CLINICAL INVESTIGATION PLAN

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG)

Reference Number: ARGOS-02

Revision:	Rev. C
Release Date:	18-FEB-2014
Sponsor:	Implandata Ophthalmic Products GmbH
	Kokenstrasse 5
	30169 Hannover
	Germany

Sponsor Signature Page

ARGOS-02

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO intraocular pressure sensor device in patients with Primary Open Angle Glaucoma (POAG)

CIP prepared by:

Jörg Breitkopf Clinical Operations Manager, Consultant	Signature	18-FEB-2014 Date
Mary Stimmel-Peeters Medical Writer, Consultant	Signature	Date
Prof. Dr. rer. nat. Ralf-Dieter Hilgers Statistician, University Aachen	Signature	Date

CIP reviewed and approved by:

Max Ostermeier Managing Director, Sponsor	Signature	Date
Stefan Meyer Chief Technology Officer, Sponsor	Signature	Date

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ARGOS-02

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Coordinating Investigator Signature Page

ARGOS-02

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO intraocular pressure sensor device in patients with Primary Open Angle Glaucoma (POAG)

Prof. Dr. med. Carl Erb

Signature

18.02.2014

Date

Institution

PRIVATINSTITUT FÜR ANGEWANDTE AUGENHEILKUNDE BERLIN

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Country Lead Investigators

ARGOS-02

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO intraocular pressure sensor device in patients with Primary Open Angle Glaucoma (POAG)

Germany

Prof. Dr. med. Hagen Thieme

Prof. Dr. med. Hagen Thieme

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18.2.2014

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Investigator Signature Page

ARGOS-02

A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO intraocular pressure sensor device in patients with Primary Open Angle Glaucoma (POAG)

Investigator Statement

I have read this protocol and agree to conduct this study in accordance with all stipulations of the Clinical Investigation Plan, any applicable standards for the conduct of clinical investigations with human patients, any requirements imposed by the responsible competent authority/ethics committee, any other applicable local, institutional or legal requirements and in accordance with the principles outlined in the Declaration of Helsinki.

<Investigator Name>

_____ _____

Signature Date

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Responsibilities and Contact Information

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Investigational Sites	A list of investigational sites is filed separately in the TMF. A final list will be shown in the clinical investigation report.
Data Management and Statistics	**Prof. Dr. rer. nat. Ralf-Dieter Hilgers** University Clinic Aachen Department of Medical Statistics Pauwelsstrasse 30 52074 Aachen, Germany Phone: +49 (0) 241 8089359 Email: rhilgers@ukaachen.de

Clinical Safety	**MDSS GmbH** Schiffgraben 41 30175 Hannover, Germany Phone: +49 (0) 511 6262 8630 Fax: +49 (0) 511 6262 8633 Email: info@mdss.com
Data Safety Monitoring Board (DSMB)	A list of members of the DSMB is filed separately in the TMF together with the DSMB charter.

SYNOPSIS

Title	A prospective, open-label, multicenter clinical investigation to assess the safety and performance of the ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG)
Study Number	ARGOS-02
Sponsor	Implandata Ophthalmic Products GmbH
Name of IMD	**ARGOS-IO System** The ARGOS-IO system is composed of the implant and its accessories: **Implant**: ARGOS-IO pressure sensor implant **Accessories:** MESOGRAPH reading device, Implant Injector and telemetric Multiline Connector
Indication	Patients with Primary Open Angle Glaucoma (POAG) and indicated cataract surgery
Study Purpose	The purpose of this study is to evaluate the safety and performance of the ARGOS-IO system in patients with POAG and indicated cataract surgery.
Study Design	This clinical investigation prospective, open-label, multicenter, single-arm clinical investigation will be conducted in two stages using a Simon two-stage design. Subjects will be enrolled as follows: **First stage:** 11 patients **Second stage:** 11 patients An interim analysis will be performed when the 11 patients of the first stage have completed their 3 month follow-up visits. The trial will be stopped if 2 or more patients have experienced a serious adverse device events (SADE) at this time. Otherwise enrollment will be resumed and the trial continued until an additional 11 patients have been enrolled in stage 2 and received ARGOS-IO implants. A conclusion for safety will be made if in total no more than 2 of the total of 22 patients experience an SADE.
Sample Size Considerations	The primary aim of this study is to show “safety”, which will be evaluated based on the percentage of subjects who experience an SADE (= “non-safety), as defined in the primary endpoints.

	For the study as a whole, "safety" will be determined based on the following decision rule: if in stage 1 the non-safety event rate is greater than 25%, the trial will be stopped (type 1 error rate of 0.05). If the non-safety event rate is lower than 25%, the study will be continued into stage 2. It will be declared a success if the final non-safety event rate is less than 6% (type II error rate of 0.20) The calculation is based on a two-stage Simon design optimizing the minimum expected sample size with parameters **α=**0.05, **β=**0.20, $p_0 = 0.75$, $p_1 = 0.94$.
Subject Population	This study will enroll subjects with POAG and indicated cataract surgery until a maximum of 22 have undergone implantation with the ARGOS-IO pressure sensor.
Study Objectives	**<u>Primary Objectives</u>** **Safety** To evaluate the safety and tolerability of ARGOS-IO pressure sensor implantation by assessing the incidence of SADEs in the 3 months immediately following implantation. **Performance** To evaluate the limits of agreement between measurements with the Goldmann Applanation tonometry (GAT) and the ARGOS-IO system between day 30 through day 180. **<u>Secondary Objectives</u>** **Safety** • To evaluate the safety and tolerability of ARGOS-IO pressure sensor implantation by assessing the incidence of adverse events and adverse device events between 3 months and 12 months following implantation. **Performance** • To evaluate the performance of the ARGOS-IO system up to 12 months after implantation.
Patient Selection	**Inclusion Criteria** Eligible subjects must meet all the following inclusion criteria: 1. Mentally competent and willing to provide written Informed consent 2. Male or female aged ≥ 40 years ≤ 85 years on the day of screening

	Female subjects of childbearing potential (not surgically sterilized or more than one year post-menopausal) must be willing to use adequate contraception throughout the trial and must have a negative pregnancy test (urine beta-hCG) within 24 hours prior to ARGOS-IO pressure sensor implantation. 3. Diagnosis of primary open-angle glaucoma (POAG) including high pressure glaucoma (HPG), normal pressure glaucoma (NPG) and ocular hypertension (OH) as defined by the European Glaucoma Society guideline (Heijl, Traverso, & al, 2008) requiring regular IOP measurements 4. Sufficiently controlled IOP 5. Phakic eyes 6. Only one eye per patient may be implanted with the ARGOS-IO implant 7. Cataract surgery indicated. The medical indication for a cataract operation must be given irrespective of the study participation. Potential study patients will be solicited for participation in the clinical trial only after the patient has given consent to the cataract operation 8. Pre-operative anterior chamber depth (ACD) ≥ 2.5 mm as measured from the corneal endothelium 9. Axis length > 22 mm 10. Endothelial cell density of the cornea ≥ 2000 cells/mm² 11. Subjects able and willing to attend all scheduled visits and comply with all study procedures **Exclusion Criteria** Eligible subjects must not meet any of the following exclusion criteria: 1. Any other type of glaucoma other than primary open-angle glaucoma as defined in inclusion criteria 3 2. Severe POAG patients with a macular degeneration and visual field loss of -20dB or worse 3. Exsudative age-related macular degeneration, instable macular degeneration 30 days prior to inclusion, or macular edema 4. Retinal detachment 5. Corneal diseases 6. Diabetes mellitus 7. Connective tissue diseases 8. History or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-IO implantation

	9. Intraocular surgical procedure(s) within 6 months prior to ARGOS-IO implantation or any surgical procedure such as refractive eye surgery that can affect the assessment of IOP by Goldmann Applanation tonometry 10. History of eye tumor 11. Ocular disease other than glaucoma that may affect assessment of visual acuity and/or IOP by Goldmann Applanation tonometry (choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy) 12. Anterior chamber configuration that puts the subject at high risk to develop an angle closure glaucoma 13. History of extensive keloid formation 14. Severe dry eye syndrome 15. Subjects who will need to undergo ancillary procedures in the study eye at the time of implantation or during the post-operative study period 16. Any known intolerance or hypersensitivity to topical anesthetics, mydriatics, plaster or silicone (component of the device) 17. Existence of other active medical eye implant and/or other active medical implants in the head/neck region 18. Any contraindication for IOL implantation such as choroidal hemorrhage, concomitant severe eye disease, excessive vitreous loss, extremely shallow anterior chamber, microphthalmos, non-age-related cataract, posterior capsular rupture, severe corneal dystrophy, untractable IOP, zonular separation, color vision deficiencies 19. Severe generalized disease resulting in a life expectancy shorter than a year 20. Any clinical evidence that the investigator feels would place the subject at increased risk with the placement of the device 21. Currently pregnant or breastfeeding 22. Participation in any study involving an investigational drug or device within the past 30 days or ongoing participation in a study with an investigational drug or device 23. Patients who are not suitable for the study based on the surgeon's evaluation 24. Patients unable or unwilling to understand or comply with required study procedures 25. Patients with psychiatric disorders influencing their judgement or autonomy

	26. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization. 27. Enrollment of the fellow eye in this clinical study
Study Procedures	**Screening (SC)** Consecutive potential subjects will undergo informed consent process up to 28 days prior to surgery. Consenting subjects will be screened. Screening visit will include: • Demographics • Medical history • Pregnancy tests for females of child-bearing potential <u>General</u> • Optical biometry (IOL Master) • Visual acuity (ETDRS) • Perimetry • Concomitant medication <u>Anterior segment measurement</u> • Slit-lamp biomicroscopy • Optical coherence tomography (OCT) • Confocal Microscopy • Gonioscopy <u>Posterior segment measurement</u> • Biomicroscopy • Optical coherence tomography (OCT) • Fundus photography <u>IOP measurement</u> • Goldmann Applanation tonometry (GAT) **<u>Surgery (V01)</u>** On day of surgery or one day prior to surgery, subjects will again be assessed for eligibility requirements including pregnancy testing for females of childbearing potential. Subjects who continue to meet eligibility requirements will undergo cataract surgery with ARGOS-IO pressure sensor implantation using the implant injector and standard clinical procedures. If it

	becomes apparent during the surgery that the subject is not a suitable candidate for the ARGOS-IO pressure sensor implant, the cataract surgery will be carried out using standard of care and the subject removed from the study. At Visit 01, data will be collected regarding: General • Implantation procedure questionnaire (surgeon) • AE/ADE/SAE/SADE • Concomitant medication • Device deficiency **Follow-up (V02 to V11)** The follow-up period after surgery will consist of 10 visits (Day 1 until D360). The examinations performed at each visit are listed without mentioning the single visit in parentheses. Examinations that are carried out only at distinct visits are indicated in parentheses. The follow-up visits will include : General • Optical Biometry (IOL Master) (V09) • Visual acuity (EDTRS) • Perimetry (V07, V09, V11) • External Eye Photography • User acceptance questionnaire (patient) (V11) • User acceptance questionnaire (investigator) (V11) • AEs/ADEs, SAEs/SADEs • Concomitant medication • Device deficiency Anterior Segment • Slit-lamp biomicroscopy • Optical coherence tomography (OCT) (V07, V09, V11) • Confocal Microscopy (V07, V09, V11) • Gonioscopy (V07, V09, V11) Posterior segment measurement • Biomicroscopy • Optical coherence tomography (OCT) (V07, V09, V11)

	• Fundus photography (V07, V09, V11) IOP measurement • Goldmann Applanation tonometry (GAT) • ARGOS-IO system measurement Measurements will be performed in series of 1 GAT measurement followed by 3 consecutive measurements with the ARGOS-IO system, with not more than 10 minutes between the GAT and the ARGOS-IO system measurements of a single series and a minimum of 60 minutes between the end of the one series and the start of the next. At V02, V03 and V04 only GAT measurements will be made (at beginning and end of visit). At V06, V08 and V10 two series of measurements will be made (at beginning and end of visit). At visits V05, V07, V09 and V11 four series of measurements will be made. • ARGOS-IO system self-measurement at home (Visit 05 to Visit 11)
Data Analysis and Statistics	**Primary Endpoints** **Safety** - Number of patients experiencing a device related SAE defined as any adverse event that both o Is considered by the Investigator to have a possible, probable or definite relationship to the device and o That meets any of the following criteria of a serious adverse event: ▪ Resulted in death, permanent damage or disability or a congenital anomaly ▪ Was life threatening ▪ Required hospitalization or intervention to prevent permanent impairment or damage **Performance** - Agreement between measurements made using GAT and the ARGOS-IO system from V05 (day 30) through V09 (day 180). If multiple ARGOS-IO system measurements have been made at time points for which paired GAT/ARGOS-IO system measurements are to be compared, the mean of the replicate ARGOS-IO system measurements will be used for

	agreement evaluation. The agreement evaluation is based on the assumption, that the measurements are constant over the measurement period. **<u>Secondary Endpoints</u>** **Safety** - Incidence, nature, severity and seriousness of observed adverse events and adverse device events in the 3 months following implantation. - Incidence, nature, severity and seriousness of observed adverse events and adverse device events in the 6 months following implantation. - Incidence, nature, severity and seriousness of observed adverse events and adverse device events in the 12 months following implantation. **Performance** - Limits of agreement between measurements made using GAT and the ARGOS-IO system from V05 (day 30) through V11 (day 360). - Performance of the ARGOS-IO system after 6 months by means of incidence of observed device malfunctions. - Performance of the ARGOS-IO system after 12 months by means of incidence of observed device malfunctions. - User acceptance of the implantation procedure by means of evaluation of implantation procedure questionnaires (investigators). - User acceptance of the ARGOS-IO system at the investigational site by means of evaluation of investigator acceptance questionnaires (investigators). - User acceptance of the ARGOS-IO system at home by means of evaluation of patient acceptance questionnaires (patients). - Daily IOP self-measurement profiles (patients). **<u>Definition of the analysis populations</u>** The safety population comprises all subjects for whom ARGOS-IO pressure sensor implantation was attempted, whether or not the implantation was successful. In this clinical investigation the intention-to-treat (ITT) population comprises the same subjects as defined in the safety population.

	Statistical analysis **Safety analysis** Incidence of SADE in the 3 month period immediately following implantation. The decision on safety follows the rule of the SIMON optimum two-stage design (parameters: **α**=0.05, **β**=0.20, $p_0 = 0.75$, $p_1 = 0.94$, minimize expected samples size). A corresponding 95% confidence interval will be given for the portion of SADE within the safety population. The confidence interval for the SADE rate will be calculated using the method proposed by Koyama (Koyama & Chen, 2008). These calculations will be based on the number of patients experiencing an SADE. Moreover, safety will be described in detail by frequency, seriousness, severity, nature and duration of events. Adverse events and the number of subjects reporting adverse events will be tabulated by system organ class and preferred terms. Adverse device events, device deficiencies and the number of subjects reporting adverse device events and device deficiencies will be tabulated by event/deficiency description. **Performance analysis** The Bland-Altman approach will be used to establish limits of agreement between the IOP measurements from GAT and the ARGOS-IO system within the ITT population. Two-sided 95% confidence intervals will be calculated accounting for repeated measurements based on the method proposed by Zou (2011). Other secondary performance endpoints will be analyzed by descriptive and explorative statistical methods. **Interim Analysis** An interim analysis to assess SADE will be performed, when the first 11 patients have completed the 3 month follow-up visit.
Safety Monitoring	A data safety monitoring board (DSMB) will be established prior to enrollment of the first patient. The DSMB is to review the safety data, including SAEs/SADEs, on a regular basis and will advise on any changes required in the conduct this clinical investigation. The DSMB will also review the data of the interim analysis and give recommendations to the Sponsor to either continue the clinical investigation (with or without an amendment of

	the clinical investigation plan) or to stop enrolment into the clinical investigation based on safety concerns.
Data Collection	Data will be collected using a paper-based Case Report Form (CRF).
Study Duration	The overall study duration for each individual patient is up to 13 months. Subjects will undergo screening for a maximum of 28 days prior to surgery and will be followed for 12 months afterwards. The overall recruitment period is expected to last 6 months. The estimated total duration of the study from first patient screened to last patient last visit is 21 months.

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LISTINGS OF FIGURES AND TABLES

2. ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
α	Type I error
ACA	Anterior Chamber Angle
ACD	Anterior Chamber Depth
ADE	Adverse Device Event
AE	Adverse Event
AS	Anterior Segment
ASADE	Anticipated serious adverse device effect
ASIC	Application specific integrated circuit
β	Type II error
Beta-hCG	Beta-subunit of human chorionic gonadotropin
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
C	Celsius
CA	Competent Authority
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
D	Day
dB	Decibel
DCT	Dynamic contour tonometry
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
EEPROM	Electrically erasable programmable read-only memory
ETDRS	Early Treatment Diabetic Retinopathy Study
EtO	Ethylene oxide
FAS	Full-analysis-set
GAT	Goldmann Applanation Tonometry
GCP	Good Clinical Practice
GDD	Glaucoma Drainage Device
HPG	High pressure glaucoma
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
IFU	Instruction for Use

IO	Intraocular
IOL	Intraocular lens
IOP	Intraocular Pressure
ISF	Investigator Site File
ISO	International Organization for Standardization
ITT	Intention to treat
KPro	Keratoprosthesis
LAL	Limulus amebocyte lysate
MD	Macular degeneration
MHz	Megahertz
Mm	Millimeter
mmHg	millimeter(s) of mercury (a unit of pressure equal to the pressure that can support a column of mercury 1 millimeter high)
MPG	Medizinproduktegesetz
MRI	Magnetic resonance imaging
N	Sample number
NCT	Non-contact tonometry
ND:YAG	Neodymium doped yttrium aluminum garnet
OCT	Optical coherence tomography
OH	Ocular hypertension
P	Pressure
p_0	Proportion of patients in stage 1 with positive outcome
p_1	Proportion of patients overall with positive outcome
PIC	Patient informed consent
POAG	Primary open angle glaucoma
PS	Posterior Segment
Rev.	Revision
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEM	Scanning electron microscope
SDV	Source Data Verification
T	Tesla
TMF	Trial Master File
V	Visit
VA	Visual acuity

USADE	Unanticipated serious adverse device effect
WTW	White-to-white

3. BACKGROUND INFORMATION

3.1 Glaucoma

An estimated 1 in 40 adults over the age of 40 has glaucoma, a group of conditions that result in damage to the optic nerve head, is characterized by a progressive thinning of the retinal nerve fiber layer and the neuroretinal rim that appears as a central depression in the optic disc. It leads to loss of visual field and if not controlled eventually to blindness, of which it is the second most common cause worldwide (Quigley, 2011) (Mansouri & Shaarawy, 2011) (King, 2013). There are two types of primary glaucoma. In primary open angle glaucoma (POAG), which accounts for approximately 70% of the glaucoma cases seen, aqueous outflow from the eye is restricted, possibly due to increased resistance in the trabecular meshwork. In closed angle glaucoma, ocular tissue, usually the iris, obstructs the drainage pathway (King, 2013).

3.2 Glaucoma Treatment

Glaucoma often remains asymptomatic until late in the disease, when irreversible vision problems become evident. Although it may be present with normal intraocular pressures (IOP), the higher the IOP, the more rapidly the damage progresses (Quigley, 2011). Reduction of IOP is the only known treatment, the main goal of which is the prevention of visual disability in the patient's lifetime (King, 2013). Lowering the IOP of patients with POAG by 20 to 40% can halve the rate of progressive damage (Quigley, 2011).

