change from baseline and the IOP-related SSIs:
  - ≥6 mmHg to ≤ 21 mmHg
  - ≥6 mmHg to ≤ 18 mmHg
  - ≥6 mmHg to ≤ 15 mmHg
  - ≥6 mmHg to ≤ 12 mmHg
- The survival analysis (Kaplan Meier curve) for the time to the first IOP-related SSIs will be performed. The survival analysis will also be performed for the time to first take the systemic IOP-lowering medications

11.5 SAFETY ANALYSIS

All safety analyses will be performed on the ITT population based on all available data.

11.5.1 ADVERSE EVENT

Adverse events (AEs) will be classified as intraoperative or postoperative. The number and the percent of eyes reporting at least 1 adverse event of a given type will be summarized. Additionally, the number of reports of each type of AEs will be provided.

For each AE, the number and the percent of eyes reported with the event will be summarized by the severity level. For eyes with multiple reports of the same type of AE, the maximum severity will be used. Similarly, the AE relationship to the procedure will be summarized. For eyes with multiple reports of the same type of AE, the closest relationship to the procedure will be used.

11.5.2 BEST CORRECTED VISUAL ACUITY (BCVA)

The number and percent of eyes reporting with BCVA of 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, worse than 20/40 to 20/80, worse than 20/80 to 20/200, and worse than 20/200 at each visit will be summarized. The number and

percent of eyes reporting BCVA of increase ≥ 10 letters, increase 10 letters, increase ≥ 5 letters to < 10 letters, within 5 letters change, decrease ≥ 5 letters to < 10 letters, decrease 10 letters, and decrease ≥ 10 letters at each postoperative visit will be calculated.

11.5.3 OTHER SAFETY OUTCOMES

The number and percent of eyes reported with each kind of slit lamp findings, gonioscopy findings, and dilated fundus examination findings at each visit will be provided.

The descriptive statistics for the continuous variables will be derived for the visual field mean deviation (MD) and pattern standard deviation (PSD).

11.6 INTERIM ANALYSES

The primary analysis for this study will occur after the final subject reaches their 12-month follow-up. Endpoints listed below will be analyzed at an interim analysis performed when at least 50% subjects complete 6 month follow-up and when 100% patients complete 6 month follow-up.

Effectiveness endpoints:

1. Reduction in mean IOP from screening visit; and
2. Reduction in mean number of IOP-lowering medications from screening visit
3. Percent of eyes with a ≥20% reduction in IOP with no increase in IOP-lowering medications compared to screening visit
4. Percent of eyes with IOP between 6 and 18 mmHg with no increase in IOP-lowering medications compared to screening visit

Safety endpoints:

1. Rates of ocular adverse events (intraoperative, postoperative)
2. Reduction in best corrected visual acuity (BCVA) from baseline (note: reduction in BCVA due to PCO will not be treated as a safety event)

It is noteworthy that the two interim analyses are based on the 6-month measurements, not the washout IOP at 12 months for the primary and secondary effectiveness endpoint. Additionally, the interim analyses are not for claiming effectiveness of the study device and the study will not be terminated due to the 6-month outcomes. Therefore, the study p-values are not adjusted for the planned interim analyses.

11.7 DEVIATION FROM THE STATISTICAL PLAN

Any deviations from the statistical plan will be noted in the final report.

12 MONITORING PROCEDURES

Sight Sciences or contract research organization (CRO) personnel will monitor the study in a manner consistent with FDA regulations, good clinical practices and the clinical research standards adopted by Sight Sciences. Study monitoring will involve the following elements:

- Site Qualification: Sight Sciences or CRO personnel will meet with investigators and clinical study staff prior to the initiation of the study in order to review the adequacy of the subject population, facilities, and equipment with respect to the needs of the study, and to familiarize the investigator with the study protocol. If Sight Sciences or the CRO have recently been involved with an investigator for another study, a site qualification visit may not be necessary.
- Site Initiation: Sight Sciences and/or CRO personnel will meet with the investigator(s) and clinical study staff when the site is ready to begin enrolling subjects in order to train them in how to properly select subjects, perform the study procedure, and record study data. This visit will include, but not be limited to a review of the following:
  - Detailed review of the protocol
  - Informed consent procedures
  - Instructions for the surgical procedure
  - Records and reports
- Interim Monitoring: Sight Sciences or CRO personnel will visit the clinical site routinely during the study to review charts and to perform source document verification, to ensure proper adherence to the study protocol, and to review regulatory documents. Interim monitoring visits and telephone consultation will occur as necessary during the course of the study to ensure the proper progress and documentation of the study findings.
- Study Closure: At the conclusion of the trial there will be a study closure visit during which several actions, including but not limited to the following, will be performed:
  - A final inspection of the study binder
  - Accountability and return of all devices and study materials to the sponsor
  - Discussion of record retention requirements with the investigator
  - Close-out notification to the IRB

13 DATA AND QUALITY MANAGEMENT

13.1 DATABASE MANAGEMENT

The study database will be designed using an electric data capture (EDC) system that is compliant with 21 CFR Part 11 and relevant guidance documents. The EDC will be developed and maintained by an independent, qualified data management firm.

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

13.2 SUBJECT IDENTIFICATION

The subjects will be identified by a five-digit subject number composed of a one-digit study identification number, a two-digit center identification number followed by a two-digit sequential subject number. The subject identification will be assigned when informed consent is obtained. In this way, information contained in the study records will be kept as confidential as possible.

13.3 SUBJECT ACCOUNTABILITY

All subjects enrolled and treated in this clinical investigation shall be monitored for the duration of the investigation. The clinical investigation shall be considered completed when all subjects that have been enrolled in the investigation have reached the final reporting period, excluding subjects who were withdrawn.

13.4 CONFIDENTIALITY

All medical records associated with the clinical investigation will be made available for review by Sight Sciences personnel, its contract research organization (CRO) and governmental/regulatory agencies involved. The results of the study may be published in the future for scientific and marketing purposes, but the identity (name) of each subject will not be revealed. All records will be stored in a secure area at the investigator's facility, the CRO, the data management firm and at Sight Sciences, Inc.

13.5 SOURCE DATA AND CASE REPORT FORMS

Source data will be entered into a validated electronic system at each site by trained personnel in accordance with 21 CFR Part 11 requirements. Electronic entries will be 100% verified against corresponding source data at the sites and queried/corrected if needed to the extent possible. Medical site records serve as source data. In addition,

data that are collected exclusively for the purpose of this study and not normally recorded in the subjects' medical records can be collected directly on the study worksheets provided by the sponsor and these study worksheets will serve as the source data.

Source data and study worksheets are to be maintained at the site in the subject records or in the medical records. All entries must be made in black or blue ink and changes must be made by strike-through only with date and initials or signature. All source documents must be completed and signed by the authorized study personnel (e.g., study coordinator). No "white-out" is to be used on the source documents.

13.6 RETENTION PERIOD

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

14 PROTOCOL MODIFICATIONS AND DEVIATIONS

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

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

All protocol deviations will be documented using the Protocol Deviation form.

15 DEVICE FAILURES AND MALFUNCTIONS

All device failures or malfunctions should be recorded on the Device Deficiency Form and reported to Sight Sciences Customer Service [redacted]

16 ETHICAL CONSIDERATIONS

16.1 DECLARATION OF HELSINKI

This study shall be conducted in accordance with the Declaration of Helsinki (Appendix D).

16.2 INSTITUTIONAL REVIEW BOARDS (IRB)

The study shall not begin at a site until approval has been obtained from the reviewing IRB. It is the Investigators' responsibility to obtain and maintain written approval of the study protocol and Informed Consent documents from the appropriate IRB. It is also the Investigators' responsibility to notify that body about any amendments to these documents and to follow the IRBs rules regarding the reporting of Adverse Events and Protocol Deviations related to the device and/or this study. Copies of all written approvals (identifying the study, the submitted and approved documents and the date reviewed) and the approved versions of the documents must be provided to Sight Sciences or its CRO.

The Investigators must file all correspondence with the IRB and forward copies of such correspondence to Sight Sciences.

16.3 INFORMED CONSENT FORM (ICF)

An Informed Consent template that covers all protocol procedures and follows GCP Guidelines will be prepared by Sight Sciences and made available to each Investigator. The Investigator may adapt these templates to the requirements of the local IRB and of the institution where the study is conducted, but any revisions made to the ICF must be submitted to the sponsor for review prior to submission to the IRB. A copy of each IRB-approved ICF version is to be made available to Sight Sciences and its CRO. The approved, IRB-stamped ICF is to be kept in its full length in the study Regulatory Binder. Original, signed ICFs are to be maintained in the subject's study records and must be made available for monitoring review.

16.4 PUBLIC LISTING OF STUDY

The study will be listed on the NIH website www.clinicaltrials.gov.