IOP reducing treatments generally begin with eye drops containing prostaglandin analogues or ß-adrenergic antagonists, although as in other chronic asymptomatic diseases, patient adherence to treatment is often poor. If eye drops do not satisfactorily reduce IOP, surgical methods such as laser trabeculoplasty or trabeculectomy to reduce production of intraocular fluid, or insertion of an artificial shunt into the anterior chamber to increase its drainage may be used (Quigley, 2011)

3.3 Measurement of IOP

3.3.1 Principle and Gold Standard

Glaucoma generally develops slowly, with no obvious symptoms. For this reason the only way to determine if treatment is working is to monitor IOP regularly. The only method currently available to measure IOP directly requires the insertion of a large gauge needle into the eye and is rarely if ever used. Under normal clinical conditions, IOP is determined indirectly with one of numerous available

tonometer devices. Most of these are based on the Imbert-Fick principle that the force needed to flatten a defined area of a sphere is proportional to the pressure inside the sphere resisting the deformation (Frampton, 2012), (Kakaday, Hewitt, Voelcker, Li, & Craig, 2009).

3.3.2 Available Devices

A number of different tonometric devices are available. These can be categorized based on whether or not they involve direct corneal contact.

3.3.2.1 Direct Tonometers

The Goldmann Applanation Tonometer (GAT) was first described in the 1950's and is considered to this day to be the gold standard to which all other methods for measuring IOP are compared. It measures the force required to applanate the cornea by pressing a probe of defined area directly against it. The Perkins Tonometer is a hand-held tonometer that works on the same principles as the Goldmann Tonometer (Burr, et al., 2012).

Dynamic contour tonometry (DCT) determines IOP by measuring the force required to mold the cornea to the shape of the concave probe (Frampton, 2012), while rebound tonometers calculate it from the induction current produced when a small plastic-tipped magnetized metal probe is bounced against the cornea (Burr, et al., 2012).

The TonoPen is a hand-held portable tonometer that uses a transducer in its probe tip to measures the force required to applanate/indent the cornea, while the Ocuton S, another hand-held tonometer, requires direct contact of its prism with the cornea (Cihara, 2008).

The Sensimed Triggerfish, a new system consisting of a micro-electromechanical strain gauge embedded in a disposable silicon contact lens, an adhesive antenna and a portable recorder, allows 24 hour out-patient monitoring of changes in the diameter of the corneoscleral junction that results from changes in IOP (Mansouri & Shaarawy, 2011).

3.3.2.2 Non-contact tonometers

In non-contact (air-puff) tonometry (NCT) a rapid air pulse is used to applanate the cornea. Advantages to NCT include lack of direct contact with the eye and hence no need for anesthesia, and low/no risk of corneal abrasion or infection transmission. The probe of the Ocular Response Analyzer applies a slightly stronger force to actually indent the cornea and uses a pneumatic sensor to take two measurements, the force at which the cornea is applanated initially and the that at which it applanates

as it returns to normal. The difference between these two pressures is due to the viscous damping of the cornea (Frampton, 2012).

In transpalpebral tonometry, IOP is calculated from the rebound of a free-falling rod as it hits the tarsal plate of the eyelid over the sclera (Burr, et al., 2012)

3.3.3 Limitations

The accuracy of most of these devices is limited to the degree that the secondary biometric parameters they measure are affected by factors other than IOP, such as corneal thickness (Krug, Kompa, & Schrage, 2002). The majority of the direct tonometers require use of corneal anesthetics. The greatest limitation however is that almost all of the devices are cumbersome and require skill and training to use, which in effect limits their use to the clinic /office setting.

The cost and inconvenience of the required office visits result in treatment decisions that are made based on only a few IOP measurements taken months apart. However fluctuations in IOP due to patient activity and circadian rhythm are normal. The level of imprecision in repeated IOP measurements has been estimated at +/- 5 mmHg, meaning that to be 95% certain there is any treatment effect, a difference greater than 7 mmHg must be seen between single pre- and post-treatment IOP levels (Rotchford & King, 2012). When 24 hour IOP profiles are taken, which require patients be admitted to the clinic, peak values – thought to be the most relevant for patient outcome in the long term – are seen outside of normal office hours in 80% of the cases, resulting in changes to treatment (Liang, Lee, & Shields, 2009) (Mansouri & Shaarawy, 2011).

For these reasons, alternative methods are being sought that would allow more frequent IOP assessments in the home setting.

According to company information, Sensimed Triggerfish measures a “profile of 24h ocular dimensional changes”, displayed in [arbitrary units], rather than changes in IOP in [mmHg]. To date, it is unknown how the measured changes in corneal curvature relate to IOP, especially in magnitude.

4. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

4.1 Summary description of the investigational device and its intended purpose

The ARGOS-IO system was developed for the wireless, contactless measurement of the hydrostatic pressure of the aqueous humor (IOP, intraocular pressure) in patients with diagnosed glaucoma, or

elevated or instable IOP that places them at a risk of ocular damage and loss of visual acuity. It is made up of four components: the ARGOS-IO implant, the external hand-held Mesograph reading device, the implant injector and the Multiline Connector.

The ARGOS-IO implant is comprised of a micro-electromechanical system application specific integrated circuit (ASIC) bound to a micro-coil of gold and encapsulated in a silicone-rubber material that has been widely used for intraocular lenses. It is intended to be implanted during cataract surgery, and to remain in place indefinitely. The implant is introduced into the area between the intraocular lens and the iris (ciliary sulcus) using standard procedures that employ an implant injector similar to those commonly used to insert IOLs.

Activation of the Mesograph reading device in the near vicinity of the eye establishes an inductive current between it and the micro-coil, thereby supplying the ASIC with power and permitting data transmission. Pressure-sensor cells and an A/D converter incorporated in the ASIC measure IOP directly and transmit the digitized data to the reader. When connected to the reader at the site or the patient's home, the Multiline Connector uploads the data recorded by the reader to a secure dedicated data base that can be accessed remotely by the Investigator. Data is redundantly stored in non-volatile memory inside the reader device, preventing data loss in case of an error.

Because the sensors are implanted in the eye, the ARGOS-IO pressure sensor measures IOP directly, without interference from corneal properties or due to operator skill. It enables numerous IOP measurements daily, providing a complete IOP profile for the entire interval between office visits, and allowing timely detection of both peaks due to patient activities and circadian rhythms and trends due to disease progression. It also permits easy patient self-monitoring, thereby providing patients immediate feedback on their IOP, which in turn should encourage adherence to the treatment regimen.

4.2 Description of the investigational device including any materials that will be in contact with tissues or body fluids

The ASIC and micro-coil components of the implant are hermetically encapsulated in a biocompatible silicone-rubber material (Nusil MED-6820) commonly used for ophthalmic implants. This layer of material:

- Forms a biocompatible, soft and atraumatic surface of the implant in order to avoid trauma to the tissues surrounding the implant
- Prevents and protects the patient from substances being washed out from the electronic module and leaking into the aqueous humor
- Provides a hermetic leak-proof seal around the electronic module, protecting it from the electrolytes and water contained in aqueous humor.

In the event that the silicone coating were to become breached the patient may indirectly come into contact with the materials of the ASIC and the micro-coil as well. The sponsor commissioned a detailed risk assessment performed by NAMSA Advisory Services, Atlanta, USA to determine if these materials would pose any risk of an adverse biological effect to the patient. The materials under investigation comprised silicon, silicon dioxide, silicon nitride, gold, and traces of aluminum, titanium, phosphorus, arsenic, borium, polyimide and tungsten-titanium. The report states that all materials have been used previously within the eye and are considered to pose little if any risk (Cao, M, 2010).

The implant is required to fit into the ciliary sulcus which is a relatively tight area in a phakic eye, but is deeper in the pseudophakic eye. The implant shape and profile is designed to:

- Be folded prior to implantation and to be manipulated through a relatively tight up to 5 mm corneo-scleral tunnel
- Not block the optical axis of the eye
- Avoid the IOL, although it may be in direct contact with parts of it
- Have a minimum profile and thickness
- Have rounded edges in order to avoid trauma when in long term contact with the surrounding tissue.

The implant contains four haptics to maintain positional stability. In addition, the two haptics on either side of the ASIC act as a spacer to prevent the ASIC from being pressed into the surrounding tissue. Two flattened allantoid protrusions running from the bottom middle to the ASIC on the posterior

surface of the ring serve to facilitate unfolding of the implant after insertion into the eye, as well as to decrease force exerted on the ASIC by the ocular structures.

The implant is packaged in multiple layers conforming to EN ISO 11607-1:2006 and then sterilized with ethylene oxide.

4.3 Details about the manufacturer of the investigational device

The sponsor Implandata Ophthalmic Products GmbH is the manufacturer of the implant and the Mesograph reading device. The implant injector is manufactured by DEUTSCHMANN INSTRUMENTS, Germany. The Multiline Connector to transfer the data from the reading device to a secure customized database via GSM technology, is manufactured by Medscale systems GmbH.

4.4 Device and accessories identification

Each ARGOS-IO pressure sensor implant will be identified by a unique 32-bit hexadecimal serial number stored in non-volatile memory on the ASIC. The reading device will be identified by a unique seven digit serial number.

4.5 Device accountability and storage

The investigational team at each site is responsible for ensuring investigational device accountability throughout the course of the study in accordance with regulatory requirements. Upon receipt of the devices, the investigator or designee will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by the sponsor. A copy of the receipt will be retained in the Investigator Site File.

Site staff will carefully record the serial number of each implant and reading device, as well as the ID number of the patient for which they were used, on the device accountability forms provided by the Sponsor. An accurate documentation of device accountability will be available for verification by the monitor at each monitoring visit. In addition, each patient will be given an implant pass identifying his/her device with type and serial number and listing further information including implantation date, sponsor contact information, implanting clinic and surgeon and warnings relevant to interactions with other medical procedures and devices as well as with metal detectors.

Investigational device accountability records will include:

- Confirmation of Device delivery to the study site
- Device inventory at the site
- Device allocation to patients, including date of Device implantation, patient number and device identification number (serial number).

The sponsor's monitoring staff will verify that the study site's device accountability records match the records of used devices recorded in the CRFs.

The device must not be used for any purpose other than the present study. Unused devices will be returned to the sponsor at the end of the study period in accordance with the sponsor's instructions.

The investigator or authorized designee will alert the responsible monitor as soon as possible of any expected or potential shortage of devices during the study, so that the sponsor can organize the shipment of extra devices. Some extra devices will be provided in case any devices cannot be used.

The investigational devices must be kept in a secure place with restricted access. The shelf life of the device is 6 months under temperature conditions ranging from 0° C to +60° C.

4.6 Necessary training and experience requirements

It is assured that ophthalmic surgeons performing the surgery will be adequately trained on the ARGOS-IO pressure sensor implantation. Site personnel responsible for device handling including accountability, storage and shipment procedures will be trained during the initiation visit. If new site personnel are assigned during the study, they will be trained by the principal investigator or the monitor.

Surgical implantation

- Only specially trained ophthalmic surgeons may perform the implantation. These surgeons must be made familiar with the handling and implantation of the ARGOS-IO pressure sensor either by special training through Sponsor representatives or by consultation of the User Manual, provided as a separate document.

Intraocular pressure measurement using the Mesograph Reading Device:

- Intraocular pressure (IOP) measurement may be carried out by any trained individual including patients and assistants. Health care professionals will be trained by sponsor representatives or their delegates. Trial staff will instruct patients on the use of the reading device for IOP self-measurement at home at visit 05. Patients will also be given separate written handling instructions provided by the Sponsor.

Setup of reading device, downloading of measurement data:

- Only specially trained site personnel may set up the reading device or download data from it. Special attention must be paid to maintaining data protection in this connection. Training will be provided by Sponsor representatives.

Evaluation of data:

- The data obtained by the ARGOS-IO system measurement will only be used for the evaluation of the trial outcome. The ophthalmologist will use only the IOP measurements made with GAT for diagnosis, therapeutic assessments and decisions about additional medical treatments.

4.7 Description of any specific medical or surgical procedures involved in the use of the investigational device.

Ophthalmic surgeons should perform the cataract surgery according to their local routine working procedures for cataract surgery. The implantation of the ARGOS-IO pressure sensor should occur according to the training received prior to any surgery given by the Sponsor.

Detailed implantation instructions are presented in the Instructions for Use (IFU) (Implandata Ophthalmic Products GmbH, 2014) and the Investigator's Brochure (IB) (Implandata, 2014).

5. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

5.1 Evaluation of pre-clinical testing/assessment

5.1.1 In-vitro Testing

5.1.1.1 Functional Testing

The ARGOS-IO pressure sensor is intended to remain permanently implanted and as such must retain accuracy and precision indefinitely. Six devices were subjected to simulated physiological conditions and assessed using calibrated lab reference sensors over the entire absolute pressure and temperature range. The sensor was found to have an initial drift of less than 3 mmHg per year that stabilized over time, a pressure accuracy of +/- 1.32 mmHg, and a temperature accuracy of +/- 0.14°C. Aging had no significant impact on the device (Görtz, M, 2010).

The system has been tested (01-RE-18-A) for safety in accordance with the relevant standards (ASTM F 2052 (Displacement), F 2182 (Heating), F2119-07 (Artifacts) by means of magnetic resonance tomography (MRT) devices and found to be safe in MRT with a magnetic field strength up to 3 T. It is unlikely that there is a danger in MRT devices with higher field strengths; the manufacturer is to be contacted if an examination in such a device should be necessary.

For similar applications it was shown that an embedding of electronic components for implantation in the human body in the manner of the ARGOS-IO implant allows a stability of > 20 years (Donaldson, 1991).

Since the implant's mechanical and thermal stress after the implantation is regarded as minimal, it is assumed that a lifespan of > 10 years is achievable.

5.1.1.2 Biocompatibility and Cytotoxicity

The ARGOS-IO implant is intended to be permanently implanted and as such will have constant contact with tissue and tissue fluid. The three individual components of the implant (encapsulation, ASIC and micro-coil) as well as the complete implant were tested for biocompatibility and cytotoxicity.

The encapsulation material, MED-6820 silicone, which forms a hermetic seal around the ASIC and micro-coil, is the only component with which tissues are intended to have contact. This material has

been used for years in the manufacture of intraocular implants. The manufacturer, Nusil Silicone Technologies has tested the material for cytotoxicity, sensitization, acute intracutaneous reactivity, acute systemic toxicity, material mediated pyrogenicity, genotoxicity and implantation. The material was found to be non-toxic, non-sensitizing, non-irritating, non-pyrogenic and non-mutagenic. Carcinogenicity tests were deemed to be unnecessary because the Ames test for genotoxicity was negative and the material has been in use for so long. More detail can be found in the IB and the Master Access File provided by Nusil.

In the event that the MED-6820 coating becomes breeched, the patient will be exposed indirectly to the materials making up the ASIC and the micro-coil. The consultancy NAMSA Advisory Services performed an analysis of the risks posed by exposure to the materials contained in these components (silicon, silicon dioxide and traces of silicon nitride, gold, aluminum, titanium, phosphorus, arsenic, borium, polyimide and tungsten-titanium) and found that all been used previously in the eye and would pose little risk of adverse biological effects. Additional detail can be found in the IB and the NAMSA report (Cao, M, 2010).

The Sponsor conducted cytotoxicity testing according to ISO 10993-5 on the device as a whole (ISO10993). No relevant cytotoxicity was found with the device in direct or indirect cell contact (Niedhart, C; Müller, U, 2011).

5.1.1.3 Sterilization Verification

Encapsulation and packaging of the implants are carried out under monitored clean room conditions by Mecora GmbH, an ISO 13485 certified contract manufacturer.

Once packaged, the devices are transferred to a second ISO certified manufacturer, Sterigenics Germany GmbH, where they undergo ethylene oxide sterilization according to EN ISO 11135-1:2007 and AAMI TIR16:2009 requirements. Various tests have been performed on the EtO sterilized product:

- Residual EtO analysis (ISO 10993-7:2008/DIN EN ISO 10993-7:2009)
- Product sterility testing (ISO 11737:2006)
- Bioburden testing (ISO 11737:2006)
- Endotoxin (LAL) testing: additional test that has been implemented for the last small batch release process (ISO 11979-8:2006).

To date, small batch release process was conducted according to ISO 11737-1:2006 on 4 consecutive batches and no contamination was found (Sterigenics).

5.1.1.4 Compatibility with other Medical devices and Examination methods

The influence of silicone oil, which can be utilized in surgical interventions on the retina as a temporary tamponade, on the ARGOS-IO implant was examined (Investigator's brochure, 01-RE-17A). Small quantities of silicone oil can find their way into superficial layers of the sensor encapsulation under certain circumstances. The influence of silicone oil on the sensor is slight, but it is recommended to review the sensor measurement in comparison with an alternative IOP measurement method. This fundamentally applies to any ocular intervention.

An implantation of a glaucoma drainage device (GDD) may not be possible in the standard method (see document 01-RE-09A in the IB). In such cases the investigator must be contacted before the intervention.

The investigator must be contacted before any surgical ocular intervention.

5.1.1.5 Simulated Implantation in Enucleated Porcine Eyes

The effects of implantation were tested on 5 devices, which underwent functionality testing before being implanted in freshly enucleated porcine eyes using the same techniques, including folding, intended for the implantation of the device in humans, again after implantation using standard implantation procedures, and after removal through dissection and storage under physiological conditions for at least 14 days, at which time they were also examined microscopically and via SEM. There were no measureable deterioration in the device performance and no signs of any damage to either the sensors or the surface of the devices (Dreher, WF; Kern, N; Warres, C, 2010).

5.1.2 Animal Studies

In conjunction with removal of the natural crystalline lens, Todani et al (Todani, et al., 2011) implanted transducers in either the ciliary sulcus (5 eyes) or the vitreous cavity (1 eye) of 6 rabbits eyes and subjected a 7th rabbit to sham. All 7 rabbits showed transient, mild anterior chamber inflammation consistent with the procedure in the initial post-surgical period. No signs of toxicity or intolerability were seen over a follow-up of up to 25 months, including in histological examination of 2 eyes enucleated at 5.5 and 20 months. Two devices showed a downward drift. In one of these, a sudden

downward drift of 2 mm Hg per month that resolved when manometry was performed on the eye was seen approximately 1 year after implantation. A second device showed a sudden drop in readings at approx. 1.5 years, but remained stable in comparison to pneumotonometry. IOP measurements with the transducers otherwise showed good repeatability as well as good agreement with measurements made by direct manometry (Todani, et al., 2011).

In an additional study involving one rabbit from the above mentioned study, an antenna combined with a motion detector was employed to permit reliable IOP readings to be made without human involvement (Paschalis, et al., 2014).

5.2 Evaluation of clinical data

To date, nine patients have been implanted with the ARGOS-IO pressure sensor.

In a case study performed at the Beirut Eye Specialist Hospital, Lebanon, in cooperation with the Boston Eye Group, USA, lasting from June 2011 to June 2012, the ARGOS-IO pressure sensor was implanted in the ciliary sulcus of a 66 year old woman following phacoemulsification of the cataract and “in-the-bag” implantation of a Rayner 620 plate haptic IOL. Following an unsuccessful attempt to place the implant in the anterior chamber, the first implant was removed and replaced with a second, which was placed directly in the sulcus space with the sensor side towards the cornea. Post-operative recovery was normal, with no persistent intraocular inflammation, pigment dispersion or angle narrowing. YAG capsulotomy was required at weeks 6 and 31. Good concordance with GAT was observed, with a p-value of 0.527 found using the Brown-Forsythe test. A wide range of IOP values were obtained during office hours (16.7 to 31.5 mmHg), at home (12.2 to 43.5 mm Hg), as well as during a 4-day period of nocturnal measurements (1.5 to 33.1mmHg). At the patient’s last site visit in December 2012, 18 months following implantation, the sensor continued to function properly. No deficiencies or adverse effects were noted at this time. At the end of 2013, approximately 30 months post-implantation, the patient’s attending ophthalmologist reported that the sensor remained in situ and continued to function (Melki, Todani, & Cherfan, 2014).