17 STUDY ADMINISTRATION

17.1 EARLY TERMINATION OR SUSPENSION OF THE STUDY OR AN INVESTIGATIONAL SITE

Sight Sciences may terminate the study, in which case the investigators and associated IRBs will be notified in writing. Possible reasons for study termination include but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the study subjects implanted with the device
- Withdrawal of FDA clearance of the OMNI device.
- Insufficient enrollment in the study

Sight Sciences reserves the right to stop the study at a particular site any time after the initiation visit if there have been no subject enrollments or if there have been significant protocol deviations/violations at the site.

Likewise, a principal investigator may terminate the study at his/her institution. This decision must be followed by written notification to Sight Sciences within five working days, stating the reasons for termination.

If the study is terminated, every effort should be made to obtain final follow-up from all subjects.

In the event that there are significant human use issues with the device, the investigator will be consulted to make a determination of whether the study should be terminated or not.

17.2 INVESTIGATOR RESPONSIBILITIES

17.2.1 GENERAL RESPONSIBILITIES OF INVESTIGATORS

An Investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations, for protecting the rights, safety, and welfare of subjects under the Investigator's care, and for the control of devices under investigation. An Investigator also is responsible for ensuring that informed consent is obtained in accordance with 21 CFR part 50.

17.2.2 SPECIFIC RESPONSIBILITIES OF INVESTIGATORS

1. Awaiting approval - An Investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB approval.

2. Subject Qualification -The Investigator is responsible for ensuring that all subjects entering the study conform to the subject selection criteria.

3. Compliance - An Investigator shall conduct an investigation in accordance with the signed agreement with the Sponsor, the investigational plan, all applicable FDA regulations, and any conditions of approval imposed by an IRB.

17.2.3 INVESTIGATOR RECORDS

A participating Investigator shall maintain the following accurate, complete, and current records relating to the Investigator's participation in an investigation for the period specified in Section 13.6:

1. All correspondence with another Investigator, an IRB, the Sponsor, a monitor, or FDA, including required reports.

2. Records of each subject's case history and exposure to the device. Case histories include the study CRF's/worksheets and supporting data including, for example, signed and dated consent forms and medical records. Such records shall include:

    a) Documents evidencing informed consent.

    b) All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

3. The protocol, with documents showing the dates and reasons for each deviation from the protocol.

4. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

17.2.4 INVESTIGATOR REPORTS

An Investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects - An Investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.

2. Withdrawal of IRB Approval - An Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.

3. Progress - An Investigator shall submit progress reports on the investigation to the Sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
4. Deviations from the Investigational Plan - An Investigator shall document and report to the Sponsor any deviation from the investigational plan.
5. Informed Consent - If an Investigator enrolls a subject without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.
6. Final Report - An Investigator shall, within 3 months after termination or completion of the investigation or the Investigator's part of the investigation, submit a final report to the Sponsor and the reviewing IRB.
7. Other - An Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

17.3 INVESTIGATOR AGREEMENT

The principal investigators in each center shall agree to the clinical protocol and any amendments and indicate their approval and agreement by signing and dating the cover page of the study protocol and the Investigator Responsibility Agreement.

18 PUBLICATION POLICY

Sight Sciences recognizes the value of disseminating research results. It is understood that the Study is part of the Multi-Center Clinical Trial and publication of results is expected. This publications policy applies to journal articles, conference abstracts, and conference presentations (posters and slides) covering Sight Sciences-sponsored clinical studies. This policy is in addition to any arrangement contained in the Clinical Trial Agreement between Sight Sciences and the investigator.

<u>Multi-Site Data</u>
Clinical site investigators are encouraged to propose publications and abstracts that include clinical or research data from multiple clinical sites; such projects will be coordinated by Sight Sciences. Authorship of papers and abstracts resulting from these projects will be determined collaboratively according to the following guidelines:

- The first author on such publications will be the person who primarily wrote the paper and took the lead on the research. In the case of clinical trial papers where all authors contributed equally, authorship order may be based on site enrollment or other criteria at Sight Sciences' discretion.
- Other authors include those who significantly contributed to the specific work.
- At least one person from each clinical site whose study subjects appear in the work will be acknowledged in the manuscript/presentation in some way, either

as an author group member, a non-author contributor, or listed in the acknowledgements, depending on the particular policies of the journal or conference.

Single Site Data

After publication of the multi-center study results in a peer-reviewed journal, or if Sponsor has not submitted a manuscript for publication in a peer-reviewed journal within twelve (12) months after the study has been completed, whichever occurs first, Investigators may publish the results of the Study generated by the Investigator, subject to the obligations of the Clinical Trial Agreement between Sight Sciences and the Investigator, and the prior approval of Sponsor in writing.