In a case study conducted from May 2009 to May 2011 at the Santo Domingo Centro Láser, Dominican Republic, in cooperation with the Boston Massachusetts Eye and Ear Infirmary (Harvard Medical School), USA, the ARGOS-IO pressure sensor was implanted in conjunction with a Boston Keratoprosthesis Type I (which prevents IOP measurement using available instruments) and corneal grafts in two male patients, aged 18 (patient I) and 23 (patient II), who had severe corneal scarring

with fluctuating vision and poorly controlled secondary glaucoma (frequently reported in patients qualifying for KPro implantation) resulting from severe ammonia burns. Following extracapsular cataract extraction, the ARGOS-IO pressure sensor was implanted into the ciliary sulcus, after which a Boston KPro Type I keratoprothesis device was implanted in a carrier corneal graft to replace the central opaque cornea. Topical antibiotic treatment was instilled and a soft lens applied, after which the eye was patched and shielded. Postoperative medication for both patients included topical antibiotics, steroids and anti-glaucoma medication. Both patients showed only the post-operative reactions known for Boston KPro implantation. These post-operative reactions gradually subsided over 1-2 months on standard doses of topical antibiotics and steroids. Subsequently, no cells in the anterior chamber, retroprosthesis, epi-retinal membrane or retinal detachment were identified.

At day 1 Patient I had a visual acuity of 20/200. At one week after surgery, the visual acuity improved to 20/30 and after one month all postoperative signs of inflammation had resolved. After four months post-surgery, this patient's IOP increased over 40 mmHg despite aggressive anti-glaucoma medication treatment. An Ahmed drainage device was then implanted, which significantly lowered the IOP. After 5 months, the visual acuity was 20/70 and no signs of inflammation were detected. IOP remained between 20-25 mmHg despite topical medication. Gradual opacification of the posterior capsule developed and necessitated YAG laser capsulotomy after 22 months. After 24 months, visual acuity was 20/60 and there was no evidence of inflammation in the anterior chamber.

In patient II, vision remained at only light perception despite clear media after surgery. One month after surgery, all signs of inflammation had resolved. IOP remained consistently high, which resulted in an Ahmed drainage device implantation after 8 months. IOP could be reduced for some time, but the glaucoma damage was considered end-stage. The ARGOS-IO system IOP readings appeared very reasonable and promising when compared to finger palpation. Peaks in IOP were detected in a timely manner, facilitating the adjustment or initiation of medical treatments or medical procedures. To date, both patients are still implanted with the ARGOS-IO pressure sensor and functionality is checked at regular hospital visits. (Lopez, Melki, & Dohlmann, 2013).

In a pilot study (ARGOS-01) performed at the University Eye Clinic Aachen, Germany, lasting from 2011 to 2013 (last patient out 28 November 2013), six glaucoma patients (2 normal pressure glaucoma, 4 POAG; 2 male; mean age 73 years) received an ARGOS-IO implant in their ciliary sulcus in conjunction with phacoemulsification and IOL implantation for cataract.

In the first week following surgery, all patients showed signs of trauma to the anterior chamber in the form of

- Mild to moderate conjunctival irritation and corneal edema (all patients)
- Mild (1 patient), moderate (1 patient) or major (4 patients) anterior chamber cells
- Minor (3 patients) moderate (1 patient) or major (3 patients) Tyndall flares

During this week, five patients also had fibrin reactions (two major, three minor), two of which were associated with hypopyons < 1mm. Samples were taken from two patients were both found to be sterile. All five patients were treated with topical steroids and antibiotics. The patients experiencing sterile hypopyons were also treated with systemic steroids and antibiotics following standard procedures. All patients recovered without sequelae by day 21. Because the inflammation in all cases cleared quickly and did not return, as would have been expected if it was a reaction to the implant itself, it was concluded by the DSMB that the reaction was most likely caused by the operational procedure. On the basis of this information, the DSMB concluded that the implantation and use of the ARGOS IO pressure sensor in further study patients is justifiable (Implandata, 2013).

In addition, one participant had minor Descemet folds at day 3 to 7, and another both mild pigment dispersion and endothelial sediment at days 1-3 and 4-7. With the exception of two patients who continued to have mild to moderate corneal edema and conjunctival irritation throughout the study, these symptoms abated in all other patients before day 28. Two isolated incidents of conjunctival irritation and corneal edema and one of anterior chamber cells were seen at individual visits later in the study. Other adverse effects observed included transillumination (two patients), pigment dispersion (five patients), pupil distortion (five patients, flattening of the anterior chamber (three patients) and posterior lens opacification (three patients).

There were no apparent changes in corneal thickness or endothelial cell density as measured with Pentacam and Confoscan, respectively. The anterior angle was found to be open to the ciliary body in all patients at all gonioscopy examinations. Anterior synechiae were noted in one patient at 12 months (Implandata, 2014).

To date, nine patients have been successfully implanted with the earlier ARGOS-IO implant design, with which there is to date a combined 279 patient-months experience.

Table 1. Combined Patient Months with the ARGOS-IO Implant

Study	Combined patient months
Case study (Lebanon): ARGOS-IO (n=1)	57
Case study (Dominican Republic): Boston KPro + ARGOS-IO (n=2)	89
Pilot study (Germany): ARGOS-IO (n=6)	133
Total combined patient months	**279**

5.3 Justification for Design and Evaluation Relevant to Use in Human Subjects

If it is demonstrated to be safe and reliable in humans, the ARGOS-IO system would offer several valuable advantages to current devices for the measurement of IOP:

- Frequent measurements in the patient's daily environment
- Complete IOP profile upon which to base treatment decisions, as opposed to single IOP measurement every 3 months
- Detection of peaks and trends
- Ability of patient to self-monitor, with accompanying increase in motivation to adhere to treatment

The device has been shown to be well tolerated and to have good agreement with manometry in rabbits, with use durations ranging up to four years (Todani, et al., 2011). Once implanted, it was easily used, and has even been employed together with a motion detector to permit reliable IOP readings to be made without human involvement in laboratory animals (Paschalis, et al., 2014).

In an initial case study, a single POAG patient received an earlier ARGOS-IO implant, which then was followed for 18 months. The IOP measurements obtained in this patient with the ARGOS-IO system showed a good agreement with those obtained using GAT at the same time points. With the exception of posterior opacification that required two YAG capsulotomy procedures to correct, no significant AEs were reported. This incident could also have been a result of the normal cataract surgery with IOL implant (Melki, Todani, & Cherfan, 2014)

Two patients who received an earlier ARGOS-IO implant in conjunction with a Boston Keratoprosthesis Type 1 in a carrier corneal graft, showed no significant AEs. IOP measurements obtained with the

ARGOS-IO system demonstrated reasonable IOP comparability when compared to finger palpation in these patients in whom use of alternative tonometry methods were not possible. Peaks in IOP could be detected timely, permitting medical treatments and procedures to be adjusted or initiated.

In a recently completed early feasibility study (ARGOS-01), six glaucoma patients (4 POAG and 2 NPG) at a single university eye clinic in Germany had an earlier version of the ARGOS-IO pressure sensors implanted in the ciliary sulcus concomitantly to cataract surgery. Promising concurrence was seen between IOP profiles obtained with ARGOS-IO, GAT and DCT over the 12 months follow-up period and the ARGOS-IO system was easily used by the patients in the home setting. However, after two fibrin reactions classified as procedure-related SAEs were observed, as were multiple adverse events possibly caused by the size and/or form of the implant, the sponsor stopped the study to investigate the cause.

Analysis of an extensive databank of eye MRIs, obtained from MRI Research Inc., a company supported by the American National Institute of Health National Eye Institute, demonstrated that the ciliary sulcus undergoes a distortion in the first months following cataract extraction. This distortion, which is extenuated by the use of single piece IOLs such as those received by all patients in the ARGOS-01 study, caused a radial force to be exerted on the ARGOS-IO pressure sensor. In vitro testing was then conducted using a tool specially designed to mimic such pressure in a controlled manner. It was determined that when exposed to such force, the original ARGOS-IO pressure sensor prototype produces aberrant pressure readings and develops a curvature in its horizontal plane.

As a result of these tests and the ARGOS-01 study, modifications were made to the form of the device and the implantation procedure to improve the device's safety profile. The implant thickness was reduced from 0.9 mm to 0.5 mm overall, tapering to a rounded outer edge of only 0.1 mm, and haptics were added to the device to better maintain its positional stability and to reduce mechanical stresses of the sensor on the eye. In addition, four haptic arms and two allantoid protrusions on the posterior surface of the ring were added to the ring to improve its positional stability, facilitate unfolding and better distribute pressure on the ring. When subjected to radial force, the redesigned sensor ring did not show the abnormalities in pressure readings or the plane distortions seen in the earlier version..

The implant is also now available in three different diameters to allow selection of the implant size that best fits the individual participant. Related procedural changes, including the use of a cartridge injector similar to those used to insert foldable IOLs to insert the implant and first use of the sensor at 30 days post-surgery instead of at day 1 to 3 as in the previous study, are expected to reduce potential

stress to the patients' anterior chambers during surgery and the initial post-surgical period. Together, these changes are expected to reduce irritation of the iris and pressure drifting observed in the ARGOS-01 study.

Due to the unique form of the human eye, and the exacting nature of the fit, it is not possible to assess the effects of the design modification in animals.

At this point further clinical investigations are required to assess the safety and performance of the modified ARGOS-IO system. It should become apparent in the first stage of this study if these changes were sufficient to reduce the rate of inflammatory reaction. If as anticipated the investigation is successful, an innovative device will be made available that will permit easy measurement of IOP on a daily basis in the hospital, at the ophthalmologist and/or at home. This in turn will permit more frequent and exacting adjustments to treatment, thereby slowing disease progression and the blindness that accompanies it.

6. RISK EVALUATION

6.1 Anticipated clinical benefits

Reduction of IOP is to date the only proven therapy for glaucoma (Quigley, 2011). Improved control of IOP is linked to better long-term outcomes for glaucoma patients (King, 2013). Most of the currently available methods to measure IOP require office or clinic visits and are not feasible for frequent, round-the-clock or continuous use or for use in the patient's daily environment. At the same time, IOP fluctuates as a result of the patient's daily activities and circadian rhythm. Peak values – which are thought to be the most significant for long-term outcomes – are often not detected. Under normal clinical conditions for example in Germany, IOP of patients with diagnosed glaucoma is measured only once every 3 months, which does not provide enough information to adequately adjust patient treatment. The ARGOS-IO system will make numerous IOP measurements every day on a permanent basis, requiring only that the patient hold the external reader near the eye to activate the implant and download the readings several times daily. The physician is able to access the readings so recorded, thereby obtaining a complete profile of IOP changes, including peak values and values as influenced by all patient activities, for the entire time interval since the last treatment visit.

One objective of this study is to verify the device's accuracy in the patient population. Until this is done, only the control readings made via GAT will be used as the basis for treatment decisions. Study patients will however benefit from a more intensive than normal monitoring of their IOP during the study and are enabled to measure IOP daily themselves between D30 and D360. If and when the device's usefulness has been verified, the patients and the general patient population will benefit from the increased insight gained from a continuous long-term monitoring of IOP independent from visits to the ophthalmologist. If the device proves successful, the Sponsor plans to develop an internet platform that will permit the physician to remotely access information from individual readings, allowing patients' IOP to be monitored between visits. This should permit a more rapid response to changes in IOP and a better fine-tuning of treatment protocols.

Because glaucoma progresses slowly and does not generally cause any immediate symptoms, patients have no way of registering the success or failure of their treatment between clinic visits. As a result, as with other chronic diseases, adherence to prescribed treatment regimens may be poor (Hermann, Bron, & Creuzot-Garcher, 2010). The consequences of poor IOP control are however serious and irreversible loss of vision and accompanying handicap. The frequent feedback the patient will receive from the device is expected to motivate better compliance with the treatment regimen, thereby facilitating improved IOP control and optimizing long-term patient outcome.

6.2 Risk Management Process

Potential risks related to the intended use and foreseeable misuse of the ARGOS-IO system are identified and mitigated on an ongoing basis according to the risk management analysis prescribed by ISO 14971:2012 in combination with ISO/TR 24971: 2013 and detailed in the document ARGOS-IO Implant: Risk Management Report (01-RE-00D). The analysis is updated at least once annually, including the specific time points: before the start of the clinical investigation of the device, at the completion of the first phase of the study, at each interim analysis and whenever significant new information regarding the risk profile or AEs becomes available. Risks were identified based on a list of questions contained in Annex C of ISO 14971:2012, information and data obtained from published standards, scientific technical data, field data from similar devices already in use, clinical and preclinical evidence, results of appropriate investigations and expert opinion.

The sources listed above were also used to assign rankings for severity of possible harms and probability of occurrence for each identified risk. The rankings used are defined in Table 2 and Table 3, respectively.

Table 2. Levels of Severity used for Risk Assessment

Level of Severity		Possible Harm
	1	No harm
	2	Very brief, harmless discomfort
	3	Short term discomfort
	4	Minor damage or disablement, no expert medical intervention required
	5	Minor damage or disablement, that may require expert medical intervention
	6	Slight damage or disablement that requires expert medical intervention
	7	Temporary damage or marked disablement that requires expert medical intervention
	8	Permanent damage or disablement without further disease
	9	In combination with the diseases potentially lethal damage or disablement
	10	Patient death

Source: (Meyer, S, 2014)

Table 3. Levels of Probability used for Risk Assessment of ARGOS-IO system

Level of Probability		Frequency of Occurrence
	1	Improbable
	2	1 in 10^5 uses
	3	1 in $5x10^4$ uses
	4	1 in 10^4 uses
	5	1 in $5x10^3$ uses
	6	1 in 10^3 uses
	7	1 in $5x10^2$ uses
	8	1 in 10^2 uses
	9	1 in 10 uses
	10	Every use

Source: (Meyer, S, 2014)

A dichotomy was seen in severity of risks, with all risks having a severity higher than 7 related to the implant itself or the surgical procedure and those having a severity of 7 or less related to IOP measurements. On the basis of both severity and probability, the identified risks were categorized as either acceptable, as low as reasonably possible given the available risk mitigation measures or unacceptable. The rankings used are shown in Table 4.

Table 4. Risk Acceptability Matrix

Probability \ Severity	1	2	3	4	5	6	7	8	9	10
1	y	y	y	y	y	y	y	y	n	n
2	y	y	y	y	y	y	y	y	n	n
3	y	y	y	y	y	y	y	y	n	n
4	y	y	y	y	y	y	y	a	n	n
5	y	y	y	y	y	y	a	n	n	n
6	y	y	y	y	y	y	n	n	n	n
7	y	y	y	y	y	y	n	n	n	n
8	y	y	y	y	y	a	n	n	n	n
9	y	y	y	y	y	n	n	n	n	n
10	y	y	Y	y	a	n	n	n	n	n

Source: (Meyer, S, 2014)

Risk control measures were undertaken to reduce the probability of unacceptable and borderline acceptable risks. Where ever possible, priority was given to mitigating the risk first through design changes to eliminate it and if this was not feasible, by integrating protective measures in the medical device itself or in the manufacturing process to minimize the risk. Risks due to human factors that could not be eliminated or checked in advance, such as mistakes in the implant or explant procedures will be mitigated by including clear warnings and cautions in the literature and packaging accompanying the device and by limiting implantation use to experience ophthalmic surgeons. Finally, the resulting measures were reassessed to ensure that no new risks had been introduced during the mitigation process.

6.3 Anticipated Adverse Device Effects associated with the ARGOS-IO sensor device and their control

Anticipated potential risks of a long-term implantation of the ARGOS-IO pressure sensor are associated with:

- Surgical implantation of the ARGOS-IO pressure sensor
- Possible side effects and/or tolerance in the early or deferred post-operative period
- Possible crowding of ocular structures due to presence of the implant
- Side effects of the wireless IOP measurement
- Incompatibility with other surgical procedures or medical devices, such as silicone oil tamponade, glaucoma drainage device (GDD) and cochlear implants
- Incompatibility of interactions of the ARGOS-IO implant with topically applied ophthalmic medications and vice versa
- Potential unplanned explantation of the ARGOS-IO implant from the eye

In addition, the following risks, although not expected with the ARGOS-IO implant, have been associated with similar devices:

- Uncontrolled increase in IOP
- Changes in anterior chamber structures including ACD and ACA
- Fibrin reactions
- Anterior chamber hemorrhage
- Endophthalmitis
- Amotio Retinae

At the end of the risk mitigation process, possible risks were identified that could not be assessed in pre-clinical trials. These risks, which are the subject of the clinical investigation, include (Meyer, S, 2014):

- **Risks caused by ARGOS-IO implant size and/or form:** If the implant is too large for an individual, it could cause mechanical stresses on the sensor and the surrounding eye structure, leading to effects on the eye structure and/or affecting the function of the sensor. If the implant is too small, it could allow the implant to become visible in low light conditions or

cause positional instability. Both localized pressure and positional instability could also result from the form of the implant. Possible adverse device effects that could result include:

- **Angle Block:** The implant could theoretically push the iris forward, creating an angle block that leads to subsequent IOP elevation.
- **Aqueous flow inhibition:** Because the aqueous flows from the ciliary body through the pupil into the anterior chamber, it is remotely possible that the implant could interfere with the aqueous flow. According to animal studies and consultation with the advising physicians, it is unlikely that the implant will inhibit the flow of aqueous through the pupil.
- **Blockage of the optical axis:** There is a remote chance that the patient may experience shadowing or aperture effects as a consequence of the limited inner diameter of the device. This issue would be compounded if the implant becomes dislocated.
- **Irritation / Inflammation of the Eye, Iris Pigment Abrasion:** Tests in animals indicated a low level of irritation in the long term and inflammation levels as expected in the short term following eye surgery. However, due to the position of the implant within the human eye, there is a chance of higher levels of irritation and inflammation. Mild to moderate pigment dispersion was observed late in the ARGOS-01 study.
- **Incompatibility with the IOL:** Because both are being implanted in a confined area, there is a possibility that they will interfere with each other.

- **Mitigation: The following measures were undertaken to mitigate the above mentioned effects:**
  - It was concluded that due to the large volume of the natural lens that is removed during cataract surgery, there should be enough space in normal eyes for both the IOL and the ARGOS-IO implant without mutual interference. The ARGOS-IO pressure sensor implantation is contraindicated in eyes with an axial length less than 22 mm and an anterior chamber depth less than 2.5 mm. Eyes with an axial length less than 22 mm are excluded from the study. Physicians using state-of-the-art imaging technology are likely to identify, and exclude patients with a very shallow anterior segment.

- To ensure aqueous flow remains uninhibited, a surgical iridectomy is mandatory in the clinical trial.
- The inner and outer diameters of the implant were chosen to limit the chance of shadowing and aperture effects. In the ARGOS-02 study, the ASIC will be placed at the 12 o'clock position where any such effects will be limited by the morphology of the eye.
- A silicone material often used for IOLs was chosen for the surface of the implant. It has well known biocompatibility properties, a soft surface and rounded, smooth edges. Possible small material flashes are soft and non-traumatic.
- As a consequence of the ARGOS-01 study results, several changes were made to the form of the ARGOS-IO implant. The changes include the following:
  - Thickness of the implant has been reduced from 0.9 mm to 0.5 mm overall, tapering to a rounded outer edge of only 0.1 mm. The previous prototype had a uniform thickness including the outer edges.
  - Three different ARGOS-IO implant sizes (11.3 mm, 11.7 mm, 12.1 mm) are available to allow the selection of an optimal size for each patient by using WTW measurements.
  - Four haptic arms were added to the plane of the ring and two flat, rounded, allantoid protrusions were added to its posterior surface to both improve positional stability, facilitate unfolding after implantation and to better distribute pressure resulting.