Publications Review Policy

Investigators must submit all presentations, posters, abstracts and manuscripts pertaining to this study to Sight Sciences for review in advance of their submission. Sight Sciences conducts this review to protect its proprietary rights to information, inventions, or products developed under the Study. Please use the following guideline to determine the absolute minimum advance time for submitting an item to Sight Sciences for review:

- Presentations/Posters: 5 business days in advance of presentation
- Abstracts: 5 business days in advance of submission
- Manuscripts: 30 calendar days in advance of submission for publication

In accordance with the Clinical Trial Agreement, these items must receive written approval from Sight Sciences in order for them to be submitted or presented. If an item is not received in the timeframe listed above, approval may not be granted due to insufficient time for considered review. In addition, since most of our Clinical Trial Agreements require that Sight Sciences has 60 days to review publications, Sight Sciences reserves the rights granted in those Agreements if circumstances require a longer review.

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20 APPENDIX A – METHODS FOR EXAMS, TESTS AND QUESTIONNAIRES

20.1 LIST OF STUDY PROCEDURES

1. Informed Consent
2. Demographics, Medical & Ocular History
3. Medication Log
4. BCVA
5. Visual Field (Humphrey 24-2 SITA)
6. IOP (Goldmann Tonometry)
7. Unmedicated Diurnal IOP
8. Slit Lamp Exam
9. Gonioscopy
10. Dilated Fundus Exam/C:D Ratio
11. Eligibility Assesment
12. Cataract Extraction + ab-interno transluminal viscoelastic delivery + Trabeculotomy
13. AE Assessment

20.2 SEVERITY OF GLAUCOMA

Severity of glaucoma is graded as documented in subjects' medical charts using the coding guidelines shown in Figure 3.

Figure 3: AAO/AGS/ICD-10 Glaucoma Stage Definitions

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AGS

GLAUCOMA STAGE DEFINITIONS

Mild or Early Stage Glaucoma

ICD-10 7th digit "1"

- Optic nerve abnormalities consistent with glaucoma
- but NO visual field abnormalities on any visual field test
- OR abnormalities present only on short-wave-length automated perimetry or frequency doubling perimetry

Moderate Stage Glaucoma

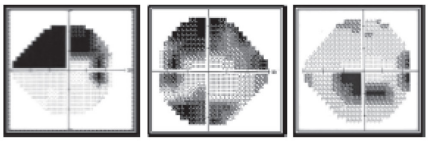
ICD-10 7th digit "2"

- Optic nerve abnormalities consistent with glaucoma
- AND glaucomatous visual field abnormalities in ONE hemifield and
- NOT within 5 degrees of fixation (note: 5 degrees = involvement of spots nearest fixation)

Advanced, Late, Severe Stage

ICD-10 7th digit "3"

- Optic nerve abnormalities consistent with glaucoma
- AND glaucomatous visual field abnormalities in BOTH hemifields
- AND/OR loss within 5 degrees of fixation in at least one hemifield



Indeterminate Stage

ICD-10 7th digit "4"

- Visual fields not performed yet
- Patient incapable of visual field testing
- Unreliable/uninterpretable visual field testing

Unspecified

ICD-10 7th digit "0"

- Stage not recorded in chart
- Remember to document stage in record!

ICD-10

For ICD-10, not all glaucoma diagnoses require the use of Staging at the 7th digit.

These are the Codes in ICD-10 that **do not have a laterality digit: Code the Stage for the most severely affected eye, if required in the 7th digit.**

1. Unspecified open-angle glaucoma **H40.10-** (Requires Stage digit for most severely affected eye)
2. Unspecified primary angle-closure glaucoma **H40.20-** (Requires Stage digit for most severely affected eye)
3. Other specified glaucoma **H40.89** (Stage is not used)
4. Unspecified glaucoma **H40.9** (Stage is not used)

Risk Factors for OAG Suspect Codes

- African American or Hispanic race
- Family history of glaucoma in 1st degree relative
- Thin central corneal thickness
- High IOP
- Pseudoexfoliation or pigment dispersion syndrome

≥ 3 risk factors = high risk
≤ 2 risk factors = low risk

Publication Date: February 2015 **Revised: August 2017**

20.4 VISUAL ACUITY

ETDRS Testing Method
Best-corrected visual acuity at Baseline and all scheduled follow-up visits will be measured using the ETDRS charts at 1 or 4 meters.

The ETDRS chart must be placed at a distance of 4.00 meters (13 feet and 1.5 inches, or 157.5 inches) from cornea to chart surface, when using a 4-meter chart. For the patients unable to read the topmost line of 4.00 meter chart VA testing should be done using 1 meter chart. For testing at 1 meter, the distance must be 1.00 (39 and 3/8 inches). A measuring tape or meter stick should always be available to verify the chart distance, even if the examining chair is supposed to be immovable or if reference marks are placed on the floor or walls. (Custodial and other staff have been known to move room furnishings about and clean-off marks from the floor or wall while performing their duties, necessitating re-establishing the correct distances for the lane.)

The 1-meter distance is measured from the eye of the participant, seated comfortably in a chair with his/her back firmly placed against the chair, to the center of the 2nd or 4th letter of the 3rd line of the chart. The measuring device can be homemade (e.g., a dowel rod accurately cut to a length of 1.00 m) or 1 meter ruler may be purchased.

Note: If it is necessary to refract at the 1-meter distance, remember to add +0.75 sphere to the trial frame. Subtract the +0.75 sphere from the final refraction obtained at the 1-meter distance before recording the refraction on the form.

Methods

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

A maximum effort should be made to identify each letter on the chart. When the subject says he/she cannot read a letter, the subject should be encouraged to guess. If the subject identified two (2) letters (e.g., A or B), the subject should be asked to choose one letter and, if necessary, to guess. When it becomes evident that no further meaningful readings can be made despite encouragement to read or guess, the examiner should stop the testing for that eye. However, all letters on the last line should be attempted as letter difficulties vary and the last letter may be the only one read correctly. The number of letters missed or read incorrectly should be noted.

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

Recording and Scoring Best-Corrected Visual Acuity

Using the Visual Acuity Worksheet, circle each letter the subject identifies correctly, write total correct for each row in the place provided, and compute the total correct for all rows. Do not mark letters read incorrectly or not read at all. Each letter read correctly is recorded as one. Only move to the next line if 4 or more letters are read correctly.

The number of correct letters will be recorded on the study worksheets and entered into the EDC.

20.5 MEASUREMENT OF INTRAOCULAR PRESSURE

Each time IOP is measured, the physician or technician should use a Goldmann tonometer. Take two measurements of IOP. If the measurements differ by more than 2 mmHg, take a third measurement. If two measurements are taken, record the mean on the case report form. If three measurements are taken, record the median on the case report form.

At all scheduled visits every attempt should be made to have these measurements taken at the same time interval to minimize the effect of daily fluctuations in pressure.

Guidelines for performing Goldmann tonometry are as follows:

1. The subject is told the purpose of the test and is reassured that the measurement is not painful. The subject is instructed to relax, maintain his or her position, and hold his or her eyes open widely.
2. One drop of a topical anesthetic, such as 0.5% proparacaine or 0.4% benoxinate, is placed in each eye, and the tip of a moistened fluorescein strip is touched to the tear layer on the inner surface of each lower lid. Alternatively, one drop of a combined anesthetic-fluorescein strip is touched to the tear layer on the inner surface of each lower lid. The tonometer and prism are set in correct position on the slit lamp.
3. The tension knob is set at 1 g. If the knob is set at 0, the prism head may vibrate when it touches the eye and damage the corneal epithelium. The 1 g position is used before each measurement. As a rule, it is more accurate to measure intraocular pressure by increasing rather than decreasing the force of applanation.
4. The 0 graduation mark of the prism is set at the white line on the prism holder. If the subject has more than 3 diopters of corneal astigmatism, the

area of contact between the cornea and the prism is elliptic rather than circular. In this situation the prism should be rotated to 45 degrees from the long axis of the ellipse-that is, the prism graduation corresponding to the least curved meridian of the cornea should be set at the red mark on the prism holder. An alternative approach is to average the intraocular pressure readings obtained with the axis of the prism horizontal and then vertical.