- **Inaccuracy, imprecision and sensor drift:** measurements taken with the ARGOS-IO are ultimately to be used to guide treatment decisions. If the measurements are incorrect, inappropriate treatment and inadequate control of IOP could result.
  - **Mitigation:** accuracy, precision and sensor drift were tested and validated in bench tests and animal trials. A main objective of this clinical investigation is to evaluate these properties in humans. The ARGOS-01 study showed that although IOP values obtained with the ARGOS-IO system were constantly higher than those measured with GAT or DCT, there was good correlation between the IOP patterns over time. In this

study, only IOP values determined by GAT will be used to guide treatment decisions. Because the risk of undetected device failure will always remain, cautions are included in the IFU (ARGOS-IO Implant) and IB requiring that IOP values obtained with the ARGOS-IO system be confirmed with an alternative method of IOP measurement such as GAT on a regular basis.

- **Usability issues:** issues involving the handling and usability of the device, especially by the patient during self-tonometry have been considered.
    - **Mitigation:** Appropriate data will be collected during the clinical investigation to evaluate the practicality of the device.

6.4 Risks and Benefits associated with the participation in the clinical investigation

- **ARGOS-IO system associated risks** – As described in section 6.2, a full risk analysis was performed during the development of the ARGOS-IO system to anticipate and eliminate or at least minimize all foreseeable ARGOS-IO system-related risks. However – as with any new device – it is possible that unknown risks remain that will only become apparent as more experience is gained with the device. The safety of the study patients is of paramount importance and will be monitored throughout the study at all times. If at any time a safety issue arises that is thought to be related to the ARGOS-IO implant, to the specific procedures necessary to implant it, or to its use to measure IOP, appropriate measures will be initiated immediately to minimize risk to current and future study patients. All investigators will be kept informed of such issues. The ARGOS-IO was designed to be able to remain in the eye even in the event of failure. If it must be removed, for example due to adverse effects, the risks of removal correspond to those associated with implantation.

- **Data Privacy Risks** – Health data about study patients will be collected and transferred to an electronic database. Although, all currently required methods will be used to protect patients' privacy, the security of such databases can never be completely ensured. For this reason, no information that can identify study patients other than the pseudonymising participate number will be used on the database or on any study documentation other than the patient log, which will remain at the site. Potential patients will be informed of the data privacy policy during the informed consent process.

- Because of patients' vulnerable nature, there is a risk that they may either feel obligated to participate in the study or that their knowledge of the study may influence their decision whether or not to undergo cataract surgery at this time. To mitigate these risks, only patients who have already consented to cataract surgery will be informed of the study and all potential study patients will be told explicitly that they are free to choose not to participate, and that refusing will not affect their treatment except in regards to the ARGOS-IO system.

- It is possible that the study will show the ARGOS-IO system is not suitable for its intended use. In this event, future patients will be spared exposure to the ARGOS-IO system and information may have been gained to develop alternatives. Patients in this study may still have benefitted from their participation in the form of a closer follow-up and a positive altruistic feeling.

- Patients will be requested to attend visits on a regular basis. It is possible that this will be uncomfortable or inconvenient for them. Patients will be reminded that the information they provide is confidential, that it will be used to better the care they and fellow patients receive, and that their continued participation is voluntary.

6.5 Possible Interactions with Concomitant Medical Treatments

Interaction of the ARGOS-IO implant with other medical treatments and devices is possible both during the implantation, which is intended to occur concomitantly with cataract removal and implantation of an IOL, and indefinitely following implantation due to the intended permanence of the implantation and the continuing use of the external reader.

Possible interactions of the ARGOS-IO implant with other devices and/or substances used in treatments of the eye:

- **Instrumentation and substances used during the implantation procedure:**
    - Forceps for folding and extra- and intraocular manipulation of the implant
    - Folding fixture or injector
    - Other instruments commonly used for manipulation during intraocular implantation procedures: to prevent damage to the surface of the implant, it is important to avoid contact of the implant with sharp or pointed instruments such as toothed forceps
    - Viscoelastic surgical devices

- **Intraocular lenses** (no silicone lenses should be used in conjunction with the ARGOS-IO implant)
- **Keratoprothesis devices**
- **Glaucoma Drainage Devices:** GDD implantation is considered to be a final escalation stage for use in severe cases of refractory IOP elevation. The ARGOS-IO may be incompatible with insertion of the GDD tubing into the anterior chamber of the eye in certain anatomies. However, there are alternative methods of GDD tube implantation that will be compatible with ARGOS-IO implant.
- **Surgical Trabeculectomy:** this procedure is not likely to be affected by the implantation of the device.
- **High power ND:YAG Laser:** It is highly probable that After Cataract removal will be required in this patient population. If the laser is pointed directly at the implant it is likely to cause damage to the implant's electronic components. However, because laser beams can be precisely guided and controlled, pointing the laser beam at the contact would be likely only result from a grave treatment error.
- **Laser Trabeculoplasty:** it is unlikely that the ARGOS-IO will be a hindrance for laser trabeculoplasty.
- **Trabeculectomy:** it is unlikely that the ARGOS-IO will be a hindrance for trabeculectomy.
- **Interaction of the device with topically applied ophthalmic medications:** Although the device could theoretically affect effectiveness of the medication, thereby compromising therapeutic success for medication could interfere with functionality of the device, these risks are considered very unlikely. Chapman et al (1992) studied the absorption of common topical ophthalmic medications by silicone IOLs in vitro and found pharmaceutically negligible absorption. As the ARGOS-IO implant, which is encapsulated by a similar silicone material, has a surface area that is slightly larger than an IOL, the amount of absorption is expected to be slightly greater. However, given the low concentrations of pharmaceuticals found in the aqueous humor, and the low rates of absorption, effects are expected to be insignificant. In addition, although the encapsulation material is known to allow diffusion of several substances in the gas phase, the bubble free encapsulation method as well as the hermetic sealing of all chip openings with a hermetic gold cap make corrosion unlikely. No drug-device interaction was observed either during pre-clinical studies in rabbits (Paschalis, et al., 2014), during the

case studies or the ARGOS-01 study. Data will be collected in this investigation to allow further assessment of this risk.

- **Interaction of the device with topically applied ophthalmic ointments:** Isolated cases of silicone IOL contaminations caused by the seeping of antibiotic and steroid ointments applied to the eye following surgery through the incision have been reported. These cases, considered to be caused by incorrect bandaging procedures following surgery, required subsequent in explantation of the IOL (Werner, Apple, & Mamalis, 2010).
- **Silicone Oil used in Vitroretinal Surgery:** Silicone oil used in vitroretinal surgery has been reported to deteriorate the optical properties of silicone IOLs. This has however only been a problem in patients having severe vitroretinal disease requiring radical treatment with silicone oil (Werner, Apple, & Mamalis, 2010). The influence of silicone oil on the (non-optical) ARGOS-IO implant has been tested by the sponsor (01-RE-17A). No direct influence has been detected. However, if silicone oil has to be used in conjunction with the ARGOS-IO implant, performance has to be closely monitored.
- **Ocular dyes:** Although some dyes have been reported to permanently discolor some types of IOLs, silicone lenses are not known to be affected by commonly used ophthalmic dyes 0 (Werner, Apple, & Mamalis, 2010).

Interactions with other general medical procedures:

- **Magnetic Resonance Imaging (MRI):** testing has demonstrated safety of use of MRI (up to a magnetic field strength of 3T) with the ARGOS-IO pressure sensor, however imaging artifacts are likely to be seen in the proximity of the implant. The manufacturer should be consulted before the subject undergoes an MRI examination.
- **X-ray:** medical X-rays are unlikely to cause deletion of the EEPROM from the ASIC. Gamma radiation must not be used on the ARGOS-IO because it will very likely erase the EEPROM.

Interactions with other active implanted medical devices:

- **Cochlear Implants:** the ARGOS-IO is contraindicated in patients with cochlear implants
- **Brain nerve stimulators:** the ARGOS-IO is contraindicated in patients with nerve stimulators
- **Pacemakers:** the ARGOS-IO reader must not be activated in direct proximity to a pacemaker generator

- **Implantable cardioverter defibrillator (ICD):** the ARGOS-IO reader device must not be activated in direct proximity to an ICD generator.
- **Other devices generating high-frequency electromagnetic fields:** although it is conceivable that the device could be influenced by exposure to high-frequency electromagnetic energy, because it operates only on a narrow band length (13.56 MHz) the likelihood of this occurring is small. However interaction with oncological therapy or other hypothermia devices having high performance levels cannot be ruled out.

6.6 Possible Alternative Treatments

To be enrolled in this study, all patients must have glaucoma and cataracts requiring surgery.

Potential study patients must have consented to undergo cataract surgery with concurrent implantation of an IOL prior to enrollment in the study. If they decide not to participate in the study, they will undergo the same cataract surgery regardless of whether they participate in the study or not. The only differences will be any adaptations to the surgery required by the ARGOS-IO implant related procedures, such as a slightly larger incision size (4.5 mm), the iridectomy and the slightly longer surgery time.

Alternative methods for monitoring IOP are described in section 3.3.2 of this CIP as well as in the IB. The objective of this study is to evaluate the accuracy and reliability of IOP measurements with the ARGOS-IO system. Until these have been demonstrated, IOP will continue to be monitored using the standard GAT method. If potential subjects choose not to participate in the study, their IOP levels will continue to be monitored using GAT or other approved IOP measuring devices.

6.7 Risk/Benefit Assessment

Identified risks associated with the implantation and use of the ARGOS-IO system have been identified and minimized through the risk management process. This process, which is described in sections 6.1 to 6.5 of this CIP, and in more detail in the IB and the Risk Management Report, followed all relevant guidelines and industry standards. Unidentified residual risks of the ARGOS-IO system may remain. Although the risk profile for the patient is not expected to differ significantly from those seen with predicate devices such as IOLs and surgical procedures, that have been used in the clinical setting for decades, higher than expected safety events were seen in the ARGOS-01 study, in which an earlier ARGOS-IO implant prototype was used:

- fibrin reactions (4 from 6 patients)
- pigment dispersion (6 from 6 patients)
- pupillary distortion (5 from 6 patients)

As a consequence, modifications were made to the form of the device, the implantation procedure and the eligibility criteria to mitigate risk. Ongoing collection and analysis of information about any adverse events related to the device that do occur will allow rapid identification of previously unknown risks. The implementation of a two-stage design will also prevent the exposure of further patients to the device if risks are higher than currently anticipated.

These risks are to be balanced against the medical benefit of the quasi-continuous IOP measurement permitted by the device. Ophthalmologists will obtain valuable information about individual patients to better guide their treatment, and better insight into the progression of glaucoma in general. The ability of patients to actively monitor their condition on a daily basis will motivate them to better adhere to their prescribed treatment regimen for a condition that progresses gradually with few if any short term symptoms but devastating irreversible consequences.

Given the serious and permanent long-term consequences of poor IOP control in glaucoma patients and the difficulties associated with current methods of IOP monitoring, the residual risks of the ARGOS-IO system and their probability of occurrence are clearly within the range found acceptable for other similar ophthalmic devices currently on the market.

7. OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

7.1 Objectives

The aim of this trial is to verify the safety and performance of the ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG) and indicated cataract surgery. The measurements of intraocular pressure through the pressure sensor shall be compared with Goldmann Applanation Tonometry (GAT), which is generally accepted as the clinical gold standard. The ARGOS-IO pressure sensor will be implanted during cataract surgery and is to remain permanently in the eye.

7.1.1 Primary Objectives

7.1.1.1 Safety

- The primary objective of this clinical investigation is to evaluate the safety and tolerability of the ARGOS-IO pressure sensor in the first 3 months following implantation.

7.1.1.2 Performance

- To evaluate the performance of the ARGOS-IO system compared to GAT from day 30 through day 180.

7.1.2 Secondary Objectives

7.1.2.1 Safety

- To evaluate the safety and tolerability of ARGOS-IO pressure sensor implantation between 3 and 12 months

7.1.2.2 Performance

- To evaluate the performance of the ARGOS-IO system compared to GAT up to 12 months after implantation.

7.2 Primary and secondary hypothesis, to be accepted or rejected by statistical data from the investigation

- The specific hypothesis to be tested in this single arm two-stage design study is, that the SADE rate is at most 6%.
- If this hypothesis is proven, agreement of the measurements made with the ARGOS-IO system to those with GAT will be described by evaluation of the bias and limits of agreement.

7.3 Claims and intended performance of the IMD to be verified

This study aims to estimate the agreement of measurements taken with the ARGOS IO system to those obtained using GAT and to collect further information on the occurrence of AEs and ADEs and about the reliability of the device in humans.

7.4 Risks and anticipated adverse device effects to be assessed

Information will be collected on all AEs and ADEs. Particular attention will be paid to the following AEs, for which increased risks are considered possible:

- Uncontrolled increase in IOP
- Changes in anterior chamber structures including ACD and ACA
- Fibrin reactions
- Anterior chamber hemorrhage
- Endophthalmitis
- Amotio Retinae
- Pigment dispersion during surgery
- Postsurgical pigment dispersion
- Hypopyons
- Pupillary distortion
- Peripheral flattening or raising of the AC, including position and extent.

8. DESIGN OF THE CLINICAL INVESTIGATION

8.1 General Aspects

8.1.1 Description of the type of clinical investigation

The trial will be conducted as an open, prospective, multicenter single-arm clinical trial using the two-stage design described by Simon (Simon, 1989). In the first stage, 11 patients will have an ARGOS-IO pressure sensor implanted, after which enrollment will be halted until the patients have completed their 3 months follow-up visits and an interim analysis has been performed. The interim analysis will be reviewed by the DSMB. If two or more of these 11 patients in the first stage are found to have had an SADE, further enrollment into the study will be stopped. If not, enrollment will resume until another 11 patients have had an ARGOS-IO pressure sensor implanted. If two or fewer of the total 22 patients experience an SADE, a conclusion for safety will made at the 5% significance level. A corresponding 95% confidence interval for the SADE rate will be calculated according to the procedure of Koyoma (2008).

All patients who receive an ARGOS-IO implant will return for 10 follow-up visits to the clinic (day 1, 3, 10, 30, 60, 90, 120, 180, 240, 360) during the 12-month post-surgical period (see Table 6: Assessment Schedule). To allow comparison of the IOP measurement methods, IOP measurements will be made at every visit with GAT and with the ARGOS-IO systems beginning at V5 (day 30).

8.1.2 Description of the measures to be taken to minimize or avoid bias

No randomization and blinding/masking procedures will be used in this study. To avoid bias resulting from prior knowledge of the IOP value from the ARGOS-IO system on the measurement obtained with GAT, GAT will be used first.

8.1.3 Primary and secondary endpoints

8.1.3.1 Primary endpoints

Safety

- Number of patients experiencing a device related SAE defined as any adverse event that both
  - Is considered by the Investigator to have a possible, probable or definite relationship to the device and
  - That meets any of the following criteria of a serious adverse event:
    - Resulted in death, permanent damage or disability or a congenital anomaly
    - Was life threatening
    - Required hospitalization or intervention to prevent permanent impairment or damage

Performance

- Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system from V05 (day 30) through V09 (day 180).

8.1.3.2 Secondary endpoints

Safety

- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the 3 months immediately following implantation of the ARGOS-IO pressure sensor.
- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the first 6 months following implantation of the ARGOS-IO pressure sensor

- Incidence, nature, seriousness, severity and duration of adverse events and adverse device events in the 12 months following implantation of the ARGOS-IO pressure sensor.

Performance

- Limits of agreement between IOP measurements made using GAT and the ARGOS-IO system from V05 (day 30) through V11 (day 360).
- Incidence of device deficiencies in the 6 months following implantation
- Incidence of device deficiencies in the 12 months following implantation
- User acceptance of the implantation procedure by means of evaluation of the Implantation Procedure Questionnaire (Investigators)
- User acceptance of the ARGOS-IO system at the investigational site by means of evaluation of the Investigator Acceptance Questionnaire (Investigators)
- User acceptance of the ARGOS-IO system at home by means of evaluation of the Patient Acceptance Questionnaire (patients)
- Daily IOP self-measurement profiles (patients).

8.1.4 Equipment to be used to assess the clinical investigation variables and arrangements for monitoring maintenance and calibration

Sites will use their own ophthalmology diagnostic devices. The CRA will verify that the sites maintain and calibrate these devices on a regular basis.

8.1.5 Any procedures for the replacement of subjects

Screen failures (withdrawn for any reason up to implant) will be replaced. Subjects who withdraw their consent after implantation will not be replaced.

8.2 Investigational device(s) and comparator(s)

8.2.1 Description of the exposure to the investigational device(s) or comparators, if used

The ARGOS-IO pressure sensor is intended to be permanently implanted. Subjects will be exposed to the tip of the ARGOS-IO pressure sensor implant injector transiently during the implantation procedure and transiently to low-levels of electromagnetic energy induced by the MESOGRAPH reading device

during the reading sessions, at which time their skin may also be exposed to the MESOGRAPH outer surface.

The ARGOS-IO system will be directly compared to the non-invasive Goldmann Applanation tonometry (GAT). Therefore, subjects will not be exposed to any other active implantable comparators.

8.2.2 Justification of the choice of comparator

GAT is the standard tonometry method to which all other tonometers have traditionally been compared.

8.2.3 Other medical devices or medication to be used

No other investigational medical devices or medications will be used specifically for this clinical investigation, except for standard of care during surgery, standard devices for ophthalmic diagnostics, surgery follow up or Glaucoma treatment.

8.2.4 Number of investigational devices to be used

The ARGOS-IO pressure sensor will be implanted in up to 22 patients diagnosed with Primary Open Angle Glaucoma (POAG) and indicated cataract surgery. Sites will initially be provided with implants in all available sizes. Upon usage, individual implants will be resupplied. Approximately 90 devices (30 devices per implant size including replacement devices, if needed) will be required for this study.

8.3 Subjects

8.3.1 Inclusion Criteria

In order to ensure that the study population is representative of the eligible patient population, the Investigator must ensure that all patients who meet the following inclusion criteria are offered enrolment in the study. The investigator may not apply any additional eligibility criteria. Eligible subjects must meet all the following inclusion criteria:

1. Mentally competent and willing to provide written Informed consent.
2. Male or female aged ≥ 40 ≤ 85 years on the day of screening.
   Female subjects of childbearing potential (not surgically sterilized or more than one year post-menopausal) must be willing to use adequate contraception throughout the trial and must

have a negative pregnancy test (urine beta-hCG) within 24 hours prior to ARGOS-IO pressure sensor implantation.

3. Diagnosis of primary open-angle glaucoma (POAG) including high pressure glaucoma (HPG), normal pressure glaucoma (NPG) and ocular hypertension (OH) as defined by the European Glaucoma Society guideline (Heijl, Traverso, & al, 2008) requiring regular IOP measurements.
4. Sufficiently controlled IOP.
5. Phakic eyes.
6. Only one eye per patient may be implanted with the ARGOS-IO implant.
7. Cataract surgery indicated. The medical indication for a cataract operation must be given irrespective of the study participation. Potential study patients will be solicited for participation in the clinical trial only after the patient has given consent to the cataract operation.
8. Pre-operative anterior chamber depth (ACD) ≥ 2.5 mm as measured from the corneal endothelium.
9. Axis length > 22 mm.
10. Endothelial cell density of the cornea ≥ 2000 cells/mm².
11. Subjects able and willing to attend all scheduled visits and comply with all study procedures.