5. The cobalt filter is used with the slit beam opened maximally. The angle between the illumination and the microscope should be approximately 60º. The room illumination is reduced.
6. The subject is seated in a comfortable position on an adjustable stool or examining chair facing the slit lamp. The heights of the slit lamp, chair and chin rest are adjusted until the subject is comfortable and in the correct position for the measurement. The subject's chin is supported by the chin rest and the forehead by the forehead bar. The forehead bar should be well above the subject's eyebrows so the frontalis muscle can be used to open the eyes widely. The subject's collar and tie should be loosened if necessary. The subject should breathe normally during the test to avoid Valsalva's maneuver.
7. The palpebral fissure is a little wider if the subject looks up. However, the gaze should be no more than 15° above the horizontal to prevent an elevation of intraocular pressure that is especially marked in the presence of restrictive neuromuscular disease. A fixation light may be placed in front of the fellow eye. The subject should blink his eyes once or twice to spread the fluorescein-stained tear film over the cornea and then should keep his eyes open widely. In some subjects it is necessary for the examiner to hold the eyelids open with the thumb and forefinger of one hand. Care must be taken not to place any pressure on the globe because this raises intraocular pressure.
8. The operator sits opposite the subject in position to look through the microscope. The clinician moves the assembly toward the subject. When the black circle near the tip of the prism moves slightly, it indicates contact between the prism and the globe.
9. Alternatively, the assembly is advanced toward the subject until the limbal zone has bluish hue. The biprism should not touch the lids or lashes because this stimulates blinking and squeezing. Touching the lids also thickens the fluorescein rings, which may cause an overestimation of intraocular pressure.
10. The clinician observes the applanation through the biprism at low power. A monocular view is obtained of the central applanated zone and the surrounding fluorescein stained tear film. Using the control stick, the observer raises and lowers and centers of the assembly until two equal semicircles are seen in the center of the field of view. If the two semicircles are not equal in size, intraocular pressure is overestimated. The clinician turns the tension knob in both directions to ensure that the instrument is in good position. If the semicircles cannot be made "too small," the instrument

is too far forward. If the semicircles cannot be made "too large," the instrument is too far from the eye.

11. The fluorescein rings should be approximately 0.25 to 0.3 mm in thickness, that is, one tenth the diameter of the flattened area. If the rings are too narrow, the subject should blink two or three times to replenish the fluorescein; additional fluorescein may be added if necessary. If the fluorescein rings are too wide, the subject should dry his eyes lightly with a tissue, and the front surface of the prism should be dried with lint-free material. An excessively wide fluorescein ring is less of a problem than a very narrow ring but can cause the intraocular pressure to be overestimated.
12. The fluorescein rings normally undergo a rhythmic movement in response to the cardiac cycle. The tension knob is rotated until the inner borders of the fluorescein rings touch each other at the midpoint of their pulsations. The intraocular pressure is the mean of these 2 readings.
13. Intraocular pressure is measured in the study eye twice. If the 2 readings differ by 2 mmHg or less the average is the IOP. If the 2 readings differ by > 2 mm Hg, a third reading is taken.
14. The reading obtained in grams is multiplied by 10 to give the intraocular pressure in millimeters of mercury. This value is recorded along with the date, time of day, list of ocular medications, and time of last instillation of ocular medication if IOP is measured on different days, an attempt should be made to standardize the time.

Errors in measurement can arise from a number of factors, including the following:

1. Inadequate fluorescein staining of the tear film causes an underestimation of intraocular pressure.
2. Elevating the eyes more than 15° above the horizontal causes an overestimation of intraocular pressure. Widening the lid fissure excessively causes an overestimation of intraocular pressure.
3. Repeated tonometry reduces intraocular pressure, causing an underestimation of the true level. This effect is greatest between the first and second readings, but the trend continues through a number of repetitions.
4. A scarred, irregular cornea distorts the fluorescein rings and makes it difficult to estimate intraocular pressure.
5. The thickness of the cornea affects intraocular pressure readings. If the cornea is thick because of edema, intraocular pressure is underestimated. If the cornea is thick because of additional tissue, intraocular pressure is overestimated. The Goldmann tonometer is accurate after epikeratophakia.
6. If the examiner presses on the globe or if the subject squeezes his eyelids, intraocular pressure is overestimated.

7. If corneal astigmatism is greater than 3 diopters, intraocular pressure is underestimated for with the rule astigmatism and overestimated for against the rule astigmatism. The intraocular pressure reading is inaccurate 1 mm Hg for every 3 diopters of astigmatism.

Calibration and Documentation
The calibration of the tonometer will be checked at least once every three months with the weight system at 0, 2, and 6 grams as supplied by the manufacturer. When the calibration steps provide readings within ± 2 mmHg of the target value for each weight, the tonometer is considered adequately calibrated. However, if the variation exceeds this amount, a different adequately calibrated instrument should be used for IOP measurements.