8.3.2 Exclusion Criteria

Eligible subjects must **not** meet any of the following exclusion criteria:

1. Any other type of glaucoma other than primary open-angle glaucoma as defined in inclusion criteria 3
2. Severe POAG patients with a macular degeneration and visual field loss of -20dB or worse
3. Exsudative age-related macular degeneration, instable macular degeneration 30 days prior to inclusion or macular edema
4. Retinal detachment
5. Corneal diseases
6. Diabetes mellitus
7. Connective tissue diseases

8. History or evidence of severe inflammatory eye diseases (i.e. uveitis, retinitis, scleritis) in one or both eyes within 6 months prior to ARGOS-IO pressure sensor implantation.
9. Intraocular surgical procedure(s) within 6 months prior to ARGOS-IO pressure sensor implantation or any surgical procedure such as refractive eye surgery that can affect the assessment of IOP by Goldmann Applanation tonometry.
10. History of eye tumor.
11. Ocular disease other than glaucoma that may affect assessment of visual acuity and/or IOP by Goldmann Applanation tonometry (choroidal hemorrhage or detachment, lens subluxation, thyroid ophthalmopathy).
12. Anterior chamber configuration that puts the subject at high risk to develop an angle closure glaucoma.
13. History of extensive keloid formation.
14. Severe dry eye syndrome.
15. Subjects who will need to undergo ancillary procedures in the study eye at the time of implantation or during the post-operative study period.
16. Any known intolerance or hypersensitivity to topical anesthetics, mydriatics, plaster or silicone (component of the device).
17. Existence of other active medical eye implant and/or other active medical implants in the head/neck region.
18. Any contraindications for IOL implantation such as choroidal hemorrhage, concomitant severe eye diseases, excessive vitreous loss, extremely shallow anterior chamber, microphthalmos, non-age-related cataract, posterior capsular rupture, severe corneal dystrophy, untractable IOP, zonular separation, color vision deficiencies
19. Severe generalized disease resulting in a life expectancy shorter than a year.
20. Any clinical evidence that the investigator feels would place the subject at increased risk with the placement of the device.
21. Currently pregnant or breastfeeding.

22. Participation in any study involving an investigational drug or device within the past 30 days or ongoing participation in a study with an investigational drug or device.
23. Patients who are not suitable for the study based on the surgeon's evaluation.
24. Patients unable or unwilling to understand or comply with required study procedures.
25. Patients with psychiatric disorders influencing their judgment or autonomy
26. Subject and/or an immediate family member is an employee of the investigational site directly affiliated with this study, the sponsor or the contract research organization.
27. Enrollment of the fellow eye in this clinical study.

8.3.3 Discontinuation or Withdrawal Criteria

8.3.3.1 Study stopping rules

As described in section 9, the study will be conducted in two stages. In the first stage, 11 subjects will receive ARGOS-IO implants, after which implantation will be halted. Once these subjects have completed their 3 months follow-up visits, the interim results will be evaluated by the DSMB. The study will be stopped for safety reasons if at the time of the interim analysis two or more of these 11 subjects have had SADEs or if the DSMB otherwise determines that severe safety risks to the subjects exist.

If more than two patients in the first stage of the study experience SADEs, the study will be stopped for safety reasons.

The study may be discontinued at any time for administrative reasons; if new negative data about the investigational device resulting from this or any other studies becomes available; and/or on advice of the DSMB, the sponsor, the investigators, and/or the EC or regulatory authorities.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the Regulatory Authorities and the ECs of the reason for termination or suspension. If the study is prematurely terminated for any reason, the investigator should promptly inform the study subjects and assure they receive appropriate therapy and/or follow-up.

The study can be terminated at any time for any reason by the sponsor.

8.3.3.2 Screen Failures

Screen failures are subjects who have signed the informed consent form but fail to meet eligibility criteria for enrolment e.g. they do not meet one or more of the inclusion criteria or do meet one or more of the exclusion criteria. Such subjects will return to standard treatment and will not be enrolled in the study. The only data collected on them will be the date of their screening visit, the date they gave informed consent and reason they are a screen failure. This data will be entered on the demography and study discharge pages in the CRF.

8.3.3.3 Premature subject withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time. The investigator must determine whether voluntary withdrawal is due to safety concerns.

All subjects who withdraw from the study after implantation and before completing the follow-up visits per protocol will be considered to be drop-outs. Subjects who drop-out or are withdrawn after implantation will not be replaced. Unless the patient revokes his/her permission to use it, any data collected up to the point of the patient's withdrawal will be included in the safety analysis. The data of all subjects who undergo implantation of the ARGOS-IO pressure sensor will be included in the efficacy analysis under the Full Analysis Set.

A patient will be withdrawn for any of the following reasons:

- The patient withdraws informed consent.
- It is determined during surgery that the patient is not feasible for ARGOS-IO pressure sensor implantation.
- The ARGOS-IO pressure sensor must be removed or replaced for any reason.

If the patient permits, all end-of-study assessments indicated in the visit schedule should be performed for implanted early discontinuing subjects.

Any subject who has been discontinued from the study because of an AE related to a study device or procedure will be followed as deemed appropriate by the investigator until resolution or stabilization of the event. This will be documented in the medical chart and in the CRF. Any patient who has been discontinued from the study because of an AE not related to a study device or procedure will be followed as deemed appropriate by the investigator.

The investigator will classify the termination reason of each subject at the end of the study in the termination page of the CRF according to the following:

- AE
- Non-compliance with clinical investigation plan (CIP)
- Lost to follow up
- Voluntary withdrawal not for AE
- Other reason.

8.3.3.4 Completed Subjects

A completed subject is considered to be a subject that completed all procedures as defined by the clinical investigation plan.

8.3.3.5 Subjects lost to follow-up

If a subject fails to appear for a follow-up examination, reasonable effort should be made to locate or contact them to at least to determine their health status while fully respecting the subject's rights. Reasonable effort consists of at least three documented attempts to contact the patient by phone or post. These efforts should be documented in both the source documents and the subject's CRF.

8.3.3.6 Pregnancy

If a patient becomes pregnant between screening and surgery, she will be withdrawn from the study. If a subject becomes pregnant between surgery and the end of the study, she may remain in the study if she wishes. Her follow-up will be limited at the discretion of the Investigator until the end of the pregnancy as necessary to protect her health and that of the fetus/embryo. The pregnancy will be documented as an AE and as a protocol deviation. The pregnancy will be followed until the end to determine its outcome.

8.3.4 Point of enrolment

A subject is considered as being enrolled into the clinical investigation when he/she gives consent in writing to participate in this investigation.

8.3.5 Total expected duration of the clinical investigation

The estimated total duration of the study from first patient screened to last patient last visit is 21 months.

8.3.6 Expected duration of each subject's participation

The maximum duration of each patient's participation in this clinical intervention is 13 months. The point of enrolment is considered to be the time point at which potentially eligible subjects sign the informed consent form. Surgery will be performed within 28 days of this time point. The patient will be followed-up for 12 months post-surgery to obtain data on safety and performance.

8.3.7 Number of subjects required

According to the sample size calculation described in section 9.2, 22 patients are considered to be adequate in order to gain sufficient data to support the analysis of the study endpoints.

8.3.8 Estimated time needed to select the planned number of subjects

The estimated recruitment time is considered to be 3 months for the first stage of the study and 3 months for the second.

8.4 STUDY PROCEDURES

8.4.1 Informed Consent

Eligible patients may only be included in the study after providing written informed consent as described in Section 12.1. Failure to obtain signed informed consent renders the patient ineligible for the study.

8.4.2 Allocation of Patient Number

Each subject is uniquely identified in the study by a combination of his/her country identifier, number and patient number. The number is assigned by the sponsor to the investigational site. Upon signing the Informed Consent Form, the subject is assigned a patient number by the investigator. The patient number will be composed of the country letter code (DE) and a 5-digit string with a 2-digit center identifier and a 3 digit patient identifier. This 3 digit patient identifier corresponds to the chronological order of enrollment in the center (e.g. the 21st subject included in the study in Germany at site 01 will

be patient DE-01-021). Once the patient number has been assigned to a subject, a number will not be reused even if the subject is a screen failure.

8.4.3 Methods and timing for assessing, recording, and analyzing parameters

During the study, subjects will attend 12 clinic visits, including 1 screening visit (up to 28 days prior to surgery), 1 surgery visit (day 0 = V01 surgery), and 10 follow-up visits (days 1, 3, 10, 30, 60, 90 120, 180, 240 and 360). The assessment schedule in Table 6 summarizes all visits and the assessments to be performed at each. The visit window given in the table should be adhered to as closely as possible.

8.4.3.1 Safety

At each follow-up visit, the Investigator will examine the patient and record information about any new or ongoing adverse events, adverse device events or clinically significant anomalies. In addition, the Investigator or designated site staff will ask the patient non-leading questions to ascertain if the patient experienced any adverse events or adverse device events between visits.

8.4.3.2 Performance

Starting at V05, IOP level will be assessed at every follow-up visit with both GAT and the ARGOS-IO system. Measurements will be performed in series of 1 GAT measurement followed by 3 consecutive measurements with the ARGOS-IO system, with no more than 10 minutes between the GAT and the first of the ARGOS-IO system measurements in the series. Two series of measurements, one each at the beginning and end of the visit, will be made at visits 06, 08 and 10. Four series of measurements, at the beginning (1), in the middle (2) and at the end (1) will be made at each of visits 05, 07, 09 and 11. There will be a minimum of 60 minutes between the last ARGOS-IO system measurement of one series and the GAT measurement of the next.

To assess device deficiencies, at each follow-up visit site staff will record any deficiencies observed during the visit and will examine the patient's hand-held reader device and ask patients non-leading questions starting at V06 (D60) to determine if any device deficiencies occurred during the home use.

To ensure accuracy and comparability of the recorded parameters, all responsible site personnel will be thoroughly instructed on the agreed measurement methods. In particular, to ensure that IOP measurements will be comparable between each patient's individual assessments as well as between the different subjects and sites.

To access the user acceptance of the implantation procedure and the general usability of the ARGOS-IO system, surgeons, personnel performing the ARGOS-IO system measurements and patients (self-measurement) will be asked to complete user acceptance questionnaires.

8.4.4 Assessments

8.4.4.1 Patient demographics/other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all subjects include: year of birth, sex, race, weight, height, educational level, pre-treatments and source of patient referral.

8.4.4.2 Medical history

Relevant medical history/current medical condition data includes data until start of ARGOS-IO pressure sensor implantation. Relevant medical history should be supplemented by review of the subject's medical chart and/or by documented dialog with the subject's referring physician. If possible, diagnoses and not symptoms are to be recorded.

8.4.4.3 Pregnancy test

Urine dip stick test at screening (SC) and before surgery (V01) will be performed in female patients of childbearing potential. The test type and results will be recorded in the subject's source documents. A positive result necessitates the exclusion of the subject from the study. For further details please refer to section 7.3.6.

8.4.4.4 Concomitant medication, treatments and devices

There are no restrictions for the use of concomitant medications and treatments required for ophthalmological or systemic diseases during this clinical investigation. The use of concomitant medication and treatments will be documented in the patient's file and in the CRF.

8.4.4.5 AEs/ADEs/SAEs/SADEs

Starting with the implantation of the ARGOS-IO pressure sensor, all AEs/ADEs/SAEs/SADEs will be recorded.

8.4.4.6 Device Malfunctions

Starting with the implantation of the ARGOS-IO system IOP measurements at V05 (D30), all observed device malfunctions will be recorded.

8.4.4.7 Questionnaires

In the study, three types of questionnaires will be used to assess potential strength and weaknesses of the ARGOS-IO system. Surgeons are asked to complete an implantation procedure questionnaire after each implantation at V01 (D0). At V11 (D360), the site staff responsible for IOP measurement as well as the patients will be asked to complete a user acceptance questionnaire for the MESOGRAPH reading device and the general measurement procedure.

The aim of these questionnaires is to gain more information about the level of user-acceptance of the ARGOS-IO system during implantation and during IOP measurement. The data collected with these questionnaires is only of exploratory nature and will not be included in the analysis. Results will provide the sponsor with data that could influence future device system improvements.

8.4.4.8 Optical Biometry (IOL Master®)

The IOL Master (Carl Zeiss Meditec, Germany) uses the principle of optical biometry partial coherence interferometry (PCI) to measure the axial length of the globe. The IOL Master is a non-contact optical biometry assessment method to determine which power of the intraocular lens (IOL) should be implanted during cataract surgery. Standard site procedure will be followed.

8.4.4.9 Visual acuity (VA)

The best corrected visual acuity will be determined after objective and subjective determination of refraction with the ETDRS chart in accordance with the ETDRS protocol. The number of characters read and the reading distance will be recorded. The standard testing distance is 4 meters.

8.4.4.10 Visual field (Perimetry)

The purpose of visual field testing is to determine both the outer limits of visual perception by the peripheral retina and the varying qualities of vision within that area. Perimetry is performed to obtain an accurate examination of the peripheral extent of the visual field. Automated perimeters will be used either with standard glaucoma field, field 30-2 or equivalent.

8.4.4.11 External Eye Photography

Standard external eye photography will be performed in order to document potential changes to the outer eye involving the iris or pupil structure.

8.4.4.12 Anterior eye segment measurement

Slit-lamp biomicroscopy (undilated, anterior segment)

Slit-lamp biomicroscopy involves the examination of the external ocular structures and the front of the eye. The following anatomic parameters will be assessed by using the slit-lamp biomicroscopy through an undilated pupil:

a) Lids
b) Conjunctiva
c) Cornea
d) Anterior chamber
e) Iris
f) Pupil
g) Lens
h) Anterior vitreous.

Optical coherence tomography (OCT)

Standard anterior segment OCT will be used to evaluate effects on change in chamber angle after surgery and to assess the central corneal thickness.

Confocal microscopy

Standard confocal microscopy will be performed to determine corneal endothelial cell density.

8.4.4.13 Gonioscopy

Gonioscopy

Standard gonioscopy will be used to confirm the glaucoma classification and to assess other problems within the anterior chamber, such as the presence of foreign bodies hidden in the recess of the angle. The method clearly confirms the POAG diagnosis by distinguishing primary open-angle glaucoma from secondary open-angle glaucoma. The gonioscopic grading system according to Spaeth (Spaeth, 1971) is used in this clinical investigation.

ARGOS-IO implant size assessment

The ARGOS-IO implant size will be determined based on the horizontal White-to-White (WTW) measurement obtained with the IOL Master. At least three WTW measurements will be taken and the average calculated. The average in mm will then determine the right ARGOS-IO implant size (Table 5).

Table 5. Recommended ARGOS-IO Implant Sizes

WTW Measurement (mm)	Recommended ARGOS-IO ring size (mm)
11.2 to 11.59	11.3
11.6 to 11.99	11.7
12.0 to 12.4	12.1

8.4.4.14 Posterior eye segment measurement

Biomicroscopy (dilated, fundus)

The posterior eye segment will be examined using a slit lamp in combination with a 90D or "Superfield" or comparable lenses. The following parameters will be assessed through a pupil dilated using mydriatic agents:

a) Optic nerve lesions
b) Other posterior pole lesions
c) Vitreous opacities
d) Optic nerve head
e) Fundus lesions
f) Retinal arteries and veins (AV)
g) Macular area
h) Fundus periphery
i) Normal and abnormal variations of the fundus.

Optical coherence tomography (OCT)

Posterior segment OCT will be used to assess macular structures and the peripapillary nerve fiber layer.

Fundus photography

Standard fundus photography will be performed at screening and at V07, V09 and V11 to document potential changes to the interior surface of the eye, including the retina.

8.4.4.15 Intraocular pressure (IOP) measurement

Intraocular pressure (IOP) will be measured using two techniques. Goldmann Applanation Tonometry (GAT) will be performed in the clinic at every visit. Beginning at V05, IOP measurement will also be performed with the ARGOS-IO system, both by site personnel at clinic visits and by the patient at home between visits. Only GAT will be used to guide any treatment decisions. The GAT must be performed by preferably one or at maximum two dedicated investigators at each site to reduce potential bias.

IOP measurement in the clinic

Each IOP measurement will be conducted as a series of 1x GAT followed by 3x ARGOS-IO system, except for Visits SC through V04 when only GAT will be used. When series of measurements are made, the GAT must always be used first to avoid operator bias. There should be no more than 10 minutes between the GAT measurement and the first of the ARGOS-IO system measurements in a series, and at least 60 minutes will lie between the last measurement with the ARGOS-IO system in one series and the GAT of the next.

IOP will be measured at least two times at every visit, preferably at the beginning and end of the visit. At Visits 05, 07, 09 and 11, IOP will be measured 4 times. Again, effort should be made to ensure there are at least 60 minutes between measurement series.

ARGOS-IO system measurement by the patient at home

At V05 (D30), after detailed instruction in their use, the patients will receive an individual Mesograph reading device and the Multiline Connector to perform self-tonometry at home. The patients will be requested to perform at least 4 IOP measurements with the Mesograph daily, evenly spread throughout the day. They will also be requested to connect the reader to the Multiline Connector on a regular basis to transfer the recorded IOP data directly into the secure database. No manual recording of data by the patient will be required.

Patients shall be instructed to bring the Mesograph reading device to every visit to permit site staff to check its functionality and to delete the measured IOP data from the device. The device routinely stores up to 3.000 measurements.

8.5 ARGOS-IO pressure sensor implantation

8.5.1 IOL implantation

Ophthalmic surgeons should perform the surgery according to their local routine working procedure for IOL implantation.

8.5.2 ARGOS-IO pressure sensor implantation

After implantation of the IOL, the ARGOS-IO pressure sensor ring will be inserted into the ciliary sulcus using the IOL implant injector provided by the sponsor. Please refer to the IFU for the ARGOS-IO implant and the IB for a detailed description of the process.

If during surgery, the ophthalmic surgeon decides for any reason that ARGOS-IO pressure sensor implantation is not in the subject's best interest, the surgeon will stop the ARGOS-IO pressure sensor implantation and will proceed as dictated by the subject's condition and standard of care.

8.5.3 Concomitant medication and devices during surgical procedure

Medication and devices routinely used during surgery (such as anesthesia, etc.) will not normally be recorded in the CRF. However, if there is a SAE during surgery, all medication administered during surgery will also be recorded.

8.5.4 Concomitant medication after implantation

The use of concomitant medication is at the discretion of the Investigator. Prophylactic use of steroid therapy and antibiotics according to standard local procedure is recommended following surgery.

8.5.5 Concomitant therapy in case of inflammatory events after implantation

If the patient shows signs of an inflammatory reaction following implantation, treatment such as administration of local and/or systemic steroid and antibiotic therapy is recommended, according to the local procedure regimens. In the event a hypopyon develops, an anterior chamber biopsy is recommended to determine whether it is sterile or due to an infectious agent.

8.6 ARGOS-IO pressure sensor explantation, if medically necessitated

The ARGOS-IO implant can be explanted at any time, when medically indicated. In case the ARGOS-IO implant has to be removed, follow the following steps:

- Corneal incision (approximately 3 mm) with appropriate instrument
- Viscoelastic injection to stabilize the anterior chamber
- Transect the ARGOS-IO implant at the microcoil area with appropriate scissors (e.g. Vannas scissors)
- Extrude one end of the transected implant through the wound with forceps and gently pull the rest of the implant out of the eye.
- Close the corneal incision with a suture following standard procedure.

8.7 Study Visits

8.7.1 Screening visit, SC (Day -28 to 0)

Only patients who have already independently agreed to undergo cataract surgery will be approached by the trial team about participation in the study.

At the SC, the investigator will conduct the informed consent process (section 12.1), ensuring that the subject's signature has been obtained on the patient informed consent (PIC) form and that the subject has received a copy before any study specific procedures are conducted. Once the PIC is signed, the subject will be assigned a patient number (section 8.2) and the Investigator will determine if the subject meets the eligibility criteria, the surgery visit will be scheduled and the screening fax form completed and faxed to the sponsor.

In addition, the following procedures will be performed at this visit:

- Collection of background information about the subject including: demographics, medical history with prior treatments and current medications.
- Pregnancy test, when applicable
- Visual acuity (ETDRS)
- Visual field (perimetry)
- Optical Biometry (IOL Master) including ARGOS-IO implant size assessment
- External eye photography
- Anterior Segment measurements (Slit-lamp biomicroscopy, AS-OCT, gonioscopy and confocal microscopy)
- Posterior Segment measurement (Biomicroscopy , PS-OCT, fundus photography)
- IOP measurement with GAT

- Instruct subjects on the need to report as soon as possible any SAEs occurring at any time during the study (starting from surgery, Visit 1)
- Complete the screening fax form and send to sponsor
- Complete the CRF.

8.7.2 Surgery, Visit 1 (Day 0)

The following procedures may be carried out one day before surgery (in subjects already hospitalized for the surgery) or on the day of surgery:

- Verify that the subject continues to meet eligibility criteria
- For female subjects of childbearing potential: collect urine for pregnancy test. A test done within 24 hours prior to surgery must be negative
- Perform external eye photography prior to surgery.

The following procedures are to be performed on the day of the surgery:

- Cataract surgery and ARGOS-IO pressure sensor implantation as described in section 8.5, including the recording of any AEs, SAEs starting from implantation of the ARGOS-IO pressure sensor; any concomitant medication related to SAE/SADEs during surgery; and any device malfunctions.
- Completion of the implantation procedure questionnaire (surgeon) and the CRF
- Complete the patient inclusion form and fax it to the sponsor
- Instruct subjects on the need to report promptly any SAE that may occur at any time during the study.
- Arrange a date for Visit 2 (V02).
- The duration of the patient's hospitalization is at the discretion of the Investigator. Recommended duration is 1 to 3 days, but durations of up to 7 days will not be considered in themselves to be SAEs.

8.7.3 Follow-up visits 02 to 04 (early post-surgical): days 1, 3 and 10

Procedures to be conducted at the early post-surgical visits include:

- Visual acuity
- External eye photography
- Recording of AEs/SAEs/ADEs/SADEs, concomitant medications (all)
- Anterior Segment Measurements: Slit-lamp microscopy only
- Posterior Segment Measurements: Biomicroscopy only
- IOP Measurement (GAT only)
- Complete the CRF and arrange the next visit.

8.7.4 Follow-up visits 05 to 11: days 30, 60, 90, 120, 180, 240 and 360

Procedures to be conducted at the early post-surgical visits include:

- Visual acuity
- Perimetry (Visits 07, 09 and 11 only)
- External eye photography
- Recording of AEs/SAEs/ADEs/SADEs, concomitant medications (all)
- Anterior Segment Measurements:
    - Slit-lamp microscopy at all visits
    - AS-OCT, gonioscopy and confocal microscopy at V07, V09 and V11
- Posterior Segment Measurements:
    - Biomicroscopy at all visits
    - PS-OCT, gonioscopy and fundus photography at V07, V09 and V11
- IOP Measurement: GAT and ARGOS-IO system
    - 4 series at visits 05, 07, 09 and 11
    - 2 series at Visits 06, 08 and 10
    - ARGOS-IO system self-measurement (by patients at home between visits)
- Complete the CRF and arrange the next visit

Visit 11 is in addition the study discharge visit. At this visit, patients will complete a User Acceptance Questionnaire for patients and the Investigator will complete a User Acceptance Questionnaire for Investigators. Site personnel will collect the Mesograph reader from the patient. After this visit, patients will return to standard care. They will be informed about the planned surveillance registry and asked if they wish to participate.

8.8 Visit schedule and assessments

Table 6. lists all assessments and indicates with an “X” the visits at which they and related assessments are to be performed. The visit window given in the table should be adhered to as closely as possible.

Table 6. Assessment Schedule

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11
Indicative Days (D)	**Up to 28 days before surgery**	**D0**	**D1**	**D3**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D60 +/- 5 Days**	**D90 +/- 10 Days**	**D120 +/- 10 Days**	**D180 +/- 10 Days**	**D240 +/- 10 Days**	**D360 +/- 10 Days**
GENERAL												
Informed consent signed	X											
Allocation of subject number	X											
Inclusion & exclusion criteria	X	X[1]										
Demography	X											
Past and current significant medical history	X											
Pregnancy test (urine beta-hCG)	X	X[2]										
Optical Biometry (IOL Master)	X[3]											
Cataract surgery and ARGOS-IO pressure sensor implantation		X										
Visual acuity (ETDRS)[4]	X		X	X	X	X	X	X	X	X	X	X
Perimetry[5]	X							X		X		X
External eye photography[6]	X	X	X	X	X	X	X	X	X	X	X	X
User acceptance questionnaire (patient)												X
Implantation procedure questionnaire (surgeon)		X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
AE/ADE/SAE/SADE		X	X	X	X	X	X	X	X	X	X	X
Device malfunction		X	X	X	X	X	X	X	X	X	X	X
ANTERIOR SEGMENT												
Slit-lamp biomicroscopy[7]	X		X	X	X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)[8]	X							X		X		X
Gonioscopy[9]	X							X		X		X
Confocal Microscopy[10]	X							X		X		X
POSTERIOR SEGMENT												
Biomicroscopy[11]	X		X	X	X	X	X	X	X	X	X	X
Optical coherence tomography (OCT)[12]	X							X		X		X
Fundus photography	X							X		X		X

Visit	SC	V01	V02	V03	V04	V05	V06	V07	V08	V09	V10	V11
Indicative Days (D)	**Up to 28 days before surgery**	**D0**	**D1**	**D3**	**D10 +/- 1 Day**	**D30 +/- 5 Days**	**D60 +/- 5 Days**	**D90 +/- 10 Days**	**D120 +/- 10 Days**	**D180 +/- 10 Days**	**D240 +/- 10 Days**	**D360 +/- 10 Days**
IOP Measurement												
Goldmann Applanation tonometry[13]	X		X	X	X	X	X	X	X	X	*X*	X
ARGOS-IO pressure sensor measurement[13]						X[14]	X	X[14]	X	X[14]	X	X[14]
ARGOS-IO pressure sensor self-measurement[15]						X	X	X	X	X	X	*X*

[1] Eligibility must be reassessed at V01 prior to surgery.

[2] For females of childbearing potential, a pregnancy test performed within 24 hours preceding surgery must be negative to confirm eligibility.

[3] The Optical Biometry measurement using the IOL Master made at SC will be used to determine the implant sizes (IOL and ARGOS-IO implant).

[4] The best corrected visual acuity will be determined after objective and subjective determination of refraction with the ETDRS chart in accordance with the EDTRS protocol.

[5] Perimetry is performed to obtain an accurate examination of the peripheral extent of the visual field. Automated perimeters will be used either with standard glaucoma field, field 30-2 or equivalent.

[6] External eye photography is performed through a slit lamp camera or equivalent. The outer eye shall be photographed in order to document potential changes to the iris or pupil structure.

[7] Slit-lamp biomicroscopy is performed though an undilated pupil to assess the following anatomic parameters of the anterior segment: lids, conjunctiva, cornea, anterior chamber, iris, pupil, lens and anterior vitreous.

[8] Anterior segment OCT is performed to evaluate effects on change in chamber angle after surgery and to assess the central corneal thickness.

[9] Standard gonioscopy is used to confirm glaucoma classification and to determine predilation angle evaluation, the presence of iris tumors, foreign bodies, anterior synechiae and to predict the anterior chamber angle. The gonioscopic grading system according to Spaeth is used in this clinical investigation.

[10] Standard confocal microscopy is used to determine the corneal endothelial cell density.

[11] Posterior segment biomicroscopy is performed though a dilated pupil using mydriatic agents by means of indirect ophthalmoscopy on a slit lamp with the aid of a 90D or “Superfield” or comparable lenses. This method is used to evaluate the following parameters: optic nerve lesions, other posterior pole lesions, vitreous opacities, optic nerve head, fundus lesions, retinal arteries and veins (AV), macular area, fundus periphery, normal and abnormal variations of the fundus.

[12] Posterior segment OCT is used to assess macular structures and the peripapillary nerve fiber layer.

[13] IOP measurements will be made in series of 1 Goldmann Applanation tonometry (GAT) standard measurements followed by 3 ARGOS-IO system measurements, the first of which must occur within 10 minutes of the GAT. A series of measurements will be made at both the beginning and end of each visit. An interval of at least 60 minutes should lie between the last measurement of one series and the first measurement in the next.

[14] At visits 5, 7, 9 and 11 at least 4 series of IOP measurements will be performed, with at least 60 minutes between the last measurement in one series and the first measurement in the next.

[15] All patients will receive a MESOGRAPH reading device at Visit 05 in order to measure the IOP daily at home. Measurements shall be taken at least 4 times per day (morning, noon, afternoon, evening). The MESOGRAPH reading device will be connected to an external GSM module, which will transfer the measured value directly to a secure database. Investigators can log into the database in order to track the pressure levels of their patients as required.

9. STATISTICS

9.1 Statistical design, method and analytical procedures

The primary purpose of this investigation is to assess safety of the investigational device. This will be judged statistically based on the number of individual patients experiencing serious device-related adverse events (SADEs). The study will be implemented in a two-stage design equivalent to the Simon optimum design to minimize the expected sample size (Simon, 1989). In the first stage, enrollment will be halted after 11 patients have received ARGOS-IO implants. An interim analysis will be conducted when these 11 patients have been followed-up for 3 months. If two or more patients experience SADEs in this time, the study will be stopped for safety reasons (Type I error rate = 0.05). If fewer than two have experienced SADEs, enrollment will be resumed and will be continued until a total of 22 patients have received ARGOS-IO implants. A final decision for safety will be drawn, if overall two or fewer of the total 22 patients have an SADE [SIMON optimum two stage design to minimize expected sample sizes, parameters: α=0.05, β=0.20, $p_0 = 0.75$ (proportion in stage 1 without SADE), $p_1 = 0.94$ (proportion overall without SADE)]. A corresponding 95% confidence interval for the proportion of the safety population with SADEs will be calculated using the method proposed by Koyoma and Chen (2008).

Table 7. Study design

	First Stage	Overall
SADE-free Subjects		
Proportion	$p_0 = 0.75$	$p_1 = 0.94$
Minimum number required	10	20
Subjects with SADE		
Proportion	$1 - p_0 = 0.25$	$1 - p_1 = 0.06$
Maximum number allowed	1	2
Total Number of Subjects	11	22

9.1.1 Demographic and baseline characteristics

Demographic characteristics (year of birth, sex, race, weight, height, educational level, pre-treatments and source of patient referral), length of time since diagnosis of glaucoma, anti-glaucoma medication, and other previous and concurrent treatments will be tabulated for the FAS.

9.1.2 Patient Disposition

The number and percentage of screened, enrolled and implanted patients, as well as those who complete the follow-up will be tabulated for the FAS and ITT population. The number and percentage of screen failures and early withdrawals will also be tabulated, along with the reason for the screen failure or drop-out.

9.1.3 Safety Analysis

The safety rate within the safety population will be estimated with a 95% confidence interval taking into account the two-stage Simon design.

9.1.4 Performance Analysis

The Bland-Altman method, which compares the mean of paired measurements to their difference will be used to determine the upper and lower limits of agreement expected to contain 95% of the IOP value pairs obtained with the ARGOS-IO system and GAT. The two-sided 95% confidence intervals for each of these limits will be calculated using the Mover method (Zou, 2011) to account for repeated observations. IOP values will be displayed as Bland-Altman plots of individual measurement pairs by measurement technique for each individual participant as well as mean plots over time.

Because the ARGOS-IO implant is in direct contact with the aqueous humor and gives a digital readout of IOP, it is anticipated to objectively measure the true IOP. In comparison, although GAT is considered the gold standard, it measures IOP indirectly through applanation of the cornea and is known to be influenced by corneal thickness and biomechanical properties (Burr, et al., 2012). In addition, measurements with GAT are known to be subject to operator bias.

Consequently, the absolute IOP values obtained with the ARGOS-IO system are expected to show a systematic shift in measurements compared to those obtained from indirect methods. However, deviation between the IOP measurements obtained with ARGOS-IO system and GAT over time should agree well with the shape of those obtained with the other methods. The limits of agreement will be calculated to provide an estimate of the agreement to allow direct comparison of values obtained with different methods.

9.2 Sample Size Calculation

The sample size calculation was based on the study's purpose of establishing safety.

To minimize the required sample size and consequently the number of patients exposed to risk while at the same time maximizing the chances of detecting safety events, a two-stage design based on the rate of non-events was chosen (Simon, 1989). The event of interest was defined as a serious device-related adverse events (SADEs). Based on a probability of non-events of p_0=0.75 for the first stage and an overall acceptable probability of p_1=0.94, a sample size of at least 11 evaluable patients in the first stage and additional 11 patients in the second stage are required. This maintains a type 1 error probability of 5% and the power of 80% based on minimizing the maximal sample size and results in an expected sample size of 13.2 patients.

9.3 Level of significance and the power of the clinical investigation

Significance level is set to 0.05, Power to 80%.

9.4 Expected drop-out rates

This section is not applicable.

9.5 Pass/fail criteria to be applied to the results of the clinical investigation

This investigation will be considered a success if fewer than two of the total 22 patients (stage 1 and 2) experience SADEs during the follow-up period.

9.6 Interim analysis

One interim analysis is planned for this study. It will take place when all patients in the first stage have completed the first 3 months of the follow-up period and will determine whether or not to continue the study to the second stage based on the number of patients experiencing an SADE..

9.7 Criteria for termination of the clinical investigation on statistical grounds

The participation of an individual site in the study will be discontinued if the sponsor, the investigator or the responsible ethics committee deems it necessary for any reason.

The complete study will be discontinued:

- If the sponsor and/or any responsible regulatory authority or ethic committee judge/s it necessary for any reason. See also section 8.9 Early Patient Withdrawal and section 12.10 Criteria for Suspension and Premature Termination of Study
- If, during the course of the study, the DSMB comes to the conclusion that further implantation of the ARGOS-IO pressure sensor would subject study patients to undue risk
- If more than 1 patient in the first stage of the study experiences SADEs during the first 3 months of the post-surgical follow-up period.

Patients who until that time had had an ARGOS-IO pressure sensor implanted will continue to be followed up.

9.8 Procedures for reporting of deviations from the original statistical plan

Significant deviations from the original statistical analysis plan will be listed and clarified in the final clinical investigation report.

9.9 Specification of Subgroups for Analysis

In order to investigate the impact of certain characteristics on performance, the co-primary endpoints will also be examined by the following variables:

- Gender
- Post-surgery complications
- Successful implantation
- Age groups
- Concomitant medication
- Pre-treatment
- Size of ARGOS-IO implant
- Country of investigational site
- Educational level.

9.10 Treatment of missing, unused and spurious data, including drop-outs and withdrawals

The handling of missing data will be detailed in the statistical analysis plan.

9.11 Datasets to be analyzed

9.11.1 Safety population

The data of all patients, with successful implantation of the ARGOS-IO implant, will be used for the safety evaluation.

9.11.2 The Full-Analysis-Set (FAS) population

The FAS population comprises all subjects in whom an ARGOS-IO pressure sensor was successfully implanted. Measurements recorded by the patient will not be included into the evaluation of the FAS population. Additional information about the drop-outs: all patients who revoke their consent and agreement preoperatively will be regarded as screen failures and will not be included in the statistical evaluation. All patients who revoke their consent and agreement postoperatively will be considered withdrawals and their data will be evaluated in the safety analysis.

9.12 Exclusion of particular information from the testing of the hypothesis

No particular information is planned for exclusion from the analysis.

9.13 Number of subjects at each site

It is planned to enroll an approximately equal number of subjects at each site.

10. DATA MANAGEMENT

10.1 Site Monitoring

The study will be monitored in compliance with the Declaration of Helsinki, ISO 14155:2011, the Clinical Investigation Plan (CIP) and all applicable national and local regulations. All monitoring activities will be conducted by trained and qualified monitors, who will document each individual monitoring visit. In general, during monitoring visits the monitor will ensure that the study is being conducted according to the CIP, ISO 14155:2011, ICH GCP (International Conference on Harmonisation Good Clinical Practice) and other applicable regulations, and will compare the CRF entries to original

source data. He/she will also make sure the informed consent procedure has been appropriately carried out and will ensure that all SAEs have been reported within applicable timeframes. He/she will also ensure that investigational device accountability has been maintained and will, after completion of the study, perform final accountability and arrange return or destruction of investigational products. Detailed monitoring procedures will be described in a separate monitoring plan.

10.2 Data collection

Data will be collected through a paper-based Case Report Form (CRF) provided by the sponsor or its designee to the centers prior to study start. The site will enter study data directly into the CRF during or as soon after the visit as possible.

10.3 Database Management and Quality Control

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. This includes maintaining any source documentation related to the study. The anonymity of participating subjects must be maintained. The sites will maintain a list of the subjects´ names and the Patient ID assigned to each individual patient. Documents that identify the subject beyond the Patient ID will not be submitted to the sponsor (e.g. the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow inspections by the regulatory authorities and audits by the study monitor or sponsor representatives.

The investigator must promptly review the completed CRFs for each subject. As the person ultimately responsible for the accuracy of all CRF data, the investigator must confirm the entries with his/her signature at the end of each documented subject's visit in the CRF.

After data review, a paper-based query will be generated by data management for any missing, out of range or questionable data and sent to the physician for completion. The physician will answer the query and this answer will be documented. All queries must be answered and the database locked before any (interim) analysis of the data may begin.

10.4 Verification, validation and security of electronic data system

It has been verified by the sponsor that only validated and secure electronic data systems will be used in this clinical investigation. Electronic data systems include the clinical data management database

and the ARGOS-IO system measurement database. Database validation and security follow the respective national and international requirements.

10.5 Data retention and Retention period

10.5.1 Investigator Records Retention

All study documents must be retained by the investigator for a period of at least 15 years after completion of the study. The investigator at each investigational site must maintain adequate records of the clinical study, including:

- Completed case report forms
- Medical records
- Signed informed consent forms
- Product accountability
- Shipment and receipt records
- Adverse Events reports
- All correspondence between the Investigator and the Ethics Committee, Regulatory Authorities, the sponsor and the CRO
- Any other pertinent data relevant to the study

The investigator must not destroy any study specific documentation before receiving written permission for this from the sponsor. Hospital records will be archived according to local regulations.