The investigator must maintain written documentation in a log (hardcopy or electronic format acceptable) of the calibration of each tonometer used at the beginning and throughout the study period, and make these records available to study monitors for review. Documentation must describe the unit (by model and serial number or other permanent identifier), the date of each calibration, the name or initials of the person performing the calibration, and an indication as to whether or not the unit passed the calibration. If not calibrated successfully, a note should be entered in the log about contacting the authorized manufacturer's representative for repair and what repairs were required. Following any repair, another calibration should be documented prior to clinical use.

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

20.6 VISUAL FIELD EXAMINATION

Visual fields must be automated threshold visual fields, 24-2 Humphrey Stimulus III. The SITA Standard must be used for the visual field conducted at the pre-operative evaluation and all subsequent evaluations. Visual fields must be reliable at screening for eligibility, defined as less than 33% false positives, false negatives, and fixation losses. A visual field done within 90 days prior to the subject informed consent date and in accordance with the 24-2 SITA Standard requirements can be used for the baseline evaluation. For visual fields that do not meet the reliability standards, the test should be repeated within two weeks.

Visual fields are to be performed with a non-dilated pupil unless, in the opinion of the investigator, the pupil is so miotic that dilation is required (e.g., < 3mm). If dilation was performed at screening, it should be performed at all subsequent visual field

examinations. However, dilation should not be performed before the IOP measurement on the appropriate visits.

It is recommended that the following set up occur for the visual field:
SITA Standard 24-2 test

- using the white, size III stimulus,
- Foveal Threshold ON,
- Head Tracking ON and
- Vertex Monitoring OFF.

The appropriate trial lens as defined by the perimeter should be used.

20.7 DILATED FUNDUS EXAMINATION

A mydriatic should be used to dilate the pupil so that an examination of the fundus can be conducted with an indirect ophthalmoscope and slit lamp biomicroscopy (with contact lens, Hruby lens or 60-, 66-, 78-, or 90 diopter lens). The appearance of the optic disc, macula, vessels and periphery should be evaluated and reported on the Baseline form. A measurement of the cup to disc ratio should be made and reported.

20.8 SLIT LAMP EXAMINATION

The clinician will examine the conjunctiva, cornea, anterior chamber, lens and anterior vitreous of the eye with the aid of a slit lamp, which is a table-mounted binocular microscope. Fluorescein dye will be instilled into the ocular cul-de-sac to facilitate this examination. In addition to the following, any evidence of pigment dispersion visible in slit lamp examination should be evaluated and noted.

Iris

Findings of Atrophy/Erosion; Peaking; and Rubeosis should be noted. Each will be evaluated using a scale of None (0), Mild (+1), Moderate (+2) and Severe (+3).

Cornea - Edema

None (0)	Transparent and clear or less than mild
Mild (+1)	Dull glassy appearance
Moderate (+2)	Dull glassy appearance of epithelium with large number of vacuoles
Severe (+3)	Epithelial bullae and/or stromal edema, localized or diffuse, with or without stromal striae

Cornea - Staining/Erosion

None (0)	No fluorescein staining of epithelium, OR less than mild
Mild (+1)	Slight fluorescein staining confined to a small focus
Moderate (+2)	Regionally dense fluorescein staining (1 mm or greater in diameter) with underlying structure moderately visible
Severe (+3)	Marked fluorescein staining or epithelial loss

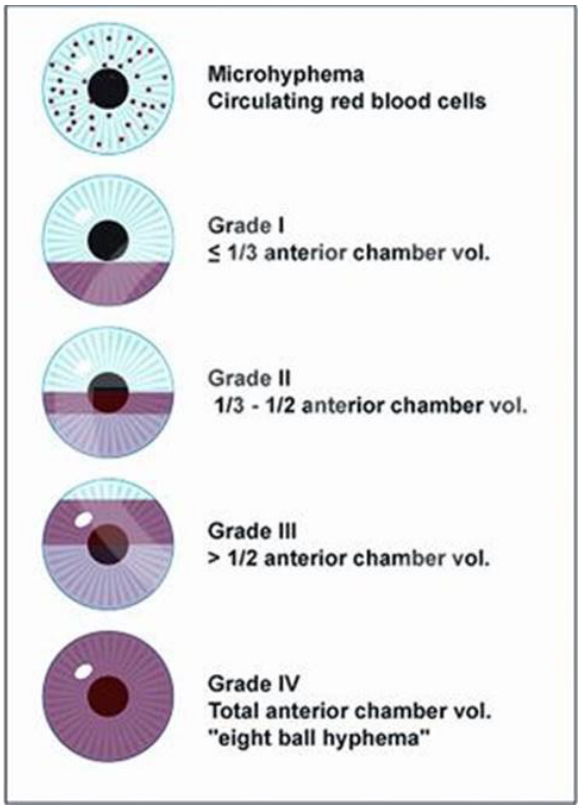
Anterior Chamber
The following system is recommended for grading of aqueous cells and flare using a slit beam 1.0 mm wide and 1.0 mm long.