10.5.2 Sponsor Records Retention

The sponsor will maintain the following records for at least 15 years after the last device has been manufactured or until the company ceases to exist:

- All correspondence pertaining to the investigation
- Signed and dated Investigator Agreements and signed and dated investigator curriculum vitae that were current at the time of the study
- Copies of all EC approval letters, the EC review and approval procedures, and relevant EC correspondence
- Names and addresses of the institutions where the clinical investigation was conducted, as well as records of approval from site administration

- Correspondence with authorities as required by national legislation
- Insurance certificates
- Adverse Events report forms
- Names/contact addresses of monitors
- Statistical analyses and underlying supporting data
- Final and all interim reports of the clinical investigation
- Study training records for site personnel and sponsor/CRO personnel.
- Quality assurance

To assure accurate, complete and reliable data, the sponsor or its representatives will do the following:

- Provide instructional material to the investigational sites as appropriate
- Perform a detailed initiation visit to instruct and train the investigational site personnel concerning the investigational device and all relevant study procedures
- Perform regular monitoring visits at the investigational sites
- Be available for consultation and stay in contact with study site personnel by mail telephone and fax
- Review and evaluate CRF data on a regular basis
- Conduct assessment of the site's electronic patient database.

In addition, the sponsor or its representatives may periodically check a sample of subject data recorded against source documents at the study site.

To ensure the safety of study patients, and to ensure accurate, complete, and reliable data, the investigator will keep records of clinical notes and subject medical records in the patient files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ethical committees with direct access to original source documents.

The study may be audited by the sponsor or its representatives at any time. Such an audit will be conducted according to a specific audit plan. Investigators will be given notice before an audit occurs.

The regulatory authorities, both national and foreign, may inspect the study site at any time. The

Investigator is responsible for notifying the sponsor of such an inspection immediately upon gaining knowledge of it. During the audit or inspection, the investigator/institution will permit the auditor, and

regulatory inspector(s) direct access to all relevant medical records and other source data, study related files and CRFs.

11. ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

11.1.1 Definitions

The following definitions are based on ISO 14155:2011 and MEDDEV 2.7/3 (2010).

11.1.2 Adverse Event (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a subject, whether or not related to the investigational medical device

NOTE 1: This definition includes events related to the investigational medical device or the control.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

11.1.2.1 Adverse Device Effect (ADE)

Any Adverse Event (AE) that is related to the use of the investigational medical device is defined as Adverse Device Effect (ADE).

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

11.1.2.2 Serious Adverse Events

A Serious Adverse Event is defined as any Adverse Event that:

- Led to death
- Led to a serious deterioration in the health of a subject that:
    1. Resulted in a life-threatening illness or injury

2. Resulted in a permanent impairment of a body structure or body function
3. Required in-patient hospitalization or prolongation of existing hospitalization
4. Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function

- Led to fetal distress, fetal death or a congenital abnormality or birth defect

NOTE: An Adverse Event is considered 'Serious' if any one of the conditions 1, 2, 3, or 4 applies in combination with serious deterioration in health (e.g. a pre-planned hospitalization for a pre-existing condition, without a serious deterioration in health, is not considered to be a SAE).

NOTE for Germany: In Germany the term SAE is defined according to §2 Section 5 MPSV [Medical Devices Safety Plan Ordinance].

11.1.2.3 Serious Adverse Device Effect (SADE)

An Adverse Device Effect that has resulted in any of the consequences characteristic of a SAE.

11.1.2.4 Anticipated Serious Adverse Device Effect (ASADE)

A Serious Adverse Device Effect (SADE) which by its nature, incidence, severity or outcome has been identified in the risk analysis report is defined as an Anticipated Serious Adverse Device Effect (ASADE).

11.1.2.5 Unanticipated Serious Adverse Device Effect (USADE)

A Serious Adverse Device Effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report is defined as an Unanticipated Serious Adverse Device Effect (USADE).

11.1.2.6 Device Deficiency

An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance is defined as a Device Deficiency.

NOTE: Device Deficiencies include malfunctions, use errors, and inadequate labeling.

11.1.3 Recording of Adverse Events (AEs)

All Adverse Events (AEs) will be documented from the point of surgery until the subject is discharged from the study.

AEs will be collected with a non-leading question at each visit: “Have you had any new or worsening health problems since the last visit?” as well as by reporting those events directly observed and spontaneously reported by the subject. Clearly related signs, symptoms and abnormal diagnostic procedures should preferably be grouped together and recorded as a single diagnosis or syndrome whenever possible. Seriousness, **severity** (mild, moderate or severe), outcome and **relationship to investigational device** as well as expectedness and **action taken** will be recorded in the AE page of the CRF. **Start and end date and time** of the event will also be recorded.

Seriousness

Seriousness will be recorded as described in section 11.1.2.2.

Intensity/Severity

Severity of AEs will be assessed according to the following definitions:

- *Mild:* sign or symptom of the AE is apparent but is easily tolerated by the subject
- *Moderate:* the AE interferes somewhat with the subject’s usual activities (disturbing)
- *Severe:* the AE prevents the subject from working or performing his/her usual activities (unacceptable).

Relationship to study device

Assessment of causality is based on the following considerations: associative connections (time and/or place), pharmacological explanations, previous knowledge of the device, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The investigator will assess causal relationship to the investigational device according to following classifications:

- ***None*:** The time course between use of the device and occurrence or worsening of the AE rules out causal relationship; and/or another cause is confirmed and no indication for involvement of the study device in the occurrence/worsening of the AE exists
- ***Unlikely:*** The time course between use of the device and occurrence/worsening of the AE makes causal relationship unlikely; and/or the known effects of the device provides no indication for involvement of the study device in the occurrence/worsening of the AE; and/or

although it is conceivable based on previous knowledge that study device may have causal relationship to occurrence/worsening of the AE, another cause is much more probable; and/or another cause is confirmed and involvement of the study device in the occurrence/worsening of the AE is unlikely

- ***Possible:*** It is conceivable based on previous knowledge that study device may have causal relationship to the occurrence/worsening of the AE but other factors exist that are equally likely to be causative factors; or although the previous knowledge on study device does not provide any support for causal relationship, no other possible causative factors exist.
- ***Probable:*** Time relationship exists; and previous knowledge on study device supports causal relationship although another cause cannot be ruled out.
- ***Definite:*** The criteria for probable relationship are fulfilled and no other possible causative factors exist.

Action taken

The investigator will document the action taken in relation to the investigational device and to other treatments. The categories in relation to the investigational device are:

- No action taken
- Device removed
- Subject withdrawn from the study
- Other, specify

The categories in relation to other treatments are:

- No action
- Medication given (must be specified in the concomitant medication page)
- Non-medication treatment given (must be specified)
- Hospitalization
- Other, specify

Outcome The investigator will document the outcome by choosing one of the following alternatives:

- Recovered
- Recovered with sequelae
- Recovering

- Not recovered
- Death
- Unknown.

All AEs will be reported on an Adverse Event Form, one for each Adverse Event, which is part of the Case Report Form. AEs will be followed for 2 years after surgery.

11.1.4 Reporting of Serious Adverse Events (SAEs)

The reporting modalities for SAEs are defined in ISO 14155, MEDDEV 2.7/3 (Dec 2010) and local laws and regulations, in compliance with the requirements of Annex X of Directive 93/42/EEC, its amendment Directive 2007/47/EC, Annex 7 of Directive 90/385/EEC and local laws and regulations. SAEs need to be reported starting from ARGOS-IO pressure sensor implantation onwards.

Information reported on the SAE form shall include (see MEDDEV 2.7/3 Appendix, SAE Report Table 8 and/or national laws and regulations):

- A description of the event
- The date of event onset
- The relatedness of the event to the procedure
- The relatedness of the event to the device
- The expectedness of a SADE
- Actions taken as a result of the event
- The outcome of the event
- The date the event was first noticed by or reported to the investigator
- The date the event was reported to the sponsor.

Initial SAE reporting may be done by telephone or email, followed by the completed SAE form. Contact information is given on each SAE form and is available in the Investigator Site File.

All other Adverse Events will be documented in the source documents and reported on the Adverse Event form in the CRF in a timely manner after the investigator first learns of the event.

Table 8. Country-specific SAE reporting requirements

Country	SAE Form to be used	Reporting Responsibilities	Governing Law	Reporting Timeline

Germany	SAE Form (current version) provided by the Federal Institute for Drugs and Medical Devices (BfArM)	Sponsor and investigator has to report the SAE to the Federal Institute for Drugs and Medical Devices (BfArM)	German Medical Device Law (MPG) and Ordinance for Safety Reporting (MPSV) paragraph 3 section 5 and paragraph 5 section 2; EU directives 90/385/EEC Annex 7 number 2.3.5 and 93/42/EEG (modified by directive 2007/47/EC) Annex X number 2.3.5	Immediate reporting after occurrence

Regulatory authorities and ECs will be informed about SAEs according to local regulations as described in Table 8.

In case of an immediately reportable Adverse Event the investigators can contact **MDSS GmbH** and the Medical Device Safety Officer **Tom Barkow** via Phone, Fax or Email.

Please send the completed form to:

MDSS GmbH
Schiffgraben 41
30175 Hannover, Germany
Phone: +49 (0) 511 6262 8630
Fax: +49 (0) 511 6262 8633
Email: info@mdss.com

The sponsor should be informed in a parallel process.

11.1.5 Device Deficiencies

The investigator will record all observed device deficiencies by completing a Device Deficiency Form.
The reporting modalities are defined in ISO 14155:2011 and MEDDEV 2.7/3 in line with the requirements of Annex X of Directive 93/42/EEC and its amendment Directive 2007/47/EC, Annex 7 of 90/385/EEC and local laws and regulations.
All device deficiencies must be reported to the sponsor immediately. Any Investigational Medical Device Deficiency that might have led to a SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate must be reported as described in Table 8.6.3 following the SAE reporting modalities.

11.1.6 Medical Care

At all times during the study, the medical care of the subject is at the discretion of the investigator. Following the study, the subjects will return for standard control visits as needed.

11.1.7 Safety monitoring

A Data Safety Monitoring Board (DSMB) was established prior to enrolment of the first subject. The composition, frequency of the meetings, and roles is detailed in the DSMB charter which was approved by the DSMB at its first meeting.

In brief, the DSMB is composed of at least 3 members including two clinicians with expertise in Glaucoma and cataract surgeries and a biostatistician. Neither sponsor employees nor investigators participating in the study may be members of the DSMB. The DSMB is to review the safety data, including reported SAEs/SADEs, on a regular basis and advise the sponsor on any changes required to the conduct of the study.

The first meeting is planned when the 11 patients in the first stage have completed their 3 month follow-up visits. Enrollment will be halted to allow the DSMB to review their data and for changes to be made to the clinical investigation plan, if recommended. The DSMB may hold additional meetings whenever deemed appropriate.

It is foreseen that the DSMB may come to one of three types of recommendations, namely:

1. Continue the study as planned --No safety issues exist and it is ethical and feasible to continue the study as planned.
2. Continue the study with protocol amendments – Ethical to continue the study but recommend an amendment to the protocol (e.g. incorporate additional or more frequent safety examinations).
3. Stop enrollment and treatment -- Sufficient evidence for a serious safety concern exists, making further implantation of ARGOS-IO pressure sensors in subjects unethical.

11.1.8 Sponsor Responsibilities

The Sponsor is responsible for reporting Serious Adverse Events, interim or annual safety reports, premature termination or suspension of the clinical investigation, and the final Study Report to Regulatory Authorities, the ECs and investigators. Refer to Table 8. and Table 9 for details.

Table 9. Sponsor Reporting Responsibilities

Reporting Responsibility	Reports to	Description
Serious Adverse Events (SAEs)	Regulatory Authorities, ECs	See Sections 11.1.2.2 for details
Interim or annual safety reporting	ECs and/or CA per local regulations	An interim or annual safety report may be required by country regulations, or may be specifically requested by the EC/CA
Premature termination or suspension of the clinical investigation	Investigators, ECs, relevant Regulatory Authorities	Provide prompt notification of termination or suspension and reasons
Final Study Report	Investigators, ECs, relevant Regulatory Authorities	The sponsor will notify the investigators of the completion or termination of the study. A Final Study Report will be submitted to the investigators and the ECs following local regulations.

12. ADMINSTRATIVE PROCEDURES AND RESPONSIBILITIES

12.1 Informed Consent

Eligible patients may only be included in the study after providing written informed consent as approved by the responsible ethic committee. The Patient Informed Consent (PIC) form must be fully signed and dated prior to any study related activities required by the protocol (including any diagnostic testing, questionnaires, or other study-related procedures). Failure to obtain signed informed consent renders the patient ineligible for the study.

A proposed PIC that complies with the ISO 14155:2011 standard and is considered appropriate for this study will be submitted to the Ethics Committees. The PIC will be translated into the local language of each country in which the study will be conducted and will contain language that is non-technical and understandable to the patient. Any changes to the PIC suggested by the investigator must be agreed to by Implandata Ophthalmic Products GmbH before submission to the EC and a copy of the EC approved version must be provided to the monitor after EC approval.

The Investigator or designated sub-investigator must explain the study to the patient in detail, talking through all points described in the PIC. The patient must be given the opportunity to ask questions and ample time to consider his/her participation. The patient will also be informed of his/her right to withdraw from the study at any time without giving a reason. If the patient is willing to participate in the study, he/she must sign and date two copies of the PIC, which must also be signed and dated at the same time by the investigator or designated sub-investigator who explained the study.

One copy of the PIC will be given to the patient and the other will be retained in the Investigator Site File (ISF).

Subject information and the PIC will be revised if new information becomes available or a CIP amendment is issued regarding patient's safety, study procedures or any aspects of the study that could potentially influence the patient's willingness to continue in the study. After the new patient information documents have been approval by EC and regulatory authorities, the patient will be informed of the changes and will be asked to sign the new consent form to confirm his/her continuation in the study. The investigator is to ensure that the patient is informed in a timely manner about any new safety-relevant information that could affect the patient's willingness to continue in the study and agrees to request the patient's consent again, if necessary.

12.2 Regulatory and Ethical Compliance

This clinical study was designed and shall be implemented and reported in accordance with ISO 14155:2011, with applicable local laws and regulations, and with the ethical principles laid down in the Declaration of Helsinki and described in the ICH-GCP guidelines.

12.3 Approval from Ethics Committee or Regulatory Authority

The Clinical Investigation Plan (CIP) and the proposed PIC must be reviewed and approved by a properly constituted Ethics Committee (EC) before study start. A signed and dated statement from the EC that the CIP and PIC have been approved by the EC must be given to Implandata Ophthalmic Products GmbH before study initiation.

The study must be reviewed and approved by the responsible Regulatory Authorities before study initiation, according to local and national regulations, if required. When an approval process is not required by the Regulatory Authority at least a notification shall be performed. Any additional requirements imposed by the EC or Regulatory Authority will be followed.

If any alterations, other than changes of an administrative nature only, are made to the study CIP, a formal CIP amendment will be issued and submitted to the relevant EC for approval. The amendment will not be implemented until EC approval, except in cases where immediate implementation is necessary to eliminate or prevent imminent hazard to the subjects.

12.4 Investigator Responsibilities for Ethics Committees and Regulatory Authorities

Prior to study start, the investigator is required to sign a protocol signature page confirming his or her agreement to conduct the study in accordance with all of the instructions and procedures found in this protocol and associated documents and to give access to all relevant data and records to Implandata Ophthalmic Products GmbH, monitors, auditors, Quality Assurance representatives, designees, Ethics Committees, and regulatory authorities as required. If an inspection of the investigational site is requested by a regulatory authority, the investigator must immediately inform Implandata Ophthalmic Products GmbH that this request has been made.

12.5 Reporting responsibilities

12.5.1 Investigator Reporting Responsibilities

The investigator or designee is responsible for completing (including review and signature) and submitting to the sponsor all case report forms, as well as reports of any Adverse Events (according to country-specific collection requirements), deaths or deviations from the clinical investigation plan. If any action is taken by the EC with respect to the investigation, the investigator will forward the information to the sponsor as soon as possible. Reports are subject to inspection and to the retention requirements as described in section 10.5. Refer to Table 6 for SAE reporting responsibilities.

12.5.2 Sponsor Reporting Responsibilities

The sponsor is responsible for reporting Serious Adverse Events, interim or annual safety reports, premature termination or suspension of the clinical investigation, and the Final Study Report. Refer to Table 7 for details.

12.6 Insurance

The sponsor maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, proof of the clinical trial insurance policy will be provided to the Ethics Committee. If required by national regulations, indemnification will be provided.

12.7 Amendments to the CIP

The sponsor will inform the investigator about any relevant changes to the CIP. Changes will be documented as an amendment to the CIP that will be signed by each investigator. Unless required to prevent harm to a subject, no changes to the CIP may be implemented by the investigator before a fully approved amendment is available. If applicable, due to the nature of the amendment and in accordance with local regulations, EC and CA notification and/or approval is also required before the amendment is implemented.

The investigator is expected to take any immediate action required to ensure the safety of any patient included in this study, regardless of any need for approval of formal protocol amendments, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified of this action promptly and the Ethics Committee responsible for the study site should be informed.

12.8 Deviations from the CIP

The investigator is not allowed to deviate from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency situation or when caused by unforeseen circumstances that are beyond the investigator's control (e.g. subject did not attend scheduled visit). Such approval will be documented in writing and maintained in the Investigator Site File (ISF) and Trial Master File (TMF).

The site will report all deviations, regardless of whether medically justifiable or taken to protect the subject in an emergency, to the sponsor in a timely manner on a protocol deviation form. In addition, the investigator is required to adhere to the Ethics Committee procedures for reporting deviations.

Deviations include, but are not limited to the following list:

- Failure to obtain informed consent prior to conducting study specific activities
- Incorrect version of the PIC used
- Subject did not attend treatment visit, or visit was outside the required timeframe
- CIP-required testing and/or measurements were not done or were done incorrectly
- Adverse Events not reported by investigators within the required timeframe as specified in the CIP
- Source data permanently lost
- Pregnancy.

A sponsor representative or monitor will review site compliance with regard to deviations at each monitoring visit. The monitor will discuss any deviations that occurred at the investigational site directly with the investigator and will summarize the findings in a follow-up letter to the site. In addition, all deviations from the CIP will be documented in the final study report.

12.9 Recording, Reporting, Analysis of CIP Deviations

The site will report all deviations, regardless of whether medically justifiable, or taken to protect the subject in an emergency, to the sponsor in a timely manner on a protocol deviation form. In addition, the investigator is required to adhere to the Ethics Committee procedures for reporting deviations.

Deviations include, but are not limited to the following list:

- Failure to obtain informed consent prior to conducting study specific activities
- Incorrect version of the PIC used
- Subject did not attend treatment visit, or visit was outside the required timeframe
- CIP-required testing and/or measurements were not done or were done incorrectly
- Adverse Events not reported by investigators within the required timeframe as specified in the CIP
- Source data permanently lost

- Pregnancy.

A sponsor representative or monitor will review site compliance with regard to deviations at each monitoring visit. The monitor will discuss any deviations that occurred at the investigational site directly with the investigator and will summarize the findings in a follow-up letter to the site. In addition, all deviations from the CIP will be documented in the final study report.

12.10 Corrective and preventive action and principal investigator disqualification criteria

See section 12.8 Deviations from CIP. After analyzing and taking corrective actions, site personnel will be retrained by the sponsor or its representatives on the relevant study procedures. All necessary measurements will be taken to prevent re-occurrence of the protocol deviation. If despite this retraining an investigational site continues to deviate from the CIP, the site will be discontinued from the study.

12.11 Suspension or Premature Termination

The sponsor may temporarily or permanently discontinue the study at a single site or at all sites for safety, ethical, compliance or other reasons. If this is necessary, the sponsor will endeavor to provide advance notification to the site. If the study is suspended or discontinued, the investigator or the sponsor will be responsible for promptly informing the ethics committee. The monitor will visit the site to conduct a study site closure visit.

12.12 Criteria for access to a breaking/masking code in the case of suspension or premature termination of the clinical investigation, if applicable

This section is not applicable.

12.13 Subject follow-up requirements

All pregnancies will be followed to birth. All on-going AEs will be followed-up until resolution or until 7 days after the last subject has been discharged from the study. All SAEs will be followed-up until resolution or stabilization.

12.14 Investigator and Site Selection

Site selection will be based on the site's experience with and access to patients requiring mitral valve repair/annuloplasty. Sites need to meet the following criteria:

- Compliance:
  - Willing to comply with the Clinical Investigation Plan (CIP), all required procedures, the Declaration of Helsinki, ISO 14155 and national and local regulations
- Expertise
  - Investigator experienced in the procedure of annuloplasty
  - Access to the patient population
- Patient recruitment potential
  - Potential of 2-8 patients in the given timeline
  - Patient enrolment and site commitment not expected to be impacted by any competing studies
- Clinical support staff
  - Study nurse/assistant/coordinator or equivalent who are adequately trained and willing to invest time in study administration and electronic data input
- Time investment
  - Investigator has sufficient time to fulfill the study requirements, including reporting, and to attend the study meetings.
- Equipment / Procedures
  - Separate rooms to perform study procedures
  - Sufficient, lockable storage capacities for study materials.

13. PUBLICATION POLICY

13.1 Study Report and Publication

The sponsor is responsible for generating a Clinical Study Report of the study after the study is completed. This report, or parts of it, must be submitted to the relevant authorities if applicable.

The publication of study results will be agreed between the sponsor and the investigator(s). The sponsor is interested in publishing the results of the study, but to prevent publication of any confidential information, the sponsor retains the right to review all publications and presentations before they are made public.

14. REFERENCES

Bland, J., & Altman, D. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, S. i: 307-310.

Burr, J., Botello-Pinzo, P., Takwoing, Y., Hernández, R., Vazques-Montes, M., Elders, A., & al, e. (2012). Surveillance for ocular hypertension: an evidence synthesis and economic evaluation. *Health Technology Assessment*, S. 16 (29).

Cao, M. (2010). *Silicone-Coated Microchip for Ocular Implantation.* Atlanta, USA: NAMSA Advisory Services.

Chapman, J. M., Cheeks, L., & Green, K. (Vol. 18, September 1992). Drug interaction with intraocular lenses of different materials. *J Cataract Refract Surg*, S. 456-459.

Cihara, E. (2008). Assessment of true intraocular pressure: the gap between theory and practical data. *Surv Ophthalmol*, S. 203-218.

Donaldson, P. (1991). Aspects of silicone rubber as an encapsulant for nerological prostheses Part 1. Osmosis. *Medical and Biological Engineering and Computing*, S. 29(1):34-49.

Dreher, WF; Kern, N; Warres, C. (2010). *56586 Characterisation of Sensor Surface.* Tübingen: NMI Natural and Medical Sciences Institute.

Frampton, P. (2012). Tonometry: Does Historical Precedent and Familiarity Constrain Development. *Ophthalmology Times*.

Görtz, M. (2010). *Exemplarische Driftmessungen und Dichtigkeitstest für den 8D12-Prozess.* Fraunhofer IMS,.

Heijl, A., Traverso, C., & al, e. (2008). *Terminology and Guidelines for Glaucoma.* European Glaucoma Society.

Hermann, M., Bron, A., & Creuzot-Garcher, C. D. (2010). Measurement of Adherence to Brimonidine Therapy for Glaucoma Using Electronic Monitoring. *J Glaucoma*, S. 8:502-508.

Implandata. (2013). *Klinischer Sicherheitsreport: Klinische Prüfung Intraokulärer Drucksensor "ARGOS", ref nr.* Implandata GmbH.

Implandata. (2014). *Clinical Investigation Report: ARGOS 01.* Hannover, Germany.

Implandata. (2014). *Investigator's Brochure: ARGOS-02 (01-RE-17A).*

Implandata Ophthalmic Products GmbH. (2014). *Instructions for Use: ARGOS-IO Implant.*

ISO 14155. (2011). *Clinical investigation of medical devices for human subjects - Good clinical practice.* International Organization for Standardization.

Kakaday, T., Hewitt, A., Voelcker, N., Li, J., & Craig, J. (2009). Advances in telemetric continuous intraocular pressure assessment. *Br J Ophthalmology*, S. 93: 992-996.

King, A. (2013). Glaucoma. *BMJ*, S. 346: 3518.

Koyama, T., & Chen, H. (2008). Proper inference from Simon's two-stage designs. *Stat Med*, S. 27 (16):3145-54.

Krug, A., Kompa, S., & Schrage, N. F. (25. 3 2002). The Aachen-keratoprothesis--a felxible KPro That Permits Intraocular Pressure Measurement. *The International Journal of Artifical Organs*, S. 238-242.

Liang, S., Lee, G., & Shields, D. (2009). Self-tonometry in Glaucoma Management -- Past, Present and Future. *Survey of Ophthalmology*, S. 54: 450-462.

Lopez, M., Melki, S., & Dohlmann, C. H. (2013). Two keratoprosthesis patients with intraocular pressure sensor - followed for two years. *Unpublished Data*.

Mansouri, K., & Shaarawy, T. (2011). Continuous intraocular pressure monitoring with a wireless ocular telemetry sensor: initial clinical experience in patients with open angle glaucoma . *Br J Ophthalmol*, S. 95: 627-629.

MEDDEV 2.7/3. (2010). *Clinical Investigations: Serious Adverse Event Reporting under Directives 90/385/EEC and 93/42/EEC.* European Commission Directorate General for Health and Consumers.

Melki, S., Todani, A., & Cherfan, G. (2013). Telemetric Intraocular Pressure Measurement: Report of First Human Implantation. *Unpublished data*.

Melki, S., Todani, A., & Cherfan, G. (2014). An Implantable Intraocular Pressure Transducer: Initial Safety Outcomes. *in press*.

Meyer, S. (2014). *ARGOS-IO Implant: Risk Management Report.* Hannover, Germany: Implandata Ophthalmic Products GmbH.

Niedhart, C; Müller, U. (2011). *Investigation Report B0062/11 Cytotoxicity Investigations.* Aachen: BMP Labor für medizinische Materialprüfung GmbH.

Paschalis, E., Cade, F., Melki, S., Pasquale, L., Dohlman, C., & Ciolino, J. (2014). Reliable intraocular pressure measurement using automated radio-wave telemetry. *Clinical Ophthalmology*, S. 8: 177-185.

Quigley, H. (2011). Glaucoma. S. 377: 1367-77.

Rotchford, A., & King, A. (2012). Repeatability of measurements of effectiveness of glaucoma medication. *Br J Ophthalmol*, S. 96: 1494-1497.

Simon, R. (10 1989). Optimal Two-Stage Designs for Phase II Clinical Trials. *Controlled Clinical Trials*, S. 1-10.

Spaeth, G. L. (Vol. 91 1971). The normal developmentof the human anterior chamber angle: a new system of descriptive grading. *Trans Opthalmol Soc UK*, S. pp. 709-739.

Todani, A., Behlau, I., Fava, M., Cade, F., Cherfan, D., Zakka, F., . . . Melki, S. (2011). Intraocular Pressure Measurement by Radio Wave Telemetry. *Invest Ophthalmol Vis Sci*, S. 52: 9573-9580.

Werner, L., Apple, D., & Mamalis, N. (2010). Opacification and coloration of Intraocular Lenses. *In R. Steinert, Cataract Surgery, 3rd Edition*.

Zou, G. (2011). Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual. *Stat Methods Med Res*, S. 0 (0): 1-13.

Addendum to Clinical Investigation Plan: A prospective, open-label, multicenter clinical investigation to assess the safety and performance of ARGOS-IO system in patients with Primary Open Angle Glaucoma (POAG)

To Current Revision: ARGOS-02_CIP_RevC_20140218

Part 1: Enrollment

Page 8, Table: Synopsis, Row: Study Design:

RevC

This clinical investigation prospective, open-label, multicenter, single-arm clinical investigation will be conducted in two stages using a Simon two-stage design. Subjects will be enrolled as follows:

First stage: 11 patients

Second stage: 11 patients

An interim analysis will be performed when the 11 patients of the first stage have completed their 3 month follow-up visits. The trial will be stopped if 2 or more patients have experienced a serious adverse device events (SADE) at this time. Otherwise enrollment will be resumed and the trial continued until an additional 11 patients have been enrolled in stage 2 and received ARGOS-IO implants. A conclusion for safety will be made if in total no more than 2 of the total of 22 patients experience an SADE.

Ammended

This prospective, open-label, multicenter, single-arm clinical investigation will enroll 22 consecutive Patients.

Enrollment will be temporarily halted in case a serious adverse device effect (SADE) occurs, and a Data and safety Monitoring Board (DSMB; see section "Safety Monitoring" on page 16) meeting will be conducted as soon as possible. The DSMB will then recommend whether to further continue the study as planned, or whether enrollment shall be stopped. A conclusion for safety will be made if in total no more than 2 of the total of 22 patients experience an SADE.

Page 8, Table: Synopsis, Row: Sample Size Considerations:

RevC

The primary aim of this study is to show "safety", which will be evaluated based on the percentage of subjects who experience an SADE (= "non-safety), as defined in the primary endpoints.

For the study as a whole, "safety" will be determined based on the following decision rule: if in stage 1 the non-safety event rate is greater than 25%, the trial will be stopped (type 1 error rate of 0.05). If

the non-safety event rate is lower than 25%, the study will be continued into stage 2. It will be declared a success if the final non-safety event rate is less than 6% (type II error rate of 0.20) The calculation is based on a two-stage Simon design optimizing the minimum expected sample size with parameters α=0.05, β=0.20, $p_0 = 0.75$, $p_1 = 0.94$.

Ammended

The primary aim of this study is to show "safety", which will be evaluated based on the percentage of subjects who experience an SADE (= "non-safety), as defined in the primary endpoints.

The study will be declared a success if the final non-safety event rate is less than 6% (type II error rate of 0.20) The calculation is based on a design optimizing the minimum expected sample size with parameters α=0.05, β=0.20, $p_0 = 0.75$, $p_1 = 0.94$.

Page 16, Table: Synopsis, Row: Safety Monitoring:

RevC

A data safety monitoring board (DSMB) will be established prior to enrollment of the first patient. The DSMB is to review the safety data, including SAEs/SADEs, on a regular basis and will advise on any changes required in the conduct this clinical investigation. The DSMB will also review the data of the interim analysis and give recommendations to the Sponsor to either continue the clinical investigation (with or without an amendment of the clinical investigation plan) or to stop enrolment into the clinical investigation based on safety concerns.

Ammended

A data safety monitoring board (DSMB) will be established prior to enrollment of the first patient. The DSMB is to review the safety data, including SAEs/SADEs, on a regular basis, or if a SADE occurs, and will advise on any changes required in the conduct of this clinical investigation.

Page 60, 8.1.1 Description of the type of clinical investigation:

RevC

The trial will be conducted as an open, prospective, multicenter single-arm clinical trial using the two- stage design described by Simon (Simon, 1989). In the first stage, 11 patients will have an ARGOS-IO pressure sensor implanted, after which enrollment will be halted until the patients have completed their 3 months follow-up visits and an interim analysis has been performed. The interim analysis will be reviewed by the DSMB. If two or more of these 11 patients in the first stage are found to have had an SADE, further enrollment into the study will be stopped. If not, enrollment will resume until another 11 patients have had an ARGOS-IO pressure sensor implanted. If two or fewer of the total 22 patients experience an SADE, a conclusion for safety will made at the 5% significance level. A corresponding 95% confidence interval for the SADE rate will be calculated according to the procedure of Koyoma (2008).

All patients who receive an ARGOS-IO implant will return for 10 follow-up visits to the clinic (day 1, 3, 10, 30, 60, 90, 120, 180, 240, 360) during the 12-month post-surgical period (see Table 6: Assessment Schedule). To allow comparison of the IOP measurement methods, IOP measurements will be made at every visit with GAT and with the ARGOS-IO systems beginning at V5 (day 30).

Ammended

The trial will be conducted as an open, prospective, multicenter single-arm clinical trial. All 22 patients will be enrolled consecutively, until a SADE occurs. In that case, the DSMB will be called, and decides whether the enrollment can be continued or not. If two or fewer of the total 22 patients experience an SADE, a conclusion for safety will made at the 5% significance level. A corresponding 95% confidence interval for the SADE rate will be calculated according to the procedure of Koyoma (2008).

All patients who receive an ARGOS-IO implant will return for 10 follow-up visits to the clinic (day 1, 3, 10, 30, 60, 90, 120, 180, 240, 360) during the 12-month post-surgical period (see Table 6: Assessment Schedule). To allow comparison of the IOP measurement methods, IOP measurements will be made at every visit with GAT and with the ARGOS-IO systems beginning at V5 (day 30).

Page 66, 8.3.3.1 Study stopping rules:

RevC

As described in section 9, the study will be conducted in two stages. In the first stage, 11 subjects will receive ARGOS-IO implants, after which implantation will be halted. Once these subjects have completed their 3 months follow-up visits, the interim results will be evaluated by the DSMB. The study will be stopped for safety reasons if at the time of the interim analysis two or more of these 11 subjects have had SADEs or if the DSMB otherwise determines that severe safety risks to the subjects exist.

If more than two patients in the first stage of the study experience SADEs, the study will be stopped for safety reasons.

The study may be discontinued at any time for administrative reasons; if new negative data about the investigational device resulting from this or any other studies becomes available; and/or on advice of the DSMB, the sponsor, the investigators, and/or the EC or regulatory authorities.

If the study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the Regulatory Authorities and the ECs of the reason for termination or suspension. If the study is prematurely terminated for any reason, the investigator should promptly inform the study subjects and assure they receive appropriate therapy and/or follow-up.

The study can be terminated at any time for any reason by the sponsor.

Ammended

Enrollment will be stopped at the occurrence of a SADE. At this point, a DSMB meeting will be called. The DSMB will then evaluate the SADE, and decides as to whether enrollment will be ended, and will also decide on how to proceed further with the conduct of the study.

The study may be discontinued at any time for administrative reasons; if new negative data about the investigational device resulting from this or any other studies becomes available; and/or on advice of the DSMB, the sponsor, the investigators, and/or the EC or regulatory authorities.

If the study is prematurely terminated or suspended, or enrollment is stopped, the sponsor will promptly inform the investigators, the Regulatory Authorities and the ECs of the reason for termination or suspension or stop of enrollment. If the study is prematurely terminated for any reason, the investigator should promptly inform the study subjects and assure they receive appropriate therapy and/or follow-up.

The study can be terminated at any time for any reason by the sponsor.

Page 84, 9.1 Statistical design, method and analytical procedures:

RevC

The primary purpose of this investigation is to assess safety of the investigational device. This will be judged statistically based on the number of individual patients experiencing serious device-related adverse events (SADEs). The study will be implemented in a two-stage design equivalent to the Simon optimum design to minimize the expected sample size (Simon, 1989). In the first stage, enrollment will be halted after 11 patients have received ARGOS-IO implants. An interim analysis will be conducted when these 11 patients have been followed-up for 3 months. If two or more patients experience SADEs in this time, the study will be stopped for safety reasons (Type I error rate = 0.05). If fewer than two have experienced SADEs, enrollment will be resumed and will be continued until a total of 22 patients have received ARGOS-IO implants. A final decision for safety will be drawn, if overall two or fewer of the total 22 patients have an SADE [SIMON optimum two stage design to minimize expected sample sizes, parameters: α=0.05, β=0.20, p_0 = 0.75 (proportion in stage 1 without SADE), p_1 = 0.94 (proportion overall without SADE)]. A corresponding 95% confidence interval for the proportion of the safety population with SADEs will be calculated using the method proposed by Koyoma and Chen (2008).

Table 1. Study design

	First Stage	Overall
SADE-free Subjects		
Proportion	$p_0 = 0.75$	$p_1 = 0.94$
Minimum number required	10	20
Subjects with SADE		
Proportion	$1 - p_0 = 0.25$	$1 - p_1 = 0.06$
Maximum number allowed	1	2
Total Number of Subjects	11	22

Ammended

The primary purpose of this investigation is to assess safety of the investigational device. This will be judged statistically based on the number of individual patients experiencing serious device-related adverse events (SADEs). Patients will be enrolled consecutively until a total of 22 patients have received ARGOS-IO implants. A final decision for safety will be drawn, if overall two or fewer of the total 22 patients have an SADE [parameters: $p_1 = 0.94$ (proportion overall without SADE)]. A corresponding 95% confidence interval for the proportion of the safety population with SADEs will be calculated using the method proposed by Koyoma and Chen (2008).

Table 2. Study design

		Overall
SADE-free Subjects		
Proportion		$p_1 = 0.94$
Minimum number required		20
Subjects with SADE		
Proportion		$1 - p_1 = 0.06$
Maximum number allowed		2
Total Number of Subjects		22

Page 87, 9.2 Sample Size Calculation:

RevC

The sample size calculation was based on the study's purpose of establishing safety.

To minimize the required sample size and consequently the number of patients exposed to risk while at the same time maximizing the chances of detecting safety events, a two-stage design based on the rate of non-events was chosen (Simon, 1989). The event of interest was defined as a serious device-related adverse events (SADEs). Based on a probability of non-events of p0=0.75 for the first stage and an overall acceptable probability of p1=0.94, a sample size of at least 11 evaluable patients in the first stage and additional 11 patients in the second stage are required. This maintains a type 1 error

probability of 5% and the power of 80% based on minimizing the maximal sample size and results in an expected sample size of 13.2 patients.

Ammended

The primary aim of this study is to show "safety", which will be evaluated based on the percentage of subjects who experience an SADE (= "non-safety), as defined in the primary endpoints.
The study will be declared a success if the final non-safety event rate is less than 6% (type II error rate of 0.20) The calculation is based on a design optimizing the minimum expected sample size with parameters α=0.05, β=0.20, p_0 = 0.75, p_1 = 0.94. According to Table 7, those parameters will be fulfilled if 2 or less SADE will occur in a sample of 22 patients.

Part 2: Interim Analysis

Page 16, Table: Synopsis, Row: Data Analysis and Statistics, Item: Interim Analysis:

RevC

An interim analysis to assess SADE will be performed, when the first 11 patients have completed the 3 month follow-up visit.

Ammended

An interim analysis to assess Safety and Performance will be performed, when the all patients have completed the 6 month follow-up visit or if an SADE occurs.

Page 87, 9.6 Interim Analysis:

RevC

One interim analysis is planned for this study. It will take place when all patients in the first stage have completed the first 3 months of the follow-up period and will determine whether or not to continue the study to the second stage based on the number of patients experiencing an SADE..

Ammended

An interim analysis is planned for this study. It will take place when all patients have completed 6 month follow-up period, or each time an SADE occurs, prior to the regular DSMB meeting

Part 3: Implant size selection

Page 74, 8.4.4.13 ARGOS-IO implant size assessment:

RevC

The ARGOS-IO implant size will be determined based on the horizontal White-to-White (WTW) measurement obtained with the IOL Master. At least three WTW measurements will be taken and the average calculated. The average in mm will then determine the right ARGOS-IO implant size (Table 5).

Ammended

The recommended ARGOS-IO implant size will be determined based on the horizontal White-to-White (WTW) measurement obtained with the IOL Master. At least three WTW measurements will be taken and the average calculated. The average in mm will be used for fitting the ARGOS-IO implant size (Table 5). The investigator may re-assess this selection if intraoperative findings prescribe a different implant size.

CIP amendment reviewed and approved by:

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