Cells
0 = < 1 cell seen
0.5+ = 1-5 cells seen
1+ = 6-15 cells seen
2+ = 16-25 cells seen
3+ = 26-50 cells seen
4+ = > 50 cells seen

Flare
0 = None
1+ = Faint
2+ = Moderate (iris and lens details clear)
3+ = Marked (iris and lens details hazy)
4+ = Intense (fibrin or plastic aqueous)

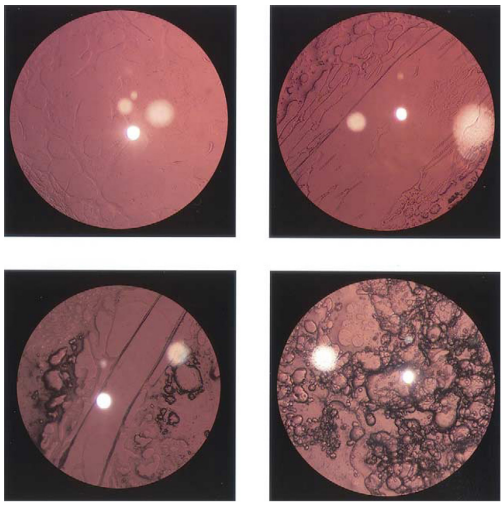
The presence of hypopyon is recorded separately. The presence of "microhyphema" or "layered hyphema" in the anterior chamber should also be recorded. Layered hyphema will be graded using the following scale (If Grade 1, also record size in mm on the CRF). [35]

[35] http://www.aao.org/image/hyphema-grading-system-2



Posterior Capsule Opacification

As a routine part of the slit lamp examination, posterior capsule opacification (PCO) will be evaluated using the following scale:



NONE

Minimal (Top left image)

Mild (Top right image)

Moderate (bottom left image)

Severe (bottom right image)

Other Slit Lamp Findings (complete for each finding)

- Trace
- Mild
- Moderate
- Severe

20.9 GONIOSCOPY

Gonioscopy will be conducted as part of the screening process to verify that the subject has an open angle and to identify any anterior synechiae as well as determine if there is any pigment dispersion. A Zeiss, Sussman or similar lens should be used and gonioscopy conducted in a dark room with a narrow, short slit beam that does not pass through the pupil and without a fixation light being used. The Shaffer method will be used as follows: grade 4, wide open (35°-45°): grade 3, moderately open (25°-34°); grade 2, moderately narrow (20°); grade 1, very narrow (10°); grade 0, closed (0°). The grade number will be reported for each quadrant of the eye in the appropriate location on the form.

20.10 OCULAR HYPOTENSIVE MEDICATIONS

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

21 APPENDIX B - DECLARATION OF HELSINKI

I. PREAMBLE

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

II. GENERAL PRINCIPLES

1. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

2. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. Medical progress is based on research that ultimately must include studies involving human subjects.

4. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures

and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

5. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

6. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

7. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

8. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

9. Medical research should be conducted in a manner that minimizes possible harm to the environment.

10. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

11. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

12. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

13. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

III. RISKS, BURDENS AND BENEFITS

- In medical practice and in medical research, most interventions involve risks and burdens.

  Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

- All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

  Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

- Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

  When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

IV. VULNERABLE GROUPS AND INDIVIDUALS

- Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

  All vulnerable groups and individuals should receive specifically considered protection.

- Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

V. SCIENTIFIC REQUIREMENTS AND RESEARCH PROTOCOLS

- Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

- The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

  The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

  In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

VI. RESEARCH ETHICS COMMITTEES

- The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

  The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

VII. PRIVACY AND CONFIDENTIALITY

- Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

VIII. INFORMED CONSENT

- Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

- In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

  After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

  All medical research subjects should be given the option of being informed about the general outcome and results of the study.

- When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

- For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

- When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

- Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

- The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

- For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

IX. USE OF PLACEBO

- The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

  Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

  Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

X. POST-TRIAL PROVISIONS

- In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

XI. RESEARCH REGISTRATION AND PUBLICATION AND DISSEMINATION OF RESULTS

- Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

- Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

XII. UNPROVEN INTERVENTIONS IN CLINICAL PRACTICE

In the treatment of an individual patient, where proven interventions do not exist, or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.